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CLINICAL TRIAL PROTOCOL

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

Compound:	**TTP399**
Compound name:	**N/A**
US IND Number:	**78,649**
EudraCT Number:	**N/A**
Protocol Number:	**TTP399-203**
Clinical Phase:	**Phase 1b/2**
Version and Date:	**Amendment 5 FINAL 08FEB2019**

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Document	Version Date	Summary of Changes
Original	30AUG2017	--
Amendment 1	28SEP2017	• Eliminated sentinel inclusion criteria # 11 for historical c-peptide value • Changed the maximum total daily dose from 1600mg to 1200 mg • Added to Section 4.2 and the Appendix that patients would also be given transmitters • Added that "Visits should occur as close to scheduled Day as possible." in Section 7.1 • Added additional patient instructions if ketoacidosis test strips are positive in Section 4.4 • Clarified dosing instructions for outpatient clinic dosing to occur with water sufficient for swallowing • Clarified at home dosing to occur approximately one hour before the meal • Updated text in Section 8.6.4 regarding collection of the glucagon/GLP-1 biomarker sample to align with Figure 5 and Table 1 • Updated language appendix with relevant Continuous Glucose Monitoring information • Corrected inconsistencies and added additional abbreviations • Corrected typographical and grammatical errors
Amendment 2	20DEC2017	• Changed the amount of insulin dosing prior to MMTTs o Reduced the amount of insulin to 50% of the patient's normal bolus insulin dose prior to the Day -7 MMTT to prevent the risk of hypoglycemia. Modifications were made in Sections 7.1.2 and 8.6 and Figure 2 o Have patients dose with 50% of the patient's normal bolus insulin dose prior to the MMTT where TTP399 is also dosed, i.e. Days 1, 8, 15 and 21. Modifications were made in Section 7.1.4, 7.1.6 and 8.6, and Figure 2
Amendment 3	10APR2018	• Provided protocol synopsis table in place of protocol summary section for clarity • Added time frame (indicated in bold) that was inadvertently omitted from exclusion criterion 1. The criterion now reads as follows: a history of DKA **within the last**

		year. • Added time frame (indicated in bold) that was inadvertently omitted from exclusion criterion regarding weight loss. The criterion now reads as follows: fluctuation of >5% in body weight **within three months prior to** the Screening visit [Sentinel Ex 6 and Part 1 and 2 Ex 9] • Added language barrier as exclusion criteria for Part 1 and 2 [Ex 23] • Added separate lines for collecting urine for safety labs and collecting urine for pregnancy tests for women in Schedule of Activities and specified pregnancy test in Section 7.1.2. for Day -7 collected to clarify • Replaced collection of patient's CGM data from *Baseline to day of last dose* to from *Screening through the Follow-up visit* to be consistent with the Informed Consent Form 11Oct2017 (Section 4.2) • Added to Section 8.2 that standardized conditions for body weight measurements could also be with "minimal clothing with no shoes or heavy accessories (e.g., jewelry or belt) • Eliminated the requirement to perform vitals on Day 1 in triplicate (for Sentinel Phase only). Single values will be collected since no safety concerns with vital signs have been identified in patients dosed to date with TTP399 and the time needed to collect triplicate values would prolong the fasting period for these patients, potentially creating unnecessary safety issues [Section 8.5 and Schedule of Events (Sentinels)]. • Section 9.8.2 Reporting of Hypoglycemia has been updated to include the specific reporting of hypoglycemia and align with the classifications published by the International Hypoglycaemia Study Group (Diabetes Care 2017, 155-157) • Changed Part 1 Interim analysis is now to occur approximately 6 weeks after 30 patients have been randomized instead of after 4 weeks of dosing. Statistical sections were modified to support this change. • Week 6 visit was added to support the interim analysis for Part 1 (Schedule of Activities), Figure 3 and Section 7.3.3 • In Part 1, eliminated all MMTTs and blood samplings associated with the MMTT. Blood collections for PK, Glucagon/GLP-1, c-peptide and retention samples were changed to occur with other lab sample collections. Sections modified include Schedule of Events, Objectives and Endpoints, Figure 3, Section 4.1, Section 8.6 and Section 7, Table 1 (Part 2), Table 2. • Change patient dosing instruction for Part 1 to occur "with their morning meal" instead of 1 hour "prior to their

		morning meal" • Updated Section 4.2 to include the continued use of unblinded Continuous Glucose Monitoring in Part 1. • Added guidance for PI regarding Insulin Dose Adjustment during the study to Section 8.11 • Added the use of diabetes treatment questionnaire(s) at Screening and Week 12 and QOL question at Week 12 for Part 1 and 2 [Schedule of events, Section 7.2.1, 7.2.7, 7.3.1, and 7.3.4, 8.12 and 8.13] • Added Table for laboratory sample collections by visit for Part 1 [Appendix 2] • Noted that enrollment of consented patients who have met screening criteria when the enrollment goals are met will continue until up to a total number of 140 patients enrolled in Parts 1 and 2 (Section 3 and 5.2) • Section 4.2 was updated to include unblinded CGM throughout the study instead of periods of blinded CGM. • Modified recording requirements and included use of CGM App in place of study diary for Part 1 (Section 4.2 and 4.3) • Updated Section 5.2 to include the requirement of patients in Part 1 to use CGM and CSII. • Excluded patients that were not compliant with CGM requirements or study drug dosing during the CGM baseline period (Week -2 and Week 0/Day 1) in Section 5.2.2 • Updated Section 6 to include additional information for drug dispensing for Part 1 • Increase BMI from ≤ 32 kg/m2 to ≤ 35 kg/m2 for Inclusion criteria 8 (Part 1 and 2) • Added reference to Section 9.7 on reporting AEs upon patient withdrawal (7.2.10 and 7.3.6) in Parts 1 and 2 • Eliminated the statement allowing the investigator to repeat a laboratory assessment once during screening [Sections 7.2.1 (Part 1) and 7.3.1 (Part 2)] • Changed "dosing of TTP399" to "dosing of study drug" in Schedule of Events and added dosing at Week -2 to align with dosing of either placebo and TTP399 • Added a Week 2 visit for Part 2 (Section 7.3.4) • Added Sections 7.2.1, 7.2.3 and 7.2.4 for phone contact (Part 1) • Noted that patients in Part 1 and 2 should continue to eat meals per their normal routine with no predetermined carbohydrate limits [Section 4.1] • Moved safety related secondary objectives and endpoints to specific safety objectives and endpoints section. [Section 2] • Section 2: Eliminated the Objectives of the interim analysis. Modified Objectives and Endpoints of the Part 1 and 2 analysis

		• Section 7.2 Includes instructions that if patients are not fasting at Week 0/Day 1 the patient visit should be rescheduled and if the patients are not fasted for other visits, the visit will be conducted, but the lab requisition form should indicate the patient was not fasted. • Added an Insulin Dose Adjustment Period of up to 3 weeks for patients in Part 1 and 2, if needed (Protocol Synopsis, Schedule of Activities and Section 7.2 and 7.3.2) • Updated Sections 3.3.2. and 3.4.1 and 3.4.2 with dose selection of 800mg QD dose and the rationale for progression into Part 1 and Part 2 • Updated in clinic dosing in Section 6.5.2 to require in clinic dosing only at Week -2 and Week 0/Day 1 due to the elimination of MMTTs. • Included statement for site to advise patients to eat their morning meal after the Week -2 and Week 0/Day 1 visits to establish a routine of dosing with their morning meal (Section 7.2.2. and Section 7.2.3) • Added clarification in Section 7.2.4 and 7.3.3 that IWRS will assign a randomization ID to the patient once the patient is randomized, the patient can no longer be considered a screen-failure. • Added enrollment ID to be provided by EDC upon entering placebo-run in period and clarification that AE reporting will begin following the administration of study drug at Week -2 (Section 7.2.2); • Updated Section 7.2.8 and 7.2.9 to provide additional clarity for Early Termination and Patient Withdrawal (Part 1) • Added study stopping rules for Part 1 to Section 3.2.1 • Updated Statistical Section [Section 10 and protocol synopsis] • Added Figure 6: Decision Flow Chart for Patient Visits Prior to Randomization in Part 1 • Modified Section 7.2.10 and 7.3.6 (Patient Withdrawal) to clarify criteria for determining exit visit(s). • Modified Section 4.5.3 to require male patients to refrain from sperm donation AND use one of the following methods of contraception starting at Week -2 rather than Day 1 • Added Signature Line for Clinical Senior Management • Added specific visits for Study Procedures in Section 7.2 rather than referencing the Schedule of Activities table • Added Appendix 3: Values or Changes Potentially of Clinical Concern • Corrected typographical and grammatical errors

Amendment 4	15NOV2018	• Increased maximum age for inclusion from 60 to 70 years (Section 5.2.1, Inclusion 4) • Reduced use of CGM prior to enrollment in the study from 3 months to 2 months and required disruption in device use for more than 2 weeks to be evaluated by the Sponsor prior to enrollment. (Section 5.2.1, Inclusion 3) • Added reference in Section 7.2.1 to address the addition of separate consent if patients need CGM supplies prior to screening visit • Added retest screening labs upon medical monitor approval (Section 7.2.1 and 7.3.1) • Updated CGM requirements to be consistent with manufacturer instructions for both Dexcom G5 and G6 (Sections 4.2, 5.2.2 and 7.2.1). • Added clarification that the PBO-Run in period be at least 13 days in duration (Section 7.2.2) • Section 6.10.1 modified to clarify that closed loop systems (e.g. MiniMed 670G system) are NOT allowed **unless** they agree to switch off the auto mode during the study and enroll in the basal adjustment period (up to three weeks) • Remove number of injections of insulin bolus as an endpoint from interim analysis. Updated interim analysis endpoints to Change from baseline in bolus insulin (number of units) OR Change from baseline for time in target glycemic range of 70-180 mg/dL (Section 2.3 and 10.5.1) • Eliminated collection of glucagon/glp-1 samples at Week 2, 4, 6 and Week 8 during Part 1. Table 1, Appendix 2 and Section 8.7.1 were modified accordingly. • Added the option to include additional interim analysis (Section 10.9 and Synopsis) • Corrected grammatical and typographical errors
Amendment 5	08FEB2019	• In protocol synopsis and throughout: o Added progression to Part 2 is based upon the absence of safety concerns resulting from ongoing safety review of accruing data upon completion of approximately 50% of patients in Part 1 o Clarified the flexibility that interim analyses for the study may or may not be done based on business needs o Modified to indicate the interim analysis for Part 1 may occur approximately 6 weeks after approximately 20 patients have been randomized o Increased to number of sites to Part 2 to up to 20 o Changed the HbA1c value for inclusion in Part 2 to 7.0-9.5%, inclusive at Screening o Changed the BMI for inclusion in Part 2 to be ≤ 39

		kg/m2 at Screening o Determined the dose of TTP399 for Part 2 to be 800 mg and removed references to potential change in dose for Part 2 o Noted that enrollment of consented patients who have met screening criteria when the enrollment goals are met will continue up to a total number of approximately 140 patients are enrolled in Parts 1 and 2 (Section 3 and 5.2) o Introduced stratification into randomization to control balance between patients who enter the study on CGM and those who do not • Changed secondary endpoint of "Change from baseline in insulin (basal, bolus or total daily) dose (number of units and/or number of injections)" to o Secondary endpoint of "Change from baseline in number of units of insulin (basal, bolus or total daily) dose)" and o Exploratory endpoint of "Change from baseline in number of bolus injections of insulin" • Clarified secondary endpoint to "Achievement of a decrease of at least 0.3% in HbA1c at Week 12 (responders)" • Modified Schedule of Events, Figure 4 and Section 7.3 to reflect the following changes for Part 2 o Eliminate Week 4 and Week 8 visits o Add Week 6 and Week 10 visits o Require Week0/Day 1 visit that to occur at least 13 days after Week -2 visit in order apply Sponsor CGM (Schedule of Activities and Figure 4, Section 7.3) o Require Week 12 visit that to occur at least 13 days after Week 10 visit in order apply Sponsor CGM (Schedule of Activities and Figure 4, Section 7.3) o Changed phone call from weekly during dosing to occur at Week -1, Week 1, Week 4 and Week 8 o Make Basal Insulin Adjustment Period (optional) as either on-site visit or phone call o Added providing glucometer and associated supplies (if needed); o Added providing electronic device to collect insulin dosing information for patients using MDI; o Add the collection of insulin data and premeal/fasting glucose during the basal insulin adjustment period • Added separate rows for registration, enrollment and randomization for clarification (Schedule of Events); • Added footnote to confirm patient is fasted prior to labs on Week 0/Day 1 visit or reschedule visit (Schedule of Events)

		• Updated in Section 3.4.2 to indicate Part 2 will be initiated upon completion of approximately 50% of patients in Part 1 in the absence of safety concerns • Consolidated instructions for dosing with meal at Week -2 and Week 0/Day 1 to include both Part 1 and 2 (Section 4.1); • Included instructions for CGM use for Part 2 (Section 4.2); • Replaced Section 4.3 (Study Diary) with Insulin Data Collection • To clarify entry criteria for Part 2, added Section 5.3 and eliminated entry criteria for Part 2 from Section 5.2; • Modified inclusion criteria 3 to address insulin delivery method (Section 5.3.1); • Added inclusion criteria 4 to specify requirements regarding use of personal CGM during the study (Section 5.3.1) • Eliminated the requirement for a urine drug screen and modified exclusion criteria 7 as follows: Documented history within the last 2 years of use of non-prescribed controlled substances or illicit drugs (Section 5.3.2). • Modified exclusion criteria 2 to exclude any patients previously treated with TTP399 (Section 5.3.2) • Added instructions for patients to store drug at room temperature “Once dispensed to patients, medication will be stored at room temperature.” (Section 6.4.2 Part 2); • Added number of bottles to be dispensed at each visit in Part 2 to Section 6.1.2 and 6.4.2; • Added clarification to Section 6.5.2 that no dose is taken the day of the Week 12 visit; • Added requirements for Insulin device use and data recording in Part 2 to section 6.10.1; • Deleted requirement for local or on-site HbA1c determination if medical history is not available (Section 7.3.1); • Clarified that screening activities are to be completed within 2 weeks of the next study visit (Section 7.3.1); • Clarified screen failure and run-in failure. o If a patient does not qualify for the trial, prior to enrolling at Week -2, he or she will be considered a screen failure (Section 7.3.1) o If a patient does not qualify for the trial after being enrolled, but prior to randomization, he or she will be considered a run-in failure (Section 7.3.5) • For Part 2, modified Section 7.3.2, Section 8.11 and Figure 6 o added the use of glucometers (in addition to personal CGMs) to review patient glucose data o reduced the glucose review period from 2 weeks to 7 days • Added language to confirm the patient is fasted at the Week 0/Day1 visit and reschedule the visit if not confirmed (Section

		7.3.4). • Added Laboratory Specimen collection (Part 2) to Appendix • Updated visit assessment collection times for Part 2 (Sections 8.2, 8.3, 8.4, 8.5, 8.8) • Section 8.7 o Updated Table 1 Summary of Blood collection samples o Added fasting plasma glucose assessment to Table 2 o Eliminated mandatory urine drug testing • Added Section 10.1 Randomization • Section 10.8 Modified to note that if a data safety monitoring board is convened for Part 2 that an endocrinologist and statistician would be included. In addition, a potentially unblinded endocrinologist will be contracted to evaluate SAEs and AEs of special concern. • Grammatical and typographical errors were corrected

SIGNATURE CONFIRMATION PAGE

Investigational Product: TTP399

Study Number: TTP399-203

Protocol 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 Dated: Final Protocol Amendment 5 dated 08FEB2019

I have reviewed and approved of the protocol listed above.

[redacted] _____

[redacted] Signature Date

vTv Therapeutics LLC

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PROTOCOL SYNOPSIS

Study Number: TTP399-203	**Phase: 1b/2**
Title of Study	A Multi-Center, Randomized, Double-Blind, Parallel-Group, Multiple-Dose Adaptive Study Assessing the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of TTP399 in Patients With Type 1 Diabetes Mellitus
Objectives	**Sentinel Phase:** The primary objectives of this part of the study were: • 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 was: • 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 **Parts 1 and 2 (Following 12 weeks of dosing)** **Primary objective** •To evaluate the pharmacodynamic (PD) effect of TTP399 following multiple day dosing (at 12 weeks) in patients with T1DM **Secondary objective** •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
Primary Endpoint	Part 1 and 2: change from baseline in HbA1c at 12 weeks
Secondary Endpoints	•Change from baseline for 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)
Exploratory Endpoint	Change from baseline in number of bolus injections of insulin
Safety Measures	Adverse events, laboratory, vital sign and electrocardiograms (ECG) parameters
Study Design	This is a Proof of Concept study to explore the effect of TTP399 as adjunctive therapy for the treatment of Type 1 diabetes. The proposed study is an adaptive three-part Phase 1b/2 study designed to evaluate the safety and pharmacokinetic profiles of the tablet formulation of TTP399 and to determine if TTP399 can replace or reduce mealtime insulin bolus and improve A1c for patients with Type 1 diabetes. An adaptive design was chosen to streamline the development of TTP399 for treatment in the Type 1 diabetes patient population using either continuous subcutaneous insulin infusion (CSII) or multiple daily doses of insulin (MDI). Go/no go decision: The analysis of the sentinel phase suggested positive results based on our progression rationale, so Part 1 will be initiated. Part 2 will be initiated upon completion of approximately 50% of patients in Part 1 in the absence of safety concerns resulting from ongoing safety review of accruing data. Modifications in the endpoints and/or the number of patients enrolled in Part 2 may or may not occur based on information from the analysis of safety and pharmacodynamic parameters in the Part 1. If modifications are needed, a protocol amendment will be filed, and an IRB review will take place before initiating Part 2.
Methodology	This is an outpatient study where all patients will wear a continuous glucose monitoring (CGM) device during designated periods. Each part of the study will have Screening period, a baseline CGM period [one week baseline period (Sentinels) or single-blind placebo run-in period of 2 weeks (Parts 1 and 2)], a dosing period [an open label dosing period of up to 3 weeks (Sentinels) and a double-blind treatment period of 12 weeks (Part 1 and Part 2)] and a follow-up visit approximately 1 week after the last dose. In addition, Parts 1 and 2 will have a basal insulin dose adjustment period of up to 3 weeks prior to the placebo run-in period, if needed. Following this basal insulin adjustment period, patients in Part 1 and 2 will have a 2-week single-blind placebo period and then be randomized (in 1:1 allocation ratio) to placebo or a single dose of TTP399. Mixed meal tolerance test (MMTT) will be done on Days -7, Day 1, 8, 15 and 21 (Sentinels only). An Interim analysis may be conducted approximately 6 weeks after approximately 20 patients have been randomized in Part 1.
Study Sites (Country)	**Sentinels:** 1 site (USA) **Part 1**: up to 5 sites (USA) **Part 2**: up to 20 sites (USA)

Number of Patients	Enrollment goal is 126 patients with up to approximately 140 total patients: up to 6 sentinels enrolled and approximately 30 in Part 1 and approximately 90 in Part 2 will be randomized
Main Criteria for Inclusion	Male and female patients aged 18 through 70 years, diagnosed with T1DM with an HbA1c value <9% (Sentinels) and 7.0-9.0% (Part 1) and 7.0-9.5% (Part 2), inclusive at Screening. Currently on MDI or CSII therapy.
Dosage, and Mode of Administration	**Sentinels:** dose escalation with TTP399 up to 1200mg daily dose once daily (QD) **Part 1 and 2**: 800 mg dose of TTP399 or placebo tablets - Oral administration once daily (QD)
Duration of Treatment	Up to 3 weeks of open label treatment (sentinels) and up to 12 weeks of double-blind treatment (Part 1 and 2)
Sample Size and Randomization	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. Patients will be randomized in parts 1 and 2 using a fixed randomization scheme (adaptive randomization is not used). Randomization is balanced 1:1 for TTP399 and placebo. Randomization identification for the subjects reflects the stage of the study for the patient (sentinel phase, Part 1, or Part 2). 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
Statistical Methodology	***Populations of analysis*:** The following population of analysis will be used for all statistical analysis: • The full analysis set (FAS) includes all randomized patients who receive any study medication and have a baseline assessment. • The per-protocol set (PPS) includes all patients in the FAS excluding patients who have major protocol violations. • The safety set (SAF) includes all patients who receive any study medication. The FAS will be used for all hypothesis tests of efficacy. The PPS is used for

	supportive efficacy analysis. The SAF will be used for safety analyses. The FAS for Part 1 will be analyzed separately from the FAS for Part 2. Analysis and presentation will also be done for Parts 1 and 2 integrated. ***Efficacy Analysis:*** 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. The primary analysis on change in HbA1c from baseline to Week 12 will use the intent-to-treat methodology and a main-effects model for analysis of covariance (ANCOVA), with adjustment for baseline HbA1c levels. A Statistical analysis plan will be finalized prior to un-blinding consistent with adaptive trials. For this adaptive study, the SAP will supersede the protocol regarding statistical methodology. Additional analysis or composite endpoints may be added. ***Safety Evaluation:*** All safety analyses will be based on the safety set (SAF). Safety is monitored in this study by collection of adverse events, vital signs, electrocardiography, and clinical laboratory measures. 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. Additional safety analyses will be done in accordance with current guidance regarding DILI, QTc changes, and MACE events. ***Interim Analysis:*** An interim analysis is planned for Part 1 of this study approximately 6 weeks after approximately 30 patients have been randomized. Additional interim analysis may or may not be done for this study. Details of the plans for this interim analysis will be described in an interim analysis plan (IAP), which will include intentions for disclosure and processes and procedures planned to protect the integrity of the ongoing study.

SCHEDULE OF ACTIVITIES

(see next page ➔)

Schedule of Activities (Sentinels)	**Screening**	**Baseline CGM and MMTT**	**Dose Escalation Periods**					**ET**	**EOS**
	Day -28 to Day -8	**Day -7 to Day -1**	**Period 1 Day 1 -7**	**Period 2 Day 8 -14**	**Period 3 Day 15 -21**				
Protocol Activity	**Screening**	**Baseline MMTT w/ Insulin**	**Period 1 MMTT: 400mg TTP399**	**Period 2 MMTT: 800mg TTP399**	**Period 3 MMTT: 1200mg TTP399**				
Outpatient Visit	**Screening**	**Day -7**	**Day 1**	**Day 8**	**Day 15**	**Day 21**	**Day 22**	**ET**	**F/U**
Sign informed consent	X								
Registration/Enroll	X		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
Medication history/update	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 standing blood pressure	X	X	X[3]	X	X	X		X	X
Supine 12-lead ECG	X	X	X[4]	X	X	X		X	X
Collect blood samples for clinical chemistry and hematology	X		X	X	X	X		X	X
Collect blood for HbA1c	X		X			X		X	
Collect urine for urinalysis,	X		X	X	X	X		X	X
Collect urine for pregnancy test[5]	X[5]	X[5]	X	X	X	X		X	X[5]
Instruct patients on CGM and insulin/carb/event entries[6]		X	X	X	X	X			
Administer TTP399[7]			X	X	X	X		X	
Administer MMTT [8]		X	X	X	X	X		X	
Collect MMTT*PD samples [9]		X	X	X	X	X		X	
Collect PK samples[10]			X	X	X	X	X	X	
Collect retention sample (optional exploratory)[11]		X				X			
Upload/review CGM and insulin/carb/event entries			X	X	X	X		X	
Standardized lunch		X	X	X	X	X		X	
Dinner meal			X	X	X	X		X	
Compliance check (via pill count)				X	X	X		X	
Dispense study medication			X	X	X				
Daily contact with patient [12]			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 Day 1, Day 21 and ET (if applicable)
[3] Baseline vitals obtained prior to dosing [4] Baseline ECG obtained in triplicate, prior to dosing on Day 1, single readings all other visits
[4] Baseline ECG obtained in triplicate, prior to dosing on Day 1, single readings all other visits
[5] Urine pregnancy tests required for WCBP at all visits, except Day 22.
[6] Refer to Section 4.2 and Appendix for details
[7] Administer dose 60 minutes prior to the MMTT according the dose escalation decision for the period indicated.
[8] MMTT at the clinic will consist of 1 bottle of Ensure Plus administered 1 hour post dose and consumed within 5 minutes [Refer to Section 8.6]
[9] PD samples will be obtained prior to drinking Ensure (0, MMTT) and at times indicated in Section 8.6.4 and Figure 5.
[10] Blood samples will be obtained for TTP399 concentrations immediately prior to dosing at time 0 (PK) and at times indicated in Section 8.6.4 and Figure 5.
[11] Retention samples will be obtained (as appropriate) for patients who consent
[12] Site should talk/text to the patient at least once a day during the dosing period

Schedule of Activities (Part 1)	Screening	Basal Insulin Adjustment Period	Baseline CGM and PBO Run-In Period	Dosing Period						ET	EOS
Study Week			Week -2 to 0	Week 0-Week 12							
Visit	Screening		Week -2	Week 0	Week 2	Week 4	Week 6	Week 8	Week 12	ET	F/U
Study Day	-	-	Day -14	Day 1	Day 14	Day 28	Day 42	Day 56	Day 84	-	-
Visit duration/window		Up to 3 weeks	At least 13d		± 3d	± 3d	± 3d	± 3d	± 3d		± 3d
Sign informed consent	X										
Registration/	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	X
Medication history/update	X		X	X	X	X	X	X	X	X	X
Physical exam	X[1]			X[2]			X[2]		X[2]	X[2]	
Body weight	X		X	X	X	X	X	X	X	X	X
Sitting pulse rate and blood pressure	X		X	X[3]	X	X	X	X	X	X	X
Supine 12-lead ECG	X		X	X[4]	X	X	X	X	X	X	X
Collect blood samples for clinical chemistry, hematology, lipids and glycemic markers[12]	X			X	X	X	X	X	X	X	X
Collect Glucagon/GLP sample[8]				X					X		
Collect PK samples[8]				X	X	X	X	X	X	X	
Collect retention samples (optional, exploratory)[9]				X					X	X	
Collect urine for urinalysis	X			X	X	X	X	X	X	X	X
Collect urine for pregnancy test[5]	X[5]		X	X[5]	X	X	X	X	X	X	X[5]
Administer DTSQs	X								X		
Administer DTSQc									X		
Ask QOL question/enter answer in EDC									X		
Provide glucometer and CGM and glucometer supplies, as needed	X	X	X	X	X	X	X	X			
CGM and Insulin Pump: Provide Instructions/ Save Settings and Data//Review[6]		X	X	X	X	X	X	X	X	X	X
Collect unused drug/compliance check (via pill count)				X	X	X	X	X	X	X	
Dispense blinded study medication based on IWRS			X	X	X	X	X	X			
Administer Study drug with morning meal[7]			X	X							
Contact patient by telephone or text		X[10]		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]		

[1] Full physical exams, including height, are to be conducted at Screening
[2] Limited physical exams will be conducted at Week 0, Week 6 and Week 12 and ET (if applicable)
[3] Baseline vitals obtained in triplicate, prior to dosing on Week 0, single readings all other visits
[4] Baseline ECG obtained in triplicate, prior to dosing on Week 0, single readings all other visits
[5] 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.
[6] Refer to Section 4.2 and Section 8.11 for details regarding CGM and Insulin Pump
[7] 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.
[8] Blood samples will be obtained for TTP399 concentrations and Glucagon/GLP sample prior to dosing
[9] Retention samples will be obtained (as appropriate) for patients who consent prior to dosing at Week 0 and 12.
[10] Site should talk/text the patient approximately every 3 days during the basal insulin dose adjustment period
[11] Site should talk/text the patient every business day during the first week of the dosing period and then once a week during the dosing period
[12] Refer to Laboratory Manual for Sample Collection Instructions and Appendix 2 (Part 1) for lab tests conducted by visit

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.

ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC(0-t)	area under the plasma concentration time curve from 0 to time of last measurement
BID	twice daily
BMI	body mass index
BOCF	baseline observation carried forward
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research (FDA)
CDER	Center for Drug Evaluation and Research (FDA)
CEC	cardiovascular endpoints committee
CGM	continuous glucose monitoring
CRA	clinical research associate
CRF	case report form
Cmax	maximal plasma concentration
CRO	contract research organization
CRU	Clinical Research Unit
CS	clinically significant
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
DBL	database lock
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DTSQs	Diabetes Treatment Satisfaction Questionnaire status version
DTSQc	Diabetes Treatment Satisfaction Questionnaire change version
ECG	electrocardiogram
eCRF	electronic case report form

EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
FAS	full analysis set
FCBP	females of childbearing potential
FNCBP	females of non-childbearing potential
FIH	first in human
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GK	Glucokinase, also known as Hexokinase IV or D
GKA	Glucokinase Activator
GLP-1	glucagon-like peptide
GGT	gamma glutamyltransferase
HEENT	head, eyes, ears, nose, throat
HbA1c	glycosylated hemoglobin
HDL-C	high density lipoprotein cholesterol
IAP	interim analysis plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization (of Technical requirements for Registration of Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee (DHHS)
INR	international normalized ratio
IRB	Institutional Review Board
ICF	Insulin Correction Factor
ISF	Insulin Sensitivity Factor
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
LDL-C	low density lipoprotein cholesterol

LLN	lower limit of normal
LLT	lowest level term
LOCF	last observation carried forward
LSM	least squares means
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac event
MAD	multiple ascending dose
MAR	missing at random
MDG	mean daily glucose
MDI	multiple daily doses of insulin
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMRM	mixed model repeated measure
NAS	National Academy of Science
MMTT	mixed meal tolerance test
NMAR	not missing at random
NASH	nonalcoholic steatohepatitis
NCS	not clinically significant
NOAEL	no observable adverse effect level
NYHA	New York Heart Association
OTC	over-the-counter
PCS	potentially clinically significant
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetics
PPS	per protocol set
RBC	red blood cells
RDW	RBC distribution width
QD	once daily

QOL	quality of life
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDH	sorbitol dehydrogenase
SID	patient identification [number]
SOC	system organ class
SUSAR	serious and unexpected adverse event
SSF	study site file
T1/2	Terminal elimination half-life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	Treatment-Emergent Adverse Event
TEAV	Treatment-Emergent Abnormal Value
TG	triglyceride(s)
Tmax	Time of maximal plasma concentration
UDS	urine drug screen
ULN	upper limit of normal
vTv	vTv Therapeutics LLC
WCBP	women of child bearing potential
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This is an adaptive Phase 1b/2 study with three parts, the sentinel phase which is an open label, dose escalation of approximately 6 patients with Type 1 diabetes (T1DM) on CSII and CGM (sentinels) with up to 8 visits, Part 1 with approximately 30 randomized patients with type 1 diabetes on CSII dosing for 12 weeks with up to 10 visits and Part 2 with approximately 90 randomized patients with type 1 diabetes on CSII or MDI with up to 9 visits. The analysis of the sentinel phase suggested positive results [as defined in Section 3.4 (Rationale for progression)], resulting in Part 1 being initiated. Part 2 will be initiated following positive results from an interim analysis of Part 1 [See Section 3.4.2 Rationale for progression into Part 2]. Completion of Parts 1 and 2 will result in approximately 120 patients dosing for 12 weeks. 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 daily 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.. Mixed meal tolerance test (MMTT) will be conducted in the Sentinel patients. 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.

1.1. Background and Rationale

While multiple oral drugs are approved for the management of hyperglycemia in type 2 diabetes (T2DM), no oral therapies are approved that improve hyperglycemia in type 1 diabetes (T1DM). There is an unmet medical need to provide people with type 1 diabetes treatment options that help them to achieve tighter blood glucose levels and reduce insulin doses without increasing the risk of hypoglycemia or ketoacidosis.

1.1.1. Type 1 Diabetes Mellitus

Type 1 diabetes (T1D) is an autoimmune disease that usually leads to absolute insulin deficiency. Multiple genetic predispositions and poorly defined environmental factors result in the autoimmune destruction of pancreatic β-cells, the site of insulin secretion [1]. T1D affects more than one million people in the United States and strikes both children and adults at any age. Most T1D patients are on insulin therapy (multiple daily injection of prandial insulin and basal insulin or continuous subcutaneous insulin infusion) to control their blood sugar, however, there is significant unmet need as maintaining proper glycemic control with insulin therapy is demanding on patients and comes with significant risk of hypoglycemia that can have serious cognitive effects as well as long term complications affecting multiple organs. Improvements in the delivery of insulin have been made recently to reduce the risk of hypoglycemia, but reduction of required insulin doses and/or increasing time in glycemic range using oral anti-diabetic therapies acting through different mechanisms could meet a significant unmet need for Type 1 diabetic patients.

1.1.2. Mechanism of Action

TTP399 is a liver-selective glucokinase activator. Glucokinase (GK), plays an essential role in blood glucose homeostasis. It catalyzes glucose phosphorylation and is the rate-limiting reaction for glycolysis [2]. In the liver, GK determine the rates of both glucose uptake and glycogen synthesis (Figure 1), and it is also thought to be essential for the regulation of various glucose-responsive genes[3,4]. Data from transgenic animals in which only liver glucokinase has been up regulated by different mechanisms clearly shows that a selective increase in hepatic glucokinase is the only requirement for the normalization of the metabolic profile in insulin deficient animals. These observations suggest that selective activation of liver GK could provide a mechanism that ensures reduction of blood glucose without the risk of hypoglycemia

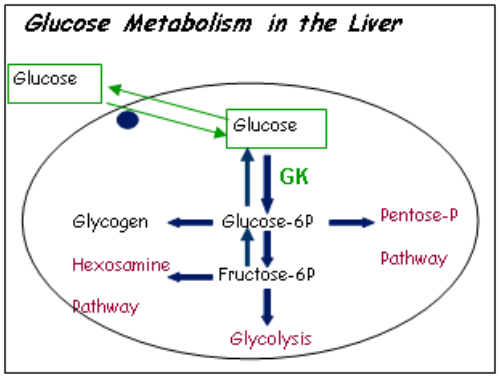


Figure 1: Schematic representation of the role of GK in the liver

1.1.3. Nonclinical Studies

Animal models have confirmed that liver-selective GK activator TTP399 significantly improves glycemic control, reduce insulin resistance, and decrease body weight without changes in β-cell mass, plasma insulin, or hepatic lipids.

The toxicokinetic data from the 9-month oral toxicity study in minipigs demonstrated approximate safety margins of 37-fold and 32-fold for AUC_{0-24} and C_{max} for the dose of 1600mg/day (800mg BID).

Refer to the IB for additional information on the non-clinical pharmacology and toxicology.

A pilot study in a model of type 1 diabetes, where following streptozotocin administration, beta-cell reduced Gottingen minipigs dosed with a liver-selective GKA with identical pharmacological properties to TTP399 provided preclinical evidence supporting the concept of liver-selective GKAs for the treatment of T1DM. Treatment with the liver selective GKA reduced by half the dose of exogenous insulin needed to maintain glycemic control in this type 1 model of minipigs. Dosing with the liver-selective GKA was well tolerated and no hypoglycemia was seen in the animals even when insulin was dosed in the absence of food.

In addition, during a 4-day period without insulin administration, treatment delayed/prevented increase in glucose and ketone bodies, reduced glucagon and maintained buffer capacity in blood.

1.1.4. Clinical Studies

Results from the preclinical program supported the initiation of 9 Phase 1 trials and 2 Phase 2 trials of TTP399. These eleven trials have evaluated 701 patients; 494 of whom received one or more doses of TTP399 (182 healthy subjects and 312 patients with T2DM). Nine of these studies were Phase 1 trials studies (up to 10 days of dosing) conducted in healthy volunteers or patients with T2DM. Two Phase 2 trials have been conducted, a Phase 2a study involving 6 weeks of dosing in patients with T2DM and a 6-month Phase 2b study in patients with T2DM on stable doses of metformin. In these studies, the incidence of adverse events was similar for healthy and T2DM patients administered TTP399 compared to placebo. There were no AEs that had an obvious treatment-related relationship to dose, no concern of hypoglycemia associated with TTP399 treatment, and no demonstrated adverse effects of TTP399 on vital signs, ECG parameters, or clinical laboratory assessments. Current studies have not revealed a maximum tolerated dose with single doses up to 1200 mg and multiple doses up to 800 mg BID being well tolerated.

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 A1c and the effect was sustained for the duration of the study without significant hypoglycemia, dyslipidemia or ketoacidosis.

Refer to the IB for additional information on clinical results.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. 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

2.3. 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

3. ADAPTIVE STUDY DESIGN AND RATIONALE:

This adaptive study to evaluate TTP399 as a potential treatment for T1DM will occur in three parts (sentinels, learning phase (Part 1) and confirming phase (Part 2)) with the opportunity to modify the study. Weekly dose escalations (anticipated from 400mg to 1200 mg daily doses of TTP399) will occur in up to 6 sentinel patients on CSII and CGM (open label) to determine the dose to be compared with placebo in approximately 120 Type 1 diabetes patients using either CSII or MDI (with a goal of approximately 30 patients in Part 1 and approximately 90 patients in Part 2). Some possible adaptations envisioned include dose regimen, endpoints and number of patients randomized into Part 1 and 2. The study population will consist of patients with T1DM who have experience using either CSII or MDI. Patients will be dosed daily with TTP399 (orally) or placebo during the treatment period. Continuous Glucose Monitoring will be used to monitor safety and efficacy and mixed meal tolerance tests will be conducted in sentinel patients. Pharmacokinetic samples will also be obtained.

The three parts of this an adaptive Phase 1b/2 study are:

- Sentinel phase: an open label, dose escalation with approximately 6 adult T1DM patients (sentinels) with up to 8 visits,
- Part 1: a placebo-controlled study with approximately 30 randomized adult type 1 diabetic patients dosing for 12 weeks with up to 10 visits and
- Part 2: a placebo-controlled study with approximately 90 total randomized adult type 1 diabetic patients with up to 9 visits.

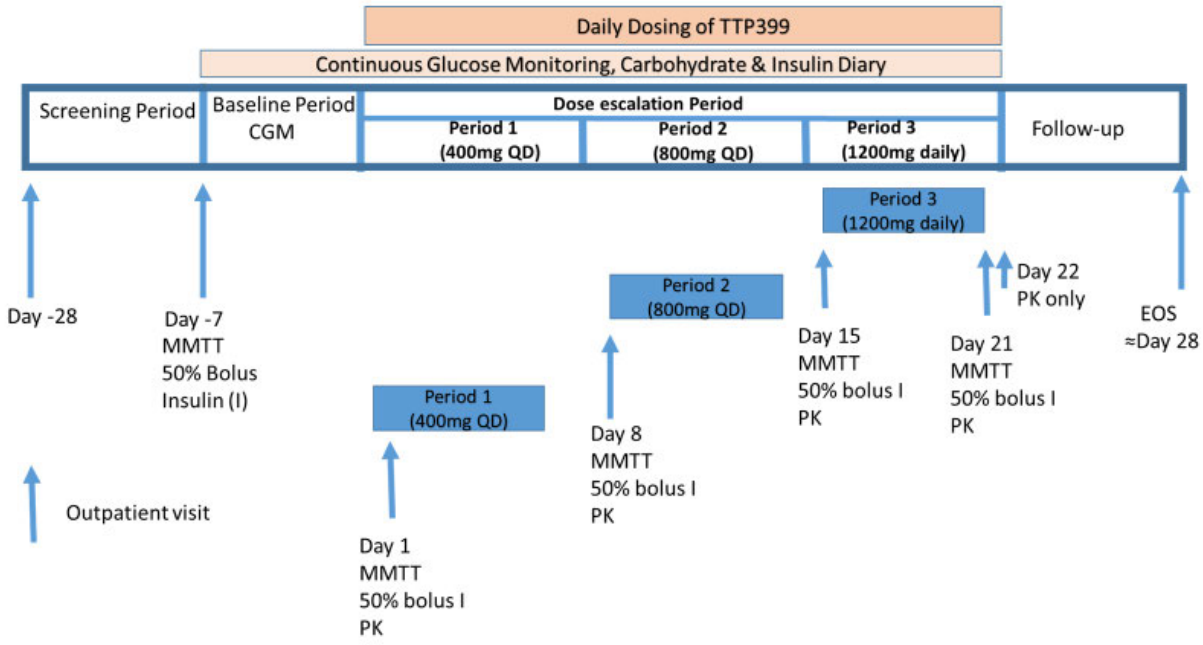
The analysis of the sentinel phase suggested positive results based on our progression rationale (Section 3.4.1), so Part 1 was initiated. Part 2 will be initiated upon completion of approximately 50% of patients in Part 1 in the absence of safety concerns resulting from ongoing safety review of accruing data . Completion of Part 1 and 2 will result in approximately 120 patients dosing for 12 weeks. Consented patients who have met screening criteria when the enrollment goals are met will be allowed to continue until up to a total number of approximately 140 patients are enrolled in the study.

3.1. Sentinel phase

This will be conducted at only one site. The Sentinel phase of this adaptive Phase 1b/2 study is to evaluate the safety, pharmacokinetics and pharmacodynamics of different dose regimens ranging from 400 to 1200mg daily doses of TTP399 in adult Type 1 Diabetic patients. The study population for the sentinel phase of the study will consist of patients with T1DM who are currently be using CGM and CSII. This study will be initiated with 6 patients in an open-label, weekly dose escalation study with up to 3 dose escalations (7 days dosing at each dose level). Patients will be dosed initially with a once daily dose of TTP399 during the treatment period. Since this is an adaptive study, dosing regimens may be modified based on patient results with regards to dose amount (up to 1200 mg per day) and frequency (BID or other alternative dosing strategies). Study stopping criteria for the sentinel patients (outlined below) are based on safety and efficacy criteria. Unblinded Continuous Glucose Monitoring will be used to monitor safety and efficacy.

See **Figure** 2 for a schematic of the study design and the SCHEDULE OF ACTIVITIES (SENTINELS) for the timing of study procedures.

Figure 2: Study Design: Sentinel Patients. Open label with dose escalation, 3 periods (7 days per period), no washout between periods; anticipated doses are listed, conducted at 1 site



3.1.1. Sentinel Phase Dose Escalation Stopping Rules

All patients in this study will be closely monitored for emergent signs or symptoms indicating possible adverse effects. Dose escalation stopping rules will be used to direct the safety committee to determine whether the maximum tolerated dose has been attained. The following is a list of dose escalation stopping rules. If dose escalation is stopped due to any of these findings, additional periods using different dosing regimens may be implemented.

3.1.1.1 Individual Patient Criteria

- If an individual patient experiences an episode of severe hypoglycemia [as defined in Section 9.8.2], the patient will be instructed to stop dosing, contact the site AND come to the site for follow-up safety visits as determined by the investigator. The patient will NOT be restarted on study drug unless there were substantial aggravating issues precipitating the episode as determined by the Investigator.

- If an individual patient experiences an episode of diabetic ketoacidosis DKA [as defined in Section 9.8.3], the patient will be instructed to stop dosing, contact the site AND come to the site for follow-up safety visits as determined by the investigator. The

patient will NOT be restarted on study drug unless there were substantial aggravating issues precipitating the episode as determined by the Investigator.

- If a patient post prandial glucose is maintained at less than 180mg/dL as determined by CGM in the absence of mealtime bolus insulin the dose given will be determined to be efficacious and only one more dose escalation for that patient will be conducted.

3.1.1.2 Dose Level Criteria

- Dose escalation will be stopped if two or more patients develop similar drug-related clinically significant laboratory, ECG or vital signs abnormalities, or dose-related severe AEs in the same organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any serious adverse event (SAE) that occurs in a patient receiving active treatment until causality is fully assessed by the PI and Sponsor. Dosing will cease if the SAE was determined to be drug-related, and may resume if determined to be not drug-related by the PI and Sponsor.

- Dose escalation will be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the vTv study team and the study site team.

- The sentinel study will be paused if 2 or more patients experience at least one episode of severe hypoglycemia [as defined in Section 9.8.2].

- The sentinel study will be paused if 2 or more patients experience at least one episode of DKA [as defined in Section 9.8.3].

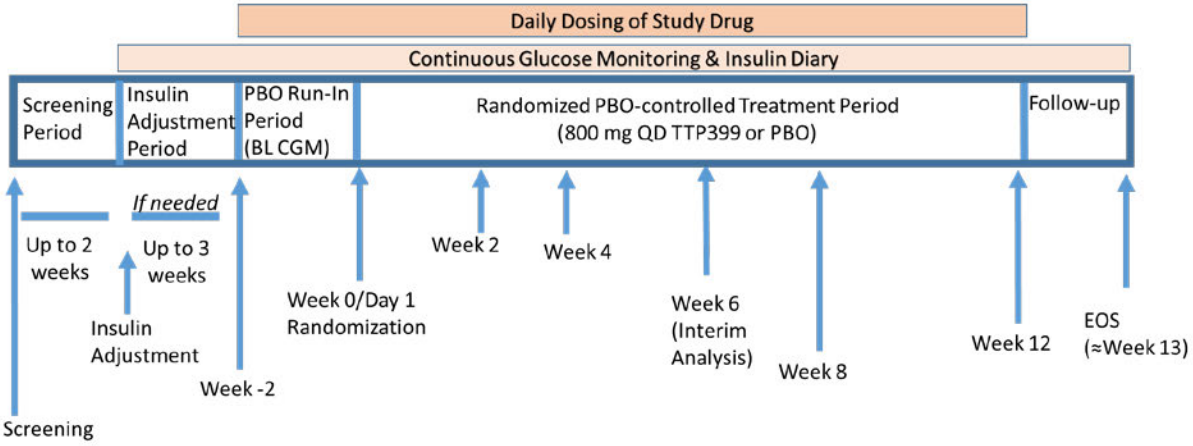
- Other findings that, at the discretion of the Study Team and Investigator, indicate that dose escalation should be halted

3.2. Parts 1 and 2

3.2.1. Part 1

Part 1 is a multi-center (up to 5 sites) double-blind placebo-controlled study with a 2-week single-blind placebo run-in period to evaluate TTP399 as a potential adjunctive treatment to insulin therapy for T1DM. The study will examine the safety and pharmacodynamic response at 12 weeks of dosing in patients randomized (1:1) to either placebo or 800 mg QD TTP399. Part 1 will enroll approximately 30 adult type 1 diabetic patients who have experience using CSII and CGM. Approximately six weeks after 30 patients are randomized, a planned interim analysis will be conducted to evaluate safety and efficacy. Unblinded Continuous Glucose Monitoring will be used to monitor safety and efficacy throughout the study. See Figure 3 for a schematic of the study design and the SCHEDULE OF ACTIVITIES (PART 1) for the timing of study procedures.

Figure 3: Study Design: Part 1- Double blind placebo-controlled randomized (1:1) with up to 5 sites, n=approximately 30 patients, treatment period 12 weeks.



Stopping Criteria Part 1

- Part 1 will be paused if 3 or more patients experience at least one episode of severe hypoglycemia defined as **each** of the following criteria being met:

  a) The patient was unable to treat him/herself, requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Neurologic impairment must be the explanation for why the patient could not treat him/herself and required the assistance of another person.

  b) Blood glucose:
     - If blood glucose was measured and was ≤ 49 mg/dL (2.7 mmol/L) using plasma referenced- home glucometers, CGM (or central laboratory), **or**

     - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

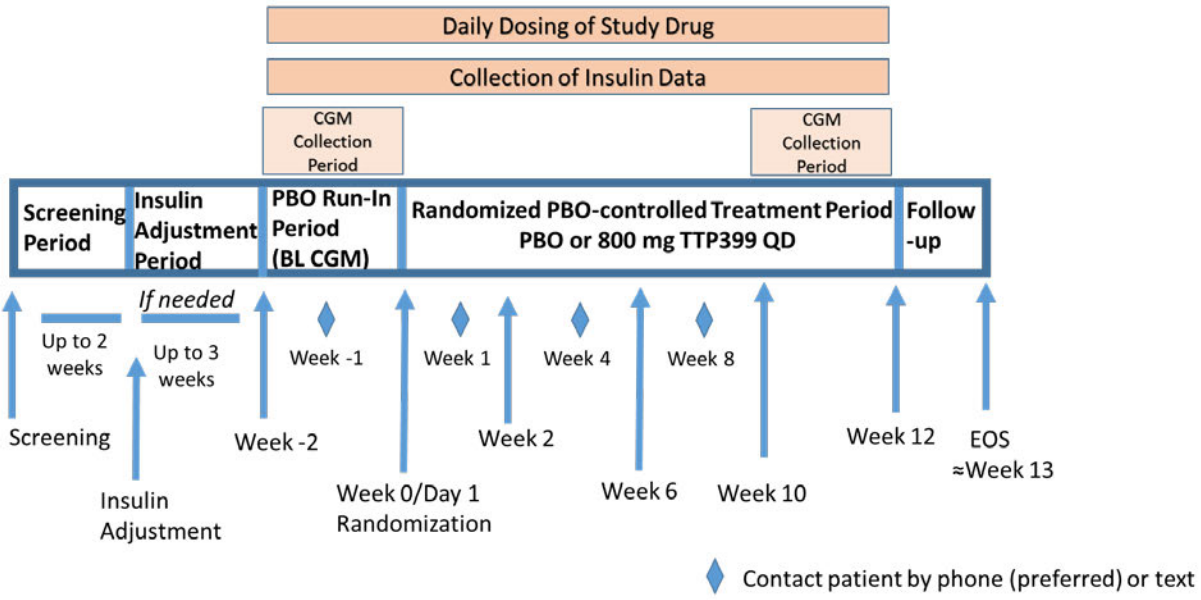
- Part 1 will be paused if 3 or more patients experience at least one episode of DKA [as defined by

  a) Increased serum β- hydroxybutyrate or urine ketones (above ULN) **AND**
  b) serum bicarbonate (total CO_2) <15mmol/L **OR** blood pH < 7.3

3.2.2. Part 2

Part 2 is a double-blind placebo control study to be conducted at up to 20 sites to evaluate TTP399 as a potential adjunct treatment for T1DM that will examine the safety, pharmacokinetic and pharmacodynamic response after 12 weeks of dosing in approximately 90 adult T1DM patients randomized (1:1) to either placebo or a dose of 800 mg QD TTP399. Since this is an adaptive study, modifications in the endpoints and/or the number of patients randomized to each treatment group in Part 2 may or may not occur based on information from the analysis of safety, PK and PD parameters in Part 1 or the Sentinels. The sponsor will provide Continuous Glucose Monitoring Devices (blinding) to be used at two timepoints during the study, including during baseline and at the end of the dosing period. Patients will be provided glucometers and glucometer related supplies to monitor glucose levels, if needed. See Figure 4 for a schematic of the study design and the SCHEDULE OF ACTIVITIES (PART 2) for the timing of study procedures.

Figure 4: Study Design: Part 2 - Double blind placebo-controlled randomized (1:1) with up to 20 sites, n=90 patients. Treatment period 12 weeks



3.3. Dose Selection Rationale

3.3.1. Rationale for Dose Selection for Sentinel Phase

The initial proposed doses for the sentinel phase of the study (400-1200 mg QD) were selected with the following objectives in mind: 1) bracket the expected therapeutic dose; 2) choose a starting dose that is well tolerated; 3) allow for conservative dose escalation; and 4) choose a maximum dose that will allow tolerability to be adequately assessed, but which is not expected to be associated with significant safety risks

Dosing above 1200 mg QD dosing is not anticipated, but additional periods evaluating higher doses (up 1200 mg daily) or alternatives to QD dosing (e.g. BID dosing) may be studied if emerging data supports that decision (i.e., if previous doses are well-tolerated and additional efficacy is expected to be achieved at higher doses).

Based on the clinical experience to date with TTP399 in Type 2 Diabetic Patients, glucose lowering in response to an MMTT has been observed at doses ranging from 400 mg -1200 mg total daily doses. Doses up to 1200 mg daily are not expected to be associated with significant safety risks.

3.3.2. Rationale for Dose selection for Parts 1 and 2:

The dose selected for Part 1 is 800 mg QD. Based on results from the sentinel phase where doses up to 1200 mg QD dosing were tolerated (1200mg QD was the highest dose evaluated) and other clinical trials conducted to date where 494 patients have received one or more doses of TTP399 (182 healthy subjects and 312 patients with T2DM) with doses up to 1600 mg daily demonstrating glucose lowering and being well tolerated).

The anticipated dose for Part 2 is also 800 mg QD. As an adaptive study, modifications in the dose regimen may occur based on information learned from Part 1. A dose regimen will be chosen to evaluate efficacy without any anticipated safety risks. Any modifications to the dose regimen will be provided to the IRB through a protocol amendment. IRB approval will occur prior to dosing patients in Part 2 if modifications are needed.

3.4. Study Progression Rationale

3.4.1. Rationale for progression into Part 1:

The sentinel phase results demonstrate that TTP399 once daily dosing up to 1200 mg QD was well tolerated in 5 patients with Type 1 Diabetes on insulin. No incidences of severe hypoglycemia or diabetic ketoacidosis occurred during this phase of the study. When compared to baseline, trends toward improved glycemic control while reducing insulin dose were observed with TTP399 treatment, providing support for the progression to the randomized, placebo control Part 1 of the study based on the following criteria outlined prior to study start:

- **TTP399 is well tolerated;**

and one or more of the following:

- **TTP399 treatment shows an improvement in one or more of the secondary outcomes, e.g. AUC 0-3hr, time in range, less hypoglycemia.**

- **TTP399 maintains glycemic control while reducing insulin dose or simplifying**

insulin regimen

And successful IRB approval of any protocol changes based on the Sentinel phase and ICF approval, as applicable.

3.4.2. Rationale for progression into Part 2:

The results of the ongoing safety review of accruing data will advise whether the TTP399 program development can move forward. Part 2 will be initiated upon completion of approximately 50% of patients in Part 1 in the absence of safety concerns.

4. STUDY REQUIREMENTS AND RESTRICTIONS:

4.1. Meals and Dietary Restrictions

For clinic visits to the site (beginning with the baseline CGM visit (Sentinels) and Week -2 (Part 1 and 2) and continuing through follow-up), patients will be instructed to arrive before their morning meal and before taking mealtime insulin and their study medications for that day, as applicable. Measures to mitigate hypoglycemia are allowed, e.g. glucose tablets.

Sentinel Patients:

For all clinic visits when MMTTs are conducted, the patients will be given lunch with a standardized carbohydrate content (between 30-100 g of carbohydrate). Each patient will select a lunch at the baseline MMTT visit [Day -7 for Sentinels]. The same lunch will be provided at all visits requiring MMTTs and be required to consume the entire meal.

For all study visits with MMTTs and PK collection, an evening meal with a standardized carbohydrate content (between 30-100 g of carbohydrate) will be provided by the site. For the baseline MMTT where no PK is collected (i.e. a shorter clinic visit), patients are not required to stay in the clinic until dinner, but should have a dinner meal with between 30-100 g of carbohydrates and record the carbohydrate content in their CGM system (Sentinels).

For days when dosing occurs at home, study medication (TTP399 or placebo) should be taken at approximately the same time every day, approximately one hour before the morning meal. Normal mealtime insulin dose (if needed) will be administered per the patient's normal routine.

Patients will be asked to manage glycemic targets to the suggested ADA general guidelines regarding glycemic targets: 80-130 mg/dl before meals and <180 mg/dl after meals.

Part 1 and Part 2 Patients:

At Week -2 and Week 0/Day1, patients will be dosed with study medication in the clinic. At these two visits, patients will eat their morning meal at the site following dosing to establish a

routine of dosing the study drug with their morning meal. There are no restrictions on the meal and it can either provided by the site or brought to the site by the patient.

From the day after Week -2 visit until the end of the dosing period (except for the Week -2 and Week 0/Day1 visits where patients are dosed in the clinic), study medication (TTP399 or placebo) should be taken at approximately the same time every day with the morning meal. Patients should be instructed to continue to eat meals per their normal routine with no predetermined carbohydrate limit. Normal mealtime insulin dose (if needed) will be administered per the patient's normal routine.

Patients will be asked to follow instructions provided by the site with a goal of reaching the ADA suggested targets: 80-130 mg/dL before meals and <180 mg/dL peak after meals. During phone calls and visits, the PI (or designee) will confirm that the patient's insulin dosing is adjusted appropriately to treat to this target glycemic range according to the guidance provided in Section 8.11.

4.2. Continuous Glucose Monitoring:

Sentinel Patients
Sentinel patients will be required to be experienced with CGM, currently be using Dexcom CGM and agree to continue to use CGM during the study. Patients will be provided with sensors and transmitters. Patient must agree change sensors one day prior to Day -7, Day 1, Day 8 and Day 15 visits. No CGM sensor changes are allowed on days of clinic visits to ensure appropriate data recording. If the sensor is not changed prior to the visit, the site will confirm that data is being collected, re-educate the patient on the requirement of the sensor change the day prior to the visit and the visit will be conducted as scheduled. See the Appendix for additional details regarding the CGM.

The unblinded CGM is required throughout the sentinel phase to monitor patient safety and patients must agree to share their real time unblinded CGM with the PI and/or designee and share their CGM data through the Dexcom CLARITY® software with the PI or designee and allow a de-identified copy to be shared with vTv. Unblinded CGM will be collected beginning with screening and continuing through the follow-up visit for Sentinel patients.

Patients enrolled in the Sentinel phase of the study will record the following in their CGM system:

- insulin bolus (mealtime insulin dose) for every meal during the duration of the study. Any changes to baseline insulin should be reported to the site for recording in the EDC.
- carbohydrate content of meals from the 4^{th} to the 6^{th} day of each dosing period
- any symptoms of hypoglycemia (and contemporaneous glucose readings if available)

- general comments including notable events that might affect glucose levels such as extreme stress or strenuous physical activity in their CGM system.

CGM records will be saved.

Part 1 Patients

Patients in Part 1 will be required to be experienced with CGM, currently be using Dexcom CGM and agree to continue to use CGM during the study. Patients will be provided with sensors and transmitters and glucometers and supplies. Patients must agree to use the CGM device per manufacture instructions with particular attention to change sensors weekly.

The unblinded CGM is required throughout Part 1 to monitor patient safety and patients must agree to share their CGM data through the Dexcom CLARITY® software with the PI or designee and allow a de-identified copy to be shared with vTv. Patients must agree to share CGM data collected up to a month prior to the screening visit *with the site* for evaluation of glycemic control and insulin adjustment needed prior to the placebo run-in period. Unblinded CGM will be collected beginning with screening and continuing through the follow-up visit for patients in Part 1.

Patients enrolled in the Part 1 of the study should record the following in their CGM App:

- Home glucometer measurements undertaken in the event the patient experiences symptoms of hypoglycemia (entered in CGM as calibration)

- Events such as extreme stress or strenuous physical activity that are associated with hypoglycemic or hyperglycemic symptoms

Part 2 Patients

At the Week -2 and Week 10 visit, patients enrolled in Part 2 will be provided with a CGM device (sponsor provided, blinded). The CGM device will be collected at the following visit (Week 0/Day1 and Week 12, respectively). The CGM data will be collected during these periods: Baseline (Week -2 to Week 0) and from Week 10 to Week 12.

If the patient also has a personal CGM, the sponsor provided CGM will be the one of record for statistical analysis.

The sponsor will provide glucometers and related glucometer supplies, as needed.

If the basal insulin dose adjustment period is needed, the patients should collect fasting/pre-meal glucose values as instructed by the study site staff for evaluation. Glucose values can be collected either using personal CGMs or glucometers provided by the sponsor. For individuals who do not have personal CGMs, sponsor provided glucometers should be used

to collect glucose values.

4.3. Insulin Data Collection

Part 2

- Both basal and bolus insulin dosing information will be collected from the basal insulin adjustment period through Week 12. Insulin dosing information should be collected from the patient's insulin pump (for patients using CSII) or the sponsor provided insulin dosing collection device (for patients using MDI).

4.4. Diabetic Ketoacidosis Monitoring:

Patients will be educated about DKA and supplied with urinalysis ketone test strips for home use and instructed to use them if they exhibit any symptoms of DKA Typical symptoms of diabetic ketoacidosis (DKA) are thirst or a very dry mouth, frequent urination, high blood glucose (blood sugar) levels, or high levels of ketones in the urine. Home monitoring should be undertaken in the event patients experience blood glucose ≥ 240mg/dL during an illness or in the presence of symptoms described above. Patients should call the study site if they measure moderate or high ketone values [Refer to Section 9.8.3 for additional information]. If the site cannot be reached the patient should seek immediate medical assistance either at urgent care or the emergency unit for further assessment.

4.5. Contraception and Pregnancy

4.5.1. Women of Non-childbearing Potential

Women of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal women, defined as women between the ages of 45 to 70 who have been amenorrheic for at least 1 year PLUS have a serum FSH level within the laboratory's reference range for postmenopausal females.
2. Women who have a documented hysterectomy and/or bilateral oophorectomy in their medical history or additional documentation. Females who claim one of these procedures but are lacking documentation can be enrolled PROVIDING a serum FSH level is in the postmenopausal range.

All women of non-child bearing potential must have a negative urine pregnancy test at screening, confirmed at baseline. A urine pregnancy test must also be conducted at follow-up.

4.5.2. Women of Childbearing Potential (WCBP)

A woman who is of childbearing potential must agree to use two methods of birth control for the duration of the study (from the day of the screening visit until 90 days after the final dose of the study medication).

Acceptable methods of birth control include implants, injectables, combined oral contraceptives, barrier contraception methods, spermicides, intrauterine devices (IUDs), transdermal contraceptives, and intravaginal contraception rings.

All WCBP must have a negative urine pregnancy test at every visit.

At every study visit, all WCBP are reminded of contraception requirements as described above, through 90 days after end of dosing. They will be instructed to notify a study site staff member immediately if they become pregnant during this time period.

4.5.3. Men

It is required that all male patients refrain from sperm donation AND use one of the following methods of contraception starting at Week -2 through 90 days after the end of dosing:

- Abstinence;
- Use of condom for males with a vasectomy;
- Men without vasectomy must use a condom starting from Day 1 and for the duration of participation in the study. If their female partner could become pregnant, she should use another form of contraception such as an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant, or a tubal ligation;

At appropriate study visits, all males are reminded of contraception requirements as described above, through 90 days after end of dosing. They will be instructed to notify a study site staff member if a female partner becomes pregnant during this time period.

4.6. Blood Donation

Patients are advised that they should not donate blood until after completion of the Follow-Up Visit.

4.7. Activity

Patients are instructed not to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests.

5. PATIENT SELECTION:

5.1. Sentinel Patients

A sufficient number of study participants will be screened in order to enroll up to 6 patients into the sentinel phase of the study. The sentinel patients will be required to have experience with and currently using CGM and use CSII.

5.1.1. Inclusion Criteria

1. Patients diagnosed with T1DM, confirmed diagnosis prior to 40 years of age and a minimum of 1 year prior to the Screening Visit
2. Using a Dexcom CGM and CSII for at least the past 3 months and has no plans to discontinue the device during the study
3. Using a CSII pump (with lispro or aspart) whose insulin dose can be uploaded by the site and no plans to discontinue using the pump during the study.
4. Demonstrate good awareness of hypoglycemia as determined by the PI (or designee)
5. Living with someone who has awareness of hypoglycemia as determined by the PI (or designee)
6. Age 18 to 60 years, inclusive, at the time of the Screening Visit
7. Patients who are willing to use adequate contraception
8. Diabetic drug therapy is solely insulin with no adjunctive drug therapy such as SGLT2 inhibitors or GLP-1 agonists
9. Have a fasting plasma glucose (FPG) according to CGM less than 270 mg/dL, inclusive at the Screening Visit
10. Have an HbA1c value of <9%, obtained at the Screening Visit from a Central Lab
11. Have TG ≤ 600 mg/dL at Screening Visit
12. Have a BMI ≤ 32 kg/m2 at the Screening Visit
13. Generally stable health without a history of major surgery or significant injuries within the last year and without an active infection. Any chronic diseases should be stable, i.e. unlikely to show significant worsening, require multiple medication changes, hospitalization or intensive monitoring during the duration of the trial.
14. Agree to follow the suggested ADA general guidelines regarding glycemic targets: 80-130 mg/dl before meals and <180 mg/dl after meals
15. Agree to share real time CGM with the PI and/or designee and grant access to de-identified data through Dexcom CLARITY® software to vTv
16. The patient is capable of giving informed consent, which includes compliance with the requirements and restrictions listed in the consent form

5.1.2. Exclusion Criteria

1. Diagnosis of T2DM, severely uncontrolled T1DM, maturity-onset diabetes of the young, insulin-requiring T2DM, other unusual or rare forms of diabetes mellitus,

diabetes resulting from a secondary disease or history of diabetic ketoacidosis within the last year.

2. Participation in a clinical trial and receipt of an investigational product within 30 days or any therapeutic protein or antibody within 90 days prior to the Screening Visit.
3. Living in the same household or related to another participant in this study.
4. Any severe episodes of hypoglycemia that required assistance by a third party within 1 year of the Screening Visit
5. Use of concomitant medications including: antidiabetic therapy other than insulin (3 months prior to the Screening Visit), systematic corticosteroids (1 month prior to the Screening Visit), weight loss medication (2 weeks prior to the Screening Visit), antipsychotic medication including olanzapine, risperidone, clozapine, quetiapine and haloperidol (3 months prior to the Screening Visit)
6. Participation in any formal weight loss program or contemplating such therapy during the trial or fluctuation of > 5% in body weight within three months prior to the Screening Visit,
7. Patient has known allergy to study drug ingredients
8. Consumption of less than 30 g of carbohydrates per meal for more than occasional meals, generally in the context of a low carbohydrate diet
9. Recent history of use of non-prescribed controlled substances or illicit drugs (within a year)
10. Current alcoholism or a history of excessive alcohol consumption within 2 years prior to the Screening Visit. Excessive alcohol consumption is defined as usual alcohol intake in excess of 7 drinks per week for females or 14 drinks per week for males, where 1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor.
11. History or presence of clinically significant disease such as chronic pancreatitis, chronic hepatitis or liver cirrhosis, myocardial infarction, clinically significant cardiac arrhythmias, congestive heart failure (NYHA class II to IV symptoms), or or HIV
12. History or presence of symptomatic autonomic neuropathy (e.g. Gastroparesis) or chronic gastrointestinal disease (e.g. celiac disease)
13. History or presence of any results from screening lab test, ECG, physical exam or vital signs that, in the opinion of the investigator or Medical Monitor, should be exclusionary for such a patient.
14. Estimated glomerular filtration rate (eGFR) < 50ml/min/1.73 m^2 at the Screening Visit
15. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5X ULN the Screening Visit.
16. A personal history of long QT syndrome.
17. A screening 12-lead ECG demonstrating QTcF interval >450 msec for males or >470 msec for females, at the Screening Visit if confirmed by a single repeat during the screening period OR the average QTcF intervals from the three ECGs performed at Day 1 exceeds the above values or a single value > 500 msec. This exclusion does not apply to patients with bundle branch block or those whose ECG indicates the presence of a pacemaker.

18. Persistent, uncontrolled hypertension at screening, defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 95 mmHg after at least 5 minutes rest at the Screening Visit if confirmed by up to 3 repeat assessments on the same or another day.
19. Blood donation of approximately 1 pint (500 mL) within 8 weeks prior to the Screening Visit or plans to donate blood during the study
20. History of hemolytic anemia, chronic transfusion requirement, or other condition rendering HbA1c results unreliable as indicator of chronic glucose levels, or hematocrit <35 g/dL for males and <33g/dL for females.
21. History of cancer, other than non-melanoma skin cancer or in-situ uterine cervical cancer that required therapy in the 5 years prior to the Screening Visit.
22. Breastfeeding
23. Positive pregnancy test at the Screening Visit, Day -7 or Day 1.
24. Unwilling or unable to follow the procedures outlined in the protocol.
25. Mental or legal incapacitation.

5.2. Part 1

A sufficient number of study participants will be screened and admitted in order to randomize approximately 30 study participants into Part 1 from up to 5 sites. The study population will consist of patients with T1DM who have experience using CSII (Part 1) and . at least 2 months of experience with CGM.

5.2.1. Inclusion Criteria

1. Patients diagnosed with T1DM, confirmed diagnosis prior to 40 years of age a minimum of 1 year prior to Screening Visit
2. Diabetic drug therapy is solely insulin with no adjunctive drug therapy such as SGLT2 inhibitors or GLP-1 agonists
3. Patients utilizing CGM and CSII (with lispro or aspart) [Part 1] for the past two months prior to enrollment (Week -2) and has no intention of discontinuing the devices during the study or either CSII (with lispro or aspart). Any disruptions greater than two weeks in CGM use in the past 2 months must be evaluated and approved by the Sponsor.
4. Age 18 to 70 years, inclusive, at the time of Screening
5. Patients who are willing to use adequate contraception
6. Have an HbA1c value of 7.0-9.0%, inclusive, obtained at Screening Visit from a Central Lab
7. Have TG ≤ 600 mg/dL at Screening Visit
8. Have a BMI ≤ 35 kg/m2 at Screening Visit
9. Generally stable health without a history of major surgery or significant injuries within the last year and without an active infection. Any chronic diseases should

be stable, i.e. unlikely to show significant worsening, require multiple medication changes, hospitalization or intensive monitoring during the duration of the trial.

10. The patient is capable of giving informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

5.2.2. Exclusion Criteria

1. Diagnosis of T2DM, severely uncontrolled T1DM, maturity-onset diabetes of the young, insulin-requiring T2DM, other unusual or rare forms of diabetes mellitus, diabetes resulting from a secondary disease or history of diabetic ketoacidosis within the last year.
2. Receipt of an investigational product within 30 days of the Screening Visit (including previous treatment with TTP399) or any therapeutic protein or antibody within 90 days prior to Screening Visit.
3. Patients have known allergic to study drug ingredients.
4. Two severe episodes of hypoglycemia that required assistance by a third party within 3 months prior to the Screening Visit or prior to the placebo run-in period
5. Use of concomitant medications including antidiabetic therapy other than insulin (within 3 months prior to Screening Visit), systemic corticosteroids (within 1 month prior to Screening Visit), weight loss medication (within 2 weeks prior to Screening Visit), and/or antipsychotic medication including olanzapine, risperidone, clozapine, quetiapine and haloperidol (within 3 months prior to Screening Visit)
6. Participation in any formal weight loss program or contemplating such therapy during the trial or fluctuation of > 5% in body weight within 3 months prior to the Screening Visit,
7. Recent history of use of non-prescribed controlled substances or illicit drugs.
8. Current alcoholism or a history of excessive alcohol consumption within 2 years prior to screening. Excessive alcohol consumption is defined as usual alcohol intake in excess of 7 drinks per week for females or 14 drinks per week for males, where 1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor.
9. History or presence of clinically significant disease such as chronic pancreatitis, chronic hepatitis or liver cirrhosis, myocardial infarction, clinically significant cardiac arrhythmias, congestive heart failure (NYHA class II to IV symptoms, or HIV.
10. History or presence of symptomatic autonomic neuropathy (e.g. Gastroparesis) or chronic gastrointestinal disease (e.g. celiac disease)

11. History or presence of any results from screening lab test, ECG, physical exam or vital signs that, in the opinion of the investigator or Medical Monitor, should be exclusionary for such a patient.
12. Estimated glomerular filtration rate (eGFR) < 50ml/min/1.73 m^2 at Screening Visit
13. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5X ULN at Screening Visit.
14. A family or personal history of long QT syndrome.
15. A Screening Visit 12-lead ECG demonstrating 1) QTcF interval >450 msec for males or >470 msec for females, if confirmed by a single repeat during the screening or placebo run-in period OR 2) the average QTcF intervals from the three ECGs performed at Week0/Day 1 exceeds the above values or a single value > 500 msec. This exclusion does not apply to patients with bundle branch block or those whose ECG indicates the presence of a pacemaker.
16. Persistent, uncontrolled hypertension from screening to prior to randomization on Week 0/Day 1, defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 95 mmHg after at least 5 minutes rest if confirmed by up to 3 repeat assessments on the same or another day.
17. Blood donation of approximately 1 pint (500 mL) within 8 weeks prior to Screening
18. History of hemolytic anemia, chronic transfusion requirement, or other condition rendering HbA1c results unreliable as indicator of chronic glucose levels, or hematocrit <35 g/dL for males and <33 g/dL for females.
19. History of cancer, other than non-melanoma skin cancer or in-situ uterine cervical cancer that required therapy in the 5 years prior to randomization.
20. Breastfeeding
21. Positive pregnancy test from Screening Visit to prior to randomization on Week 0/Day 1.
22. Unwilling or unable to follow the procedures outlined in the protocol.
23. Mental or legal incapacitation or language barrier.
24. Living in the same household or related to another participant in this study.
25. Requiring more than three weeks for basal insulin dose adjustment prior to placebo run-in period
26. Non-compliant during the placebo run-in/baseline CGM period between Week -2 and Week 0/Day 1 as defined by any of the following:
    - Less than 80% compliance with calibration of CGM, if applicable (at least twice a day)
    - Failure to change the sensor as instructed

- Less than 80% compliance with regards to dosing study medication as determined by pill count

5.3. Part 2

A sufficient number of study participants will be screened and admitted in order to randomize approximately 90 study participants into Part 2 from up to 20 sites. Patients who have met screening criteria when the enrollment goals are met will be enrolled until up to a total of approximately 140 patients enrolled in Part 1 and 2. The study population will consist of patients with T1DM who have experience using either CSII or MDI (Part 2). Patients enrolling in Part 2 are NOT required to have experience with CGM, however, patients enrolling in the study currently on personal CGM are required to have at least 2 months of experience with CGM without significant interruptions (i.e. > 2 weeks) prior to screening and agree to continue using their personal CGM throughout the study in addition to the sponsor provided CGM. If patients are not using personal CGM at screening, they should agree to not start any personal CGM during the study.

5.3.1. Inclusion Criteria

1. Patients diagnosed with T1DM, confirmed diagnosis prior to 40 years of age a minimum of 1 year prior to Screening Visit
2. Diabetic drug therapy is solely insulin with no adjunctive drug therapy such as SGLT2 inhibitors or GLP-1 agonists
3. Patients utilizing CSII or MDI with no plans to change insulin delivery method after enrollment in the study. *Closed loop systems (e.g. MiniMed 670G system) are **NOT allowed unless during the study,** the patient agrees to switch to open loop (i.e., switch off the auto mode) and enter the basal adjustment period.*
4. 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

5. Age 18 to 70 years, inclusive, at the time of Screening
6. Patients who are willing to use adequate contraception
7. Have an HbA1c value of 7.0-9.5%, inclusive obtained at Screening Visit from a Central Lab
8. Have TG ≤ 600 mg/dL at Screening Visit
9. Have a BMI ≤ 39 kg/m2 at Screening Visit

10. Generally stable health without a history of major surgery or significant injuries within the last year and without an active infection. Any chronic diseases should be stable, i.e. unlikely to show significant worsening, require multiple medication changes, hospitalization or intensive monitoring during the duration of the trial.

11. The patient is capable of giving informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

5.3.2. Exclusion Criteria

1. Diagnosis of T2DM, severely uncontrolled T1DM, maturity-onset diabetes of the young, insulin-requiring T2DM, other unusual or rare forms of diabetes mellitus, diabetes resulting from a secondary disease or history of diabetic ketoacidosis within the last year.
2. Receipt of an investigational product within 30 days of the Screening Visit or any therapeutic protein or antibody within 90 days prior to Screening Visit or any previous treatment with TTP399.
3. Patients have known allergy to study drug ingredients.
4. Two severe episodes of hypoglycemia that required assistance by a third party within 3 months prior to the Screening Visit or prior to the placebo run-in period
5. Use of concomitant medications including antidiabetic therapy other than insulin (within 3 months prior to Screening Visit), systemic corticosteroids (within 1 month prior to Screening Visit or during Basal Adjustment Period), weight loss medication (within 2 weeks prior to Screening Visit), and/or antipsychotic medication including olanzapine, risperidone, clozapine, quetiapine and haloperidol (within 3 months prior to Screening Visit).
6. Participation in any formal weight loss program or contemplating such therapy during the trial or fluctuation of > 5% in body weight within 3 months prior to the Screening Visit.
7. Documented history within the last 2 years of use of non-prescribed controlled substances or illicit drugs.
8. Current alcoholism or a history of excessive alcohol consumption within 2 years prior to screening. Excessive alcohol consumption is defined as usual alcohol intake in excess of 7 drinks per week for females or 14 drinks per week for males, where 1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor.
9. History or presence of clinically significant disease such as chronic pancreatitis, chronic hepatitis or liver cirrhosis, myocardial infarction, clinically significant

cardiac arrhythmias, congestive heart failure (NYHA class II to IV symptoms, or HIV.

10. History or presence of symptomatic autonomic neuropathy (e.g. Gastroparesis) or chronic gastrointestinal disease (e.g. celiac disease)
11. History or presence of any results from screening lab test, ECG, physical exam or vital signs that, in the opinion of the investigator or Medical Monitor, should be exclusionary for such a patient.
12. Estimated glomerular filtration rate (eGFR) < 50ml/min/1.73 m^2 at Screening Visit
13. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5X ULN at Screening Visit.
14. A family or personal history of long QT syndrome.
15. A Screening Visit 12-lead ECG demonstrating 1) QTcF interval >450 msec for males or >470 msec for females, if confirmed by a single repeat during the screening or placebo run-in period OR 2) the average QTcF intervals from the three ECGs performed at Week0/Day 1 exceeds the above values or a single value > 500 msec. This exclusion does not apply to patients with bundle branch block or those whose ECG indicates the presence of a pacemaker.
16. Persistent, uncontrolled hypertension from screening to prior to randomization on Week 0/Day 1, defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 95 mmHg after at least 5 minutes rest if confirmed by up to 3 repeat assessments on the same or another day.
17. Blood donation of approximately 1 pint (500 mL) within 8 weeks prior to Screening
18. History of hemolytic anemia, chronic transfusion requirement, or other condition rendering HbA1c results unreliable as indicator of chronic glucose levels, or hematocrit <35 g/dL for males and <33 g/dL for females.
19. History of cancer, other than non-melanoma skin cancer or in-situ uterine cervical cancer that required therapy in the 5 years prior to randomization.
20. Breastfeeding
21. Positive pregnancy test from Screening Visit to prior to randomization on Week 0/Day 1.
22. Unwilling or unable to follow the procedures outlined in the protocol.
23. Mental or legal incapacitation or language barrier.
24. Living in the same household or related to another participant in this study.
25. Requiring more than three weeks for basal insulin dose adjustment prior to placebo run-in period
26. Non-compliant during the placebo run-in/baseline CGM period between Week -2

and Week 0/Day 1 as defined by less than 80% compliance with regards to dosing study medication as determined by pill count

6. STUDY TREATMENTS

6.1. Assignment to Study Treatment

6.1.1. Sentinel Patients

The sentinel phase of the study is open label with dose escalations following each 7-day dosing at each dose level. Escalations will occur as outlined above (Figure 2) and patients will be given dosing instructions before being discharged from the clinic.

6.1.2. Parts 1 and 2

Parts 1 and 2 are a double blind, randomized study with an insulin dose adjustment period and a single blind placebo run in period. All patients that meet screening criteria at the screening visit will begin the study with an up to 3-week basal insulin dose adjustment period (if needed for insulin adjustment) followed by a 2-week single blind placebo run in period (the patient will be blinded to the placebo). Patients that continue to meet entry criteria at Week -2 will be assigned one bottle of placebo at Week -2 via an Interactive Web Response System (IWRS). Compliance of at least 80% as determined by pill count during this 2-week placebo run-in period is required in order to be randomized.

For Part 1, up to 5 US sites will recruit approximately 30 patients who will be randomized (1:1) active and placebo and treated for 12 weeks.

For Part 2, up to 20 US sites will recruit approximately 90 patients who will be randomized (1:1) active and placebo and treated for 12 weeks.

Patients will be randomized into the Double-Blind Treatment Period at the Week 0/Day 1 visit provided the patient continues to satisfy eligibility criteria, as applicable. Patients will be assigned a unique randomization number based on a site-based randomization scheme via an Interactive Web Response System (IWRS). In Part 1, at Weeks 0, 2, 4, and 6 the IWRS will assign 1 unique bottle to be dispensed and at Week 8 the IWRS will assign 2 unique bottles to be dispensed. In Part 2, at Week 0/Day 1 and Week 10 the IWRS will assign 1 unique bottle to be dispensed and at Weeks 2 and 6 the IWRS will assign 2 unique bottles to be dispensed.

6.2. Breaking the Blind

Treatments for Parts 1 and 2 are double-blind.

At the initiation of the study, the sites will be instructed on the method for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of patient safety. Whenever possible, the investigator or sub-investigator should consult with the Sponsor prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered in the case report form (CRF). Breaking the blind during the

placebo run-in will not be necessary given all patients receive placebo.

6.3. Drug Supplies

6.3.1. Sentinel Patients

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

TTP399 is packaged in 60 cc HDPE bottles with heat induction seal and child-resistant closures. Each bottle contains 35 tablets.

The bottled tablets are stored at refrigerated conditions [2° C to 8° C (36° F to 46° F).

6.3.2. Parts 1 and 2

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.

The bottled tablets are stored at the study site under refrigerated conditions [2° C to 8° C (36° F to 46° F).

6.4. Dispensing of Study Drug to Study Participants

The study site is responsible for dispensing and the accountability of study drug. A qualified staff member at the site will be responsible for dispensation of investigational product to the patients per the protocol requirements and in compliance with GCP.

6.4.1. Sentinel Group

The PI or designee will write on the bottle, prior to dispensing, the number of tablets to be taken in the morning (AM) or evening (PM) that are appropriate for the dose escalation period (e.g. for 400mg QD, 1 tablet in the AM, 0 tablets in the PM). New bottles of drug will be dispensed at Day 1, Day 8, and Day 15 and the patients are expected to return all empty and unused drug to the site on Days 8, 15 and 21. The bottle number dispensed to each patient should be recorded by the site.

6.4.2. Parts 1 and 2

Part 1

Prior to dispensing, an appropriate representative at the site will utilize the IWRS to obtain the unique bottle identification number to be dispensed to the patient. The PI or designee will

write on the bottle, prior to dispensing, the number of tablets (**2**) to be taken, the site number and the subject screening number. At Week -2, patients will be provided with **one** bottle of placebo to allow for 2 weeks of dosing. At Week 0, 2, 4 and 6 visits, patients will be provided with **one** bottle of double-blinded study medication (TTP399 or placebo) to allow for 2 weeks of dosing. At Week 8 patients will be provided with **two** bottles of double-blinded study medication (TTP399 or placebo) to allow for 4 weeks of dosing. The number of bottles dispensed and the number of tablets administered will be identical for both treatment groups.

Part 2

At Week -2, patients will be provided with **one** bottle of placebo to allow for 2 weeks of dosing. At Week 0/Day 1 and Week 10 will be provided with **one** bottle of double-blinded study medication (TTP399 or placebo) to allow for 2 weeks of dosing patients. At Week 2 and Week 6 patients will be provided with **two** bottles of double-blinded study medication (TTP399 or placebo) to allow for 4 weeks of dosing. The number of bottles dispensed, and the number of tablets administered will be identical for both treatment groups.

Once dispensed to patients, medication will be stored at room temperature.

6.5. Study Drug Administration (Dosing)

6.5.1. Sentinel Group Dosing

The Sentinel Phase includes an initial 1-week dosing period at 400 mg once-a-day and potentially 2 additional dose escalation periods of 7 days. Subsequent doses escalations may be modified, up to a maximum of 1200 mg per day, but are initially planned as 800 mg QD for the second week and 1200 mg total daily dose for the third week.

The first dose of TTP399 will be administered in the clinic for each of the dose escalation periods. The patient will be administered 1 tablet on Day 1 with a sufficient volume of water to allow swallowing, 1 hour prior to the drinking the Ensure Plus for the MMTT.

After being discharged from the Day 1 clinic visit, the patients will continue taking 1 tablet approximately 1 hour before the morning meal (i.e., 400 mg QD with morning meal) until Day 8, the next clinic visit.

Assuming the expected PK profile and no observed safety issues following 7 days of dosing, patients will return to the clinic in a fasted state to receive the next dose level. Dosing of 800 mg (2 tablets) with a sufficient volume of water to allow swallowing will occur on the first day of the second period (Day 8), 1 hour prior to drinking the Ensure Plus (MMTT) for period 2. After being discharged from the clinic, patients will continue to take 2 tablets approximately 1 hour before the morning meal at home until the next clinic visit, Day 15. Dosing of 1200 mg daily will occur on the first day of the third period (Day 15), 1 hour prior to the MMTT for period 3. The 1200 mg total daily dose will be administered as

either one or more doses per day (e.g. 1200mg approximately 1 hour before the morning meal OR 800mg approximately 1 hour before the morning meal and 400mg approximately 1 hour before the evening meal). After being discharged from the clinic, patients will continue 1200mg per day dosing at home until the next clinic visit (Day 21) where the final dose of TTP399 (1200 mg per day) will be administered. If an additional period of dose escalation is needed, the dose will not exceed 1200mg daily and will be determined based on the safety and pharmacodynamic response of previous periods. Prior to escalating dosing, the Medical Monitor, the Investigator(s) and appropriate vTv individuals will review and discuss the cumulative safety and PK results of patients in order to make a decision regarding the next dose level.

Patients will be instructed to take by mouth study medication each day at approximately the same time of day approximately 1 hour before the morning meal. Tablets should be swallowed whole and not crushed or broken. If a patient forgets to take a dose of study medication at the usual time, they should be instructed to take that dose approximately 1 hour before their next meal when they remember it, unless it is within 6 hours of the next dose. Patients will administer premeal insulin up to 15 minutes before meals per their usual routine, if needed.

If a BID regimen is used, in addition to dosing in the morning, the patient will be instructed to also dose with study drug as described above 1 hour before the evening meal.

6.5.2. Parts 1 and 2 Dosing

Outpatient Clinic Dosing - Dosing at Study Visits

Beginning at the Week -2 visit, patients will be instructed to arrive at the site after an overnight fast. At visits Week -2 and Week 0/Day 1 study drug will be administered, with a meal in the clinic, from **the bottle of drug dispensed at that visit** (i.e., as applicable, patients should turn in their previous bottle of medication and study drug should be dispensed from a new bottle of drug as assigned by the IWRS) after all assessments have been completed. Patients will be dosed with **two tablets** of study drug (either 800mg TTP399 or placebo) with a sufficient volume of water to allow swallowing. No dosing in the clinic will occur after the Week 0/Day 1 visit.

Patients will eat their morning meal at the site following dosing to establish a routine of dosing the study drug with their morning meal. There are no restrictions on the meal and it can either provided by the site or brought to the site by the patient.

Dose administration at the study site may be delegated to an appropriately qualified staff member but will remain under the direct supervision of the PI or licensed physician designee.

At home dosing

Starting the day after the Week -2 visit, patients will take 2 tablets by mouth at approximately the same time of day with the morning meal (i.e., 800 mg QD TTP399 or PBO with morning meal) until the completion of the dosing period, ***except for Week 0/Day 1 which will be administered on site.*** Patients will be instructed to take the study drug with their next meal following study visits after Week 0/Day 1. No dose is taken the day of the Week 12 visit.

Tablets should be swallowed whole and not crushed or broken. If a patient forgets to take a dose of study medication at the usual time, they should be instructed to take that dose with their next meal, unless it is within 6 hours of the next dose.

6.6. Dosing Errors

Medication errors that result, for example, from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength will be captured as a protocol deviation. In the event of medication dosing error, the site should notify the Sponsor upon discovering the mistake.

In the event of a medication error, including overdose (accidental or intentional), it will be determined by the investigator whether the medication error is clinically significant and must be captured as an adverse event on the AE EDC page. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE report.

6.7. Compliance

At home dosing

Sentinel Phase

Compliance with study medication administration for doses will be assessed during the treatment phase of the study by the number of tablets returned by the patients at the EOS visit. The expectation is that the patients will be 100% compliant for the sentinel phase, including the return of used and unused bottles. The investigators must closely monitor and provide adherence counseling to non-compliant patients to enhance their adherence to the study treatment.

Parts 1 and 2

Compliance with study medication administration for self-administered doses will be assessed during the placebo run-in period prior to randomization at Week 0/Day 1 and during the treatment phase of the study by the number of tablets returned by the patients at each visit during the treatment period. At least 80% compliance with self-administration of the study medication is expected during the placebo run in period. Patients who are not at least 80% compliant **should not** be randomized. Likewise, at least 80% compliance with self-administration of the study medication is expected from Week 0 to 12, inclusive and less

than 80% compliance will be considered noncompliant. Patients who do not return unused drug should also be considered non-compliant. The investigators must monitor and provide adherence counseling to non-compliant patients in order to enhance their adherence to the study treatment.

6.8. Drug Accountability

The Investigator is responsible for the study drug accountability, reconciliation, and record maintenance. The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational products. Forms/records must identify the investigational product, including bottle numbers (if applicable), and account for its disposition on a patient by patient basis, including specific dates and quantities. Copies of the accountability records or reports should be provided to the Sponsor after the study is completed.

Upon initial receipt of study drug supplies, an authorized designee at the study site will acknowledge receipt of the supplies, indicating shipment content and condition. The site must maintain a dated inventory record of study drug supplies, inclusive of all distributions of study drug to the clinic for administration to study participants. A copy of this inventory log or report will be provided to the Sponsor after the study is completed.

6.9. Drug Disposal

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused or partly used investigational product. Unless otherwise authorized by the Sponsor, at the end of the clinical study, all drug supplies unallocated or unused by the patients must be returned to a designated destruction facility.

6.10. Concomitant Medication(s)

6.10.1. Insulin

Sentinel Group

Patients are required to use CSII (with lispro or aspart). Basal rates will be adjusted to keep glucose levels flat or slightly increasing between meals (according to ADA goals of 80-130 mg/dL pre-prandially). Basal rates will be **specifically** evaluated on Days 3 and 6 by the study site team in collaboration with the patient, based on blood glucose levels on two of the last three days.

Basal and bolus insulin doses will be saved.

Part 1

Patients enrolled in Part 1 are required to use CSII (with lispro or aspart) . Closed loop

systems (e.g. MiniMed 670G system) are **NOT** allowed **unless during the study,** the patient agrees to switch to open loop (i.e., switch off the auto mode) and enter the basal adjustment period. Patients using the low glucose suspend feature should continue to do so during the study. During phone calls and visits, the PI (or designee) will confirm that the patient's insulin dosing is adjusted appropriately to treat to this target glycemic range according to the guidance provided in [Section 8.11]. Insulin pump parameters should be recorded in the EDC and insulin pump data should be saved.

Part 2

Patients enrolled in Part 2 can use either CSII or MDI. Patients using MDI will be provided an electronic device to collect insulin dosing information.

Note: *Closed loop systems (e.g. MiniMed 670G system) are **NOT** allowed **unless during the study,** the patient agrees to switch to open loop (i.e., switch off the auto mode) and enter the basal adjustment period. Patients using the low glucose suspend feature should continue to do so during the study.*

During phone calls and visits, the PI (or designee) will confirm that the patient's insulin dosing is adjusted appropriately to treat to this target glycemic range according to the guidance provided in [Section 8.11]. Changes in insulin dosing information should be collected.

6.10.2. Other Concomitant Medications

Any medication (prescription and over-the-counter medications) taken within 90 days prior to Screening, until the Follow-Up visit, must be recorded with indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medication at each clinic visit.

Medications or supplements prohibited or restricted at screening in exclusion criteria 5 should be similarly prohibited or restricted during the study. If during the study, the PI believes any of these medications are required or if a patient takes any of these medications during the study, the PI should contact the Sponsor for instructions on how to proceed.

Whenever possible, attempts must be made **not to** alter the doses and regimens of background medications or supplements (with the exception of insulin, as described above). Any changes made to background medications or supplements must be captured in the patient's CRF. Over-the-counter or prescription medications which are taken "as needed" (prn) are allowed unless excluded by criteria 5, but such prn use should be reported and documented at each visit.

6.10.3. Rescue/Escape/Salvage Therapy

There is no rescue therapy to reverse AEs observed following administration of TTP399.

However, when in combination with insulin, hypoglycemia should be treated according to best practices, e.g. prompt ingestion of carbohydrates or administration of glucagon.

Standard medical supportive care must be provided to manage AEs.

If during the study, a patient is prescribed an additional antidiabetic agent without the prior knowledge of the PI, the PI, upon learning of this event, should contact the Sponsor for instructions on how to proceed.

6.10.4. Hyperglycemic excursion during MMTT (Sentinels):

All MMTTs will be conducted under close medical supervision so that insulin dose adjustments can be made quickly if necessary. If the patient meets the rescue criteria of having a glucose reading > 450mg/dL and is symptomatic (e.g. vomiting) or is unwilling to continue, the patient should be dosed with insulin to correct high glucose levels under normal standards of care at the Investigator's (or Designee) discretion. The event should be recorded as hyperglycemia associated with MMTT in the patient's CRF.

7. STUDY PROCEDURES

7.1. SENTINELS

Each outpatient site visit should occur as early in the morning hours as possible. Visits should occur as close to the scheduled day as possible. Beginning with the baseline CGM visit and continuing through follow-up visits, patients will be instructed to arrive at the site before their morning meal, and before taking mealtime insulin or their study medications for that day. Additionally, ECG and vital sign assessments should precede the blood collection.

Patients are expected to bring all remaining study drug at Day 8, Day 15, Day 21 and ET (if applicable).

A complete list of all trial procedures can be found in the SCHEDULE OF ACTIVITIES (Sentinels).

7.1.1. Screening Visit

At Screening, the following procedures will be completed within 3 weeks prior to Day -7 visit to confirm that patients meet the eligibility criteria for this study:

- Obtain written informed consent before the performance of any protocol-specific procedures;
- Assign patient identification number for screening. This identifying screening number will be retained throughout the duration of study participation;
- Review inclusion/exclusion criteria;

- Complete medical history including duration of diabetes [refer to Section 8.1];
- Complete medication history of all prescription and non-prescription drugs (including daily doses for all mediations), vitamins, and herbal and dietary supplements taken within 90 days prior to the start of screening procedures;
- Record demographic information (including gender, race, and date of birth) and history of alcohol consumption;
- Perform full physical examination including height [refer to Sections 8.2 and 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) and standing blood pressure prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens according to lab kit/manual [refer to Section 8.7 and Table 2 for a list of tests];
- Obtain urine void (pregnancy test (as applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];

Instruct patients to continue their background medication(s), including insulin dosing per their normal routine.

The results of the clinical laboratory assessments and all screening procedures will be evaluated with respect to inclusion and exclusion criteria to determine the patient's eligibility. An investigator may repeat a laboratory assessment once during the screening period before a patient is considered a screen failure. If a patient does not qualify for the trial or is qualified but not randomized, the patient will be considered a screen failure.

7.1.2. Day -7 (Baseline MMTT and CGM)

On Day -7, patients will return to the site before their morning meal (measures can be taken to prevent hypoglycemia, e.g. glucose tablets). All procedures listed below should be performed as close as possible to the scheduled time. At this visit, the following procedures will be completed **prior** to the MMTT:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?"
- Update medications;
- Review Inclusion/Exclusion Criteria
- Confirm patient has complied with unblinded CGM requirements including no sensor changes the day of the visit [Appendix];
- Confirm the patient's CGM reading is between 80 and 200 mg/dL [if glucose is not within range, refer to Section 8.6 for appropriate procedures]
- Obtain body weight [refer to Section 8.2];
- Obtain urine void for pregnancy test for WCBP;

- Obtain supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) and standing blood pressure prior to blood sampling [refer to Section 8.5];
- Prior to the MMTT, confirm that it has been at least 4 hrs from last insulin bolus and at least 1hr after their last glucose tablet
- Administer MMTT [See Section 8.6 for detailed information]

    - Dose **with half the** normal mealtime insulin prior to MMTT (according to normal insulin dosing schedule before meals, within 15 minutes of the MMTT).
    - Provide patient with 1 bottle of Ensure Plus and instruct the patient to consume within 5 minutes and record time of consumption.
    - Patient will be observed closely during the MMTT and the insulin dose will be adjusted as needed for patient safety **(**i.e., if the patient meets the rescue criteria of having a glucose readings > 450mg/dL and is symptomatic, the patient should be dosed with insulin to correct high glucose levels. [Refer to Section 6.10.4 for additional details regarding rescue therapy for hyperglycemia during MMTT].
    - Collect MMTT pharmacodynamic samples (glucose, c-peptide, GLP-1/Glucagon and retention sample for non-genomic biomarkers (as applicable based on consent) as indicated in Section 8.6.4 and Figure 5

Following completion of the above procedures:

- Provide patient with standardized lunch meal per their selection and instruct the patient to consume the entire meal with insulin bolus, if needed (See Section 4.1 for standardized lunch meal requirements).
- Instruct patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;
- Confirm patient understanding of CGM and event entry requirements [See Section 4.2]
- Remind patient to return to the study site for the following visit with CGM and related supplies;

7.1.3. Day -1

- On Day -1 remind patient to return to site on Day 1 before their morning meal (measures can be taken to prevent hypoglycemia, e.g. glucose tablets) and bring CGM and related supplies;

7.1.4. Days 1, 8 and 15

On Day 1, 8, and 15, patients will return to the site before their morning meal (measures can be taken to prevent hypoglycemia, e.g. glucose tablets)

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Review Inclusion/Exclusion Criteria (Day 1 only)
- Perform limited physical exam (Day 1 only) [refer to Section 8.3]
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (Triplicate on Day 1, Single readings all other days) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) and standing blood pressure prior to blood sampling (Triplicate on Day 1, Single values all other days) [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.8 and Table 2];
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Upload and review CGM and event entry information [Section 4.2];
- Confirm dosing compliance by a pill count (Day 8 and 15 only) [See Section 6.7]
- Confirm patient has complied with unblinded CGM requirements including no sensor changes the day of the visit [Appendix];
- Prior to the MMTT, confirm that it has been at least 4 hrs from last insulin bolus and at least 1hr after their last glucose tablet
- Dispense study drug along with instructions for at home dosing for the next period [Refer to Section 6.4 and 6.5];
- Administer MMTT [See Section 8.6 for detailed information]
    - Administer study drug 1 hour prior to drinking the Ensure Plus Dose **with half the** normal mealtime insulin prior to MMTT (according to normal insulin dosing schedule before meals, within 15 minutes of the MMTT).
    - Collect pharmacokinetic samples as indicated in the SCHEDULE OF ACTIVITIES (Sentinels) with time 0 (PK) collected immediately prior to dosing
    - Provide patient with 1 bottle of Ensure Plus and instruct the patient to consume within 5 minutes.
        - Patient will be observed closely during the MMTT and the insulin dose will be adjusted as needed for patient safety **(**i.e., if the patient meets the rescue criteria of having a glucose readings > 450mg/dL and is symptomatic, the patient should be dosed with insulin to correct high glucose levels. [Refer to Section 6.10.4 for additional details regarding rescue therapy for hyperglycemia during MMTT].
    - Collect MMTT pharmacodynamic samples (glucose) as indicated in Section 8.6.4 and Figure 5

Following completion of the pharmacodynamic sample collection:

- Provide patient with standardized lunch meal per their selection and instruct the patient to consume the entire meal with insulin bolus, if needed (See Section 4.1 for standardized lunch meal requirements and Section 8.6.1 for guidelines for insulin adjustments).

- Provide patient with a dinner meal (Section 8.6.1 for guidelines for insulin adjustment guidance);
- Instruct patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;
- Confirm patient understanding of CGM and CGM recording requirements [See Section 4.2]
- Remind patient to return to the study site for the next study visit in a week
    - with study drug, CGM and related supplies;
    - before their morning meal (measures can be taken to prevent hypoglycemia, e.g. glucose tablets)

Upon completion of the above procedures,

- The patient will remain in the clinic for observation until the PI or designee determines it is safe for the patient to be discharged.

7.1.5. Days 2-7, 9-14, 16-20

- Contact the patient daily (phone or text) to assess safety and insulin dosing adjustments

7.1.6. Day 21 (or Last Day of Dosing)

If three dose escalation periods are conducted, the visit will occur on the last day of dosing (Day 21). If the vTv study team, in collaboration with the PI, decide to add an additional dosing period or stop dose escalation prior to the third period, a final MMTT will be conducted on the last day of dosing of the last dosing period conducted (for example if period 2 is the last dose escalation period, the Last day of dosing would be on Day 14 and if a period 4 is added, the Last day of dosing would be Day 27).

On the last day of dosing during the last period, patients will return to the site before their morning meal (measures can be taken to prevent hypoglycemia, e.g. glucose tablets.

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Perform limited physical exam [refer to Section 8.3]
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) and standing blood pressure prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit/manual [refer to Section 8.7 and Table 1]:

- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Upload and review CGM and event entry information [Section 4.2];
- Confirm dosing compliance by a pill count [See Section 6.7];
- Confirm patient has complied with unblinded CGM requirements including no sensor changes the day of the visit [Appendix];
- Prior to the MMTT, confirm that it has been at least 4 hrs from last bolus and at least 1hr after their last glucose tablet
- Administer MMTT [See Section 8.6 for detailed information]

    - Administer study drug 1 hour prior to drinking the Ensure Plus
    - Dose **with half the** normal mealtime insulin prior to MMTT (according to normal insulin dosing schedule before meals, within 15 minutes of the MMTT).

    - Collect pharmacokinetic samples as indicated in the SCHEDULE OF ACTIVITIES (Sentinels) with time 0 (PK) collected immediately prior to dosing
    - Provide patient with 1 bottle of Ensure Plus and instruct the patient to consume within 5 minutes. Patient will be observed closely during the MMTT and the insulin dose will be adjusted as needed for patient safety **(**i.e., if the patient meets the rescue criteria of having a glucose readings > 450mg/dL and is symptomatic, the patient should be dosed with insulin to correct high glucose levels. [Refer to Section 6.10.4]).
    - Collect MMTT pharmacodynamic samples (glucose, c-peptide, GLP-1/Glucagon and retention sample for non-genomic biomarkers (as applicable based on consent) as indicated in Section 8.6.4 and Figure 5

Following completion of the pharmacodynamic sample collection:

- Provide patient with standardized lunch meal per their selection and instruct the patient to consume the entire meal with insulin bolus, if needed (See Section 4.1 for standardized lunch meal requirements and Section 8.6.1 for guidelines for insulin adjustments).
- Provide the patient with a dinner meal.

Upon completion of the above procedures (except the collection of the 24hr PK timepoint,

- The patient will remain in the clinic for observation until the PI or designee determines it is safe for the patient to be discharged.
- Remind the patient to return to the clinic for the 24hr PK timepoint collection (fasting is NOT required)
- Contact the patient (phone or text) daily to assess safety and insulin dosing adjustments.

7.1.7. Day 22 (or day after the Last Dose)

- Collect blood for TTP399 PK at approximately 24h (within a 3 hour window) following Day 21 dosing (fasting is not required)
- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”

- Patients will be instructed to return to the clinic for a follow-up visit 7-10 after their final dose.

7.1.8. Follow-up (F/U); 7-10 days following the final dose

Patients will return to the study site before their morning meal (measures can be taken to prevent hypoglycemia, e.g. glucose tablets) for a follow-up visit at 7-10 days after the last dose. If an Early Termination visit is conducted the Follow-up visit will occur 7-10 days after the Early Termination visit. Out of window visits are allowed in circumstances where the patient cannot return within the appropriate window. In both cases, there should be consultation with the sponsor.

The following procedures should occur at the visit:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) and standing blood pressure prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit/manual [refer to Section 8.7 and Table 2 for list of tests];
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Save CGM and insulin pump data;

Completion of the follow-up visit marks the end of the patients' participation in the study.

- The Investigator may provide guidance to the patient regarding management of their T1DM and related conditions
- A breakfast meal may be provided (optional).

Glucometer and supplies for home glucose or DKA monitoring (if supplied by the site) can be returned to the patients for their use, if permitted by local country regulations.

7.1.9. Early Termination (ET) Visit Procedures

When a patient withdraws from the study, an Early Termination visit will be conducted as follows:

If the patient has been dosing with study drug, uninterrupted, for the last 5 days AND consents to dose their final dose at the study site and comply with procedures in the Day 21 and Day 22, visit procedures at the ET will be conducted as described for the Day 21 and Day 22 visit.

If there is a safety concern that precludes additional dosing, the patients should not be dosed and procedures associate with a MMTT and PK collection should not be conducted.

For patients who have not dosed for the last 5 days (uninterrupted) or do NOT consent to procedures associated with a MMTT and dosing on site, a follow-up visit approximately 7 days after the last dose will be conducted and no ET visit will occur.

7.1.10. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Every effort should be made to document patient outcome. The Investigator should inquire about the reason for withdrawal. The patient must return all unused study medication to the site.

The following visits should be conducted upon termination depending on the patients recent dosing history:

- An Early Termination visit should be conducted if the patient has been dosing with the latest dose escalation continuously for at least 5 days.
    - If the patient consents to take the final dose at the site and comply with activities associate with a MMTT (including collection of PK, PD and retention samples (if applicable), the site should conduct a MMTT and related activities along with safety assessments (e.g. vital signs, ECG and physical exams) at the ET visit.
    - Patients who continue to consent should have a Follow-up Visit 7-10 days after their ET visit.

- Otherwise a follow-up visit should be conducted.

If the patient withdraws consent for further assessments, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who terminate early may result in additional enrollment of patients to accommodate dropouts, at the Sponsor's discretion.

7.2. PART 1

Each outpatient site visit should occur as early in the morning hours as possible. Beginning with the Week -2 and continuing through follow-up visits, patients will be instructed to arrive at the site following an **overnight fast** (with the exception of glucose tablets taken for safety purposes), before their morning meal, before taking mealtime insulin and before taking their study medications for that day. An overnight fast must be observed prior to safety laboratory

sample collection. Patients arriving at Week 0/Day 1 that do not meet the fasting requirements should be rescheduled for another visit. At other visits, if a patient arrives at the site without fasting lab samples should be collected and a protocol deviation should be noted. The site should note on the lab requisition form whether or not the patient was fasted.

ECG and vital sign assessments should precede the blood collection.

A complete list of all trial procedures can be found in the SCHEDULE OF ACTIVITIES (Part 1).

7.2.1. Screening Visit

A signed and dated IRB approved informed consent form (ICF) will be obtained from each patient at the Screening Visit before the performance of any protocol-specific procedures.

It is possible a patient is identified who requires CGM supplies to assist with stabilization of their CGM history for up to two months prior to the Screening Visit. The sponsor must be contacted and agree to provide CGM supplies if needed prior to the Screening Visit. Once sponsor approval is obtained, a separate IRB approved CGM supply informed consent will be administered prior to providing these supplies to the patient. During this time, the patient is not considered active in screening (screened) or a participant in the study. The patient will be considered active in screening if they return for the Screening Visit and the full study ICF is obtained.

Investigators will assign a unique patient screening identification number at the Screening Visit sequentially to each patient who has signed the informed consent document. The screening ID is computer-generated. This identifying screening number will be retained throughout the duration of study participation.

At Screening, the following procedures will be completed within 2 weeks prior to the Insulin Dose Adjustment Period (if needed) or Week -2 visit to confirm that patients meet the eligibility criteria for this study:

- Obtain written informed consent;
- Assign patient identification (SID) number for screening obtained from the IWRS;
- Review inclusion/exclusion criteria;
- Complete medical history including duration of diabetes [refer to Section 8.1];
- Complete medication history of all prescription, investigational study medication and non-prescription drugs (including daily doses for all mediations), vitamins, and herbal and dietary supplements taken within 90 days prior to the start of screening procedures;
- Record demographic information (including gender, race, and date of birth) and history of alcohol consumption;
- Provide DTSQs for patient to complete;
- Perform full physical examination including height [refer to Sections 8.2 and 8.3];

- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens according to the lab kit [refer to Section 8.7 and Table 1 (Part 1) and Appendix 2]
- Obtain urine void (pregnancy test (all women) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- The site will provide the patient CGM supplies, if needed.

Instruct patients to continue their background medication(s) including their normal insulin dose.

The results of the clinical laboratory assessments and all screening procedures will be evaluated with respect to inclusion and exclusion criteria to determine the patient's eligibility. An investigator may repeat a laboratory assessment during the screening period upon medical monitor approval. If a patient does not qualify for the trial, he or she will be considered a screen failure.

7.2.1. Basal Insulin Dose Adjustment Period (Insulin Adjustment Visit): up to 3 weeks in duration

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) the basal adjustment period (up to three weeks) is required following the patient turning off the auto mode.

- The PI, or designee, will review the patient's CGM data over the previous 2 weeks;
    - If after reviewing the patient's CGM data over the previous two weeks, no basal insulin adjustments are needed (i.e., in general, the patient generally reaches the glycemic targets of fasting/pre-meal: 80-130 mg/dL), the site will proceed to conduct the Week -2 visit and the patient will enter the placebo-controlled run-in period.
    - If basal insulin adjustments are needed, the patient in collaboration with the PI and site staff will optimize the patient's basal insulin dose. The site should:
        - Contact patient twice a week during this period to review the previous 3-5 days of the patient's glucose profile and recommend basal insulin dose adjustments based on insulin dose adjustments in Section 8.11.

- If during this period no adjustments have been needed for a week, the patient will be scheduled for a Week -2 visit to begin the placebo run in period

  Insulin dose adjustments will be made for up to 3 weeks, after which the PI or designee will determine if the patient is eligible for the study or if the patient will be considered a screen fail based on the patient generally reaching the glycemic targets of fasting/pre-meal: 80-130 mg/dL.

- The site will provide the patient with a glucometer and glucometer and CGM supplies;

7.2.2. Week -2 (Placebo Run-In Period): At least 13 days in duration

On Week -2, patients will return to the site. Patients who qualify and consent to participate in the study will enroll (be assigned an enrollment ID) and will begin the single-blind placebo-run-in period.

At this visit, the following procedures will be completed **prior** to dosing:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?” and record any changes in medical history;
- Update medications;
- Review Inclusion/Exclusion Criteria;
- Obtain body weight [refer to Section 8.2];
- Obtain supine 12-lead electrocardiogram (ECG) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) [refer to Section 8.5];
- Obtain urine void for pregnancy test (WCBP only);
- Record Insulin pump settings in the EDC [refer to Section 8.11];
- Dispense study drug according to the IWRS [Refer to Sections 6.1.2 and 6.4.2];
- Administer the first dose of study drug in the clinic. Date and time of administration should be recorded in the EDC [Section 6.5.2];
- Have patient eat their morning meal (either provided by the site or brought to the site by the patient) to establish a routine of dosing the study drug with their morning meal;
- Adverse-event reporting will begin immediately following administration of study drug.

Prior to discharging the patient from the visit:

- Provide instructions for at home dosing for the next period [Refer to Section 6.5.2]
- Instruct patients regarding identification/ management of hypoglycemia, hyperglycemia and diabetic ketoacidosis;

- Provide the patient with a glucometer (if not already provided at Insulin Adjustment Visit) and glucometer and CGM supplies (if needed);
- Confirm patient understanding of CGM and CGM App requirements [See Section 4.2 (Part 1)];
- Remind patient to return to the study site for the following visit in two weeks with CGM, study drug and related supplies;

7.2.1. Phone Contact at Week -1

Contact patient by phone (voice preferred, but text acceptable) about midway through the placebo run-in period to:

- Ask the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?"
- Confirm patient is complying with CGM requirements *or* re-educate patient if needed
- Remind patient to arrive at the next site visit (in approximately 1 week) after an overnight fast, prior to taking insulin or study drug

7.2.2. Week 0/Day 1

On Week 0/Day 1 patients will return to the site after an overnight fast (except water or glucose tablets if needed for low blood glucose). If the patient is not fasted or the subject did not return the Week -2 study drug, the visit should be rescheduled.

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Confirm patient is fasting. If not fasted, the visit should be rescheduled;
- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?" and record any changes in medical history;
- Collect prior periods study drug and perform compliance check prior to dispensing and dosing at the visit;
- Update concomitant medications;
- Review Inclusion/Exclusion Criteria to confirm eligibility, including compliance of study medication (at least 80% required) and CGM requirements (sensor change and calibrations, if applicable) [Section 4.2];
- Conduct limited physical exam [refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (Triplicate) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (Triplicate) [refer to Section 8.5];

- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 1) and Appendix 2];
- Collect pharmacokinetic sample prior to dosing;
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Save/review CGM and insulin pump data and record insulin pump settings [Section 4.2 and Section 8.11];
- Provide any insulin dosing adjustment information based on the glycemic values using the guidance in Section 8.11;
- Randomize the patient to one of the double-blind treatment regimens;
  Note: IWRS will assign a randomization ID to the patient once the patient is randomized, the patient can no longer be considered a screen-failure.
- Dispense study drug according to the IWRS [Refer to Sections 6.1.2 and 6.4.2];
- Dose with study drug; document date and time of administration;
- Have patient eat their morning meal (either provided by the site or brought to the site by the patient) to establish a routine of dosing the study drug with their morning meal;
- Adverse-event reporting for double-blind treatment period will begin immediately following the administration of the first dose of double-blind study medication.

Prior to discharging the patient from the visit:

- Provide instructions for at home dosing for the next period [Refer to Section 6.5.2];
- Instruct patients regarding identification/ management of hypoglycemia, hyperglycemia and diabetic ketoacidosis;
- Confirm patient understanding of use of unblinded CGM and App recording requirements [See Section 4.2 and 4.3];
- Provide the patient with glucometer and CGM supplies (if needed);
- Remind patient to return to the study site for the next study visit in approximately two weeks with study drug, CGM and related supplies for a safety visit;

7.2.3. Phone Contact during the first two weeks of dosing:

Contact patient by phone (voice) every business day for the first week and once during the second week to:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Review glucose and insulin data with the patient
  - Provide any insulin dosing adjustments based on the glycemic values of last 2-3 days using the guidance in Section 8.11;
  - Query circumstances around any extreme episodes of hypoglycemia or hyperglycemia and record relevant information (e.g. glucometer readings or contributing factors)
- Record any insulin adjustments to the pump in the EDC [Refer to Section 8.11]

7.2.4. Phone contact at Week 3, 5, 7, 9, 10, 11 (± 3 days) [During weeks that there are no clinic visits]

Contact patient by phone (voice) **once a week** (except weeks when patients have a site visit) to:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?"
- Review glucose and insulin data with the patient
  - Provide any insulin dosing adjustments based on the glycemic values of last 2-3 days using the guidance in Section 8.11;
  - Query circumstances around any extreme episodes of hypoglycemia or hyperglycemia and record relevant information (e.g. glucometer readings or contributing factors);
  - Remind patient to arrive at the next site visit after an overnight fast, prior to taking insulin or study drug.
- Record any insulin adjustments to the pump in the EDC [Refer to Section 8.11]

7.2.5. Week 2, 4, 6 and 8

On Week 2, 4, 6 and 8 patients will return to the site following an overnight fast (except water) or glucose tablets for safety.

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?";
- Collect prior periods study drug and perform compliance check;
- Update concomitant medications;
- Conduct limited physical exam [**Week 6 only**, refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single tracing) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (single readings) [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 1) and Appendix 2];
- Collect pharmacokinetic sample prior to dosing;
- Obtain urine void (pregnancy test (WCBP only) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Save/review CGM and insulin pump data and record insulin pump settings [Section 4.2 and Section 8.11];

- Provide any insulin dosing adjustment information based on the glycemic values using the guidance in Section 8.11;
- Review compliance of study medication and CGM requirements and re-educate if needed;
- Dispense study drug according to the IWRS [At **Week 2, 4, and 6 of 1 bottle** of study drug will be dispensed At **Week 8 ONLY, 2 bottles** of study drug will be dispensed, Refer to Sections 6.1.2 and 6.4.2];

Prior to discharging the patient from the visit:

- Instruct patients to dose with study drug before their next meal;
- Provide instructions for at home dosing for the next period [Refer to Section 6.5.2]
- Remind patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;
- Confirm patient understanding of use of unblinded CGM and App recording requirements [See Section 4.2 and 4.3];
- Provide the patient with glucometer and CGM supplies (if needed);
- Remind patient to return to the study site for the next study visit with study drug, CGM and related supplies;
- Contact the patient (phone or text) at least once a week to assess safety and insulin dosing adjustments with guidance provided in Section 8.11

7.2.6. Week 12

On Week 12 patients will return to the site after an overnight fast (except water).
At this visit, the following procedures will be completed:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Collect prior periods study drug and perform compliance check;
- Update concomitant medications;
- Provide DTSQs and DTSQc for patient to complete [refer to Section 8.12];
- Ask Quality of Life Question and enter answer in EDC [refer to Section 8.13];
- Conduct limited physical exam [refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single tracing) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 1) and Appendix 2];
- Collect pharmacokinetic sample prior to dosing;
- Obtain urine void (pregnancy test (WCBP only) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Save/review CGM and insulin pump data and record insulin pump settings [Section 4.2

and Section 8.11];

Prior to discharge from the visit:

- Instruct patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;
- Remind patient to return to the study site for the next study visit in approximately 7-10 days for a follow-up visit.

7.2.7. Follow-up; 7-10 days following the final dose

The Follow-up visit is considered not to be part of the double-blind treatment period. Patients will return to the study site after an overnight fast (except water) for a follow-up visit at approximately 7-10 days after the last dose.

The following procedures should occur at the visit:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update concomitant medications;
- Conduct limited physical exam [refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single tracing) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.8, Table 2 and Appendix 2];
- Obtain urine void (pregnancy test (all women) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Save/review CGM and record insulin pump data [Section 4.2 and Section 8.11];

Completion of the follow-up visit marks the end of the patients' participation in the study.

CGM and Glucometer and supplies for home glucose and DKA monitoring (if supplied by the site) can be returned to the patients for their use, if permitted by local country regulations.

7.2.8. Early Termination (ET) Procedures [Same as Week 12 (except treatment questionnaire and QOL question]

When a patient withdraws from the study, an Early Termination visit is only required as defined in Section 7.2.9. An ET visit is considered to be part of the double-blind treatment

period, and patients are presumed to be on treatment for an ET visit to occur. If the patient has not had a dose of double-blind study medication within 10 days, the ET visit should not occur—a FU visit is to occur. If the ET visit occurs at the time of a protocol-planned scheduled visit, the site will record the scheduled visit which applies to the ET visit. If the ET visit occurs between protocol-planned scheduled visits, the site will record that the ET visit occurs at an unscheduled assessment time. The patient should return to the site after a 12 hour fast (except water) for an ET Visit. At this visit, the following procedures will be completed:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Conduct limited physical exam [refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single tracing) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 1) and Appendix 2];
- Collect pharmacokinetic sample prior to dosing
- Obtain urine void (pregnancy test (WCBP only) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Save/review CGM and insulin pump data [Section 4.2 and Section 8.11];

Prior to discharge from the visit:

- Instruct patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;
- Remind patient to return to the study site for the next study visit in approximately 7-10 days for a follow-up visit.

7.2.9. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Every effort should be made to document patient outcome. The Investigator should inquire about the reason for withdrawal. The patient must return all unused study medication to the site and should return to the site for one or two visits, as described below.

Any AEs should be followed based on the following criteria:

Follow-up of any ongoing AE (including any clinically significant laboratory abnormality) should be conducted as follows:

- If the Investigator determines the AE is *not related* to the study product or study procedures, the AE will be followed until resolution, or 60 days from end of study participation.
- All AEs with a relationship other than *not related* will be followed until resolution, or until the patient is lost to follow-up.

At the discretion of the Investigator or designated licensed physician and Medical Monitor, the length of AE follow-up may be attenuated, with written rationale by the Investigator or designated licensed physician.

Upon termination, all patients who continue to consent will have a Follow-up Visit approximately 7-10 days after the last dose). Procedures leading up to the Follow-up Visit will depend on the patient's recent dosing and how long the patient has been on treatment. The following table summarizes what exit visits should be conducted upon termination assuming patient still consents:

Patient dosing/treatment status at termination:	**Other applicable conditions:**	**Exit Visits to be conducted:**
Patient has not received 4 weeks of treatment	None	Conduct Follow-up Visit approximately 7-10 days after last dose
Patient **has not** dosed within 10 days of initiating termination procedures	None	Only conduct Follow-up Visit
Patient has dosed within 10 days of initiating termination procedures	Patient has reach 12 weeks of treatment (i.e., reached the Week 12 visit window of 12 weeks ± 3 days). Patient will be considered to have completed treatment but not complete the study.	Conduct Week 12 visit then a Follow-up Visit approximately 7-10 days later

	Patient has completed at least the Week 4 Visit but has not reached 12 weeks of treatment	Conduct Early Termination Visit then a Follow-up Visit approximately 7-10 days later

If the patient withdraws consent for further assessments, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who terminate early may result in additional enrollment of patients to accommodate dropouts, at the Sponsor's discretion.

7.3. PART 2

A complete list of all trial procedures can be found in the SCHEDULE OF ACTIVITIES (Part 2).

Each outpatient site visit should occur as early in the morning hours as possible. Beginning with the Week0/Day1 visit and continuing through follow-up visits (except the Week 10 visit), patients will be instructed to arrive at the site following an **overnight fast**, before their morning meal, before taking mealtime insulin and before taking their study medications for that day. An overnight fast must be observed prior to safety and efficacy laboratory sample collection. Additionally, ECG and vital sign assessments should precede the blood collection.

Patients are expected to bring all remaining study drug at Week 0/Day 1 and Week 26, 10 and 12 and ET (if applicable).

7.3.1. Screening Visit

A signed and dated IRB approved informed consent form (ICF) will be obtained from each patient at the Screening Visit before the performance of any protocol-specific procedures.

Investigators will assign a unique patient screening identification number at the Screening Visit 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 Screening, the following procedures will be completed within 2 weeks prior to the next visit [either the basal adjustment period (if needed) or Week -2visit (if no basal adjustment is needed)] to confirm that patients meet the eligibility criteria for this study:

- Obtain written informed consent;
- Assign patient identification (SID) number for screening;

- Review inclusion/exclusion criteria;
- Complete medical history including duration of diabetes [refer to Section 8.1];
- Complete medication history of all prescription and non-prescription drugs (including daily doses for all mediations), vitamins, and herbal and dietary supplements taken within 30 days prior to the start of screening procedures;
- Record demographic information (including gender, race, and date of birth) and history of use alcohol consumption;
- Provide DTSQs for patient to complete [Refer to Section 8.12];
- Perform full physical examination including height [refer to Sections 8.2 and 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling [refer to Section 8.5];
- Collect clinical laboratory specimens according to the lab kit [refer to Section 8.7, Table 1 (Part 2) and Appendix Part 2]
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];

Instruct patients to continue their background medication(s) including their normal insulin dose.

The results of the clinical laboratory assessments and all screening procedures will be evaluated with respect to inclusion and exclusion criteria to determine the patient's eligibility. An investigator may repeat a laboratory assessment during the screening period upon medical monitor approval. If a patient does not qualify for the trial, prior to enrolling at Week -2, he or she will be considered a screen failure.

7.3.2. Basal Insulin Dose Adjustment Period (Insulin Adjustment Period): up to 3 weeks in duration

Once a patient has met all the entry criteria at the screening visit, the site will schedule a visit or phone call, if preferred, to determine if the patient's basal insulin dose needs to be optimized.

- The PI, or designee, will review the patient's CGM or glucometer data over the previous 7 days;
    - If after reviewing the patient's glucose data over the previous 7 days, no basal insulin adjustments are needed (i.e., in general, the patient generally reaches the glycemic targets of fasting/pre-meal: 80-130 mg/dL), the site will proceed to conduct the Week -2 visit and the patient will enter the placebo-controlled run-in period.

- If basal insulin adjustments are needed, the patient in collaboration with the PI and site staff will optimize the patient's basal insulin dose. The site should:

  - Contact patient twice a week during this period to review the previous 3-5 days of the patient's glucose profile and recommend insulin dose adjustments based on insulin dose adjustments in Section 8.11.

  - If during this period no adjustments have been needed for a week, the patient will be scheduled for a Week -2 visit to begin the placebo run in period

    Insulin dose adjustments will be made for up to 3 weeks, after which the PI or designee will determine if the patient is eligible for the study or if the patient will be considered a screen fail based on the patient generally reaching the glycemic targets of fasting/pre-meal: 80-130 mg/dL.

- Provide the patient with a glucometer and associated supplies (if needed);
- Provide patients using MDI, the electronic device to collect insulin dosing information to use throughout the trial;
- Collect basal and bolus insulin dosing information;
- Collect fasting/pre-meal glucose measurements;

7.3.3. Week -2 (Baseline: Initiation of Baseline Sponsor Provided (Blinded) CGM)

All procedures listed below should be performed as close as possible to the scheduled time.

On Week -2, patients will return to the site after an overnight fast (except water). At this visit, the following procedures will be completed **prior** to dosing:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?"
- Update medications;
- Review Inclusion/Exclusion Criteria;
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling [refer to Section 8.5];
- Obtain urine void (pregnancy test (if applicable);
- Complete enrollment form in EDC once all ongoing entry criteria have been evaluated but before dosing;
  Note: IWRS will assign an enrollment ID to the patient once the patient is enrolled, the

patient can no longer be considered screen failure.

- Apply sponsor CGM and provide instructions [See Section 4.2];
- Provide patients using MDI, the electronic device to collect insulin dosing information to use throughout the trial (if not already provided at previous visit);
- Collect basal and bolus insulin dosing information;
- Dispense study drug according to the IWRS along with instructions for at home dosing for the next period [Refer to Section 6.4.2 and 6.5.2];
- Dose with study drug with normal insulin dose and their morning meal (either provided by the site or brought to the site by the patient) to establish a routine of dosing the study drug with their morning meal);
- Document date and time of study drug administration;

Prior to discharging the patient from the visit:

- Instruct patients regarding identification/ management of hypoglycemia, hyperglycemia and diabetic ketoacidosis;
- Provide the patient with glucometer and other supplies (if needed);
- Remind patient to return to the study site for the next study visit in approximately two weeks with study drug and personal CGM (if applicable) or glucometer for a safety visit;

7.3.4. Phone Contact during the placebo run-in period (approximately Week -1)

Contact patient by phone approximately one week after the Week -2 visit:

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Confirm sponsor CGM sensor is still attached, with no adherence issues. For sensor issues, subjects may need to return to the site for replacement.
- Query circumstances around any extreme episodes of hypoglycemia or hyperglycemia and record relevant information (e.g. glucometer readings or contributing factors)

7.3.5. Week 0/Day 1

On Week 0/Day 1 patients will return to the site after an overnight fast (except water or glucose tablets if needed for low blood glucose). If the patient is not fasted or the subject did not return the Week -2 study drug, the visit should be rescheduled.

Visit should be scheduled no earlier than 13 days after the prior Week -2 visit to allow for at least 13 days of collection for the sponsor provided CGM.

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Confirm patient is fasting. If not fasted, the visit should be rescheduled;
- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?” and record any changes in medical history;
- Collect prior periods study drug and perform compliance check prior to dispensing and dosing at the visit;
- Update concomitant medications;
  - Review Inclusion/Exclusion Criteria to confirm eligibility;
    Note: if a patient does not qualify for the trial after being enrolled, but prior to randomization, he or she will be considered a run-in failure.
- Conduct limited physical exam [refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (Triplicate) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (Triplicate) [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 1) and Appendix 2 (Part 2)];
- Collect pharmacokinetic samples prior to dosing;
- Collect retention samples if applicable (optional);
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Collect CGM device and data;
- Collect basal and bolus insulin dosing information;
- Provide any insulin dosing adjustment information based on the glycemic values using the guidance in Section 8.11;
- Randomize the patient to one of the double-blind treatment regimens;
  Note: IWRS will assign a randomization ID to the patient once the patient is randomized, the patient can no longer be considered Run-In failure.
- Dispense study drug according to the IWRS [Refer to Sections 6.1.2 and 6.4.2];
- Dose with study drug; document date and time of administration;
- Have patient eat their morning meal (either provided by the site or brought to the site by the patient) to establish a routine of dosing the study drug with their morning meal;
- Adverse-event reporting for double-blind treatment period will begin immediately following the administration of the first dose of double-blind study medication.

Prior to discharging the patient from the visit:

- Provide instructions for at home dosing for the next period [Refer to Section 6.5.2];
- Instruct patients regarding identification/ management of hypoglycemia, hyperglycemia and diabetic ketoacidosis;
- Provide the patient with glucometer and other supplies (if needed);
- Remind patient to return to the study site for the next study visit in approximately two weeks with study drug and personal CGM (if applicable) or glucometer for a safety visit;

7.3.6. Phone Contact during the first week of dosing (approximately Week 1)

Contact patient by phone approximately one week after the Week 0/Day 1 visit

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Query circumstances around any extreme episodes of hypoglycemia or hyperglycemia and record relevant information (e.g. glucometer readings or contributing factors)
- Record any insulin adjustments in the EDC [Refer to Section 8.11]

7.3.7. Week 2 and Week 6

On Week 2 and Week 6, patients will return to the site after an overnight fast (except water).

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Conduct inquiry about potential symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update concomitant medications;
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single readings) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (single readings) [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 2) and Appendix 2 (Part 2];
- Collect pharmacokinetic sample prior to dosing (Week 6 only);
- Collect retention samples, if applicable (optional) (Week 6 only);
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Collect basal and bolus insulin dosing;
- Provide any insulin dosing adjustment information based on the glycemic values using the guidance in Section 8.11;
- Collect prior periods study drug and perform compliance check;
- Dispense study drug according to the IWRS along with instructions for at home dosing for the next period [Refer to Section 6.4.2 and 6.5.2]

Following completion of the above procedures:

- Remind patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;
- Provide the patient with glucometer and supplies (if needed);
- Remind patient to return to the study site for the next study visit with study drug and personal CGM (if applicable) or glucometer;

7.3.8. Phone Contact during double-blind dosing period (approximately Week 4 and 8)

Contact patient by phone at approximately Week 4 and Week 8

- Assess for potential adverse events by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?"
- Review glucose and insulin data with the patient
  - Provide any insulin dosing adjustments based on the glycemic values of last 2-3 days using the guidance in Section 8.11;
- Query circumstances around any extreme episodes of hypoglycemia or hyperglycemia and record relevant information (e.g. glucometer readings or contributing factors)
- Record any insulin adjustments in the EDC [Refer to Section 8.11]

7.3.9. Week 10

On Week 10, patients are NOT required to be fasted for this visit.

- Conduct inquiry about potential symptoms by asking the patients to respond to a non-leading question such as "how have you been feeling?" and "has anything changed since your last visit?" Update medications;
- Collect urine for pregnancy test if applicable;
- Collect prior periods study drug and perform compliance check prior to dispensing and dosing at the visit;
- Dispense study drug according to the IWRS along with instructions for at home dosing for the next period [Refer to Section 6.4.2 and 6.1.2]
- Apply sponsor CGM and review requirements [See Section 4.2];
- Collect basal and bolus insulin dosing information;

Prior to discharging the patient from the visit:

- Remind patients regarding identification/ management of hypoglycemia, hyperglycemia and diabetic ketoacidosis;
- Provide the patient with glucometer and other supplies (if needed);
- Remind patient to return to the study site for the next study visit in approximately two weeks with study drug and sponsor CGM and personal CGM (if applicable) or glucometer;

7.3.10. Week 12

On Week 12, patients will return to the site after an overnight fast (except water). Visit should be scheduled no earlier than 13 days following the Week 10 visit to allow for at least 13 days of collection for the sponsor provided CGM.

At this visit, the following procedures will be completed **prior** to administration of study medication:

- Conduct inquiry about potential symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Provide DTSQs and DTSQc for patient to complete [refer to Section 8.12];
- Ask Quality of Life Question and enter answer in EDC [refer to Section 8.13];
- Conduct limited physical exam [refer to Section 8.3]
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single reading) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (single reading) [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 2) and Appendix 2 (Part 2)];
- Collect pharmacokinetic samples;
- Collect retention samples, if applicable (optional)
- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Collect CGM device and data;
- Collect basal and bolus insulin dosing information;
- Collect prior periods study drug and perform compliance check;

Following completion of the above procedures:

- Remind patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;

7.3.11. Follow-up (F/U); 7-10 days following the last dose

Patients will return to the study site after an overnight fast (except water) for a follow-up visit at 7-10 days after the last dose. If the last dose occurs at the Early Termination visit or within 10 days of the ET, a Follow-up visit will occur 7-10 days after the Early Termination visit. If an Early Termination visit is conducted the Follow-up visit will occur 7-10 days after the Early Termination visit.

The following procedures should occur at the visit:

- Conduct inquiry about baseline symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (single readings) [refer to Section 8.5];
- Collect clinical laboratory specimens according to lab manual/kit [refer to Section 8.7, Table 1 (Part 2) and Appendix 2 (Part 2)];
- Obtain urine void (pregnancy test (women only) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];

Completion of the follow-up visit marks the end of the patients' participation in the study.

- The Investigator may provide guidance to the patient regarding management of their T1DM and related conditions

CGM and study related supplies for home glucose, insulin dosing and DKA monitoring (if supplied by the site) can be returned to the patients for their use, if permitted by local country regulations.

7.3.1. Early Termination (ET) Procedures [Same as Week 12 (except treatment questionnaire and QOL question]

See Section 7.3 as to when to conduct an ET visit.

- Conduct inquiry about potential symptoms by asking the patients to respond to a non-leading question such as “how have you been feeling?” and “has anything changed since your last visit?”
- Update medications;
- Conduct limited physical exam [refer to Section 8.3];
- Obtain body weight [refer to Section 8.2];
- Obtain standard supine 12-lead electrocardiogram (ECG) prior to blood sampling (single readings) [refer to Section 8.4];
- Obtain sitting vitals (blood pressure and pulse rate) prior to blood sampling (single readings) [refer to Section 8.5];
- Collect clinical laboratory specimens per lab kit [refer to Section 8.7 and Table 1 (Part 2)];
- Collect pharmacokinetic samples;
- Collect retention samples, if applicable (optional);
- Collect prior periods study drug and perform compliance check;

- Obtain urine void (pregnancy test (if applicable) and urinalysis) [refer to Section 8.7.2 and Table 2 for list of tests];
- Collect insulin data, insulin pump settings (patients using pumps) or basal insulin dose (for patients using MDI) in the EDC as directed in the Study Procedures Manual;

Following completion of the above procedures:

- Remind patients regarding identification/ management of hypoglycemia and hyperglycemia and diabetic ketoacidosis;

7.3.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Every effort should be made to document patient outcome. The Investigator should inquire about the reason for withdrawal. The patient must return all unused study medication to the site and should return to the site for one or two visits, as described below.
Any AEs should be followed based on the following criteria:

Follow-up of any ongoing AE (including any clinically significant laboratory abnormality) should be conducted as follows:

- If the Investigator determines the AE is *not related* to the study product or study procedures, the AE will be followed until resolution, or 60 days from end of study participation.

- All AEs with a relationship other than *not related* will be followed until resolution, or until the patient is lost to follow-up.

At the discretion of the Investigator or designated licensed physician and Medical Monitor, the length of AE follow-up may be attenuated, with written rationale by the Investigator or designated licensed physician.

Upon termination, all patients who continue to consent will have a Follow-up Visit approximately 7-10 days after the last dose. Procedures leading up to the Follow-up Visit will depend on the patient's recent dosing and how long the patient has been on treatment. The following table summarizes what exit visits should be conducted upon termination assuming patient still consents:

Patient dosing/treatment status at termination:	**Other applicable conditions:**	**Exit Visits to be conducted:**
Patient has not received 4 weeks of treatment	None	Do not complete Early Termination visit. Conduct Follow-up Visit approximately 7-10 days after last dose.
Patient **has not** dosed within 10 days of initiating termination procedures	None	Do not complete Early Termination visit. Only conduct Follow-up Visit
Patient has dosed within 10 days of initiating termination procedures	Patient has reach 12 weeks of treatment (i.e., reached the Week 12 visit window of 12 weeks ± 3 days). Patient will be considered to have completed treatment but not complete the study.	Do not complete Early Termination visit. Conduct Week 12 visit then a Follow-up Visit approximately 7-10 days later
	Patient has completed at least the Week 6 Visit but has not reached 12 weeks of treatment	Conduct Early Termination Visit then a Follow-up Visit approximately 7-10 days later

If the patient withdraws consent for further assessments, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who terminate early may result in additional enrollment of patients to accommodate dropouts, at the Sponsor's discretion.

8. ASSESSMENTS

8.1. Medical History

Medical history should list all ongoing conditions, significant historical conditions, surgical sterilizations, postmenopausal onset and onset of T1DM. Any changes in the patient's medical

condition from screening until the time of dosing during the placebo run-in period should be captured as medical history except for SAEs and events associated with study specific procedures which will be captured as AEs as noted in Section 9.2.

8.2. Body Measurements

Height (cm or in) will be measured at the Screening Visit, without shoes.

A single body weight recording will be made at each of the pre-defined nominal time points outlined in the SCHEDULE OF ACTIVITIES (Sentinels) and Screening, Week -2, Week 0/Day 1, Week 2, Week 4, Week 6, Week 8, Week 12, Early Termination (if applicable) and Follow-Up for Part 1. In Part 2, a single body weight recording will be made at Screening, Week -2, Week 0/Day 1, Week 2, Week 6 and Week 12, Early Termination (if applicable) and Follow-Up.

Weight will be recorded using a calibrated scale (with the same scale used for the duration of the study) which reports weight in either pounds or kilograms.

Weight measurements must be undertaken under standardized conditions, including patients wearing undergarments and a hospital gown (and no shoes) or minimal clothing with no shoes or heavy accessories (e.g., jewelry or belt).

BMI will be calculated as body weight (kg)/height $(m)^2$.

8.3. Physical Examination

A complete physical examination will be conducted by a physician, trained physician's assistant, or nurse practitioner at Screening. The complete examination will include the following: head, eyes, ears, nose, mouth, throat, abdomen, and skin; respiratory system, cardiovascular system, musculoskeletal system; central and peripheral nervous system, and lymphatic system.

A limited physical exam will be conducted at Day 1 and Day 21 (Sentinels) and Week 0/Day 1, Week 6 (Part 1 only) and Week 12 (Part 1 and Part 2) [and Early Termination, if applicable] and will include brief exam of: HEENT (head, eyes, ears, nose, throat), skin, heart, lungs, abdomen, and extremities.

Clinically significant physical examination changes that occur after dosing during the placebo run-in period will be captured as an adverse event.

8.4. 12-Lead ECG

Supine 12 lead ECGs will be obtained at the predefined nominal timepoints outlined in the SCHEDULE OF ACTIVITIES(Sentinels) and Screening, Week -2, Week 0/Day 1, Week 2, Week 4, Week 6, Week 8, Week 12, Early Termination (if applicable) and Follow-Up for Part 1. In Part 2, ECG recordings will be made at Screening, Week -2, Week 0/Day 1, Week

2, Week 6 and Week 12, Early Termination (if applicable) and Follow-Up. ECGs should be performed in triplicate at Week 0/Day 1 (Part 1 and 2) and as single values at all other visits. ECGs should be obtained prior to blood collection and prior to dosing.

- 12 lead ECGs should be performed after the patient has rested quietly for at least 10 minutes in a supine position.
- ECGs should be performed in triplicate at Day 1 (Sentinels) or Week 0/Day 1 (Part 1 and 2) and as single tracings at all other visits.
- Each original recording will be evaluated by the PI or designee following the measurement. The interpretation of results will follow the categories "normal," "abnormal, NCS," or "abnormal, CS." Abnormal interpretations must include the specific nature of the abnormality (ies), (e.g. left bundle branch block, bradycardia, old MI). An abnormal measurement may be repeated at the discretion of the PI or designee. If an abnormal ECG measurement made after dosing is considered clinically significant, the abnormality will be recorded as an AE in the EDC.

8.5. Vital Signs

Vitals should be collected at the predefined nominal timepoints outlined in the SCHEDULE OF ACTIVITIES for Sentinels and sitting vital signs (blood pressure and pulse rate) will be measured at Screening, Week -2, Week 0/Day 1, Week 2, Week 4, Week 6, Week 8, Week 12, Early Termination (if applicable) and Follow-Up for Part 1. In Part 2, vital signs will be measured at Screening, Week -2, Week 0/Day 1, Week 2, Week 6 and Week 12, Early Termination (if applicable) and Follow-Up.

Vitals should be performed in triplicate at Week 0/Day 1 (Part 1 and 2) and as single values at all other visits.

Vitals should be collected via an automated device using an oscillometric (and not auscultatory) method as follows:

- Sitting blood pressure and pulse rate will be measured with the patient's arm supported at the level of the heart and recorded to the nearest mmHg. The same arm will be used throughout the study. The patient should be rested and sitting with both feet on the ground for at least 5 minutes before the blood pressure is obtained.
- Assessment of pulse rate may be manual or from an automated device. However, when done manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds. The method for measuring pulse rate should be used consistently for each patient throughout the study.
- Assessment of vitals should be undertaken before collection of blood samples.
- Vitals should be performed in triplicate at Week 0 (Part 1 and 2) and as single values at all other visits.

- In the Sentinel phase, after conducting the sitting blood pressure, **patients will stand and standing blood pressure** (orthostatic blood pressure) will be measured within 2 minutes. Standing blood pressure will be performed as single value.

Out of range vital signs as defined in Appendix 3 (Values or Changes Potentially of Clinical Concern) will be reviewed by the PI or designee and designated as CS or NCS. Vitals may be repeated at the PI or designee discretion. If the abnormal vital signs are observed after dosing and considered clinically significant, the abnormality will be recorded as an AE in the EDC.

8.6. MMTT (SENTINELS ONLY)

Patients will be instructed to target a fasting blood glucose between 80 and 200 mg/dL for visits where MMTT will be conducted (Sentinels: Days -7, 1, 8, 15 and 21).. MMTT will be conducted at least 4 hours after the last bolus of insulin (except for the insulin bolus within 15 minutes of the MMTT) and at least 1 hour after any glucose tablet consumption. MMTTs not following these rules will be excluded from analysis of post meal response.

- If the patient' s blood glucose is >200 mg/dL upon arrival to the clinic, the patient will be given TTP399 and pharmacokinetic samples will be taken according to the Schedule of Activities and MMTT conducted accordingly (starting 1 hour after dosing). If after 45 minutes of dosing with TTP399, blood glucose is still > 200 mg/dL, a correction dose of insulin along will be given prior to the MMTT. The MMTT will be initiated 60 minutes after the dose of TTP399 was administered. If a correction dose of insulin is administered, the pharmacodynamic blood samples will NOT be taken.

- If the patient's blood glucose is below 70 mg/dL, the patients will be treated with glucose. Once glucose levels are above 80 mg/dL, the patient will be given TTP399 and pharmacokinetic samples will be taken. An hour after dosing, the MMTT will be conducted according to the SCHEDULE OF ACTIVITIES and pharmacodynamic samples will be collected (Figure 5, Sentinels).

Patients will be dosed with 50% of their normal bolus mealtime insulin within 15 minutes of the MTTT. If patients change their normal bolus mealtime insulin during the study, the normal bolus mealtime insulin will be considered the current insulin dose.

To initiate the MMTT, patients will receive 1 bottle of Ensure Plus Homemade Vanilla Liquid [350 calories, 8 fl oz (237ml), 51 g carbohydrate, 11 g fat, 13 g of protein] in place of their morning meal. Patients will be required to consume the Ensure Plus within 5 minutes and the time of the first sip should be recorded as the start time in the EDC.

All MMTTs will be conducted under close medical supervision so insulin dose adjustments can be made quickly if necessary. If the patient meets the rescue criteria of having a glucose readings > 450mg/dL and is symptomatic (e.g. vomiting) or is unwilling to continue, the patient should be dosed with insulin to correct high glucose levels under normal standards of

care at the Investigator's (or Designee) discretion. The event should be recorded as hyperglycemia associated with MMTT in the patient's CRF.

8.6.1. Basal and Bolus Insulin Adjustments (Sentinel phase only):

The patient, in collaboration with site team, will adjust bolus insulin to aim for glucose levels consistent with ADA goals of a postprandial glucose of less than 180 mg/dL and before meal glucose levels 80-130 mg/dL. If the first dose of TTP399 does not significantly curtail glucose post-prandially, patients will be given either 25%, 50% or 75% of normal carbohydrate associated insulin dose for their next meal (based on the magnitude of the glucose spike in comparison to their baseline MMTT) and 100% of correction associated peak. Higher doses up to 100% of normal carbohydrate dosing will be administered based on glycemic responses after subsequent meals.

Basal rates will be adjusted to keep glucose levels flat or slightly increasing between meals (according to ADA goals of 80-130 mg/dL pre-prandially). Basal rates will be **specifically** evaluated on Days 3 and 6, based on blood glucose levels on 2 of the last 3 days

8.6.2. Standardized lunch following MMTT (Sentinel Phase only):

For all clinic visits when MMTTs are conducted, the patients will be given lunch with a standardized carbohydrate content (between 30-100 g of carbohydrate). Each patient will select a lunch on Day -7 (Sentinel). The same lunch will be provided at all visits requiring MMTTs. The amount of carbohydrates in the meal will be recorded in the EDC.

8.6.3. Dinner requirements following MMTT (Sentinel Phase only):

For all-day study visits with MMTTs and PK collection, an evening meal with a standardized carbohydrate content (between 30-100 g of carbohydrate) will be provided by the site. For the baseline MMTT where no PK is collected (i.e. a shorter clinic visit), patients are not required to stay in the clinic until dinner, but should have a dinner meal with between 30-100 g of carbohydrates and record the carbohydrate content in their CGM (Sentinels).

8.6.4. Sampling Schedule for MMTT (Pharmacokinetic and Pharmacodynamic Samples) (Sentinel Phase only)

Pharmacodynamic Samples

Sentinels

- Glucose samples will be obtained prior to MMTT time 0 (MMTT) and 30, 60, 90, 120, 150, and 180 min following the MMTT with every MMTT.

- C-peptide samples will be obtained prior to MMTT (time 0, MMTT and at 60min post MMTT (60, MMTT) at baseline (Day -7) and at last dose (Day 21) if patient has detectable c-peptide at Day -7.

- A Glucagon/GLP-1 sample will be obtained prior to MMTT (time 0, MMTT and at 10, 20, 30, 60 and 120 min post MMTT (60, MMTT) at baseline (Day -7) and at last dose (Day 21)

Pharmacokinetic Samples (Sentinel Phase only)

Sentinels

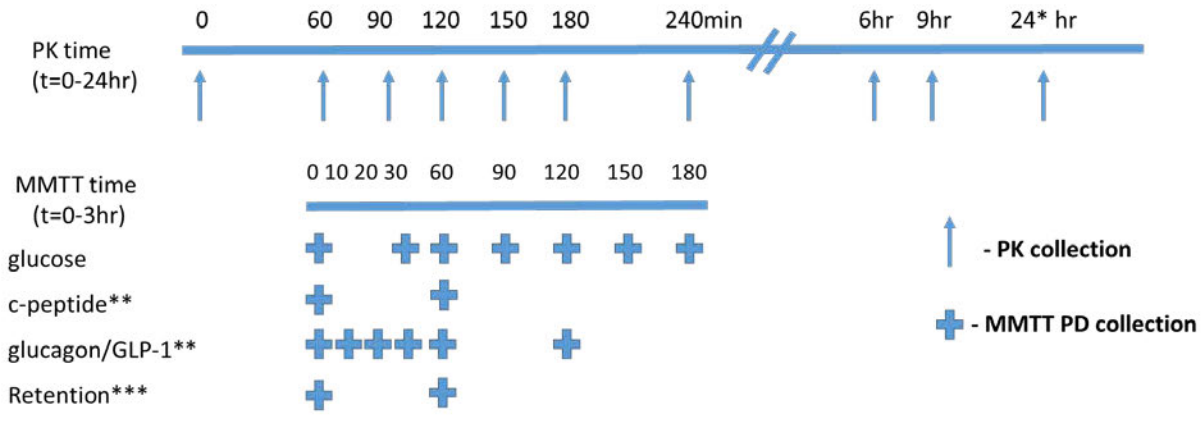
- On Day 1, Day 8, Day 15 and Day 21, blood samples will be obtained for TTP399 concentrations immediately prior to dosing at time 0 (PK) and 60, 90, 120, 150, 180, 240, 360 (6hr) and 540min (9hr) relative to dosing. On Day 22 (or the day AFTER the last dose administered in the clinic) an additional 24hr PK sample will be obtained (a window of 3 hours is allowable for the 24hr PK sample).

Retention Samples (Sentinel Phase only)

Sentinels

- Retention samples will be collected for non-genomic biomarkers (as applicable based on consent) at time 0, MMTT and at 60min post MMTT (60, MMTT) at baseline (Day -7) and at last dose (Day 21)

Figure 5: Sampling schedule for MMTT in Sentinel Phase



* In the Sentinel phase, a 24 hr PK sample will be taken approximately 24 hours (with a 3 hour window) after the last dose administered in the clinic (Day 22 or ET)
** c-peptide and glucagon/GLP-1 will be collected ONLY on Day -7 and Day 21 (or ET, if applicable)
*** The retention samples will only be collected for patients who consent

8.7. Safety and Efficacy Laboratory Assessments

8.7.1. Blood Volume

Total blood sampling volume from each individual patient for scheduled visits is estimated to be approximately 360 mL for Sentinel patients, 148 mL for Part 1 patients and 123mL for Part 2 patients, as shown below.

Table 1 Summary of Frequency and Approximate Volume of Blood Collection

Summary of Frequency and Approximate Volume of Blood Collection - Sentinels

SENTINELS Sample Type	Maximum proposed sample Volume (mL)	Number of Sampling Times				Total Volume[a] (mL)
		Screening /Baseline MMTT	**Dose escalation Period**	**Follow-Up Visit (F/U)**	**Total Number of Samples**	
Clinical Laboratory Tests (hematology and chemistry)	10.5	1	4	1	6	63
HbA1c	4	1	2		3	12
Plasma glucose with MMTT	2	1X7	4X7		35	70
c-peptide with MMTT	2	1X2	1X2		4	8
Glucagon and GLP-1 w MMTT[b]	2	1X6	1X6		12	24
PK (TTP399)	4	---	4X11	---	44	160
Retention sample (optional)	4	1X2	1X2		4	16
TOTAL						353

a. Additional blood samples/volume may be taken for repeats and safety testing.

b. In addition to glucagon and GLP-1 additional exploratory analytes that may be analyzed in the glucagon/GLP-1 sample include amylin, ghrelin, GIP, IL-6, Leptin, MCP-1, PP, PYY and TNF-α

Table 1 – Summary of Frequency and Approximate Volume of Blood Collection- Part 1

PART 1 Sample Type	Maximum proposed sample Volume (mL)	**Number of Sampling Times**				**Total Volume[a] (mL)**
		Screening	**Double-Blind Treatment**	**Follow-Up Visit (F/U)**	**Total Number of Samples**	
Clinical Laboratory Tests (hematology, chemistry, and glycemic markers[b])	10.5	1	6	1	8	84
HbA1c	4	1	6		7	28
Fasting c-peptide	2		2		2	4
Fasting glucagon and GLP-1 [c]	2		2		2	4
PK (TTP399)	4	---	6	---	6	24
Retention sample (optional)	4		2	---	2	4
TOTAL						148

a. Additional blood samples/volume may be taken for repeats and safety testing.

b. In addition to HbA1c, glycemia biomarkers to be collected in Part 1 include fructosamine and Glycomark (1,5 anhydroglucitrol)

c. In addition to glucagon and GLP-1 additional exploratory analytes (non-genomic) that may be analyzed in the glucagon/GLP-1 sample include amylin, ghrelin, GIP, IL-6, Leptin, MCP-1, PP, PYY and TNF-α

Table 1 - Summary of Frequency and Approximate Volume of Blood Collection- Part 2

PART 2 Sample Type	Maximum proposed sample Volume (mL)	Number of Sampling Times				Total Volume[a] (mL)
		Screening	**Double-Blind Treatment**	**Follow-Up Visit (F/U)**	**Total Number of Samples**	
Clinical Laboratory Tests (hematology, chemistry and glycemia biomarkers[b])	10.5	1	4	1	6	63
HbA1c	4	1	4	1	6	24
PK (TTP399)	4	---	3	---	3	12
Fasting c-peptide	2	-	3	-	3	6
Fasting Glucagon[c]	2		3		3	6
Retention sample (optional)	4	---	3	---	3	12
TOTAL						123

a. Additional blood samples/volume may be taken for repeats and safety testing.

b. In addition to HbA1c and glucagon, glycemic biomarkers to be collected in Part 2 include fructosamine, 1,5 anhydroglucitrol, and c-peptide

c. In addition to glucagon additional exploratory analytes (non-genomic) that may be analyzed in the glucagon sample include amylin, ghrelin, GLP-1, GIP, IL-6, Leptin, MCP-1, PP, PYY and TNF-α

8.7.2. Clinical Laboratory Assessments

The clinical laboratory tests listed in Table 2 will be performed at the pre-specified timepoints outlined in the SCHEDULE OF ACTIVITIES and Appendix 2 for Part 1 indicated for the specific part of the study. At all visits after giving informed consent, patient will report to the site prior to their morning meal. Unscheduled clinical lab tests may be obtained at any time during the study to assess any perceived safety concerns.

Efforts should be made to obtain all blood samples at a similar clock time (e.g., 0800 hours) at each visit to the study site.

Results that are out of range will be interpreted as “abnormal, not clinically significant (NCS),” or “abnormal, clinically significant (CS).” An abnormal laboratory result may be repeated at the PI’s or licensed physician designee’s discretion. If the abnormal laboratory result is considered clinically significant and occurs after dosing, the abnormality will be recorded as AE in the EDC.
Refer to Section 9.1 for the criteria for determining whether an abnormal laboratory test

finding should be reported as an adverse event.

All biological samples will be assayed by a Sponsor-identified laboratory using a validated analytical method. Details regarding the sample processing, handling, storage, and shipment will be described in the study-specific central laboratory manual prior to the initiation of the study.

Table 2 Laboratory Tests

Hematology	Chemistry	Glycemic markers	Urinalysis	Others
Hemoglobin Hematocrit RBC Count MCH, MCV, MCHC & RDW Platelet Count WBC Count Leukocyte differential (percent and total neutrophils, monocytes, eosinophils, basophils, lymphocytes)	BUN Creatinine Ca^{++} (total) Electrolytes (Na^+, K^+, Cl^-) Total CO_2 (Bicarbonate) AST/ ALT Alkaline Phosphatase Total bilirubin Direct (conjugated) bilirubin [a] Uric Acid Albumin Total Protein Ketones Lactate Free fatty acids GGT (Part 1 and 2) Fasting plasma glucose	HbA1c Fructosamine (Part 1 and 2 only) 1,5 anhydroglucitrol (Part 1 and 2 only) Fasting Ultra sensitive C-peptide (Part 1 and 2 only) Fasting Glucagon (Part 1 and 2 only)	Specific Gravity pH Glucose (qual) Protein (qual) Blood (qual) Ketones Leukocyte esterase Nitrites Microscopy [b]	Pregnancy test (urine) Urine drug screen [c] Lipid panel (total cholesterol, HDL-C, LDL-C, triglycerides) **PD Markers with MMTT (Sentinels only) [d]** Ultra sensitive C-peptide Glucose, Glucagon, GLP-1

RBC: red blood cell; WBC: white blood cell; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW: RBC Distribution Width; Abs: absolute; BUN: blood urea nitrogen; Ca^{++}: calcium; Na^+: sodium; K^+: potassium; Cl^-: chloride; AST (SGOT): aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ALT (SGPT): alanine aminotransferase (Serum glutamic pyruvic transaminase); qual: qualitative; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

a. Direct bilirubin will be measured at Screening. During the Treatment Period, both direct and indirect bilirubin will ONLY be measured when total bilirubin is greater than upper limit of the reference range.

If total bilirubin is lower than the upper limit of the reference range, neither direct nor indirect bilirubin will be measured

b. Only if dipstick is positive for blood, protein, ketones, leukocyte esterase, or nitrites. Microscopy will include epithelial cells, red blood cells, white blood cells, bacteria, casts (hyaline, granular, cellular), crystals, and mucus.

c. At Screening and Baseline for Part 2 only, and at additional times if needed based on PI discretion.

d. In addition to glucagon and GLP-1 additional exploratory analytes (non-genomic) that may be analyzed in the glucagon/GLP-1 sample include amylin, ghrelin, GIP, IL-6, Leptin, MCP-1, PP, PYY and TNF-α

Pregnancy test (urine) should be obtained from women of childbearing potential at each visit and for women of non-childbearing potential at Screening, Week 0/Day 1 and Follow-Up. The results must be negative for the patient to enroll and continue in the study.

8.8. Pharmacokinetic Assessment

During the Sentinel Phase blood samples for assessment of TTP399 plasma concentrations will be collected concurrent to the MMTTs according to the visits shown in the Section 8.6.4 and Figure 5.

During Part 1 blood samples for assessment of TTP399 plasma concentrations will be collected at Week 0/Day 1, Week 2, 4, 6 and 8 and 12. At Week 0 the sample should be collected prior to dosing.

During Part 2 blood samples for assessment of TTP399 plasma concentrations will be collected prior to dosing according to the Schedule of events at Week 0, Week 2, Week 6, and Week 12 and ET, if applicable.

The date/time of the blood draw and the date/time of the last dose of study medication prior to the blood draw should be captured on the EDC.

Specific details regarding PK collection, processing, and shipment will be provided in the laboratory manual.

Samples will be analyzed for TTP399 concentrations using a previously developed and validated bioanalytical method. Samples may also be analyzed for TTP399 metabolite concentrations at the Sponsor's discretion. Samples will be kept until completion of the clinical study report.

8.9. Pharmacodynamic*MMTT Panel (Sentinels only)

In addition to the single sampling of glycemic markers (HbA1c, fructosamine, and 1,5 AG) at study visits, blood samples for pharmacodynamics will be collected prior to dosing and

during MMTT according to the times listed for in the Section 8.6.4 and Figure 5 (Sentinels).

Specific details regarding collection, processing, and shipment will be provided in the laboratory manual.

Samples will be kept until completion of the clinical study report.

8.10. Blood Sampling: Plasma Storage and Retention

A 4 mL blood sample will be collected for potential future analysis of plasma biomarkers (non-genomic). Sample will be collected according to the SCHEDULE OF ACTIVITIES (Sentinels) and at Week 0 and Week 12 or Early Termination (if applicable) for Parts 1 and 2. Specific details regarding retention sample collection, processing, and shipment will be provided in the laboratory manual.

A separate consent form may be provided for this voluntary sampling if not already included in the IRB approved study protocol consent form.

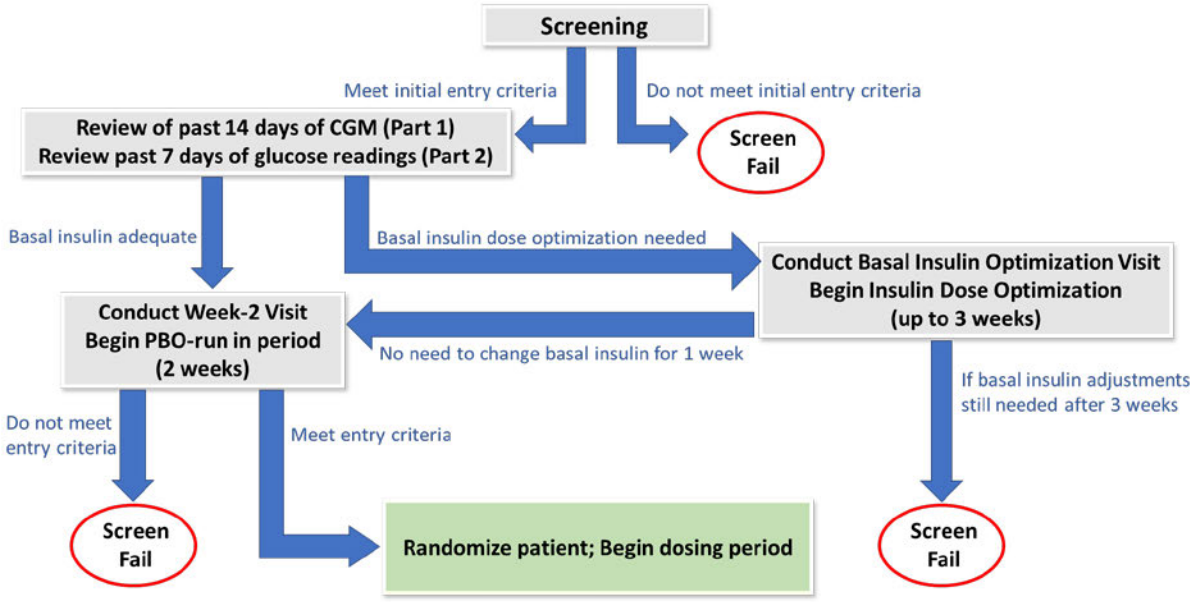
8.11. Management of Patients' Glycemic Control and Insulin Dose Adjustments

Patients will be counseled on identification and management of hypoglycemia and hyperglycemia. Glucose levels will be monitored using unblinded continuous glucose monitoring (if patients already have CGM) and self-monitoring of blood glucose using glucometers if unblinded CGM glucose values are not available. **Sentinel** patients are required to have a good hypoglycemic awareness and live with someone who has a good hypoglycemia awareness.

Parts 1 and 2, only

Prior to the placebo run-in period, the PI or designee will determine if the patient’s basal insulin dose needs to be optimized to meet the fasting/pre-meal glucose target generally from 80-130mg/dL. If the PI determines that basal insulin dose adjustment is needed, the PI or designee, in collaboration with the patient, will optimize the basal insulin dose for up to 3 weeks prior to the placebo run-in period. If basal insulin dosing is adequate, the patient will move directly into the placebo-run in period. (See Figure 6 below).

Figure 6: Decision Flow Chart for Patient Visits Prior to Randomization



*Adjust basal insulin to target fasting/pre-meal glucose levels generally between 80-130 mg/dL

The PI or designee will use the following guidance in combination with the recent glucose data to instruct the patient on insulin adjustments needed.

BASAL INSULIN DOSE ADJUSTMENT PERIOD (up to 3 weeks before Week -2)
The PI or designee will review the past 14 days of CGM data (Part 1) or fasting/pre-meal glucose levels for the past 7 days using either CGM or glucometer data (Part 2) and determine if a basal insulin dose adjustment period is needed. **If basal insulin adjustments are needed,** the basal rate should be assessed and adjusted to target fasting/pre-meal glucose levels generally between 80-130 mg/dL **If Low Blood Glucose:** Make immediate insulin adjustment. **If Elevated Blood Glucose:** Verify trends 2–3 days before adjusting insulin.
DURING PLACEBO RUN-IN PERIOD (2 weeks prior to randomization)
Do not make insulin adjustments except in response to safety concerns. **Record** in the EDC: o CSII: basal rate, Active Insulin Time and type of Pump, ICF and ICR o MDI: basal insulin dosing information, ICR and ISF
DURING DOUBLE-BLIND PERIOD:
First day of dosing (Week0/Day 1):
Reduce bolus insulin: **INCREASE** insulin to carb ratio (ICR, g/U) by 1-3 g/U (10-30%, usually 20%), e.g., if the ICR is 10g/U during run-in period increase the ICR to 11 or 13g/U, usually 12g/U. **And** **INCREASE** insulin sensitivity factor (ISF) by 10-30%, usually 20%, e.g. if the ISF is 40g/U during run-in period increase the ISF to 44-52% or, usually 48g/U. **Record** in the EDC: o CSII: basal rate, active insulin time, ICF and ICR o MDI: basal insulin dosing information, ICR and ISF
During the first two weeks of dosing:
Adjust insulin to the following glycemic targets: o Fasting/pre-meal: 80-130 mg/dL o Post-meal peak: < 180 mg/dL (post-meal peak < 200mg/dL may be acceptable target at the PI's discretion) **If Low Blood Glucose:** Make immediate insulin adjustment. **If Elevated Blood Glucose:** Verify trends 2–3 days before adjusting insulin. The adjustment of bolus insulin should be accomplished by **adjusting ICR and ISF** **Record** any adjustments in the EDC: o CSII: basal rate, active insulin time, ICF and ICR o MDI: basal insulin dosing information, ICR and ISF
After two weeks of dosing:
Adjust insulin to the following glycemic targets: o Fasting/pre-meal: 80-130 mg/dL o Post-meal peak: < 180 mg/dL (post-meal peak < 200mg/dL may be acceptable target at the PI's discretion) **If Low Blood Glucose:** Make immediate insulin adjustment. **If Elevated Blood Glucose:** Verify trends during patient calls and visits before adjusting insulin. The adjustment of bolus insulin should be accomplished by **adjusting ICR and ISF** **Record** any adjustments in the EDC: o CSII: basal rate, active insulin time, ICF and ICR o MDI: basal insulin dosing information, ICR and ISF

8.12. Diabetes Treatment Satisfaction Questionnaires

The Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) will be completed at the Screening Visit.

The Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) and the Diabetes Treatment Satisfaction Questionnaire change version DTSQc will be completed at the Week 12 visit.

8.13. Quality of Life (QOL) Question

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 slightly worse, no change, slightly improved, moderately improved, markedly improved.

9. ADVERSE EVENTS REPORTING

9.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical product. Study drug treatment does not necessarily have a causal relationship with the AE. An AE, therefore, can be any unfavorable change in structure, function, or chemistry (including abnormal clinical laboratory, vital signs, or ECG findings), symptoms, signs, or diseases temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product, as defined by ICH.

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

  Test result is considered to be an adverse event by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

9.2. Reporting Period

The adverse event reporting process will commence upon signing informed consent according to the rules below.

- SAE:
  SAE reporting will commence from the time the participant provides informed consent through last patient visit at follow-up. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to study treatment is suspected.

- Events associated with study-specific procedures:
  Events associated with study-specific procedures prior to initial administration of study drug will be tracked as AEs from the time when the study participant signed the ICF. The study-related procedure might include discontinuation from or decrease in current therapy, a study-specific assessment or scale, or a study-specific procedure.

- Non-serious AEs not related to study procedures:
  - Non-serious AEs not related to study procedures that occur **prior** to the first dose of study drug will be captured under medical history
  - Non-serious AEs not related to study procedures that occur **after** the first dose of study drug will be captured as TEAEs

- Adverse events reported during the single-blind placebo-run-in period will be captured as having onset after first dose of single-blind placebo administration but before first dose of double-blind study medication. Adverse events reported during the double-blind treatment period will be captured as having onset after first dose of double-blind study medication. The appropriate box corresponding to the period in which the TEAE occurred should be ticked in the CRF.

9.3. Assessment of Severity

The following definitions of severity should be used in the evaluation of AEs:

- Mild: an AE that is easily tolerated and does not interfere with daily activities.
- Moderate: an AE that is sufficiently discomforting so as to interfere with daily activities.
- Severe: an AE that prevents normal everyday activity.

9.4. Assessment of Relationship to Study Drug

The Investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the Investigator must record the causal relationship in the EDC. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the Investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the Investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the Investigator determines a serious adverse event is associated with study procedures, the Investigator must record this causal relationship in the source documents and EDC, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

The following definitions of relationship to study drug should be used to characterize the suspected causality of each AE, based on the Principal Investigator's or licensed physician consideration of all available information:

Related: A direct cause and effect relationship between the AE and the study drug is reasonably related to the study drug in the judgment of the investigator.

Not Related: The AE is not reasonably related to the study drug in the judgment of the investigator.

9.5. Serious Adverse Events

An SAE is any AE that is fatal or life-threatening (see below), results in persistent or significant disability (see below) or incapacity, requires inpatient hospitalization or prolongation of an existing hospitalization, or is a congenital anomaly/birth defect.

Other important medical events that may not result in death, be life-threatening, or require hospitalization should also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.5.1. Life Threatening Adverse Events

A life-threatening AE is any AE that, in the view of the PI or designated licensed physician, places the study participant at immediate risk of death from the reaction as it occurred. A life-threatening AE would not be an AE that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

9.5.2. Disability

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

9.5.3. Unexpected Adverse Event

An unexpected adverse drug experience is defined as "any adverse drug experience, the specificity or severity of which is not consistent with the current IB. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB only listed cerebral vascular accidents. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the IB), rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product." [5]

Serious and Unexpected adverse events (SUSARs) should be reported to the IRB as per IRB reporting requirements.

9.6. Documentation of Adverse Events

The condition of each study participant will be monitored throughout the study. Signs and symptoms of possible AEs may be observed by the staff, elicited by asking an open or indirect question (e.g., "How have you been feeling?"), or volunteered by the study participant. All AEs, whether observed by the PI or study site staff, elicited from the study participant, or volunteered by the study participant, will be recorded on the adverse event page(s) of the CRF. Data will include start and end dates, concomitant medications given for the AE, PI-specified or designated licensed physician-specified severity, relationship to study drug, and action taken. All AEs should be reported to the Study Sponsor.

9.7. Reporting Requirements

Follow-up of any ongoing AE (including any clinically significant laboratory abnormality) should be conducted as follows:

- If the Investigator determines the AE is *not related* to the study product or study procedures, the AE will be followed until resolution, or 60 days from end of study participation.

- All AEs with a relationship other than *not related* will be followed until

resolution, or until the patient is lost to follow-up.

At the discretion of the Investigator or designated licensed physician and Medical Monitor, the length of AE follow-up may be attenuated, with written rationale by the Investigator or designated licensed physician.

9.7.1. Serious Adverse Events Reporting Requirements

Knowledge of an SAE occurring or worsening in a patient at any time during the trial must be reported within 24 hours to the Sponsor. The Study Site is responsible for reporting the event to the relevant IRB in accordance with the IRB's specific requirements for reporting SAEs. The PI or designee should not wait to receive additional or follow-up information before an initial notification is made to the Sponsor.

Instructions related to SAE reporting, along with reporting forms, will be provided by the Sponsor to the Study Site and should be maintained in the Study Site File (SSF).

Reports relative to the patient's subsequent course must be submitted to the Sponsor until the event has subsided or, in the case of permanent impairment, until the condition stabilizes. These reports need not be submitted within 24 hours of first knowledge of each item of new information, unless the new information results in a change in diagnosis or represents a significant worsening of the patient's condition.

The PI or designee should immediately notify the Sponsor and the IRB if he/she learns of any post-study serious adverse event, which in his/her opinion is reasonably possibly related to the use of the study drug.

9.8. Adverse Events of Special Interest

9.8.1. Monitoring of MACE Events

Major adverse cardiac events (MACE) will be tracked in Part 1 and 2.
For this study, a MACE event is defined as one of the following:

- Cardiovascular mortality
- Myocardial infarction
- Stroke.

It is not expected there will be an adequate number of MACE events to support reasonable statistical analysis, and it is not expected that there will be many MACE events. If and when the number of MACE events exceeds 10 for the study, a cardiovascular endpoints committee (CEC) will be convened to adjudicate MACE events, provided less than 90% of the study visits have occurred. If there are 10 or fewer MACE events in the study as of an advanced stage of the study (when it is 90% over, based on planned study visits), it will be deemed unnecessary to convene the CEC.

9.8.2. Documenting and Reporting of Hypoglycemia

Hypoglycemia is of special concern in this population and should be described to the patients. Home glucose monitoring must be undertaken in the event patients experience symptoms of hypoglycemia. Patients should be instructed on self-management of a hypoglycemic episode (e.g., prompt ingestion of carbohydrates).

For the Sentinels, any episode of hypoglycemia associated with symptoms must be captured on the patient's diary and in the EDC as an AE with symptoms and contemporaneous glucose measurements if they are available.

For Part 1 and Part 2, hypoglycemic adverse events will be assessed and reported in three categories:

- **severe** hypoglycemia (**each** of the following criteria **must** be met):
    - The patient was unable to treat him/herself, requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Neurologic impairment must be the explanation for why the patient could not treat him/herself and required the assistance of another person.
    - Blood glucose:
        - If blood glucose was measured and was ≤ 49 mg/dL (2.7 mmol/L) using plasma referenced- home glucometers, CGM (or central laboratory), **or**
        - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.
- **documented symptomatic** hypoglycemia if typical symptoms **are** accompanied by measured glucose ≤70mg/dL using plasma-referenced home glucometers (or central laboratory) or
- **probable symptomatic** hypoglycemia if typical symptoms are not accompanied by a glucose determination as described above but are presumably caused by a plasma concentration ≤70mg/dL.

Treatment should be discontinued for a patient following an episode of severe hypoglycemia, if in the investigator's judgment the episode was both:

- unexpected with no substantial aggravating issues precipitating the episode
- unavoidable in the future, through dose adjustments of insulin and patient education.

Episodes of severe hypoglycemia will be evaluated by an independent data monitor in Part 1

and Part 2.

- Events that do **not** meet the criteria for severe hypoglycemia will be characterized as mild or moderate in severity.

Reporting of Hypoglycemia

Hypoglycemia will be reported following the classification published by the International Hypoglycaemia Study Group[6] as follows:

Severe hypoglycemia (level 3):
In order to be considered **severe** hypoglycemia **each** of the following criteria **must** be met:

1. The patient was unable to treat him/herself, requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Neurologic impairment must be the explanation for why the patient could not treat him/herself and required the assistance of another person.

2. Blood glucose:
    a. If blood glucose was measured and was ≤ 49 mg/dL (2.7 mmol/L) using plasma referenced- home glucometers, CGM (or central laboratory), **or**
    b. If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

Clinically important hypoglycemia (level 2):

A glucose level of less than 54 mg/dl (3.0 mmol/l) with or without typical symptoms of hypoglycemia. This will be quantified as:

- The percentage of CGM values that are below the threshold of <54 mg/dL [3.0 mmol/L]) or the number of minutes or hours below these thresholds.
- As the number of hypoglycemic events that occur over the given CGM reporting period

A hypoglycemic event should be defined as follows:

- Beginning of a CGM event: readings below the threshold for at least 15 min is considered an event. For example, at least 15 min <54 mg/dL (3.0 mmol/L) to define a clinically significant (level 2) hypoglycemic event.
- End of a CGM event: readings for 15 min at ≥70 mg/dL (3.9 mmol/L).
- A second hypoglycemic event outcome of prolonged hypoglycemia is considered when CGM levels are <54 mg/dL (3.0 mmol/L) for consecutive 120 min or more.

Glucose alert value (or level 1):

A glucose value of 70–54 mg/dL (3.9–3.0 mmol/L) with or without symptoms. This will be quantified as the percentage of CGM values between 70–54 mg/dL (3.9–3.0 mmol/L) or the number of minutes or hours between these thresholds.

9.8.3. Management of Diabetic Ketoacidosis

Typical symptoms of diabetic ketoacidosis (DKA) are thirst or a very dry mouth, frequent urination, high blood glucose (blood sugar) levels, or high levels of ketones in the urine. DKA is an AE of special concern in this population and should be described to the patients. Home monitoring should be undertaken in the event patients experience blood glucose ≥ 240mg/dL during an illness or in the presence of symptoms described above. Patients should call the study site if they measure moderate or high ketone values.

Diabetic Ketoacidosis (DKA) is defined by

c) Increased serum β- hydroxybutyrate or urine ketones (above ULN)
AND
d) serum bicarbonate (total CO_2) <15mmol/L **OR** blood pH < 7.3

Episodes of diabetic ketoacidosis will be adjudicated by an independent data monitor in Part 1 and Part 2.

9.8.4. Potential Cases of Drug Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below, in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury. (These events should be considered important medical events and reported as serious adverse events.)

Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

a. Participants with AST or ALT baseline values within the normal range who subsequently present with AST or ALT ≥ 3 times the upper limit of normal with a total bilirubin ≥ 2 times the upper limit of normal with no evidence of 1) hemolysis, 2) cholestasis (elevated alkaline phosphatase ≥ 2 times the upper limit of normal or not available) or 3) Gilbert's Syndrome (common benign condition associated with intermittent elevations of primarily indirect, unconjugated, bilirubin to approximately 2 x upper limit of normal (ULN)).

b. Participants with pre-existing AST or ALT baseline values above the normal range who subsequently present with AST or ALT ≥ 2 times the baseline values and ≥ 3

times the upper limit of normal with a total bilirubin ≥ 2 times the upper limit of normal with no evidence of 1) hemolysis, 2) cholestasis (elevated alkaline phosphatase ≥ 2 times the upper limit of normal or not available) or 3) Gilbert's Syndrome (common benign condition associated with intermittent elevations of primarily indirect, unconjugated, bilirubin to approximately 2 x upper limit of normal (ULN)).

Increases defined above should be confirmed with repeat testing within 48 to 72 hours. In. addition to repeating AST and ALT, additional laboratory tests should include albumin, amylase, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. Symptoms should be assessed.

Close observation should be immediately initiated if symptoms persist and/or repeat testing confirms the abnormalities described above. Evaluation should include repeating laboratory tests (two or three time weekly; frequency may decrease to once a week or less if abnormalities stabilize or trial drug is discontinued and the patient is asymptomatic), a detailed medical history, and physical assessment. A detailed history includes relevant information, such as history of symptoms or concurrent illnesses, concomitant medication use (including review of acetaminophen use and herbal/dietary supplements), alcohol consumption, recreational drug use, and special diets. Additionally, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Ruling out acute hepatitis A, B, C, D, and E infection, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis (NASH), hypoxic/ischemic hepatopathy, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, parvovirus, biliary tract disease (gall bladder/ductal imaging may be warranted). All cases confirmed on repeat testing, with no other cause for LFT abnormalities identified at the time should be considered potential drug induced liver injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs.

9.9. Pregnancy

Any pregnancy in a female study participant or the female sexual partner of a male study participant that occurs during the study or if the site becomes aware of a pregnancy within 90 days after the final dose of study drug must be reported to the Sponsor within 72 hours of this information being reported to the study site. Any pregnancy complication or elective termination for medical reasons must be recorded as an AE or SAE (if applicable). Any pregnancy should be followed at least until delivery.

10. DATA ANALYSIS / STATISTICAL METHODS

The statistical considerations summarized in the following subsection outline the plan for data analysis of this study. A Statistical Analysis Plan (SAP) will be finalized prior to un-blinding the data from the study. The SAP will supersede the protocol for analyses. Any deviations from the planned analyses will be described and justified in the final integrated

study report. The analysis plans for this study will reflect sound methodologies appropriate for an adaptive study.

Continuous variables will be presented showing number of observations available, mean, median, minimum, maximum, 1st and 3rd quartiles, and standard deviations (or standard errors, depending on the variable) by visit. Categorical variables will be presented showing frequencies and percentages by visit.

All tests will be 2-sided and use an overall study-wise $\alpha = 0.05$ unless otherwise stated. SAS Version 9.1 or later will be used. Medical dictionary for Regulatory Activities. (MedDRA) Version 16.0 or later will be used for coding adverse events. Medications will be coded using WHO Drug Dictionary (WHODD) Version March 2009 or later.

This study is planned using FDA guidance *Adaptive Design for Clinical Trials for Drugs and Biologics* (draft guidance, February 2010).

10.1. Randomization

Randomization for this study is balanced. Randomization identification for the patients reflects the stage of the study for the subject (sentinel phase, Part 1, or Part 2).

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

10.2. Sample Size Determination

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.

10.3. Statistical Hypotheses

The hypotheses to be tested are as follows:

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

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

10.4. Analysis Population

The sentinel phase and the part 1 (learning phase of the adaptive study) will not have formal statistical hypotheses. The hypotheses relate to part 2, and it is acknowledged that, in this adaptive study, the hypotheses may be modified after evaluation of accrued data at the start of dosing of patients randomized into Part 2.

The statistical analysis plan will provide details for populations of analysis combining patients over parts of the study. In general, each segment of the protocol has its own population of analysis.

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

- The full analysis set (FAS) includes all randomized patients who receive any study medication and have a baseline assessment.

- The per-protocol set (PPS) includes all patients in the FAS excluding patients who have major protocol violations.

- The safety set (SAF) includes all patients who receive any study medication.

The FAS will be used for all hypothesis tests of efficacy. The PPS is used for supportive

efficacy analysis. The SAF will be used for safety analyses. 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.

The FAS for Part 1 will be analyzed separately from the FAS for Part 2. Analysis and presentation will also be done for Parts 1 and 2 integrated.

10.5. Disposition, Demographic, and Baseline Data

A tabulation of patient disposition will be presented by study part and overall, including the number screened, the number randomized in each population group, the number dosed in each population group, the number who withdrew prior to completing the study, and reasons for withdrawal.

Demographic and baseline characteristics (disease history, medical history, and prior treatments for T1DM) will be summarized for all randomized patients and for the FAS.

10.6. Efficacy Analysis

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.

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 $\alpha = 0.05$. A statistical penalty is imposed for interim analysis. This penalty is applied regardless of whether or not there is an actual modification to the study structure, design, or analysis plans. It is noted that in this adaptive study, modification is permitted with documentation and justification.

10.6.1. Efficacy Variables of Analysis

In Part 1, the primary variable of analysis for the interim analysis is mean change from baseline in bolus insulin (number of units) or the time in target glycemic range.

In Part 2, and also in the integrated Part 1 and Part 2 analysis, the primary variable of analysis is mean change from baseline in HbA1c at 12 weeks.

Other variables of analysis include will be defined in the SAP.

10.6.2. Statistical Methodology for Primary Analysis

The primary analysis will use the intent-to-treat methodology and a main-effects model for analysis of covariance (ANCOVA), with adjustment for baseline HbA1c levels. 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.

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.

Suspicious values that appear invalid and outliers that are detected during the blind review of the data will be investigated. Methods for dealing with invalid data and outliers will be defined in the SAP, prior to unblinding. Data considered to be invalid will be set to missing. In general, except for imputation methods specifically described in this protocol, missing data will not be imputed; outliers will not be excluded unless they are considered to be erroneous or invalid values. Sensitivity analyses and exploratory analyses may be done using imputation or excluding invalid data or outliers to ensure robustness of study conclusions.

10.6.3. Statistical Methodology for Secondary and Other Efficacy Analysis

Efficacy analysis for other variables that are continuous will use ANCOVA with baseline measures as covariables, with a main effects model. Dichotomous measures (e.g., proportions of responders) will be done on the full analysis set (FAS), consisting of all randomized patients who receive at least one dose of randomized study medication. Fisher's exact test will be used at the study level for variables of analysis that are proportions. Patients obtaining achievement of the response criterion prior to Week 12 will be considered responders; all others will be considered non-responders. No imputations methods will be necessary.

For secondary variables, confidence intervals will be calculated for each group and for differences between the placebo group and the group treated with TTP399.

Subgroup Analyses

Subgroup analyses will be done as identified in the SAP.

10.7. Safety Analysis

The SAF is used for safety analysis. Adverse events, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the trial to evaluate the safety of participants.

10.7.1. Safety Variables of Analysis

Adverse Events

Definitions:

- A *treatment-emergent adverse event* (TEAE) is an event that is observed or reported after administration of study medication that was not present prior to study medication administration or an event that represents the exacerbation of a pre-existing event.
- An *adverse withdrawal* is a patient who withdrew from the study due to an adverse event.
- A *serious adverse event* (SAE) is an AE that is classified as serious according to the criteria specified in the study protocol.

Adverse events variables of analysis include:

- Proportions of patients with TEAEs by Preferred Term and decreasing frequency of TEAE
- Proportions of patients with TEAEs by System Organ Class (SOC) and Preferred Term
- Proportions of patients with adverse withdrawals

Vital Signs

Vitals signs measures of blood pressure and pulse will include the following variables of analysis:

- Mean values and mean changes of values from Baseline to Visit
- Proportions of patients with potentially clinically significant abnormal values or changes in vital signs measures.
- Proportions of patients with AEs related to vital signs

Clinical Laboratory

Clinical Laboratory hematology and clinical chemistry variables of analysis include:

- Proportions of patients with TEAVs (shifts from normal status to abnormal status)

Proportions of patients meeting DILI criteria per FDA Guidance for Industry "Drug-induced liver injury: premarketing clinical evaluation" (CDER, CBER, July 2009)
- Means and mean changes from Baseline to Visit
- Proportions of patients with new (post Baseline) potentially clinically significant values (Clinical laboratory-related AEs) or changes in laboratory values

Electrocardiography

Electrocardiography variables of analyses will include:

- Proportion of patients with Corrections to QT intervals will be made by Bazett's method and also by Fridericia'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).
- Means and mean changes from Baseline to Visit
- Proportions of patients with new (post Baseline) potentially clinically significant values (Clinical laboratory-related AEs) or changes in laboratory values

Statistical Methodology for Safety Analysis

Adverse events will be coded using MedDRA Version 16.0 or above. Adverse event coding will be done to the lowest level term (LLT). All treated patients will be included in the assessment of safety. Adverse events will be summarized by MedDRA System Organ Class and Preferred Terms. Separate tabulations will be produced for related AEs (those considered by the Investigator as drug related), SAEs, discontinuations due to AEs, and severe events.

Vital signs, ECG results, and laboratory data will be tabulated for changes over time on study. In addition, TEAV and significant findings will be summarized.

For each post-Baseline assessment, descriptive statistics are provided for the assessment value and the change from Baseline to the assessment.

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, median, standard deviation, first and third quartiles, minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages).

Baseline will be the latest available data point prior to start of treatment for all parameters.

10.8. Pharmacokinetic Analysis: TTP399 (Sentinels only)

10.8.1. Derivation of Pharmacokinetic Variables

The single- and multiple-dose plasma PK profiles of oral TTP399 will be evaluated, as data permit, using the following variables:

C_{max} Maximum plasma concentration (ng/mL), observed by inspection of individual study participant plots of plasma concentration versus time.

C_{min} Minimum plasma concentration (ng/mL), observed by inspection of individual study participant plots of plasma concentration versus time.

T_{max} Time (hr) from dosing to C_{max}, observed by inspection of individual study participant plots of plasma concentration versus time.

$t_{1/2}$ Apparent terminal elimination half-life (hr), as calculated by the following equation: $t_{1/2} = 0.693/kel$ where kel is the terminal elimination rate constant.

AUC_{0-t} Area under the plasma concentration-versus-time curve (ng×hr/mL) from Hour 0 to the last measurable plasma concentration at time t (C_t), calculated using the linear trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids.

AUC_{0-24} Area under the plasma concentration-versus-time curve (ng×hr/mL) from Hour 0 to 24 hours post dose. As the dosing interval is daily this parameter will be analogous $AUC_{0-\tau}$

10.9. Safety Monitoring

Because the sentinel phase of the study is open label, the number of patients is small, and the most likely safety issues, those related to hypoglycemia, will need immediate attention, the safety will be monitored directly by the PI and the study staff. Based on safety information obtained from Sentinels and Part 1 phases of the study, a data safety monitoring board that could be convened quickly on an *ad hoc* basis to review/examine AEs may be considered for Part 2. Minimal members of the board would include an endocrinologist and a statistician.

Regular sponsor-directed safety review of study data will be conducted on an ongoing basis (unblinded reviews occurring weekly for sentinels and blinded reviews (occurring approximately monthly in Part 1 and 2). In addition, an independent, potentially unblinded endocrinologist will be contracted to evaluate SAEs or AEs of special concern in Part 1 and 2.

10.10. Interim Analysis

An Interim Analysis Plan (IAP) will be developed prior to any unblinding of the Part 1 results (other than emergency unblinding for safety reasons). The IAP will describe the statistical methodological approach, disclosure controls, and processes intended to protect the integrity of the ongoing study. The interim analysis will follow the IAP.

An interim analysis is planned for Part 1 of this study approximately 6 weeks after approximately 20 patients have been randomized. Additional interim analysis may or may not be done. Interim analysis may or may not be unblinded. As a conservative measure to protect against alpha inflation, an adjustment of 0.001 is made to the study-wise alpha that may or may not be done.

In this adaptive study, analysis will occur for the parts of the study separately as defined. There is an adjustment for alpha as a conservative measure to control unexpected inflation of alpha, reserving 0.049 for the final analysis.

10.11. Data Management Considerations

This study will utilize electronic data capture (EDC) for data capture. The database lock will occur when all data are finalized for the study. The interim analysis will be done on a clean snapshot, but a permanent lock will not be needed for that purpose.

11. QUALITY CONTROL / MONITORING OF THE STUDY

11.1. Protocol Compliance

The study must be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the study participant requires intervention. Any significant deviation from the protocol must be reported immediately to the Study Sponsor.

11.2. Protocol Amendment

Any amendment to the protocol will be created by the Study Sponsor and must be reviewed by the PI and subsequently submitted to the IRB for approval and to the applicable regulatory authority, if required. Since this is an adaptive study, protocol amendment(s) are anticipated prior to the initiation of Part 1 and potentially at other times during the study. If the protocol amendment substantially alters the study design or increases the potential risk or discomfort to the study participants, or if required by IRB, written consent for continued participation in the study must be obtained from each study participant.

11.3. Monitoring of the Study

During study conduct, the Sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on EDCs are accurate. Additionally, the study site may be patient to quality assurance audits performed by the Sponsor, and/or to inspection by the IRB or regulatory authorities.

12. DATA HANDLING AND RECORD KEEPING

12.1. Case Report Forms / Electronic Data Record

This study will utilize electronic data capture (EDC) for the data record serving as the "Case Report Form (CRF)". The database will house both Part 1 and Part 2 in a single database, but with the delineation of patients who are in Part 1 and those who are in Part 2. The databases for each part of the study may be locked separately (hard-lock). Quality control measures will progress final data management activities from last-patient-last-visit to database lock, then un-blinding, final analysis, and final reported for each part of the study as it completes. The database lock may occur for each part of the study (Part 1 and Part 2) when the study is declared closed, when all participants have completed the study (last visit of the last patient on-study) and the data are fully monitored with all queries resolved.

The PI is responsible for ensuring that the data collected are collected and reported in a timely manner and is accurate, complete, and legible.

Data will be verified within the eCRF by the Study Site and the Study Monitor before final extraction. Any changes made during verification will be documented with a full audit trail.

Any missing or inconsistent data entries will be referred back to the PI or designee, using a data query form, and documented for each individual study participant before EDCs are frozen, signed by PI or designee; then, database will be protected from changes (database lock).

12.2. Record Retention

The PI/Study Site must retain all study records, including regulatory documents and individual study participant records, for a period of 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved, until 2 years after the investigation is discontinued, and the FDA is notified or longer if requested by Sponsor (per 21 CFR 312.62). If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation, closure of facility), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Study Sponsor, such as another Investigator, another institution, or to the Study Sponsor. The Study Sponsor needs to be notified and approval obtained before records may be transferred off-site.

13. ETHICS

13.1. Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The study protocol, protocol amendments, informed consent forms, and other relevant documents (e.g., recruitment advertisements) will be reviewed and approved by the IRB/IEC prior to site initiation. All correspondence with the IRB/IEC should be retained in the site's

trial file with copies of IRB/IEC communications forwarded to the Sponsor.

A protocol amendment may be initiated prior to IRB/IEC approval only where the change is necessary to eliminate apparent immediate hazards to the participants. Should this occur, the Investigator must notify the IRB/IEC and the Sponsor in writing immediately after the implementation of the protocol amendment.

No deviations to the protocol are permissible except when necessary to eliminate an immediate hazard to study participants. The Investigator shall notify the IRB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

13.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Participants, adopted by the General Assembly of the World Medical Association (1996).

In addition, the study will be conducted in accordance with the protocol, *ICH Guideline for Good Clinical Practice*, and applicable local regulatory requirements and laws.

13.3. Patient Information and Consent

Informed consent will be administered in accordance with the requirements of 21 CFR 50.20-27 and ICH E6 4.8, Principles of Good Clinical Practice. Before protocol-specified procedures are carried out, the PI and study staff will explain the objectives of the study, study procedures, as well as the risks involved to the study participant, his/her legally authorized representative (if applicable), and caregiver prior to their inclusion in the trial. Study participants will also be informed that they are free to withdraw from the study at any time.

Prior to performing any study-specific procedure, each study participant or the participant's caregiver will be required to read and voluntarily sign an IRB-approved ICF, indicating his/her consent to participate. This ICF will conform to the requirements of 21 CFR 50.20-27 and ICH E6 Principles of Good Clinical Practice. The Study Sponsor must agree with the final IRB-approved ICF prior to initiation of the study. Study participants will be provided adequate time to review the ICF and if they wish, may take it home to discuss their participation in the study with friends, family, and/or a physician. The original signed ICFs must remain in the study participant's file in the study site. Study participants will receive a copy of their signed ICF. An ICF will be provided to study participant specific to the part of the study in which they are participating.

14. STUDY TERMINATION CRITERIA

The Study Sponsor reserves the right to discontinue the study at any time for medical or

administrative reasons. Reasons for termination may include new toxicological or pharmacological findings or SAEs that invalidate the earlier positive risk-benefit-assessment, the incidence and/or severity of AEs in the study indicate a potential health hazard caused by treatment with the study medication, or a decision by the Sponsor to discontinue the development of the investigational medication.

15. CONFIDENTIALITY AND PUBLICATION OF STUDY RESULTS

The information in this and related documents from the Study Sponsor contains trade secrets and commercial information that are confidential and may not be disclosed unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Individual study participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the study participant's personal physician or to other appropriate medical personnel responsible for the study participant's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IRB, or the local regulatory agency.

None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of the Study Sponsor.

No patent application based on the results of the study may be made by the PI, nor may assistance be given to any third party to make such an application, without the written authorization of the Study Sponsor.

16. REFERENCES

1. American Diabetes Association, Diabetes Care: **40** (Suppl. 1), S11-S24 (2017)
2. Postic, C., Shiota, M. & Magnuson, M.A. *Recent Prog Horm Res* **56**, 195-217 (2001)
3. Ferre, T., et al. *FASEB J* **10**, 1213-1218 (1996);
4. Girard, J., Ferre, P. & Foufelle, F. *Annu Rev Nutr* **17**, 325-352 (1997).
5. 21 Code of Federal Regulation 312.32(a)
6. International Hypoglycaemia Study Group. *Diabetes Care* **40**, 155-157 (2017)

17. APPENDICES

Appendix 1: Continuous Glucose Monitoring (Sentinel phase)

CGM data will be collected for all three parts of the study. Glucose assessments as well CGM and diary entries will be used to assess the safety and efficacy of TTP399. The sponsor will provide sensors and transmitters for patient's unblinded CGM (Sentinel phase and Part 1) and require that the patients replace the sensor every 7 days as indicated by the manufacturer. The sensor should be replaced the day before any MMTT visits.

All patients in the sentinel phase are required to have experience with CGM and currently be using Dexcom CGM. These experienced patients will be provided manufacturer's instructions and will have training by study site personnel to confirm proper understanding of the device and what is expected during the study. Training will include changing and calibrating sensors and the use of the electronic diary to record bolus insulin dose, meal carbohydrate content and symptoms of hypoglycemia.

At the Day -7 visit, patients will be required to

- Confirm their sensor was changed appropriately, has been calibrated according to manufacture instructions and is recording data prior to the MMTT
- Have a smartphone and agree to download and use the DexCom Share application
- Agree to consistently enter information indicated in Section 4.2 in their CGM system
- Confirm the alert criteria are set to sufficiently monitor safety according PI judgment
- Allow PI or designee to follow real time CGM and respond to site's request to enroll in CLARITY

Unblinded CGM will be collected during the study for Sentinel patients. All available data will be captured, with the Days 4-6 of each dosing period to be used for analysis of secondary outcome measures. Sites will upload the patient's Dexcom CGM data into a study specific CLARITY account where reports, including the AGP can be created.

Appendix 2: Laboratory Specimen Collection (Part 1)

VISIT NAME	SCREENING	Week 0	Week 2	Week 4	Week 6	Week 8	Week 12/ET3	FOLLOW-UP
Study Day (Study day window ± 3 days)	-	Day 1	Day 14	Day 28	Day 42	Day 56	Day 84	-
Group Name(s)								
Chemistry Panel	X	X	X	X	X	X	X	X
Electrolyte Panel	X	X	X	X	X	X	X	X
Lipid Panel	X	X	-	X	X	-	X	-
Single point PK	-	X	X	X	X	X	X	-
Hematology & Differential Panel	X	X	X	X	X	X	X	X
Urine Panel	X	X	X	X	X	X	X	X
Single point Gluca/GLP-1	-	X					X	-
Single point c-peptide and retention	-	X	-	-	-	-	X	-
Lactate	-	X	X	X	X	X	X	-
Free Fatty Acids	-	X	-	X	X	-	X	-
HbA1C	X	X	X	X	X	X	X	-
Fructosamine	-	X	X	X	X	X	X	-
GLYCOMARK	-	X	X	X	X	X	X	-
BETA-HYDROXYBUTYRATE	-	X	X	X	X	X	X	X

Chemistry panel: Total Bilirubin, Alkaline Phosphatase, ALT, AST, Urea Nitrogen, GGT, Creatinine, Uric Acid, Calcium, Total Protein, Albumin, and Direct bilirubin (Screening only)
Electrolyte panel: Sodium, Potassium, Bicarbonate, Chloride
Lipid panel: Cholesterol, Direct HDL Cholesterol, LDL Cholesterol Calculated, Triglycerides
Hematology & Differential Panel: Hemoglobin, Hematocrit, RBC, MCH, MCHC, RBC Morphology and MCV, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils and Platelets

Laboratory Specimen Collection (Part 2)

VISIT NAME	SCREENING	Week 0	Week 2	Week 6	Week 12/ET3	FOLLOW-UP
Study Day		Day 1	Day 14	Day 42	Day 84	
Group Name(s)						
Chemistry Panel	X	X	X	X	X	X
Electrolyte Panel	X	X	X	X	X	X
Lipid Panel	X	X	X	X	X	X
Single point PK	-	X	-	X	X	-
Hematology & Differential Panel	X	X	X	X	X	X
Urine Panel	X	X	X	X	X	X
Lactate	-	X	X	X	X	X
Single point c-peptide	-	X	-	X	X	-
Single point Gluca	-	X	-	X	X	-
Single point retention	-	X	-	X	X	-
Free Fatty Acids	-	X	-	X	X	-
HbA1C	X	X	-	X	X	-
Fructosamine	-	X	-	X	X	-
GLYCOMARK	-	X	-	X	X	-
BETA-HYDROXYBUTYRATE	-	X	X	X	X	X

Chemistry panel: Total Bilirubin, Alkaline Phosphatase, ALT, AST, Urea Nitrogen, GGT, Creatinine, Uric Acid, Calcium, Total Protein, Albumin, Fasting plasma glucose and Direct bilirubin (Screening only)
Electrolyte panel: Sodium, Potassium, Bicarbonate, Chloride
Lipid panel: Cholesterol, Direct HDL Cholesterol, LDL Cholesterol Calculated, Triglycerides
Hematology & Differential Panel: Hemoglobin, Hematocrit, RBC, MCH, MCHC, RBC Morphology and MCV, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils and Platelets

Appendix 3: Values or Changes Potentially 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 20nnHg (increase or decrease)
Heart Rate	<50 bpm **and** >/=25% decrease from baseline >100 bpm **and** >/=25% increase from baseline