STATISTICAL ANALYSIS PLAN

Part 2 of Study

Title: A Multi-Center, Randomized, Double-Blind, Parallel-Group, Multiple-Dose, Adaptive Study Assessing the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of TTP399 in Adult Patients with Type 1 Diabetes Mellitus.

Protocol: TTP399-203, Amendment 5 (8 February 2019)

Study Drug: TTP399

Sponsor: vTv Therapeutics LLC

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1	Original Statistical Analysis Plan	13 December 2019	Original: no modification

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vTv Therapeutics LLC

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1 Introduction

TTP399 is a liver-selective glucokinase (GK) activator (GKA). TTP399 targets the enzyme GK, a member of the hexokinase family (hexokinase IV) that catalyzes the phosphorylation of glucose. GK acts as a glucose sensor and is a key regulator of glucose homeostasis. Studies show that mutations in the gene encoding GK can cause both hyperglycemia and hypoglycemia depending on the mutation, which suggests a critical role of GK in regulation of glucose homeostasis. Because TTP399 is liver-selective, it simulates the liver to metabolize glucose, independent of an effect on insulin secretion.

TTP399 has been investigated in 11 clinical studies in over 700 subjects (healthy volunteers and patients with T2DM), approximately 500 of whom received one or more doses of TTP399. In clinical studies evaluating T2DM patients, TTP399 has shown significant reductions in postprandial glucose, increasing % time in range and decreasing % time of hypo or hyperglycemia. In the 6-month Phase 2b clinical trial in type 2 diabetic patients on stable doses of metformin, TTP399 significantly reduced HbA1c and the effect was sustained for the duration of the study without significant hypoglycemia, dyslipidemia or ketoacidosis.

Prior studies have focused on T2DM. The mechanism of action and preclinical data suggest that the GK activator TTP399 may have benefit for the treatment of type 1 diabetes as adjunctive treatment to insulin.

The study is an adaptive study with 3 stages:

- the sentinel phase, which is an open label, GK activator dose escalation of approximately 6 patients with Type 1 diabetes (T1DM) on CGM (continuous glucose monitoring) and CSII (continuous subcutaneous insulin infusion) with up to 8 visits,
- Part 1 planned with approximately 30 randomized patients with type 1 diabetes on CSII with GK activator dosing or placebo for 12 weeks with up to 10 visits, and

- Part 2 with approximately 90 randomized patients with type 1 diabetes on CSII or MDI (multiple daily doses of insulin) on GK activator or placebo for 12 weeks with up to 9 visits.

The purpose of this statistical analysis plan (SAP) is to describe the approach of statistical analysis in order to support scientifically sound study conclusions. The approach will conform to FDA guidance as described in ICH E9, *Guidance for Industry Statistical Principles for Clinical Trials* (1998), the addendum to ICH E9, ICH E9 (R1) *Addendum On Estimands And Sensitivity Analysis In Clinical Trials To The Guideline On Statistical Principles For Clinical Trials* (2018).

1.1 Adaptive Trial

This study is an adaptive trial, which includes 3 studies under the same protocol. This SAP is focused on Part 2 of this adaptive study. This SAP conforms to standards set forth in *Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry* (CDER, CBER, November 2019). The intention of the adaptive nature of this protocol is to leverage potential advantages related to statistical analysis as depicted in the FDA final guidance.

1.2 Meta-analysis

This statistical analysis plan (SAP) is for the Part 2 of the study. The analysis of the sentinel phase suggested positive results, resulting in Part 1 being initiated. Part 2 was initiated following positive results from an analysis of Part 1. Completion of Parts 1 and 2 is anticipated to result in approximately 110 patients dosed for 12 weeks.

The intention for this study is that Part 1 subjects (dosed for 12 weeks) and Part 2 subjects (dosed for 12 weeks) will be combined in a meta-analysis using a methodology following the analysis plan for the meta-analysis, which will be similar to the methodologies specified in the SAPs for Part 1 and for Part 2. It is noted that the intention for the integrated analysis is specified in the study protocol, Section 10.4.No alpha is allocated to the meta-analysis; however, it was the intention from the design stage of this study.

1.3 Study Objectives

The study objectives for the entire study as depicted in the protocol are given below:

- ***Sentinel phase***

Objectives

The **primary objectives** of this study are:

- To investigate the pharmacokinetic (PK) profiles of the tablet formulation of TTP399 in patients with type 1 diabetes mellitus (T1DM) with continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM)
- To assess the safety and tolerability of TTP399 following 7 days of repeated dosing at up to 3 doses.

The **secondary objective** of this part of the study is:

- To evaluate the pharmacodynamic (PD) effect of TTP399 following multiple dosing (up to 7 days at up to 3 doses) in patients with T1DM to determine optimal efficacious dose to improve glycemic control and/or reduce mealtime insulin bolus

Outcome Measures

Primary Outcome Measures:

- Pharmacokinetic Measures: Cmax, Tmax, and AUC(0-τ), t1/2
- Adverse events, clinically significant changes from baseline in laboratory tests, vital signs and electrocardiograms (ECG) parameters

Secondary Outcome Measures:

- Change from baseline MMTT AUC 0-3h glucose
- Change from baseline in bolus insulin (number of units and / or number of bolus injections) for the last 3 days in each 7-day interval
- Percent change from baseline in bolus insulin for the last 3 days in each 7-day interval
- Change from baseline total daily insulin for the last 3 days in each 7-day interval
- Percent change from baseline total daily insulin for the last 3 days in each 7-day interval
- Change from baseline in average daily glucose for the last 3 days in each 7-day interval
- Percent time in target glycemic range (70-180 mg/dL); hyperglycemic range (Level 1 > 180 mg/dL; Level 2 (>250mg/dL) and hypoglycemic range (Level 1< 70mg/dL; Level 2 < 54 mg/dL)
- Percent time in target glycemic range of 70-140mg/dL during the last 3 days in each 7-day interval
- Mean post prandial (0-3hr) glucose during the last 3 days in each 7-day

interval
- Hypoglycemic events by CGM (≥15 continuous minutes of glucose reading <70mg/dL
- Glycemic variability (mean SD and CoV)
- Change from baseline of non-genomic biomarkers, glucagon and GLP-1
- Body weight

- ***Parts 1 and 2 (Following 12 weeks of dosing)***

Objectives

Primary Objective:

- To evaluate the pharmacodynamic (PD) effect of TTP399 following multiple day dosing (at 12 weeks) in patients with T1DM

Secondary Objectives:
- To evaluate the safety and tolerability of TTP399 administered for 12 weeks in T1DM patients

Exploratory Objectives
- Assess relevancy of non-genomic biomarkers in predicating responders and efficacy
- To assess changes in patient quality of life

Endpoints (Part 1 and Part 2)

Primary Endpoint:

- Change from baseline in HbA1c at 12 weeks

Secondary Endpoints:

- Change from baseline time in target glycemic range (70-180 mg/dL); hyperglycemic range (Level 1 > 180 mg/dL; Level 2 (>250mg/dL) and hypoglycemic range (Level 1< 70mg/dL; Level 2 < 54 mg/dL)
- Change from baseline in number of units of insulin (basal, bolus or total daily) dose
- Percent change from baseline in insulin (basal, bolus or total daily) dose
- Achievement of a decrease of at least 0.3% in HbA1c at Week 12 (responders)

Safety Endpoints:

- Adverse events, laboratory, vital sign and electrocardiograms (ECG) parameters

Exploratory Endpoints:

- Plasma (non-genomic) biomarkers
- Diabetes treatment satisfaction questionnaire (s)
- Change from baseline in number of bolus injections of insulin
- An analysis of responders HbA1c < 7% without any severe hypoglycemic events, weight gain, ketoacidosis

Endpoints (Part 1, Interim analysis):

An interim analysis plan that will describe the variables of analysis. Endpoints will include, but not be limited to the following:

Primary Endpoints:

- Change from baseline in bolus insulin (number of units) OR
  Change from baseline for time in target glycemic range (70-180 mg/dL)

Secondary Endpoints:

- Change from baseline for time in hyperglycemic range (Level 1 > 180 mg/dL; Level 2 >250mg/dL) and hypoglycemic range (Level 1< 70mg/dL; Level 2 < 54 mg/dL)
- Composite endpoint encompassing change from baseline HbA1c and risk of hypoglycemia as described in the SAP
- Change from baseline in average daily glucose

Safety Endpoints:

- Adverse events, laboratory, vital sign and electrocardiograms (ECG) parameters

Exploratory Endpoints:

- Change from baseline in basal or total daily insulin dose (number of units)
- Percent change from baseline in insulin (basal, bolus or total daily) dose
- Change from baseline glycemic markers (fructosamine and 1,5 anhydroglucitrol)
- Body weight
- Glycemic variability (mean SD and CoV)
- Change from baseline total daily insulin dose
- Percent change from baseline in total daily insulin.

1.4 Study Rationale

Treatment groups are TTP399 800 mg QD and placebo QD, which were selected based on prior clinical studies and research of currently available therapies and the results of the sentinel phase of the study, which evaluated doses up to 1200 mg. This study conforms to

regulatory guidance depicted in FDA adaptive design guidance: FDA guidance *Adaptive Design for Clinical Trials for Drugs and Biologics* (draft guidance, February 2010) and also the European Medicines Agency guidance *Reflection Paper On Methodological Issues In Confirmatory Clinical Trials Planned With An Adaptive Design* (October 2007). This study is an adaptive study, following advice depicted in these guidance documents from regulatory agencies regarding studies on drugs at the current stage of development of this compound.

1.5 Subject Population

The study population for Part 2 of the study includes adult patients between the ages of 18 and 70, inclusive, male or female with a historical diagnosis of T1DM at least 12 months prior to Screening, who were diagnosed with T1DM before the age of 40 years, Subjects must have HbA1c at Screening in the range of 7—9.5% (inclusive).

1.6 Study Treatment

Drug supplies will consist of 400 mg TTP399 and matching placebo tablets for oral administration.

TTP399 or matching placebo tablets will be packaged in 60 cc HDPE bottles with heat induction seal and child-resistant closures. Each bottle will contain 40 tablets.

Drug supplies should be stored at the study site in their original containers under locked, refrigerated [2° C to 8° C (36° F to 46° F)] conditions. Once dispensed to patients, medication can be stored at room temperature.

1.7 Randomization

Randomization by site is done in this study, so that each site is randomized separately. Investigators will assign a unique patient screening identification number sequentially to each patient who has signed the informed consent document. This identifying screening number will be retained throughout the duration of study participation.

At the time of randomization, patients are assigned a unique, randomization number based on site-based randomization scheme.

Part 2 introduces a stratification into the randomization to control balance between patients who enter the study on CGM and those who do not:

There are two strata:

- Patients currently on CGM with at least 2 months of experience with personal CGM without significant interruptions (i.e. > 2 consecutive weeks) prior to screening who agree to continue using their personal CGM throughout the study in addition to the Sponsor supplied CGM.
- OR patients currently not using a personal CGM prior to screening who agree not to use a personal CGM during the study

Patients will be randomized, in balanced allocation within each stratum, to one of the following treatment groups:

- TTP399 **800 mg** QD
- Placebo QD.

Approximately 90 patients will be randomized following once daily dosing regimens:

Table 1. Study Treatment Regimen

Regimen (planned number of patients)	**Dosing Regimen**	**Number of TTP399 400 mg tablets**	**Number of TTP399 Matching Placebo tablets**
A (n=45)	Placebo	0	2
B (n=45)	800 mg QD TTP399	2	0

1.8 Study Design

Each part of the study will have a screening period, a baseline period, an open label dose escalation phase (Sentinels Phase only) and a double-blind, placebo-controlled treatment period (Part 1 and 2, randomized 1:1 to placebo or TTP399). Part 1 and Part 2 will have an insulin dose adjustment period, if needed. Sentinel and Part 1 patients will have unblinded CGM the entire study and will be contacted by the site routinely to assess

safety. In Part 2 there will be two periods of sponsor provided (blinded) CGM. In addition to site visits, patients will be contacted throughout the study to assess safety as outlined in the Schedule of Activities. Phone calls are preferred, but texts are allowed. Pharmacokinetic samples will be collected throughout the study for all patients. A planned interim analysis may occur approximately 6 weeks after approximately 30 patients have been randomized in Part 1.

Each patient enrolled in Part 2 of the study will undergo screening procedures, a 2-week single-blind run-in period, a 12-week, double-blind treatment period, and a follow-up site visit. The study includes a total of up to 9 outpatient visits to the study site. Patients will visit the clinic for screening, undergo a basal insulin adjustment period of up to 3 weeks (if needed), have a single-blind placebo-run-in period, and then return to the clinic for visits on Days 1, 14, 42, and 84 for safety and efficacy assessments, followed by a safety follow-up evaluation 7 to 10 days following the final dose of double-blind study medication.

At Screening, patients will sign the Informed Consent Form and then be assessed for study eligibility.

Patients who are deemed eligible based on procedures completed at Screening will undergo a basal insulin adjustment period (if needed), and then they will return to the site at Week -2 for a placebo run-in period of at least 13 days in duration.

Randomization will occur on Day 1. Eligibility will be confirmed, and eligible patients will be randomized.

Patients will come to the study site for all site visits following an overnight fast (except water). When fasting is required, patients who do not meet the fasting requirement will not have blood or urine samples collected for laboratory assessments, but all other procedures will be carried out; those patients will be asked to return the next morning after an overnight fast for laboratory assessments.

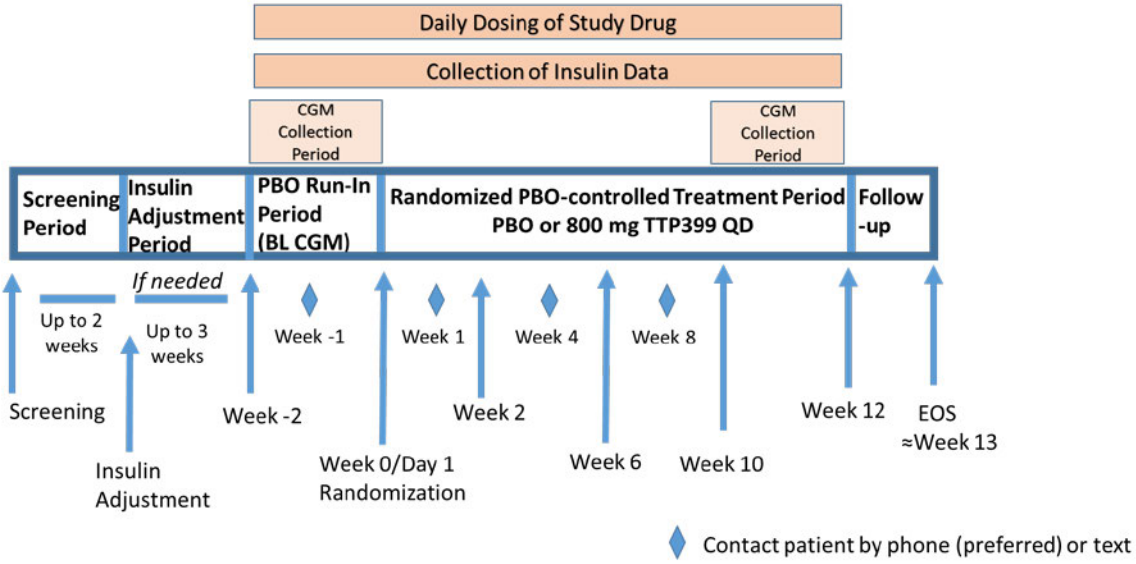
The first dose of study medication during each treatment period will be administered at the site immediately after enrollment (for the placebo run-in) or randomization (for the

double-blind treatment period). Patients will self-administer study medication (TTP399 or placebo) at home, with the exception of the morning doses administered on the first day of placebo run-in or the first day of double-blind medication, which will be administered by study staff. Morning dosing should occur at approximately the same, just prior to the morning meal.

Patients must return to the site approximately 7 to 10 days following the final dose of clinical trial material for a follow up visit. At this visit, final procedures will be completed, and the patient will be discharged from the study.

A depiction of the study design is given in Figure 1.

Figure 1. Study Design



The study is conducted at multiple sites in the U.S.

The overall structure of the study includes the following periods:

Screening: Screening procedures include obtaining informed consent and evaluations to determine eligibility for study participation. All screening procedures should occur within two weeks of the next visit (either basal insulin dose-adjustment or Week -2). .

Basal Insulin Dose Adjustment Period (Insulin Adjustment Visit): Once a patient has met all the entry criteria at the screening visit, the site will schedule a visit to determine if the patient's basal insulin dose needs to be optimized. If the patient is on a closed loop system for automated insulin delivery (e.g. MiniMed 670G) , then the basal adjustment period (up to three weeks) is required following the patient turning off the auto mode. If the patient is a new inpen™ (hereafter in this document called to as InPen) user, the basal adjustment period (up to three weeks) is also required.

Placebo-run-in Period (ending on Day 1 with first dose administration of double-blind treatment): During the placebo-run-in and baseline period, which begins at Week -2 prior to the administration of the first dose of double-blind trial medication, patients arrive at the site to receive single-blind placebo and to have Baseline assessments, including blood samples for clinical laboratory tests and for evaluation of concentrations (pharmacokinetics; PK).

Double-blind Treatment Period (Day 1 though Week 12): It is noted that "week 12" and "day 84" are used interchangeably in this study, defining a month as 28 days and a week as 7 days. During the double-blind treatment period, daily doses of oral, double-blind study medication are administered. Efficacy, dosing compliance, and safety assessments are taken, including vital signs, adverse events, electrocardiography, and concomitant medications. Blood draws are taken for PK evaluations and for biomarkers.

Follow-up Visit (7-10 days after last dose): Approximately 7 to 10 days following the last dose of study medication, final safety assessments are taken, including vital signs, adverse events, ECG, and concomitant medications.

1.9 Sample Size and Power Considerations

The protocol includes sample size considerations for Part 2 of the study. The Part 1 of the study is considered to be a pilot study within the adaptive study protocol to obtain initial placebo-controlled, double-blind study data to support the progression of the investigation to Part 2.

The following statements pertain to sample size determination for Part 2:

> "Assuming a standard deviation (SD) of 1%, 34 patients per group will provide 80% power to detect a difference between a group treated with TTP399 and the group treated with placebo of 0.7% in HbA1c using alpha = 0.049.
>
> "Randomization of 68 patients (34 patients randomized to each arm) will provide adequate power for this study to meet its objectives related to HbA1c changes.
>
> "Assuming 30% or fewer placebo-treated patients show improvement in HbA1c of 0.3% or better and assuming 60% or more patients treated with TTP399 will achieve improvement in HbA1c of 0.3% or better by Week 12, 49 patients per group will provide 80% power to detect a difference between TTP399 and placebo. Randomization of N=120 patients into the study to be included in the Part 2 analyses provides adequate power to achieve study objectives related to responder analysis.
>
> "It is noted that the randomization stratification for part 2 will be reflected in the randomization identification with a stratum digit.
>
> "It is noted that in this adaptive study, modification is permitted. (Section 10.2 of study protocol).

Rigorous calculations for the required sample size for the non-inferiority aspect of the study relative to the required sample size to achieve a conclusion of non-inferiority were not done during the development of the protocol. Using a non-inferiority margin of 0.3% (from the FDA guidance entitled Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutics Biologics for Treatment and Prevention (CDER; February 2008), the sample size required for non-inferiority is bracketed by the sample size required for adequate power for superiority of HbA1c.

1.10 Early Stopping, Data Monitoring, and Interim Analysis

This study has accommodation for one or more interim analyses. If an interim analysis is done, a separate interim analysis plan will include details of the planned analyses, disclosure, and plans to protect the integrity of the ongoing study.

Interim analysis may or may not be done for business purposes in any portion of this protocol.

1.11 Modifications from the Statistical Section of the Protocol

This SAP is consistent with the protocol with the following exceptions:

- The primary analysis is characterized more completely with change based on blinded evaluations and communications with key opinion leaders. Modifications of the statistical analysis that represent departures from the protocol are permitted in an adaptive study, and such changes are explicitly allowed in the protocol.
- A conditional sequence of hypothesis tests has been modified to reflect blinded evaluations and communications with key opinion leaders.

Any other modifications will be documented in amendments to the SAP or the clinical study report.

2 Statistical Hypotheses

The primary objective is to show superiority (using a 2-sided test) of TTP399 to placebo at 12 weeks in patients treated with insulin on a dichotomous variable to delineate patients treated with insulin plus placebo from patients treated with modified insulin with TTP399 added followed by a non-inferiority evaluation of change in HbA1c followed by a superiority evaluation of change in HbA1c .

It is noted that the insulin optimization is applied to all subjects who are not already optimized in the opinion of the investigator. After the start of double-blind study medication, intensive medical monitoring results in modifications of insulin for all patients. Under the alternative hypothesis of treatment benefit, the modification of insulin for subjects on active treatment may be altered as a result of the co-administration of TTP399. Modification of insulin for subjects on placebo is considered standard of care. It is concluded, therefore, that the placebo added to insulin standard of care is the control group for treatment with TTP399 added to a modified regimen of insulin.

The statistical evaluation including non-inferiority evaluation and hypotheses to be tested in Part 2 are as follows:

First Compound Statistical Evaluation (full alpha):

The first evaluation is non-inferiority of treatment with TTP399 800 mg daily plus a modified regimen of insulin and treatment with optimized insulin as determined by the insulin-optimization period of the study, if needed, per protocol:

- **Evaluation 1**:

  Noninferiority will be considered to have been established if the 95% confidence interval is completely bounded by the non-inferiority margin of 0.3%, which is specified in the draft guidance: *Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutics Biologics for Treatment and Prevention* (CDER; February 2008), Section V.G.1, “Typically we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative

estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials."

- The 95% confidence interval will be constructed for the difference between the two treatment groups in mean change in HbA1c to Week 12 using the ANCOVA model as described in the statistical methodology section.

- If the 95% confidence interval is entirely bounded by 0.3% (where a difference of 0.3% reflects the placebo mean is 0.3% better than the mean of the patients treated with TTP399), then the statistical conclusion will follow that treatment with 800 mg TTP399 combined with a modified regiment of insulin is non-inferior to placebo added to insulin following the usual standard of care.

Conditional on the statistical conclusion of non-inferiority of TTP399 relative to placebo, statistical evaluation continued.

It is noted that noninferiority relative to change from baseline in insulin is planned using the confidence interval approach to demonstrate that the maintenance of control of HbA1c achieved during the insulin-optimization period is not driven by an increase in insulin among subjects treated with TTP399. Formal evaluation of this aspect of non-inferiority is not planned, so the statistical evaluation is considered to be nominal rather than rigorous.

The Hochberg method is used for alpha control for Evaluation 2 and Evaluation 3.

- **Evaluation 2:**

  Superiority on HbA1c is evaluated:

  - H_{01}: The change from baseline in HbA1c at Week 12 for the group treated with 800 mg TTP399 is equal to that of the placebo group.

  - H_{11}: The change from baseline in HbA1c at Week 12 for the group treated with 800 mg TTP399 is not equal to that of the placebo group.

- **Evaluation 3:**

  It is noted that strict application of the Hochberg methodology implies that rigorous p-values may not be applicable in the event of failure to reject either hypothesis in Evaluation 2. The intersection hypothesis is, however, applicable, and it is the intention of this analysis plan to continue testing under the intersection hypothesis and interpret p-values as rigorous as opposed to nominal.

  Superiority on treatment response is evaluated:

  - H_{02}: The proportion of treatment responders at Week 12 for the group treated with 800 mg TTP399 is equal to that of the placebo group.
  - H_{12}: The proportion of treatment responders at Week 12 for the group treated with 800 mg TTP399 is not equal to that of the placebo group.

The study is declared to have met its primary endpoint if Evaluation 1 concludes TTP399 plus the modified regimen of insulin is noninferior to optimized insulin

And

Using the Hochberg method, either Evaluation 2 finds TTP399 is superior on HbA1c or Evaluation 3 finds TTP399 is superior on the proportion of treatment responders.

Conditional on achievement of endpoints, statistical evaluation continues.

Conditional Second Statistical Evaluation:

- **Evaluation 4:**

  Superiority on daytime time in range is evaluated:

  - H_{03}: The mean change in daytime time in range from baseline to Week 12 for the group treated with 800 mg TTP399 is equal to that of the placebo group.
  - H_{13}: The mean change in daytime time in range from baseline to Week 12 for the group treated with 800 mg TTP399 is not equal to that of the placebo group.

Conditional Third Statistical Evaluation:

- **Evaluation 5:**

Superiority on time in hypoglycemia using 70 mg/dl as the threshold is evaluated:

- H_{04}: The mean change in time in hypoglycemia using 70 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 is equal to that of the placebo group.

- H_{14}: The mean change in time in hypoglycemia using 70 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 is not equal to that of the placebo group.

Conditional Fourth Statistical Evaluation:

- **Evaluation 6:**

Superiority on time in hypoglycemia using 54 mg/dl as the threshold is evaluated:

- H_{05}: The mean change in time in hypoglycemia using 54 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 is equal to that of the placebo group.

- H_{15}: The mean change in time in hypoglycemia using 54 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 is not equal to that of the placebo group.

Conditional Fourth Statistical Evaluation:

- **Evaluation 7:**

Superiority on Quality of life Likert scale score is evaluated:

- H_{06}: The mean score for the single-item Likert scale for overall improvement in quality of life at Week 12 for the group treated with 800 mg TTP399 is equal to that of the placebo group.

- H_{16}: The mean score for the single-item Likert scale for overall improvement in quality of life at Week 12 for the group treated with 800 mg TTP399 is not equal to that of the placebo group.

3 Estimand Specification

This SAP is constructed to conform to regulatory guidance. In particular, this section is included as recommended by ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (30 August 2017).

In accordance with ICH E9 Addendum, the specification of the estimand is included in this SAP with the 4 attributes detailed in ICH E9 Addendum, Section A.3.1:

A. The Population, that is, the patients targeted by the scientific question:

   For this study, the population consists of subjects with type 1 diabetes who meet eligibility requirements for the study, have qualified through the basal insulin-optimization period (if needed) and the placebo run-in period, receive double-blind medication, and have at least one valid post-baseline measure of HbA1c.

B. The variable (or endpoint) to be obtained for each patient, that is required to address the scientific question:

   For this study, the primary endpoint is HbA1c with co-primary importance on treatment responsiveness (whether or not subjects are treatment responders).

C. The specification of how to account for intercurrent events to reflect the scientific question of interest:

   For this study, intercurrent events such as blood transfusion or medical treatment with prednisone or major modification in insulin regimen/doses outside the once recommended in the protocol that would render subsequent values as not protocol-meaningful will be set to missing (moved to the SDTM SUPPLB domain to facilitate sensitivity analysis that includes the values) and primary statistical methodologies of multiple imputation will be used to predict what the values were likely to be had the intercurrent event not happened.

D. The population-level summary for the variable that provides, as required, a basis for a comparison between treatment conditions:

   For this study, the population-level summary for the variable is the least-squares mean (LSM) of the treatment difference in mean change from baseline in HbA1c.

4 Populations of Analysis

In accordance with guidance from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *Statistical Principles for Clinical Trials E9* (1998), the following population of analysis will be used for all statistical analysis:

- The full analysis set (FAS) includes all randomized patients who receive at least one dose of randomized study medication with at least one valid value post-treatment value. The FAS is used for all efficacy analyses.
- The per-protocol set (PPS) includes all FAS patients who do not have significant protocol violations, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blinded data review meeting in accordance with guidance from ICH E9 (Statistical Principles).
- The safety analysis set (SAF) includes all patients who received at least one dose of study medication. The SAF is used for all safety analyses.

In accordance with ICH E9, patients lacking any valid, on-treatment assessment of HbA1c will be excluded from the FAS.

It is noted that the evaluations, reviews, and decisions planned to be made at blind data review meetings are consistent with regulatory guidance as depicted and recommended in ICH E9.

Solely to understand the influence of dropouts on study conclusions, the FAS will be partitioned into completers and dropouts.

Efficacy analysis will be done as randomized. Safety analysis will be done as treated.

PK analyses will be performed using the PK population, comprising those study participants who have received TTP399 and have sufficient PK data for analysis.

5 Specification of the Estimand

In accordance with guidance from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) ICH E9 (R1) Addendum On Estimands and Sensitivity Analysis In Clinical Trials to the Guideline to Statistical Principles tor Clinical Trials (2018), the characterization of the estimand includes the following attributes:

5.1 The Scientific Question of Interest

The scientific question of interest evaluates the potential superiority of TTP399 over placebo in the treatment of T1DM in patients who meet protocol eligibility criteria and do not require concomitant medications, blood transfusions, or other rescue therapies that would influence HbA1c measures (except for insulin), thereby rendering the subsequent values as uninterpretable for protocol-planned purposes.

5.2 The Population of Interest

The population of interest includes qualified patients who meet eligibility criteria specified in the protocol who do not require concomitant medications that would taint HbA1c measures for protocol purposes (except for insulin) or have blood transfusions and who complete 12 weeks of treatment with TTP399 or placebo.

5.3 The Variable of Interest

The endpoint or variable of primary interest is change in HbA1c. Additionally, a responder analysis is of keen interest, where a responder is a subject who shows stable or improved HbA1c at endpoint (change is zero or more), no treatment-emergent abnormal value in beta-hydroxybutyrate (BOHB), and no increase in hypoglycemic episodes below 54 mg/ml. Of key interest are parameters associated with glycemic control, including percentage of time in the target range and the coefficient of variation (CV). Important variables of interest from a safety perspective include time in hypoglycemic ranges and occurrence of adverse events of special interest, including severe hypoglycemia and DKA.

5.4 The Specification of How Intercurrent Events Are Reflected in the Scientific Question of Interest

An intercurrent event is any event that occurs after treatment initiation and either precludes observation of the variable or affects its interpretation (ICH E9 addendum, glossary).

Intercurrent events for Part 2 of this study include:

- Blood transfusion.
- Use of concomitant treatments that are known to be associated with impact on HbA1c, specifically use of steroids.
- Shift change in work schedule from day worker to night worker or other life event that may affect HbA1c, such as any situation or major protocol deviation from the usual insulin doses outside of the ones specified in the protocol.

Data from patients during periods of when the InPen or insulin pump fails cannot be interpreted for the protocol-planned purposes. Censored data will invoke statistical methodologies for coping with missingness.

5.5 The Population-Level Summary for the Variable

The mean change in HbA1c is of primary interest supported by the mean endpoint value of HbA1c to be used to compare patients treated with TTP399 with those treated with placebo. The placebo-subtracted proportion of responders is the population-level variable of interest for the responder analysis.

6 Variables of Analysis

6.1 Efficacy Variables

6.1.1 Primary Efficacy

The primary efficacy variables of analysis include the following:

- Change from baseline to Week 12 in HbA1c.
- Proportion of Responders, where a responder meets the following criteria:
    - HbA1c: has a change in HbA1c of less than zero (any improvement)
    - Ketoacidosis: has no treatment-emergent serum BOHB above the normal reference range
    - Lactic acidosis: has no treatment-emergent lactic acid above the normal reference range.
    - Hypoglycemia: has no treatment-emergent episode of severe hypoglycemia (related or not related).

6.1.2 Secondary Efficacy

Secondary variables of analysis include:

- Achievement of no more than trace ketones in urine post-treatment
- Achievement of no treatment-emergent abnormal value in serum BOHB
- Achievement of no more than trace ketones in urine or treatment-emergent abnormal value in BOHB in serum
- Change from baseline relative to:
    - Time in target glycemic range (70-180 mg/dL);
    - Time in hyperglycemic range
        - Level 1 > 180 mg/dL
        - Level 2 > 250mg/dL
    - Time in hypoglycemic range
        - Level 1 < 70mg/dL
        - Level 2 < 54 mg/dL
- Change from baseline in average daily number of units of bolus insulin dose
- Percent change from baseline in average daily insulin dose
- Achievement of a decrease of at least 0.3% in HbA1c at Week 12 (responders)

Additionally, analysis will be done on hypoglycemia both thresholds (54 mg/dl and 70 mg/dl) using the following variables:

- Change from baseline (2-week period) to Week 12 (2-week period) on the number of hypoglycemia episodes
- Proportion of patients with at least one more treatment-emergent episode of hypoglycemia at Week 12 (2-week period) relative to baseline (2-week period).
- Time-adjusted change from baseline on the number of hypoglycemia episodes.
- Proportion of patients with at least one more time-adjusted treatment-emergent episode of hypoglycemia at Week 12 than at baseline.

6.1.3 Tertiary and Exploratory Efficacy

- Standard deviation of daily CGM and associated CV%
- Plasma (non-genomic) biomarkers
- Diabetes treatment satisfaction questionnaire (s)
- Change from baseline in number of bolus injections of insulin
- An analysis of responders HbA1c < 7% without any severe hypoglycemic events, weight gain, diabetic ketoacidosis

Additionally, a quality of life (Likert Scale) question is classified as an exploratory variable of interest: At Week 12, the patient should be asked to respond to the following QOL question with one of the answers below. The answer will be entered in the EDC.

> Question: "How is your quality of life relative to study start?"
>
> Answers (choose one): markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, markedly improved.

The Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) is completed at Screening and Week 12, and the Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) is completed at the Week 12 visit. These questionnaires will be evaluated as exploratory variables of analysis in this Part.

6.2 Safety Variables

Safety is monitored in this study by collection of adverse events, vital signs, electrocardiography, and clinical laboratory measures with intensive medical monitoring for evidence of DKA or important hypoglycemic events. It is noted that all untoward events or experiences are reported as adverse events regardless of whether they are identified by clinical observation, patient reporting, physical examination, clinical laboratory test result, electrocardiography, or any other examination or test. It is noted that listings are reviewed by medically qualified individuals of vital signs, laboratory

data, electrocardiograms (ECG), and all safety data to ensure that safety signals are identified and reported in the analysis of the safety data from this study.

6.2.1 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is one that was not present at before the first dose of study medication in each period or represents the exacerbation of a pre-existing condition. It is noted that AEs that emerge during the placebo-run-in phase will be captured and reported separately from AEs that emerge during the double-blind-treatment period.

Safety variables of analysis include description of the following:

- Patients with TEAEs by Preferred Term (PT)
- Patients with TEAEs by system organ class (SOC) and PT within SOC
- Patients with any hypoglycemic TEAE by PT
- Patients with any severe TEAE
- Patients with any serious TEAE
- Patients with any related TEAE
- Patients with TEAEs that result in termination from the study

6.2.2 Vital Signs

Vital Signs variables of analysis include raw means and mean changes from baseline for the vital signs measured in this study:

- Sitting pulse rate
- Sitting systolic and diastolic blood pressures
- Bodyweight

6.2.3 Clinical laboratory assessments

Clinical laboratory variables of analysis include raw means and mean changes from baseline for the clinical laboratory measures in this study

- Hematology: hemoglobin, hematocrit, RBC count, platelet count, WBC count, total neutrophils (abs), eosinophils (abs), monocytes (abs), basophils (abs), lymphocytes (abs)
- Clinical chemistry: BUN, creatinine, calcium (total), sodium, potassium, chloride, total carbon dioxide, (bicarbonate), AST (SGOT), ALT (SGPT), alkaline phosphatase (ALK), total bilirubin, direct (conjugated) bilirubin, uric acid, albumin, total protein
- Lipid panel: total cholesterol, HDL-C, LDL-C, triglycerides
- Specialty laboratory tests: HbA1c, C-peptide, lactate, ketones, free fatty acids, GGT, fructosamine, glucagon, 1, 5 anhydroglucitrol.

A treatment-emergent abnormal value (TEAV) is a laboratory analyte that is abnormal after administration of study medication that was not present prior to the administration of study medication.

Safety variables of analysis include:

- Proportions of patients with TEAVs
- Proportions of patients with a TEAV in any liver function test (LFT) including ALT, AST, total bilirubin, alkaline phosphatase.

6.3 Pharmacokinetics Variables

Plasma trough concentrations of TTP399 will be examined as variables of analysis.

7 Statistical Methodology

Descriptive statistics will be used to summarize the data. Continuous variables will be presented showing number of observations available, mean, median, minimum, maximum, and standard deviations (or standard errors, depending on the variable) by visit. Categorical variables will be presented showing frequencies and percentages by visit.

Efficacy analyses will also be done on the FAS and, potentially, also on the PPS. If the PPS differs from the FAS by more than 10%, the analyses will be replicated on the PPS. If the PPS and the FAS do not differ by more than 10%, analysis may not be done on the PPS. Final judgments will be made at the blind data review meeting in accordance with ICH E9.

All tests will be 2-sided and use $\alpha = 0.049$ for the final analysis to accommodate planned interim analyses for which $\alpha = 0.001$ is allocated, thereby preserving a study-wise over all $\alpha = 0.05$. This penalty is applied regardless of whether or not there is an actual modification to the study structure, design, or analysis plans.

Data displays will include the following comparisons:

- **Placebo**
- **800 mg TTP399.**

MedDRA version 21.0 or later will be used. SAS version 9.4 will be used.

7.1 Follow-up Visit Data

This study includes a safety evaluation 7 to 10 days after the final dose of study medication. Due to ethical considerations, it may be necessary to allow a patient to take a protocol-prohibited rescue medication, which would render objective interpretation of subsequent assessments impossible. Data obtained at the Follow-up assessment, therefore, cannot be included in efficacy or safety analysis as part of the statistical analysis planning for this study. Data captured at this visit will be reported and summarized in data tabulations and listings, but interpretation must proceed with due caution.

7.2 Patient Disposition

A tabulation of subject disposition will be presented, including the number screened, the number treated with single-blind placebo, the number randomized, the number dosed with double-blind study medication, the number who withdrew prior to completing the study, and reasons for withdrawal for those subjects who withdrew from the study prematurely.

Subjects who are randomized, but not dosed, will be included in disposition tables and listings. A summary table will include numbers of subjects available for analysis by population of analysis, including efficacy (by analysis subgroup) and safety (all treated subjects).

Subjects who withdraw from the study during the treatment period (who terminated treatment with study medication prematurely) will be displayed separately from subjects who withdraw from the study between the end of treatment and the follow-up visit. Randomized subjects who withdraw from the study prematurely will be listed with randomization identification, age, sex, race, ethnicity, treatment group, date of first dose of double-blind medication, date of last dose of double-blind medication, date of last visit, and reason for discontinuation.

7.3 Baseline Characteristics and Demographic Data

Demographic data will be summarized for the FAS, PPS, and SAF. Summaries of continuous variables will include number of subjects, mean, median, minimum, maximum, and standard deviation. Summaries of categorical variables will include numbers of subjects in each category, by treatment and overall. The variables to be summarized will include:

- Age, gender, and race
- Weight, height, BMI
- Baseline HbA1c
- Use of InPen or Pump
- Use of personal CGM

- Age at diagnosis
- Years since diagnosis.

7.4 Extent of Exposure and Treatment Compliance

Exposure to investigational product for the SAF will be summarized including the following variables:

- Treatment duration, calculated as the number of days from the date of first dose of double-blind mediation to date of last dose, inclusive.
- Total number of doses taken
- Total dose taken (mg of TTP399, with 0 mg for placebo)
- Compliance by visit for the active study period, calculated as the number of doses taken divided by the number of days on active study, multiplied by 100% and capped at 100% for any subject.
- Overall compliance, calculated as the number of doses taken divided by 83 (the protocol-specified number of days of dosing), multiplied by 100% and capped at 100% for any subject.

Descriptive statistics will be used for assessment of treatment exposure and treatment compliance within each treatment group and among treatment groups. Continuous variables will be presented showing number of observations available, mean, median, minimum, maximum, and standard deviations by visit and summarized for the study overall. Categorical variables will be presented showing frequencies and percentages by visit and for the study overall.

7.5 Methodology for Missing Data

In general, for safety, missing data will not be imputed. Missing baseline data will be imputed with the latest available pre-dose value. In the event that no pre-dose value is available, for safety data or for insulin data, the first available data will be used for the baseline comparisons.

In general, for analyses on measures, multiple imputation methodology will be used to accommodate missingness. For dichotomous variables, non-responder imputation is used.

7.6 Analysis of Efficacy Data

The primary analysis as stated in the protocol is on change in HbA1c, and statistical methodology for measures is planned that follow standard statistical recommendations from regulatory authorities. Additionally, an important key efficacy analysis is the responder analysis, detailed in this SAP. The statistical methodology for the responder analysis is the standard Fisher's exact test.

7.6.1 Primary Efficacy

Efficacy analysis will be done on the full analysis set (FAS), consisting of all randomized subjects who receive at least one dose of randomized study medication (subjects lacking any valid post-dose HbA1c will not be included in the FAS, consistent with ICH E9 principles).

The primary analysis of the non-inferiority evaluation and the subsequent conditional superiority evaluation are done using the primary statistical methodology for change in HbA1c. The primary hypothesis test analysis will use the intent-to-treat methodology and a main-effects model for analysis of covariance (ANCOVA), with adjustment for baseline HbA1c levels and changes between screening and baseline (day 1, pre-dose assessment). Missing data will use multiple imputations methodology. Interaction terms will be examined in supportive analyses. In the event of a significant interaction term, the impact on analysis conclusion will be examined. The primary model will not include interaction terms. Assumptions underlying ANCOVA will be examined. If assumptions of ANCOVA are unwarranted and the validity of the ANCOVA becomes questionable, rank analogues will be advanced as the primary analysis. Multiple imputation (MI) methods will be used to handle missing data.

The primary analysis on treatment responders will logistic regression with baseline measure as covariables supported by the Mantel-Haenszel test controlling for randomization stratum.

The primary analysis will be conducted using the FAS following the intent-to-treat (ITT) principle.

Descriptive summaries will be produced for the actual values and change from baseline in HbA1c by treatment group, visit and overall.

Assumptions underlying ANCOVA will be examined. If assumptions of ANCOVA are unwarranted and the validity of the ANCOVA becomes questionable, rank ANCOVA will be advanced as the primary analysis.

Due to the insulin optimization period and the dramatic effect on HbA1c associated with that insulin therapy, the analysis of HbA1c will be done 4 ways:

1. Change from screening
2. Change from day 1
3. Change from the average of screening and day 1 (considered primary)

Additional analysis supporting the primary analysis will include a mixed model repeated measure (MMRM) analysis with treatment, time, and treatment-by-time interaction as fixed effects, baseline as covariate and subject as a random effect.

For completeness, an observed cases analysis will be done by visit in which no data are excluded, no data are imputed, and no data are represented at times other than when they were observed. As an alternative for handling missing data according to the rules of the primary analysis, a supportive analysis will be done using last-observation-carried-forward (LOCF).

For statistical analyses, 95% confidence intervals will be produced for the least squares means (LSM) in each treatment group, as well as the LSM differences as compared to placebo. For MMRM and ANCOVA, two-sided p-values will be displayed for the comparison against placebo.

To ensure robustness of analysis conclusions against parametric assumptions, rank analogues will be executed as supportive analysis. If the PPS differs from the FAS by more than 10%, the analyses will be replicated on the PPS. If the PPS and the FAS do not differ by more than 10%, analysis may not be done on the PPS. Final judgments will be made at the blind data review meeting in accordance with ICH E9.

All analyses will be done using the intent-to-treat (ITT) principle.

7.6.2 Secondary Efficacy

All secondary endpoints will use the FAS.

Categorical endpoints will utilize Fisher's exact test.

Continuous secondary endpoints will be summarized by treatment group and visit. MMRM will also be used to analyze those endpoints.

Statistical methodology for secondary analysis will conform to methodology for primary analysis following the ITT principle and using observed-cases approach and LOCF approach using the last assessment. The Likert-scale QoL question will be dichotomized as "improved quality of life" or "no change in quality of life or worse." Fisher's exact test will be done to compare subjects treated with TTP399 with subjects treated with placebo.

Measurement variables will be analyzed using ANCOVA and ANOVA procedures, using parametric (if warranted) and nonparametric methods. Parametric assumptions will be examined; if parametric assumptions are found to be unwarranted, rank analogues will be advanced.

Secondary efficacy analysis on measures that are continuous will examine drug effects within each treatment group using:

- Paired-t test (1-sample t-test)
- Wilcoxon (1-sample) test.

Within each treatment group, the significance of the percent change from baseline will be assessed using a paired-t test (1-sample t-test). Supportive analysis will be done using a Wilcoxon (1-sample) test.

7.6.3 Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) data will be analyzed with the following categories of interest:

- Level 2 hypoglycemia: < 54 mg/dl
- Level 1 hypoglycemia: < 70 mg/dl
- Normal or target: in the range 70-180 mg/dl
- Level 1 hyperglycemia: > 180 mg/dl
- Level 2 hyperglycemia: > 250 mg/dl

Supportive analysis will be done on the endpoint percentages of subjects in the target range or outside of the range by level.

Additionally, non-overlapping categories will be examined:

- Level 2 hypoglycemia: < 54 mg/dl
- Level 1 hypoglycemia: between 54 (inclusive) and 70 (not inclusive) mg/dl
- Normal or target: in the range 70-180 mg/dl
- Level 1 hyperglycemia: > between 180 (not inclusive) and 250 (inclusive) mg/dl
- Level 2 hyperglycemia: > 250 mg/dl

Average daily glucose at endpoint and change in average daily glucose will also be done as supportive analysis. The comprehensive analysis will also include standard deviation and CV.

7.6.3.1 Daytime analysis for Continuous Glucose Monitoring

There is particular interest in the effects of treatment with TTP399 on CGM during daytime hours when subjects are awake, eating, and moving. For purposes of analysis of daytime and nighttime (for completeness), the definitions of daytime and nighttime will be as follows:

- Daytime: 6am to 10pm (inclusive)

- Nighttime: 10pm to 6am (not inclusive).

7.6.4 Personal Devices Data for Continuous Glucose Monitoring

It is noted that patients were allowed into the protocol whether they used personal CGM devices or did not previously use them. If they reported that they did use personal CGM devices, the sponsor obtained (separate) consent for obtaining the data from the personal device. These data may or may not be used for exploratory or supportive analyses.

7.6.5 Insulin Device Data

The following data extracted from devices will be of supportive interest:

Mean over the period of

- basal insulin (Prescribed Basal insulin is used)
- bolus insulin
- Number of boluses
- Total insulin (as a measure and adjusted by bodyweight)

7.6.6 Ketones and Glucose

Although beta-hydroxybutyrate (BOHB) is a safety analyte, protection from ketoacidosis is a potential benefit for TTP399 over other treatments for T1DM, which makes the subgroup analysis for potential efficacy a useful analysis. Subjects will be categorized on BOHB as follows:

- Negative: Trace ketone in urine and in serum less than 0.20 mmoll/L (approximately 2 mg/dl)
- Mild: Plus one in urine or in serum 0.2 mmol/L (inclusive) – 0.29 mmol/L (inclusive) which is approximately 2 mg/dl – 2.9 mg/dl.
- Moderate high: Plus 2 in urine or in serum 30-40 mg/dl
- High: Plus 2 in urine or in serum 40-80 mg/dl (noninclusive)
- Marked high: Plus 3 in urine or in serum 80 mg/dl or more

Proportions of subjects will be analyzed for the following variables:

- Subjects with treatment-emergent abnormal values in BOHB
- Subjects with detectable ketones in urine beyond trace.
- Subjects with ketones in plasma or urine (TEAV in BOHB or detectable more than trace ketones in urine).

7.6.7 Interim Analysis

The study protocol includes accommodation for an interim analysis, which may or may not be done as a business decision. If interim analysis is done, details of the plans for this interim analysis will be described in an interim analysis plan, which will include intentions for disclosure and plans to protect the integrity of the ongoing study. The goal is to support the adaptive trial design for optimization of the scientific conclusions that can result from this study.

This study conforms to regulatory guidance depicted in FDA adaptive design guidance FDA guidance Adaptive Design for Clinical Trials for Drugs and Biologics (draft guidance, February 2010) and also the European Medicines Agency guidance Reflection Paper On Methodological Issues In Confirmatory Clinical Trials Planned With An Adaptive Design (October 2007).

7.6.8 Subgroup Analysis

6.5.7.1. Randomization Stratification Subgroups

Part 2 of the study includes stratified randomization with two strata:

- Patients currently on CGM with at least 2 months of experience with personal CGM without significant interruptions (i.e. > 2 consecutive weeks) prior to screening who agree to continue using their personal CGM throughout the study in addition to the Sponsor supplied CGM.
- OR patients currently not using a personal CGM prior to screening who agree not to use a personal CGM during the study

Subgroup analysis will be done for each stratum separately and combined across strata.

6.5.7.2. Subgroups defined by Age at Onset

Age at onset of TID will be used for subgroup analysis of subjects with earlier age at onset.

- Subjects with Age at Onset less than 21 years
- Subjects with Age at Onset 21 years or more

It is noted that late onset (age 40 years or more) was prohibited per the protocol; consequently, it is unnecessary to specify that subgroup as of interest.

6.5.7.3. Subgroups defined by Entry HbA1c cut at 8%

Subjects with lower HbA1c are more likely to have insulin dose reductions with TTP399 under assumptions of the mechanism of action. A subgroup analysis will be done for two subgroups:

- Subjects with Baseline HbA1c less than 8%
- Subjects with Baseline HbA1c 8% or more.

6.5.7.4. Subgroups defined by use of InPen versus Pump

Use of the InPen or not will be used for subgroup analysis.

- Subjects who use InPen
- Subject who use a pump.

6.5.7.5. Subgroups defined by Use of InPen calculator

Patients who use the InPen calculator may have a different insulin profile than those who do not. This variable will be used for subgroup analysis.

- Subjects who use InPen and use the calculator
- Subjects who use InPen and to do not the calculator
- Subjects who use a pump

6.5.7.6. Subgroups defined by C-peptide detectable or not at baseline.

Patients who have quantifiable levels of C-peptide at baseline are of particular interest. It is noted that the assay used for this study has a limit of quantitation for C-peptide of

0.004 ng/ml. Statistical analysis will be done on HbA1c in this subgroup and also on change in C-peptide.

- Subjects with baseline C-peptide is less than 0.004 ng/ml
- Subjects with baseline C-peptide is at least 0.004 ng/ml.

6.5.7.7. Subgroups defined by baseline bodyweight

Patients who have low bodyweight at entry may differ from those who are heavier at entry. Subgroup analysis defined by baseline bodyweight will include analysis of HbA1c changes and also changes in bodyweight.

- Subjects with baseline bodyweight 85 kg or more
- Subjects with baseline bodyweight less than 85 kg.

7.7 Analysis of Safety Data

7.7.1 Adverse Events

Adverse events reported in this study will be coded using MedDRA®, Version 21.0 or later. Coding will be to the lowest level terms (LLT). The verbatim text, the preferred term, and the primary SOC will be listed in subject listings. Summaries that include frequencies and proportions of subjects reporting AEs will include the preferred terms and the SOCs.

Adverse event summaries will be done by study phase: (1) pre-dose,(2) placebo run-in, and (3) double-blind treatment phase, (4) period beginning with the first dose of double-blind medication, including follow-up phase. The final category is considered the primary summary of TEAEs to support comparisons of TTP399 with placebo.

Adverse events summaries will be constructed displaying AEs in decreasing order of total frequency according to the numbers of subjects reporting the AE (not the number of reports).

- Number (percent) of subjects reporting TEAE by Treatment and overall in accordance.

A listing will be constructed that includes the subject identification, the dose group, TEAEs, MedDRA terms, seriousness, severity, causality related to study medication, causality related to insulin, elapsed time to onset, duration, and outcome.

Adverse events of special interest (AESI) will include diabetic ketoacidosis and hypoglycemia.

For purposes of analysis and reporting, hypoglycemia events will be limited to those in the first two categories (severe hypoglycemia and documented symptomatic hypoglycemia) in accordance with FDA's regulatory guidance *Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* (CDER, February 2008).

7.7.2 Hypoglycemia

- Three sources were included in this study for evaluation of safety focused on identifying important hypoglycemia: Adverse event reporting

  Adverse event reviews included specifications for blinded safety reviews (as described in safety review plan) with attention for identifying important hypoglycemia and specifications for medical monitoring also targeting hypoglycemia.

- Central Laboratory data

  Ongoing blind data review included targeted identification of values in ranges for very low (<54) and low (between 54 and 70) as reported by the laboratory data file from the core laboratory.

- Continuous glucose monitoring (CGM)

  The CGM data were included in the blind data reviews (consistent with ICH E9 guidance) with targeted identification of values in ranges for very low (<54) and low (between 54 and 70) as reported in the datafiles from the CGM sources.

7.7.3 Vital Signs

Vital signs (pulse rate, blood pressures, and weight) will be summarized by Pre-dose, Day 1 and mean values and mean change from baseline to each visit.

Clinically important values or changes in vital signs will be examined with summary tables and supportive listings for subjects meeting the criteria for values or changes of potential clinical concern (located in Section 13 of this SAP).

7.7.4 Clinical Laboratory Measurements

Because "exacerbations" of pre-existing abnormalities in laboratory analytes are examined using clinical judgment and are reported as TEAEs, additional analysis on TEAVs is limited to subjects with values that are normal prior to dosing and abnormal after dosing.

Adverse events of special interest also treatment-emergent abnormal values (TEAVs) in laboratory parameters related to liver function tests, specifically ALT, AST, bilirubin, and ALK.

Potentially clinically significant values in laboratory analytes will be examined in accordance with the table of values or changes of potential clinical significance in this SAP. Proportions of subjects in each treatment group who meet the criteria will be analyzed.

Laboratory data will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

Liver function tests have additional monitoring for this study.

To explore the potential for drug-induced liver injury consistent with *Guidance for Industry "Drug-induced liver injury: premarketing clinical evaluation"* (CDER, CBER, July 2009), subjects will be summarized and listed who meet the following criteria:

(1) Elevations in either AST or ALT of at least 3-times the upper limit of normal, and

(2) An accompanying abnormal bilirubin.

Additionally, a summary and listing will be examined for subjects with elevations in either AST or ALT of at least 3-times the upper limit of normal, regardless of bilirubin.

7.7.5 Electrocardiography

Electrocardiography data will be summarized by Baseline and mean values and mean change from baseline to each assessment.

Corrections to QT intervals will be made by Fridercia's method. Categorical analysis will be done consistent with ICH E14, "Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs" (October 2005). Subjects will be categorized and summarized according to:

- Absolute QTc interval prolongation:
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from baseline in QTc interval:
  - QTc interval increases from baseline > 30
  - QTc interval increases from baseline > 60.

For purposes of analysis, the baseline will be defined in two ways:

- Mean of triplicate values at baseline(so that the analysis for the groups and the individuals will be on change to each visit from the mean pre-dose triplicate measures value).
- Maximum of all pre-dose values (so that the analysis for the groups and the individuals will be on change to each visit from the worse pre-dose value).

An additional analysis will include change from the worst pre-dose value to the worst post-dose value.

7.8 Pharmacokinetics Analysis

Plasma trough concentrations of TTP399 will be summarized at each scheduled assessment time point with the following descriptive statistics: number of subjects (n), mean, standard deviation (SD), coefficient of variation (CV%).

7.9 Concomitant Medications

Concomitant medications will be coded and summarized using World Health Organization Drug Dictionary (WHO-DD).

8 Data Conventions

The following analysis conventions will be used in the statistical analysis.

8.1 Definition of Baseline

For safety evaluations, the baseline assessment for all measurements will be the mean of all pre-dose values that are considered to be valid taken prior to the initiation study double-blind medication

For HbA1c efficacy evaluations, the baseline measurement will be the average of the pre-treatment measures taken prior to initiation of double-blind study medication (first dose of double-blind study medication).

For CGM, the baseline measurement will be the average of the latest available days of CGM measures taken prior to initiation of double-blind study medication (first dose of double-blind study medication) and beginning with the first day of single-blind placebo study medication (first dose during placebo-run-in period), noting that there must be at least 10 days of CGM data to enable a meaningful average calculation. For insulin, the baseline measurement will be the average of the latest available days of insulin measures taken prior to initiation of double-blind study medication (first dose of double-blind study medication) and beginning with the first day of single-blind placebo study medication (first dose during placebo-run-in period).

For other efficacy evaluations, the baseline measurement will be the latest available (at least 10 days required), valid measurement taken prior to initiation of study medication (first dose).

8.2 Continuous Glucose Monitoring and insulin conventions

Continuous glucose monitoring (CGM) measures are automated by device. Insulin data are collected from InPen or pump devices (some of which is keyed) and curated by qualified data managers. It is noted that prescribed insulin is used for basal insulin, and recorded insulin is used for bolus.

Gaps may occur in either parameter. The following conventions will be used:

- There must be at least 10 days of data available to support any period calculation of summary statistics.
- Day 1 and Day 84 will not be used in any calculation of CGM or insulin.
- Other visit days will not be used, due to potential disruptions and likely gaps. An important note is that all CGM data will be included in the evaluation of hypoglycemia events.
- Data from shift workers (individuals who work outside of normal business hours) will not be used for CGM.
- Insulin data from days with pump failure will not be used.
- If there is a gap in the measure of more than 8 hours, the 24-hour period will not be used.
- If < 80% of the data are available, the measure will not be used.
- If blind review (done in accordance with ICH E9 guidance) identifies a gap for which inclusion of the day could be misleading, the day will not be used.
- If a glucose value exceeds 400 mg/dl, the event is examined blinded to treatment for evidence of significant deviation from the prescribed insulin regimen, and if blind review determines that there is likely significant deviation from the prescribed insulin regimen, the days CGM and insulin data will not be used.
- Device manufacturers for CGM have researched and documented that improvements in HbA1c as much as 1% can be observed within 3 months of beginning use of the CGM device. In this subject population in consideration for the mechanism of action for GKA, it is unexpected for a subject to experience changes in HbA1c of more than 1% in either direction. Any observed change of more than 1% will be queried to determine whether or not the use of the CGM began with the initiation of the study or whether there is some other medical explanation from the principal investigator that may reveal a major protocol deviation or a dramatic change that is not interpretable for protocol purposes. Blind review (done in accordance with ICH E9 guidance) will evaluate protocol suitability of the data, if there are explanations disallowed by the protocol; such

cases will be judged for appropriateness for use in the primary estimand. Multiple imputation based on recursive regression will be used to predict unusable data for the primary analysis (supportive analysis will be done using all available data).

- Significant holidays including Thanksgiving Day and Christmas Day are excluded from analysis of CGM.

8.3 Invalid Data

Intensive data management efforts focus on identifying invalid data, providing queries to the investigator, and having the site resolve all issues so that it is not necessary for any data to be accommodated by the sponsor. However, in the unlikely event that data from ECG, vital signs, or other data sources are deemed to be highly improbable during blinded data review (done in accordance with ICH E9 guidance) that includes medical, clinical, and data management consensus, invalid will be set to missing. Examples include pulse rate and blood pressures values when changes in antihypertensive medications have been introduced or changes in lipid measurements in the presence of changes background medications for lipid control. Conventions for determination of invalid data will be made blinded to study treatment and documented in the Data Management Plan, the minutes to a blind data review meeting (done in accordance with ICH E9 guidance), in the study data tabulation model (SDTM) datasets, in the set of tables, figures, and listings (TFLs) appended to the clinical study report (CSR), or in the text of the CSR.

8.4 Intercurrent Events

This SAP is constructed to conform to regulatory guidance. In particular, this section is included as recommended by ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (30 August 2017).

ICH E9 Addendum defined an intercurrent event as an event that occurs after treatment initiation and either precludes observation of the variable or affects its interpretation.

For this study, intercurrent events such as blood transfusion or medical treatment with prednisone that would render subsequent values as not protocol-meaningful will be set to missing (moved to the SDTM SUPPLB domain to facilitate sensitivity analysis that includes the values) and primary statistical methodologies of multiple imputation will be used to predict what the values were likely to be had the intercurrent event not happened.

It is emphasized that values representing intercurrent events as determined by blind data review (done in accordance with ICH E9 guidance) by medical, clinical, and data management will be flagged as not protocol relevant in the SDTM LB domain, and these values will be moved to the supplementary domain (SUPPLB) of the SDTM dataset; the flag in the LB dataset indicates a value has been moved for analysis purposes. These values will be considered to be missing, and the planned statistical methodologies for coping with missing data will be applied for primary analysis. Supportive analysis will be done to evaluate with impact of this value on study conclusions.

8.5 Missing Data

Blind data review is recommended by ICH E9 to identify issues that can affect analysis prior to database lock, and this SAP is updated in accordance with the recommendation.

Missing data will be handled using multiple methodologies to ensure valid conclusions and to ensure robustness against methods of handling missing data.

8.6 Dropouts

If a subject withdraws from the study, if the date of an adverse event is not available and a determination of whether or not the event is treatment emergent cannot be made, by convention the event will be considered to be treatment emergent.

8.7 Visit Windows

Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

8.8 Handling of PK Data below limit of quantitation (BLQ)

Concentration values that are below the limit of quantitation (BLQ) are set to zero for summary statistics and mean concentration-time profiles.

8.9 Handling of Dropouts or Missing PK Data

For the concentration data analysis, missing data will not be imputed; analyses will be performed only on observed data. There are to be no substitutions made to accommodate for missing data.

8.10 Unscheduled Assessments

Extra assessments (laboratory data, ECG, or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not by-visit summaries. It is noted that unscheduled data are included in summaries of change to minimum, maximum, first on treatment, last on treatment, and last available. If more than one laboratory value is available for a given visit, the observation identified by the investigator to be the scheduled assessment will be used in summaries; all observations will be presented in listings.

Data from unscheduled assessments will be included in longitudinal data summaries (e.g., minimum, maximum over time). Data planned at scheduled times for which unscheduled assessments are taken will not be reflected in by-visit summaries.

9 Analysis Deviations

All statistical analyses and summary information will be generated according to this analysis plan. Any deviation from this plan will be documented in the clinical study report. Exploratory analyses are permitted per protocol; those analyses will not be considered to be deviations.

10 Software

All analyses will be done using SAS Version 9.4.

11 Data Displays

The plans for displaying data will conform to this guideline and also to ICH E3 (*Structure and Content of clinical Study Reports)*, and to ICH E9 (*Statistical Principles for Clinical Trials*).

The following excerpt from ICH E3 (1996) applies to this SAP:

> "The guidance provided below is detailed and is intended to notify the applicant of virtually all of the information that should routinely be provided so that post-submission requests for further data clarification and analyses can be reduced as much as possible. Nonetheless, specific requirements for data presentation and/or analysis may depend on specific situations, may evolve over time, may vary from drug class to drug class, may differ among regions and cannot be described in general terms; it is therefore important to refer to specific clinical guidelines and to discuss data presentation and analyses with the reviewing authority, whenever possible. Detailed written guidance on statistical approaches is available from some authorities.
>
> "Each report should consider all of the topics described (unless clearly not relevant) although the specific sequence and grouping of topics may be changed if alternatives are more logical for a particular study" (p. 2).

In accordance with FDA and ICH guidance, tables, figures, and key data listings are planned. Exploratory and data-driven data displays may also be generated.

The following displays will be included, but are not limited to, the following:

- Investigator Enrollment Summary
- Summary of Accountability (number screened, enrolled, randomized, treated, completing, withdrawn, by reason; listing of withdrawals with study day and reason)
- Summary of Subject Tracking (enrollment, visit attendance, withdrawal)
- Summary of Demography and Background Data
- Concomitant Medication Use (selected medications)

- Summary of HbA1c
- Summary of CGM
- Summary of insulin usage
- Summary of C-peptide
- Summary of Lactate
- Summary of Glucagon
- Summary of Body Weight
- Summary of Adverse Events
- Summary of Adverse Events by severity and by relatedness (study drug or insulin)
- Summary of Adverse Events of Special Interest
- Summary of Vital Signs
- Summary of ECG Data
- Summary of Laboratory Data, including LFTs
- Listing of all Adverse Events
- Listing of all Adverse Events that resulted in Death
- Listing of all Serious Adverse Events
- Listing of all Adverse Events resulting in Study Termination
- Listing of Treatment-emergent Abnormal Values for Clinical Laboratory Data
- Listing of Clinical Laboratory Data (changes and percent changes)
- Listing of Vital Signs Data
- Listing of ECG Data
- Listing of Concentration Data

12 References

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5. Ludvik, B, Neuffer, B, Pacini, G. (2004, February). Efficacy of Ipomoea batatas (Caiapo) on diabetes control in type 2 diabetic subjects treated with diet. Diabetes Care, Volume 27, Number 2.
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7. European Medicines Agency. (2007, October). Guidance “Reflection Paper On Methodological Issues In Confirmatory Clinical Trials Planned With An Adaptive Design.”
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10. CDER and CBER (2010, February). FDA draft guidance Adaptive Design for Clinical Trials for Drugs and Biologics.
11. National Research Council. (2010). The prevention and treatment of missing data in clinical trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.
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13 Schedule of Time and Events

Schedule of Activities (Part 2)	Screening	Basal Insulin Adjustment Period	Baseline CGM Period (Week -2 to Week 0)	Dosing Period (Week 0 to Week 12)					ET	E0S
Visit	**Screening**	**Basal Insulin Adjustment**	**Week -2**	**Week 0 /Day 1**	**Week 2**	**Week 6**	**Week 10**	**Week 12**	**ET**	**F/U**
Visit duration/window		**Up to 3 weeks**	**At least 13 days**		**± 3d**	**± 3d**	**± 3d**	**At least 13 days**		
Sign informed consent	X									
Registration	X									
Enrollment			X							
Randomization				X						
Collect demographic information	X									
Review of Inclusion/Exclusion Criteria	X		X	X						
Medical history/ AE monitoring	X		X	X	X	X	X	X	X	X
Concomitant Medication history/update	X		X	X	X	X	X	X	X	X
Physical exam	X[1]			X[2]				X[2]	X[2]	
Body weight	X		X	X	X	X		X	X	X
Sitting vitals and blood pressure	X		X	X[4]	X	X		X	X	X
Supine 12-lead ECG	X		X	X[5]	X	X		X	X	X
Clinical chemistry, hematology, lipids and glycemic markers[3]	X			X[3]	X	X		X	X	X
Collect PK samples[6]				X		X		X	X	
Collect retention samples (optional, exploratory)				X		X		X	X	
Collect urine for urinalysis	X			X	X	X		X	X	X
Collect urine for pregnancy test[7]	X[7]		X	X[7]	X	X	X	X	X	X[7]
Administer DTSQs	X							X		
Administer DTSQc								X		
Ask QOL question and enter answer in EDC								X		
Provide glucometer and glucometer strips, if needed[8]		X	X	X	X	X	X			
Provide insulin dosing collection device (if needed)[9]		X	X							
Apply Sponsor CGM			X				X			
Collect and Review Sponsor CGM[10]				X				X	X	
Collect insulin dosing data and glucose data needed for insulin adjustment[11]		X	X	X	X	X	X	X		X
Administer study drug with morning meal[12]			X	X						
Collect unused drug/compliance check (via pill count)				X	X	X	X	X	X	
Dispense blinded study medication based on IWRS			X	X	X	X	X			
Contact patient by telephone or text [13]		X	X	X		X	X			

[1] Full physical exams, including height, are to be conducted at Screening
[2] Limited physical exams will be conducted at Week 0 and Week 12 and ET (if applicable)
[3] Refer to Laboratory Manual for Sample Collection Instructions and Appendix 2 (Part 2); At Week 0/Day 1 visit confirm patient is fasted prior to labs. Reschedule visit if subject is not fasted.
[4] Baseline vitals obtained in triplicate, prior to dosing on Week 0, single readings all other visits except Week 10 (no vitals)
[5] Baseline ECG obtained in triplicate, prior to dosing on Week 0, single readings all other visits except Week 10 (no ECGs)
[6] Blood samples will be obtained for TTP399 concentrations prior to dosing if dosing is conducted at visit
[7] Urine pregnancy tests should be conducted for all females at Screening, Week 0 and F/U. Urine pregnancy tests for WCBP are required at all visits.
[8] Glucometers and related supplies will be supplied to patients who don't have CGM devices or have CGM devices that require calibration.
[9] Patients using MDI will be provided an electronic device to collect insulin dosing information to use throughout the trial. Device will be provided at either the basal insulin adjustment period visit, if applicable, or the Week -2 visit if no basal insulin adjustment period is needed.
[10] For CGM collection information refer to Section 4.2 Part 2
[11] For insulin dosing collection information and instructions on insulin dose adjustments refer to Section 4.3 Part 2 and Section 8.11
[12] Administer study drug following VS, ECG, and blood and urine sample collections at Week -2 and Week 0/Day 1. Meal can be provided by the site or brought to the site by the patient.
[13] Site should contact the patient approximately every third day during insulin adjustment period and at Week -1, Week 1, Week 4, and Week 8 of the dosing period. Phone call is preferred, but text is allowed.

14 Values of Clinical Concern

Parameter	Threshold (study-specific threshold calculated)
Hematology	
Hemoglobin	<8.5 g/dL
Hematocrit	<25 %
WBC (Leukocytes)	<0.6 x LLN
Platelets	<0.5 x LLN
Total Neutrophils (Abs)	<1000/uL
Lymphocytes (Abs)	<500/μL
Chemistry	
Total bilirubin	>2.5 x ULN
AST	>3 x ULN
ALT	>3 x ULN
Alk Phosphatase	>3 x ULN
Creatinine	>2 mg/dL
BUN	>1.4 x ULN
Calcium	<6.0 mg/dL and >13.0 mg/dL
Triglycerides	Two tiers: ≥500 mg/dL and ≥ 1000mg/dL
Electrocardiogram	
PR interval	≥200 msec **and** ≥25% increase from baseline
QRS interval	≥200 msec **and** ≥25% increase from baseline
QTcF interval	≥500 msec New onset. ≥30-60 msec increase from baseline >60 msec increase from baseline
Vitals (sitting)	
SBP	≥190 mmHg (entry is < 160 mmHg) Systolic <80 mm Hg Decrease from baseline ≥30 mmHg
DBP	≥ 110 mmHg (entry is <-90 mmHg) <50 mm Hg Change from baseline of 20mmHg (increase or decrease)
Heart Rate	<50 bpm **and** >/=25% decrease from baseline >100 bpm **and** >/=25% increase from baseline

Parameters not provided with specific thresholds for clinical concern: RBC count, eosinophils, basophils, monocytes, direct or indirect bilirubin (just total as shown above), chloride, albumin, total protein, insulin, total cholesterol, HDL, LDL, urinalysis, pulse rate from VS (rely on ECG heart rate).