Title

Impact of the hepatoselective glucokinase activator TTP399 on ketoacidosis during insulin withdrawal in people with type 1 diabetes.

Journal

Diabetes, Obesity and Metabolism: a journal of pharmacology and therapeutics, 24(8)

Authors

Freeman, Jennifer
Dunn, Imogene
Dvergsten, Chris
et al.

Publication Date

2022-08-01

DOI

10.1111/dom.14697

Peer reviewed

HHS Public Access

Author manuscript

Diabetes Obes Metab. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Diabetes Obes Metab. 2022 August ; 24(8): 1439–1447. doi:10.1111/dom.14697.

Impact of the Hepatoselective Glucokinase Activator TTP399 on Ketoacidosis During Insulin Withdrawal in People with Type 1 Diabetes

Klara R. Klein, MD, PhD[1,†], **Schafer C. Boeder, MD**[2,†], **Jennifer L. R. Freeman, PhD**[3], **Imogene Dunn, PhD**[3], **Chris Dvergsten, PhD**[3], **Supradeep Madduri**[1], **Erin R. Giovannetti, FNP-C**[2], **Carmen Valcarce, PhD**[3], **John B. Buse, MD, PhD**[1,†], **Jeremy H. Pettus, MD**[2,†]

[1]Division of Endocrinology and Metabolism, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

[2]Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, La Jolla, CA.

[3]vTv Therapeutics LLC, High Point, NC, USA

Abstract

Aims—To determine the effect of TTP399, a hepatoselective glucokinase activator, on the risk of ketoacidosis during insulin withdrawal in individuals with type 1 diabetes (T1D).

Materials and methods—23 participants with T1D using insulin pump therapy were randomized to 800 mg of TTP399 (n=12) or placebo (n=11) for 7-10 days. After the treatment period, an insulin withdrawal test (IWT) was performed during which insulin pumps were removed to induce ketogenesis. The IWT was stopped after 10 hours or if blood glucose (BG) reached >399 mg/dL, beta-hydroxybutyrate (BHB) >3.0 mmol/L, or for patient discomfort. The primary endpoint was the proportion of participants who reached BHB concentrations of 1 mmol/L or greater.

Results—During the 7-10 day treatment period, mean fasting BG was significantly reduced (−27.6 vs −4.4 mg/dL, p = 0.03) and adverse events, including hypoglycemia, were fewer in the TTP399-treated arm. During the IWT, no differences were observed between TTP399 and placebo in mean serum BHB concentration, mean duration of IWT, or BHB at termination of IWT. However, serum bicarbonate was numerically higher and urine acetoacetate was quantitatively lower in the TTP399-treated participants. As a result of higher bicarbonate values, zero TTP399-treated subjects met prespecified criteria for DKA, defined as BHB >3mmol/L and serum bicarbonate <18mEq/L, compared to 42% of placebo treated subjects.

Corresponding author: Klara R. Klein, MD, PhD, Division of Endocrinology and Metabolism, Campus Box #7172, 8072 Burnett Womack, 160 Dental Circle, Chapel Hill NC 27599, Tel: (919)-966-0134, Fax (919)-966-6025, klara_klein@med.unc.edu.
†These authors contributed equally to this work

AUTHOR CONTRIBUTIONS

KRK and SCB participated in study design, data collection, analysis and manuscript drafting. JBB and JHP participated in study design, analysis, and data collection. JLRF, ID, CD, and CV participated in protocol development and analysis. ID was primarily responsible for development of the statistical analysis plan and supervision of the analyses reported. All authors edited and approved the final manuscript for submission and publication. CV is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conclusions—When used as an adjunctive therapy to insulin, TTP399 improves glycemia without increasing hypoglycemia in individuals with T1D. During acute insulin withdrawal, TTP399 did not increase BHB concentrations and decreased the incidence of DKA.

INTRODUCTION

Despite numerous advances in type 1 diabetes (T1D) insulin-based therapy, the state of T1D care remains suboptimal. Most patients do not meet glycemic control goals, have high rates of microvascular complications, an increased risk of cardiovascular disease, and high prevalence of obesity.[1] Additionally, the acute complications of T1D including severe hypoglycemia and diabetic ketoacidosis (DKA) remain unacceptably high.[2] Accordingly, there is a large unmet need to explore non-insulin, "adjunctive" therapies to reduce the acute and chronic complications in individuals with T1D.

Numerous adjunctive therapies have been explored in T1D with recent focus on glucagon like peptide-1 receptor agonists (GLP-1 RA) and sodium glucose cotransporter-2 inhibitors (SGLT-2i). While both compounds improve glucose control and reduce weight, they also have increased rates of ketosis or DKA.[3-5] For both compounds, a reduction in exogenous insulin dose is believed to be one component that leads to the increased risk of DKA. Therefore, future adjunctive therapies will need to demonstrate the ability to safely lower glucose levels in the context of lower exogenous insulin requirement, while not increasing the risk of ketoacidosis or hypoglycemia.

Hepatic glucokinase (GK) is a target of interest for the treatment of T1D that may address this need by simultaneously reducing glucose levels and ketogenesis. GK has a critical role in glucose homeostasis but has reduced activity in type 1 diabetes.[6] Chronically reduced hepatic insulin exposure observed in T1D leads to subnormal hepatic GK expression and impaired liver glucose uptake and metabolism.[7] Liver selective GK activation has the potential to restore liver glucose metabolism in individuals with T1D, thereby improving glycemia in a glucose dependent manner while shifting hepatic metabolism toward glycogen storage and away from ketogenesis.[8]

The SimpliciT1 study tested the safety and efficacy of a small molecule hepatoselective GK activator, TTP399, in participants with T1D.[9] TTP399 demonstrated significant improvements in glycemia during the 12-week treatment period versus placebo.[9] Further, there was a trend toward reduction in ketosis events, despite numerically lower insulin dose.[9] The current study was designed to further explore this trend and test the hypothesis that treatment with a GK activator would not increase rates of ketogenesis in individuals with T1D during acute insulin withdrawal.

RESEARCH DESIGN AND METHODS

Study Design and Participants

TTP399-118 was a phase 1 double-blinded, randomized, parallel-grouped, placebo-controlled multiple-dose study designed to evaluate the impact of TTP399 on ketone production following insulin withdrawal. Twenty-three adults with type 1 diabetes were

randomized to placebo (n=11) or TTP399 (n=12) at two clinical sites in the United States from April to July 2021.

The study population included adults less than 40 years of age with type 1 diabetes of at least one year duration who were on insulin pump therapy for at least three months at screening. Main eligibility criteria included HbA1c <10% (86 mmol/mol), fasting C-peptide <0.07 ng/mL, BMI ≤32 kg/m^2, and generally stable health in the opinion of investigators. Each participant provided written informed consent prior to any study procedures.

The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Participants and applicable local regulatory requirements and laws and was approved by University of North Carolina at Chapel Hill and University of California San Diego Institutional Review Boards.

Procedures

Participants who met the enrollment criteria were randomly assigned (1:1) based on a fixed randomization schedule to receive TTP399 (800 mg) or matching placebo tablets. Randomization schedule for investigational product allocation was prepared by the study sponsor and provided to the pharmacy staff for dispensing. Participants, investigators, all site personnel, and the sponsor were blinded to treatment code. The randomizing statistician and independent safety review monitor were the only unblinded people until the time of study unblinding.

The first dose of investigational product was administered at the randomization visit under observation of study staff. Participants were instructed to take the study medication every morning prior to the day of the IWT (visit 3). The treatment period lasted for 7-10 days depending on subject availability for visit 3. On the morning of the IWT, participants were instructed to bring the study product to the visit where study staff observed administration. Pill counts were performed to assess adherence. A schema of the study design is shown in Supplementary Figure 1.

On the first day of randomized product, bolus insulin dose was reduced by adjusting the insulin-to-carbohydrate ratio 0-20% depending on screening HbA1c. Participants were instructed to measure fasting ketones using a Precision Xtra blood glucose and ketone meter (Abbot Diabetes Care, California, USA) and if they exhibited any symptoms of DKA. Participants were also instructed to measure blood glucose with the study provided glucose meter for symptoms of hypoglycemia or if their continuous glucose monitor (CGM) indicated glucose <54 mg/dL.

Participants were contacted two days after randomization and the day prior to IWT to review blood glucose measurements and provide additional insulin adjustments.

On the day of the IWT, participants were instructed not to administer bolus insulin within two hours of arrival to the study site. Capillary blood glucose and ketones were checked upon arrival to confirm starting criteria (blood glucose: 80-180 mg/dL, BHB: <1.5 mmol/L). Insulin pump and blood glucose data from screening to visit 3 were downloaded.

At the start of the IWT (0 min), bedside blood glucose and ketones were checked again to confirm starting criteria, followed by insulin pump removal, and administration of the study product. The IWT was terminated at 600 min or if participants met termination criteria (bedside ketone >3.0 mmol/L, bedside glucose >399 mg/dL, persistent or bothersome symptoms to the patient, or at the investigator's discretion). Fluids were restricted to 100 cc/hr throughout the IWT.

At IWT termination, participants received fluids, subcutaneous insulin, and a high carbohydrate meal. Insulin dose was calculated using the participants insulin sensitivity factor and carbohydrate ratio. Basal insulin via insulin pump was restarted after administration of subcutaneous insulin. Participants were discharged when symptoms resolved and BHB was down-trending. A follow-up visit was conducted 3-5 days after the IWT.

Outcomes

Blood pressure, pulse, HbA1c, C-peptide, urine pregnancy tests, and safety labs (hematology, metabolic panel, lipids, and urinalysis) were collected at all visits before dosing. Electrocardiograms were collected at screening, randomization, and the follow-up visit.

The day of the IWT, serum BHB was measured prior to study product administration, every 60 min for the first 360 min, and every 30 min thereafter. Serum bicarbonate, free fatty acids (FFA), and insulin levels were collected prior to study product administration, every 120 min from 0-360 min then every 60 min. Urine ketone dipstick analysis was performed prior to dosing study product, at 240 ± 60 min, at 480 ± 60 min, and at 600 min. Pharmacokinetic samples were collected before dosing at the randomization visit and during IWT visit (pre-dose, 120, and 600 min). If IWT termination criteria were met prior to 600 min, the complete set of 600 min labs were collected at the time of study termination. All laboratory measurements were performed at a central laboratory (Labcorp Drug Development, Inc., Princeton, NJ).

The primary endpoint was the proportion of participants who had BHB concentrations of 1 mmol/L or greater which represents at least a 0.5 mmol/L increase from pre-dose level following start of insulin withdrawal test. Secondary endpoints included proportion of participants who met IWT termination criteria (bedside ketone >3.0 mmol/L, bedside glucose >399 mg/dL, persistent or bothersome symptoms to the patient), median time to reach termination criteria, and median time to reach blood ketone concentrations of 1 mmol/L which represents at least a 0.5 mmol/L increase from pre-dose level.

Safety endpoints included reported adverse events (AEs), vital signs, electrocardiography, and safety laboratory measurements. Patient-reported hypoglycemia and DKA events were considered AEs of special interest. A safety monitor who was blinded to treatment assignment evaluated AEs after each IWT. An unblinded safety analysis by statistician followed the first ten IWTs with additional cumulative analyses after the second ten IWTs. Differences observed in AEs between treatment arms were reviewed by an unblinded endocrinologist to report on safety concerns.

Statistical Analysis

The statistical analysis plan (SAP) was finalized prior to unblinding. Alpha was controlled via a conditional sequence of statistical evaluations that began with noninferiority of TTP399 relative to placebo on endpoints related to safety, which were followed by superiority evaluations. Noninferiority of TTP399 relative to placebo was evaluated for the proportion of subjects reaching thresholds of 1 mmol/L and 3 mmol/L by construction of 95% confidence intervals of the relative risk using a non-inferiority margin of 1.8.[10] Sample size calculation for non-inferiority and superiority were similar and were calculated to detect a difference between TTP399 and placebo-treated individuals. Assuming 75% of placebo-treated subjects and no more than 20% of subjects treated with TTP399 would reach the defined thresholds during the observation period, randomization of n=16 per group provided 80% power to detect a difference between subjects treated with TTP399 and those treated with placebo on median time to the event; 11 events were required for adequate statistical power. Randomization of 40 individuals were expected to enable observation of at least 11 events with at least 32 completers. However, during blinded data review, participants trended towards homogeneity, and it was determined further data would not change this trend. Twenty-three subjects were determined adequate for the planned analyses.

Intent-to-treat methodology was followed for analysis using all randomized, treated subjects with any data from the IWT. Safety analysis was done on all subjects who received any treatment with study medication.

The conditional sequential evaluation stopped when the first superiority evaluation had a p-value exceeding alpha. Subsequent analyses have nominal p-values that are informative, but do not support statistical conclusions of treatment differences. Descriptive analyses on measurements followed methods planned for other studies with analysis of covariance (ANCOVA) with baseline values as covariates supported by rank analogues, due to small sample sizes. Proportions were evaluated statistically with Fisher’s exact test. Time-to-event variables were evaluated descriptively by logrank tests.

RESULTS

Participant disposition is shown in Supplementary Figure 2. Twenty-three participants were randomized. One participant randomized to placebo refused the IWT and contributed safety data prior to IWT only. All randomized participants took at least one dose of study medication which was observed by study staff at the randomization visit. Study drug administration was also observed immediately prior to the IWT. Pill counts suggested adherence among all study subjects.

Baseline characteristics and demographics were comparable between treatment groups (Table 1). The mean ± SEM duration of diabetes was 25 ± 11 years in the placebo treated group and 18 ± 6 years in the TTP399 treated group. The average age at diagnosis was 10 ± 8 years and 14 ± 10 years in the placebo and TTP399 groups, respectively. Age (33 ± 9 years), BMI (26 ± 3 kg/m^2), and $HbA1_c$ (7.0 ± 0.8%) were similar between treatment arms. All participants used insulin pump therapy. Most participants utilized a sensor augmented

insulin pump (Placebo: 80%, TTP399: 75%). One participant in the TTP399 group did not use a CGM and monitored blood glucose with a capillary blood glucose meter.

The impact of study product on prespecified parameters during the treatment period is shown in Table 2. The change in FPG from baseline after the treatment period was significantly greater with TTP399 compared to placebo (−27.6 vs −4.4 mg/dL, respectively, p = 0.03, Table 2). During the treatment period, TTP399 did not increase BHB or FFA. Five subjects (45%) in the placebo group had treatment emergent adverse events during the treatment period prior to IWT compared to one subject (8%) in the TTP399 treated group (Table 2, Supplementary Table 1). Two participants randomized to placebo experienced level 2 hypoglycemia (<54 mg/dL) compared to none in the TTP399 group (Table 2).

Prespecified outcomes for the IWT are shown in Supplementary Table 2. The duration of each IWT prior to termination varied from 182 to 606 min. The average time for IWT termination was not different between groups (482 ± 119 vs 430 ± 114 minutes, placebo (n = 10) and TTP399 (n = 12), respectively, Supplementary Table 2). All IWTs were terminated secondary to BHB level >3.0 mmol/L, symptoms uncomfortable to the participant (generally nausea or vomiting), or completion of 600 min. No participants reached glucose concentration >399 mg/dL.

Prior to study start, insulin levels were below the level of detection in all participants. At 0 min, glucose concentration was not different between treatment groups (Supplementary Table 2). Following insulin withdrawal, plasma glucose concentration increased similarly in both groups (Figure 1A). At 0 min, BHB concentration was not different between treatments (Supplementary Table 2). Following insulin withdrawal, serum BHB concentrations increased similarly regardless of treatment (Figure 1B). There was no difference in change in BHB concentration from baseline at IWT termination (placebo: 2.06 vs TTP399: 1.90, p = 0.291, Supplementary Table 2) or final BHB concentration (Figure 1B, Supplementary Table 2). Kaplan-Meier curves of the pre-specified non-inferiority criteria are presented in Supplementary Figure 3. No difference was observed in the primary endpoint of relative risk of an event of ketone concentration ≥1 mmol/L within the first six hours (Supplementary Figure 3A, p = 0.59) or relative risk of failing to complete the 600 min IWT due to BHB >3.0 mmol/L (Supplementary Figure 3B, p = 0.79).

Following insulin withdrawal, average serum bicarbonate was numerically lower in individuals randomized to placebo compared to TTP399 at 240 minutes and at the IWT endpoint (Figure 1D, Supplementary Table 2). Only 1 out of 12 (8%) of participants randomized to TTP399 had bicarbonate <17.9 mEq/L at the end of the IWT compared to 4 out of 7 (57%) in the placebo group. The lowest bicarbonate observed in the TTP399 treated group was 16.5 mEq/L (Figure 1D). Four participants randomized to placebo had bicarbonate <16 mEq/L, one of whom had a bicarbonate of 14.1 mEq/L at IWT termination (Figure 1D). A trend towards a negative correlation was observed between serum bicarbonate and BHB concentration in the placebo group (Figure 1E, orange triangles r = −0.74, p = 0.055). Conversely, the correlation between serum bicarbonate and BHB in individuals randomized to TTP399 was flatter (Figure 1E, blue circles, r = −0.24, p = 0.45). No participants randomized to TTP399 met criteria for mild DKA (BHB >3 mmol/L

and serum bicarbonate <18mEq/L) at IWT termination compared with 42% of participants randomized to placebo (TTP399: 0 out of 12 subjects vs. Placebo: 3 out of 7 subjects, Figure 1F, G, p = 0.03). Despite no difference in serum BHB, less acetoacetate was observed in the urine of participants randomized to TTP399 compared to placebo after initiation of the IWT (Figure 2).

Treatment emergent adverse events during the IWT were more common in the TTP399 group (Table 3). Eleven (92%) of participants in the TTP399-treated group reported adverse events. Nine (75%) of participants in the TTP399 group experienced nausea versus four (40%) in the placebo group. Seven participants (58%) randomized to TTP399 stopped the IWT due to nausea compared to 3 (30%) randomized to placebo (Supplementary Figure 4). An unblinded independent endocrinologist reviewed nausea-related AEs prior to study team unblinding and concluded that nausea during the IWT was not related to higher ketones or lower bicarbonate and was therefore independent of DKA risk (Supplementary Figure 5).

DISCUSSION

This Phase 1, mechanistic study evaluated the effects of the GKA TTP399 on ketoacidosis risk in individuals with T1D on insulin pump therapy. The primary goal was to assess safety of TTP399 via a primary endpoint of non-inferiority of TTP399 compared to placebo in regard to ketone levels during acute insulin withdrawal. Indeed, TTP399 did not alter circulating concentrations of BHB or time to cessation of IWT and confirmed non-inferiority. Pre-specified secondary analyses investigated the potential for benefit. Due to higher bicarbonate concentrations in the TTP399 treatment arm, no subject treated with TTP399 met the prespecified definition of DKA while 42% of placebo-treated subjects met this criterion. Together, these data suggest that TTP399 does not increase, and may decrease, the risk of DKA in subjects with T1D.

This finding stands in direct contrast to other promising oral adjunctive therapies tested in T1D. During similar insulin withdrawal experiments, SGLT2i use significantly increased ketonemia in people with T1D during insulin withdrawal.[11] Moreover, off-label use of SGLT2i in the real world is associated with substantially increased risk of euglycemic DKA.[12] That TTP399 did not result in increased BHB during acute insulin withdrawal and instead demonstrated a trend toward lowering risk of metabolic acidosis suggests that TTP399 will not increase the risk of DKA when used in the real world.

Regarding associations between BHB and bicarbonate concentrations, the data suggest that the higher serum bicarbonate observed with TTP399 treatment was independent of BHB concentration. Interestingly, urine acetoacetate was lower by semiquantitative measurements in participants treated with TTP399, implying that the plasma acetoacetate was also lower in this group compared to placebo. The divergence between the serum BHB concentration and the urine acetoacetate concentration during the IWT was unexpected. This finding raises the question of whether TTP399 selectively reduces serum acetoacetate concentrations, thereby decreasing the overall ketone body burden and mitigating the development of acidosis. The mechanism of how TTP399 may selectively impact certain ketone bodies remains unclear.

Regardless, this study suggests that TTP399 lowers the risk of metabolic acidosis during acute insulin withdrawal.

Nausea was the most common treatment emergent AE during the IWT and occurred more frequently in participants treated with TTP399 than placebo. Nausea was more likely to be the reason for termination of the IWT in the TTP399 group than in the placebo group, however, the presence of nausea was not associated with increased concentrations of BHB or decreased concentrations of bicarbonate. Nausea universally resolved in trial participants with insulin administration. Nausea is a common symptom of ketoacidosis that can serve as an important warning sign of impending DKA.[13] TTP399-associated nausea in the setting of insulinopenia may provide additional protection from DKA by alerting individuals of pump failure or missed insulin doses, thus allowing for ketosis reversal prior to developing life-threatening metabolic acidosis.

Importantly, nausea in the TTP399-treated group only occurred during the IWT. During the 7-10 day treatment period, no episodes of nausea were observed in the TTP399 group, whereas one episode was reported in the placebo group. Overall, there were fewer adverse events during the treatment period in TTP399-treated participants than in the placebo group, again suggesting overall safety as an adjunctive therapy to insulin.

No hypoglycemic events <54 mg/dL were observed in the TTP399 group, whereas two subjects experienced a total of four hypoglycemic events <54 mg/dL in the placebo group. These data are consistent with the SimpliciT1 data which demonstrated significantly less hypoglycemic episodes in participants randomized to TTP399 compared with placebo. TTP399 also significantly reduced fasting plasma glucose compared with placebo during the 7-10 day treatment period. These data are of particular interest as 75% of the participants randomized to TTP399 utilized sensor-augmented insulin pumps. TTP399 has not previously been tested in participants using sensor-augmented insulin pumps, commonly used in T1D.

These findings add to the accumulating data indicating the safety and efficacy of TTP399 for the treatment of type 1 diabetes. Similar studies have been performed during an inpatient admission, utilizing intravenous insulin to achieve steady state prior to discontinuation of insulin,[11] but have been criticized for failing to model the insulin deficiency that occurs in the everyday lives of people with T1D.[14] Our study was performed in an outpatient clinical trials unit and was designed to mimic acute insulin withdrawal that would occur in the “real-world”, such as insulin pump failure. The study design allowed for observation of BHB concentrations across a clinically meaningful spectrum from normal to levels consistent with DKA. Additionally, the study captured realistic symptomatology associated with insulinopenia that would occur outside of a clinical trial.

In terms of study limitations, the safety criteria for the termination of the IWT were frequently met. Most participants did not complete 600 min IWT, leaving an insufficient number of subjects to evaluate differences in outcomes at 600 min. Instead, differences between groups for most outcomes were evaluated at termination of insulin withdrawal,

irrespective of the timepoint of IWT termination. This limitation was mitigated by the fact that there was no difference in the mean duration of IWT between treatment groups.

These data demonstrate that in contrast to agents like SGLT2i and GLP1 RA, TTP399 does not increase the risk of ketoacidosis when used as an adjunctive therapy to insulin in individuals with T1D. Moreover, these findings support prior studies that demonstrate that TTP399 improves glucose control and reduces hypoglycemia and suggests a protective effect of TTP399 against acidosis in people with T1D. Thus, accumulating data suggest that TTP399 has robust potential as an adjunctive therapy for T1D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMNTS

We are grateful to the participants who devoted their time and energy to this study and to the study staff whose efforts were essential in the safe and successful conduct of the trial (Alex Kass, Jamie Diner, Laura Young, and M. Sue Kirman from UNC, and Todd May, Adrienne Armstrong, and Leslie Carter from UCSD). The authors also greatly appreciate the support of Dr. Robert Rizza and Dr. Justin Gregory throughout the study.

FUNDING

The JDRF and vTv co-funded this study. Activities at the University of North Carolina were additionally supported by the NC Translational and Clinical Sciences Institute funded by a grant from the National Center for Advancing Translational Sciences (UL1TR002489), the NC Diabetes Research Center funded by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (P30DK124723) and the Department of Medicine's UNC Eastowne Clinical Research Unit. K.R.K. is supported by the University of North Carolina Department of Medicine and School of Medicine Physician Scientist Training Program.

CONFLICT OF INTEREST

KRK, SCB, SM, and ERG have no conflicts of interest.

JBB's contracted consulting fees and travel support for contracted activities are paid to the University of North Carolina by Adocia, Novo Nordisk, Senseonics, and vTv Therapeutics as well as grant support from Dexcom, NovaTarg, Novo Nordisk, Sanofi, Tolerion and vTv Therapeutics. He is also a consultant to Alkahest, Anji, AstraZeneca, Boehringer-Ingelheim, Carmot Therapeutics, Cirius Therapeutics Inc, Eli Lilly, Fortress Biotech, GentiBio, Glycadia, Glyscend, Janssen, Mellitus Health, Moderna, Pendulum Therapeutics, Praetego, Stability Health, Valo and Zealand Pharma. He holds stock/options in Glyscend, Mellitus Health, Pendulum Therapeutics, PhaseBio, Praetego, and Stability Health. He is supported by grants from the National Institutes of Health (UL1TR002489, U01DK098246, UC4DK108612, U54DK118612, P30DK124723, R33HL142680, R44DK096803, R01DK119913, R01DK112939, R01DK125831, R01DK127365) and PCORI (D1-2018C1-10853).

J.H.P reports consulting fees from Diasome, Lilly, MannKind, Novo Nordisk, and Sanofi.

REFERENCES

1. Foster NC, Beck RW, Miller KM, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019;21(2):66–72. [PubMed: 30657336]
2. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016;12(4):222–232. [PubMed: 26893262]
3. Ahren B, Hirsch IB, Pieber TR, et al. Efficacy and Safety of Liraglutide Added to Capped Insulin Treatment in Subjects With Type 1 Diabetes: The ADJUNCT TWO Randomized Trial. Diabetes Care. 2016;39(10):1693–1701. [PubMed: 27493132]

4. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. Diabetes Care. 2016;39(10):1702–1710. [PubMed: 27506222]
5. Peters AL, McGuire DK, Danne T, et al. Diabetic Ketoacidosis and Related Events With Sotagliflozin Added to Insulin in Adults With Type 1 Diabetes: A Pooled Analysis of the inTandem 1 and 2 Studies. Diabetes Care. 2020;43(11):2713–2720. [PubMed: 32928957]
6. Matschinsky FM, Wilson DF. The Central Role of Glucokinase in Glucose Homeostasis: A Perspective 50 Years After Demonstrating the Presence of the Enzyme in Islets of Langerhans. Front Physiol. 2019;10:148. [PubMed: 30949058]
7. McCarty MF. In type 1 diabetics, high-dose biotin may compensate for low hepatic insulin exposure, promoting a more normal expression of glycolytic and gluconeogenic enyzymes and thereby aiding glycemic control. Med Hypotheses. 2016;95:45–48. [PubMed: 27692165]
8. Morral N, McEvoy R, Dong H, et al. Adenovirus-mediated expression of glucokinase in the liver as an adjuvant treatment for type 1 diabetes. Hum Gene Ther. 2002;13(13):1561–1570. [PubMed: 12228011]
9. Klein KR, Freeman JLR, Dunn I, et al. The SimpliciT1 Study: A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Adaptive Study of TTP399, a Hepatoselective Glucokinase Activator, for Adjunctive Treatment of Type 1 Diabetes. Diabetes Care. 2021;44(4):960–968. [PubMed: 33622669]
10. Guidance for industry: diabetes mellitus–evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes [press release]. 2008.
11. Herring RA, Shojaee-Moradie F, Garesse R, et al. Metabolic Effects of an SGLT2 Inhibitor (Dapagliflozin) During a Period of Acute Insulin Withdrawal and Development of Ketoacidosis in People With Type 1 Diabetes. Diabetes Care. 2020;43(9):2128–2136. [PubMed: 32641376]
12. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38(9):1687–1693. [PubMed: 26078479]
13. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primers. 2020;6(1):40. [PubMed: 32409703]
14. Bolli GB, Porcellati F, Lucidi P, Fanelli CG. Comment on Herring et al. Metabolic Effects of an SGLT2 Inhibitor (Dapagliflozin) During a Period of Acute Insulin Withdrawal and Development of Ketoacidosis in People With Type 1 Diabetes. Diabetes Care 2020;43:2128-2136. Diabetes Care. 2021;44(3):e59–e60. [PubMed: 33608328]

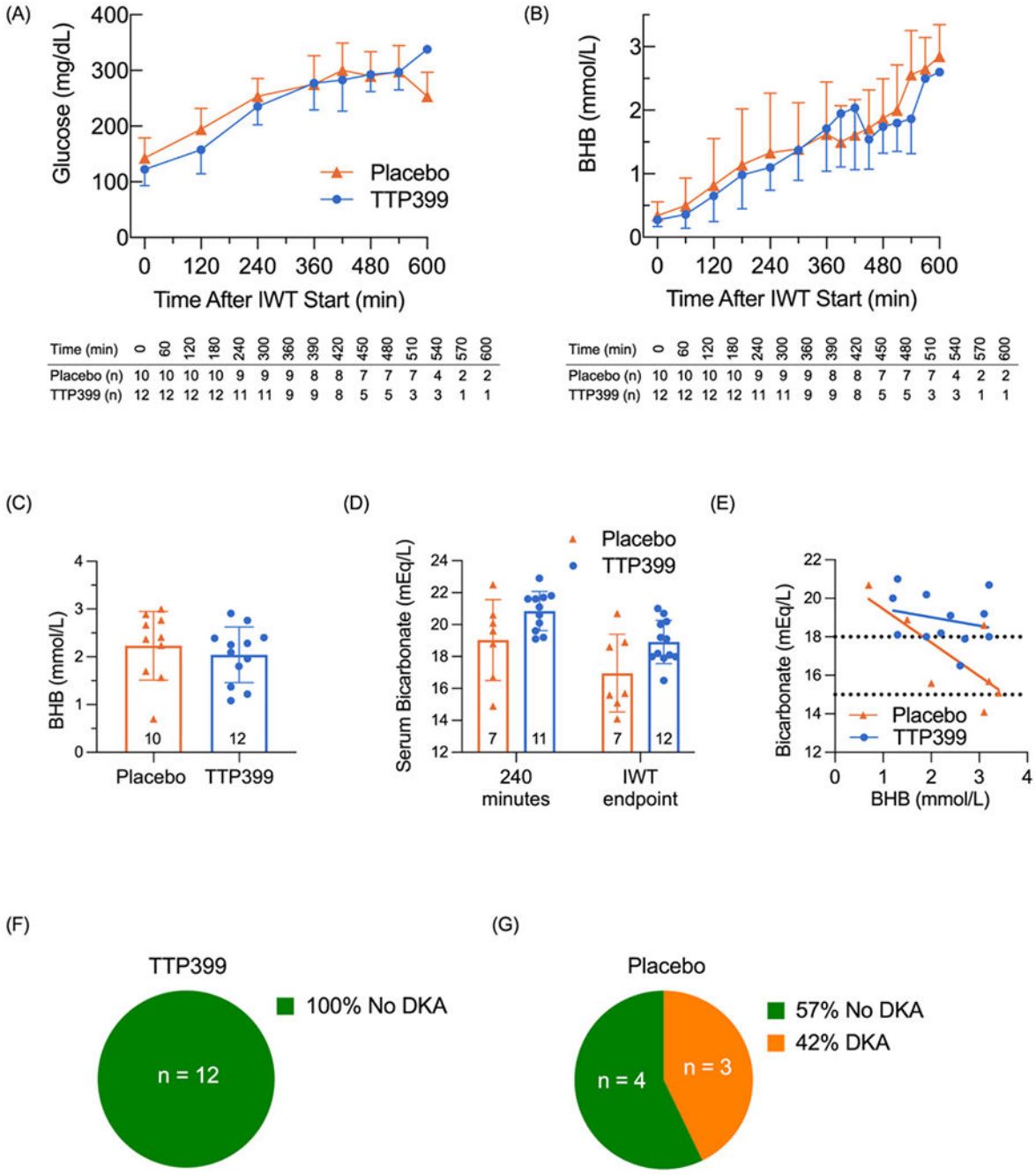

Figure 1. The effect of TTP399 on glycemia, BHB concentration, and serum bicarbonate during insulin withdrawal.

A: Glucose levels during 600-minute insulin withdrawal test (IWT). *B:* BHB concentration during 600-minute IWT. BHB and glucose were measured every hour for the first six hours and then every 30 minutes. For both *A* and *B*, the number of individuals who did not meet cessation criteria and continued to the next BHB and glucose check are listed below the graph. *C*: Average BHB concentration at the IWT endpoint. *N* for each treatment group is listed inside the bar graphs. p = ns. *D:* Average serum bicarbonate at 240m and IWT endpoint. p = ns. Serum bicarbonate is graphed for each participant. Due to laboratory

error, several of the bicarbonate data are not available. Number of bicarbonates samples at each timepoint are listed inside the bar graphs. *E:* Serum bicarbonate is graphed against serum BHB level. A negative correlation is observed for the placebo-treated group (orange triangles, p = 0.055). *F, G:* Percentage of participants randomized to TTP399 (*F*) or placebo (*G)* who met prespecified criteria for DKA. Categorical endpoints were compared between treatment groups using Fisher's exact test and yield p = 0.03. DKA was defined as BHB >3mmol/L and serum bicarbonate <18mEq/L).

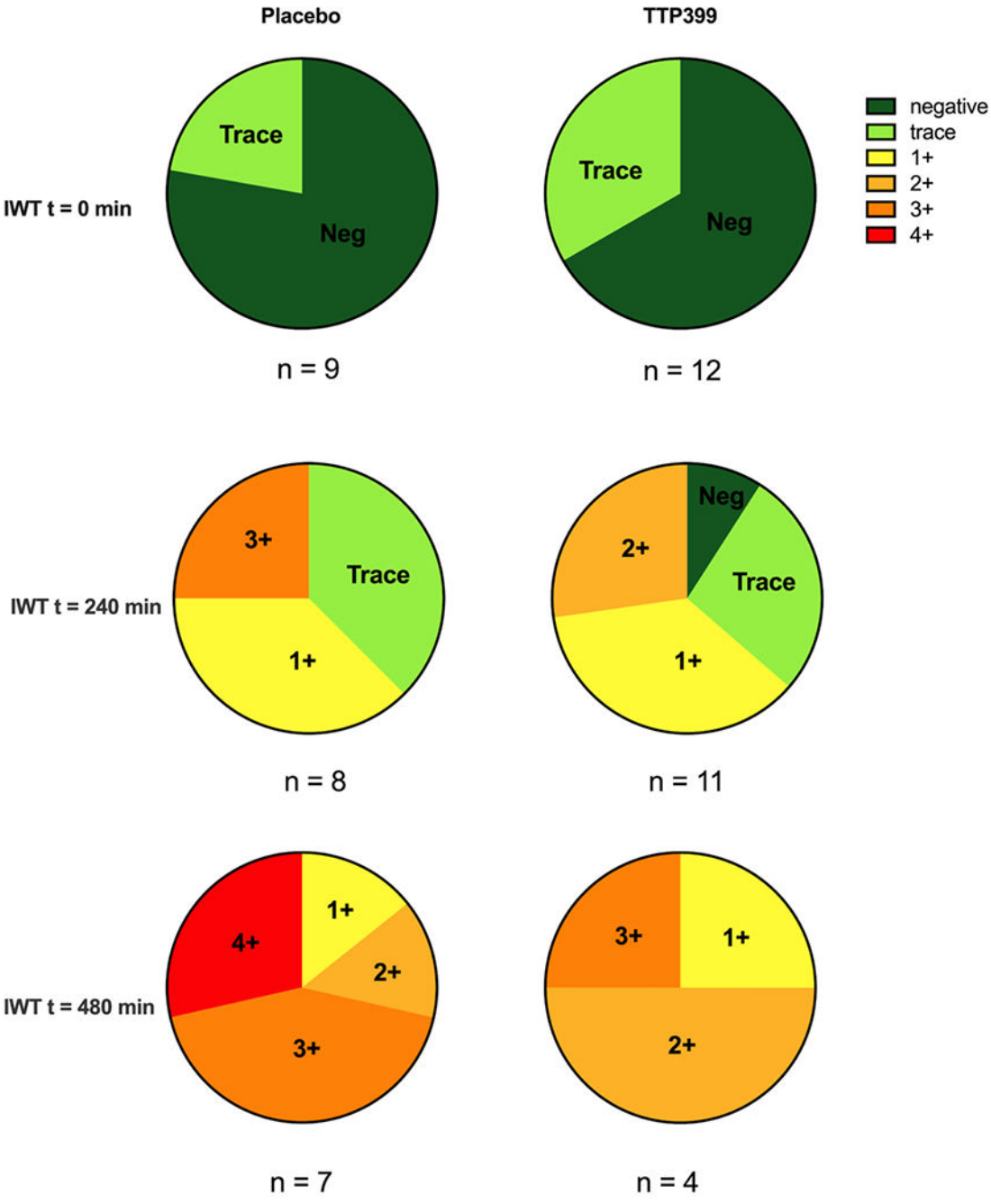

Figure 2. Semiquantitative measure of urine acetoacetate.

Semiquantitative measures of acetoacetate in urine prior to dosing study product, at 240 ± 60 min, and at 480 ± 60 min of the insulin withdrawal test. Number of urine samples at each time point are listed under each pie chart.

Table 1.

Baseline characteristics

	Placebo (n=10)	TTP399 (n=12)
Age, years	35 (11)	31 (8)
Gender – female	70%	58%
Race		
White	100 %	92 %
Black	0 %	8 %
Ethnicity – Not Hispanic or Latino	90 %	92 %
Height, cm	171 (11)	175 (9)
Weight, kg	75 (14)	79 (15)
BMI, kg/m^2	26 (3)	26 (4)
Diabetes Duration, years	25 (11)	18 (6)
Age at Diagnosis, years	10 (8)	14 (10)
HbA1c, %	6.8 (0.8)	7.1 (0.9)
Used closed loop delivery system	80 %	75 %
CGM user	100 %	92 %

Data from full analysis set as defined by randomized participants who receive at least one dose of study medication and had at least one non-missing post-treatment Insulin Withdrawal Test result.

Values are mean (standard deviation) unless otherwise indicated.

Table 2.

Impact of TTP399 on Key Laboratory Parameters and AEs During 7-10 day Treatment

	Placebo	TTP399	P
Key Laboratory Assessments, n	10	12	-
Fasting Plasma Glucose, mg/dL			
Baseline	147.2 (38.3)	150.0 (35.6)	
Change from baseline	−4.4 (16.3)	−27.6 (36.2)	0.03
Fasting Beta-Hydroxybutyrate, mmol/L [†]			
Baseline	0.14 (0.13)	0.25 (0.19)	
Change from baseline	0.10 (0.16)	−0.06 (0.17)	NS
Fasting Free Fatty Acid, mEq/L			
Baseline	0.33 (0.22)	0.52 (0.31)	
Change from baseline	0.22 (0.26)	−0.05 (0.33)	NS
Treatment Emergent AEs Unrelated to IWT, n	11	12	
Total number of subjects with at least one event	5	1	
Total number of events	9	3	
Hypoglycemia [‡]	2 (4)	0	

Laboratory data from full analysis set; AE data from the safety population. Change from baseline was calculated using labs drawn at the randomization visit and immediately prior to IWT.

[†]Beta-hydroxybutyrate values represent serum beta-hydroxybutyrate or blood ketone finger-stick measurement if serum values were unavailable.

[‡]Hypoglycemia was defined as any recorded glucose meter value of glucose < 54 mg/dL regardless of symptoms. Data is number of subjects with at least one event (number of events)

IWT: Insulin withdrawal Test, AE: Adverse event

Values are mean (standard deviation) unless otherwise indicated

Table 3.

Treatment Emergent AEs Related to IWT

	Placebo n=10	TTP399 n=12
Treatment Emergent Adverse Events Related to IWT		
Subjects with at least 1 AE, n (%)	6 (60%)	11 (92%)
Events reported, n	11	22
Events by Preferred Term †		
Nausea	4 (4)	9 (10)
Headache	3 (3)	4 (4)
Fatigue	0	2 (2)
Vomiting	0	1
Diarrhea	1	0
Pain	1	0
Vessel puncture site pain	1	0
Hypoglycemia	1	1
Dyspnea	0	1

AEs related to the IWT are those events associated with the preparation or conduct of the IWT per investigator.

† number of subjects with at least one event (total number of events).

IWT: Insulin Withdrawal Test, AE: Adverse event