Glucokinase (GK) plays an essential role in blood glucose homeostasis. In the liver, GK determines the rates of glucose uptake and glycogen synthesis. GK is also thought to be essential for the regulation of various glucose-responsive genes.

TTP399 is a liver-selective GK activator that has shown normalization of glycemic control in animal models and in subjects with type 2 diabetes (T2DM) on stable doses of metformin. These results occurred without inducing hypoglycemia or dyslipidemia. Data from preclinical studies also showed that no abnormal accumulations of glycogen or triglycerides occurred in the liver after treatment with TTP399, even at doses up to 100-fold the therapeutic dose in humans for 9-months.

The Sentinel Phase was well tolerated in eleven clinical trials conducted to date, with no demonstrated safety concerns. TTP399 has been well tolerated in eleven clinical trials conducted to date, with no demonstrated safety concerns.

In the Phase 2 studies evaluating TTP399 in T2DM subjects, TTP399 has shown significant reductions in postprandial glucose, increasing % time in range and decreasing % time in hypo or hyperglycemia. In the AGATA study, a 6-month Phase 2b clinical trial in subjects with T2DM, TTP399 significantly reduced HbA1c (placebo-subtracted change = -0.9%, p=0.01) and the effect was sustained for the duration of the study, with no demonstrated safety concerns. Data from insulin-deficient animals shows that a selective increase in hepatic GK is the only requirement for the normalization of the metabolic profile, suggesting that selective activation of liver GK could provide a mechanism to reduce blood glucose in subjects with type 1 diabetes (T1DM).

The aim of the study was to examine the safety, tolerability, pharmacokinetics and pharmacodynamics of TTP399 in subjects with T1DM on insulin-pump (CSII) and continuous glucose monitoring (CGM). The adaptive design allows for the exploration of the appropriate dose and appropriate endpoints to evaluate TTP399 in T1DM.

The Sentinel phase was an open-label, weekly dose escalation study with up to 3 dose escalations. Five adult subjects with T1DM who were using CGM and CSII were dosed with a once daily dose of 400, 800 or 1200mg of TTP399 for seven days at each dose level.

The SENTINEL study was designed as an adaptive proof-of-concept study evaluating TTP399 as a potential adjunctive treatment for T1DM in three parts (sentinel, learning phase, and confirming phase).

Introduction

TTP399 Study Design

This Adaptive Proof-of-Concept study evaluating TTP399 as a potential adjunctive treatment for T1DM will occur in three parts (sentinel, learning phase (Part 1) and confirming phase (Part 2)) (NCT03395371).

The Sentinel phase was an open-label, weekly dose escalation study with up to 3 dose escalations. Five adult subjects with T1DM who were using CGM and CSII were dosed with a once daily dose of 400, 800 or 1200mg of TTP399 for seven days at each dose level.

TTP399 has been well tolerated in eleven clinical trials conducted to date, with no demonstrated safety concerns. In the Phase 2 studies evaluating TTP399 in T2DM subjects, TTP399 has shown significant reductions in postprandial glucose, increasing % time in range and decreasing % time in hypo or hyperglycemia. In the AGATA study, a 6-month Phase 2b clinical trial in subjects with T2DM, TTP399 significantly reduced HbA1c (placebo-subtracted change = -0.9%, p=0.01) and the effect was sustained for the duration of the study, with no demonstrated safety concerns.

Data from insulin-deficient animals shows that a selective increase in hepatic GK is the only requirement for the normalization of the metabolic profile, suggesting that selective activation of liver GK could provide a mechanism to reduce blood glucose in subjects with type 1 diabetes (T1DM).

Simplici-T1: First Clinical Trial to Test Activation of Glucokinase as an Adjunctive Treatment for Type 1 Diabetes

John B. Buse1, Carmen Valcarce2, Jennifer L. Freeman2, Imogene Dunn2, Chris Dvergsten3, M. Sue Kirkman1, Alexander Kass1, Jamie Diner1, Katherine A. Bergamo3, 1UNC, Chapel Hill, NC, 2Ttv Therapeutics, High Point, NC, USA

Simplici-T1 Study Design

This Adaptive Proof of Concept study evaluating TTP399 as a potential adjunctive treatment for T1DM will occur in three parts (sentinel, learning phase (Part 1) and confirming phase (Part 2)) (NCT03395371).

The adaptive design allows for the exploration of the appropriate dose and appropriate endpoints to evaluate TTP399 in T1DM.

TTP399 has been well tolerated in eleven clinical trials conducted to date, with no demonstrated safety concerns.

In the Phase 2 studies evaluating TTP399 in T2DM subjects, TTP399 has shown significant reductions in postprandial glucose, increasing % time in range and decreasing % time in hypo or hyperglycemia. In the AGATA study, a 6-month Phase 2b clinical trial in subjects with T2DM, TTP399 significantly reduced HbA1c (placebo-subtracted change = -0.9%, p=0.01) and the effect was sustained for the duration of the study, with no demonstrated safety concerns.

Data from insulin-deficient animals shows that a selective increase in hepatic GK is the only requirement for the normalization of the metabolic profile, suggesting that selective activation of liver GK could provide a mechanism to reduce blood glucose in subjects with type 1 diabetes (T1DM).

The aim of the study was to examine the safety, tolerability, pharmacokinetics and pharmacodynamics of TTP399 in subjects with T1DM on insulin-pump (CSII) and continuous glucose monitoring (CGM). The adaptive design allows for the exploration of the appropriate dose and appropriate endpoints to evaluate TTP399 in T1DM.

The Sentinel phase was an open-label, weekly dose escalation study with up to 3 dose escalations. Five adult subjects with T1DM who were using CGM and CSII were dosed with a once daily dose of 400, 800 or 1200mg of TTP399 for seven days at each dose level.

TTP399 has been well tolerated in eleven clinical trials conducted to date, with no demonstrated safety concerns. In the Phase 2 studies evaluating TTP399 in T2DM subjects, TTP399 has shown significant reductions in postprandial glucose, increasing % time in range and decreasing % time in hypo or hyperglycemia. In the AGATA study, a 6-month Phase 2b clinical trial in subjects with T2DM, TTP399 significantly reduced HbA1c (placebo-subtracted change = -0.9%, p=0.01) and the effect was sustained for the duration of the study, with no demonstrated safety concerns. Data from insulin-deficient animals shows that a selective increase in hepatic GK is the only requirement for the normalization of the metabolic profile, suggesting that selective activation of liver GK could provide a mechanism to reduce blood glucose in subjects with type 1 diabetes (T1DM).