Selective Activation of Glucokinase (GK) in the Liver: Improves Glycemic Control and Reduces Insulin Need as Well as Risk of Ketoacidosis in Type 1 Diabetic Minipigs

vTv Therapeutics

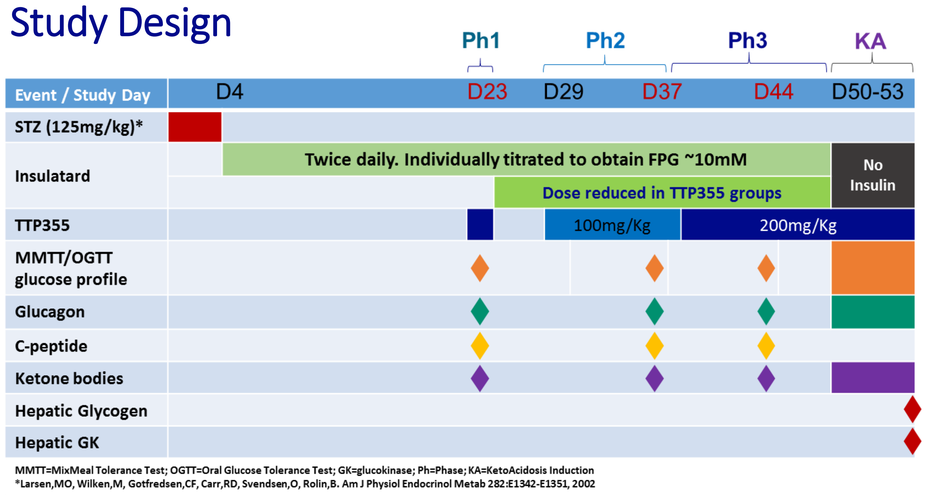
Introduction

While multiple oral drugs are approved for the management of hyperglycemia in type 2 diabetes, no oral therapies are approved that improve hyperglycemia in type 1 diabetes. 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.

TTP355 is a liver-selective glucokinase activator (GKA). Treatment with TTP355 has shown normalization of glycemic control in animal models and improvement of postprandial glucose in early stage clinical trials. Importantly, this glucose normalization occurred without significant hypoglycemia or dyslipidemia.

The objective of the present placebo-controlled study in minipigs was to investigate the potential of liver-selective GKAs as an adjunctive therapy for the treatment of type 1 diabetes. Minipigs with reduced beta-cell mass after administration of streptozotocin (STZ) were chosen as a non-rodent model of insulin-dependent diabetes.

Study Design

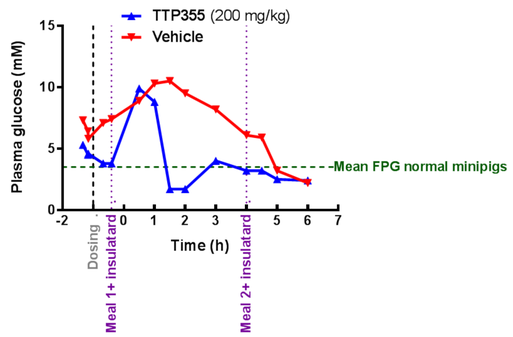


MMTT=MixMeal Tolerance Test; OGTT=Oral Glucose Tolerance Test; GK=glucokinase; Ph=Phase; KA=KetoAcidosis Induction
*Larsen,MO, Wilken,M, Gotfredsen,CF, Carr,RD, Svendsen,O, Rolin,B. Am J Physiol Endocrinol Metab 282:E1342-E1351, 2002

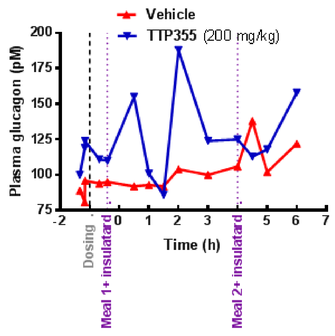
Results

Ph1: Acute Administration of TTP355 200mg with Full Insulin Dose - Asymptomatic Hypoglycemia Suggested Need for Reduction in Exogenous Insulin

Significant reduction in plasma glucose.

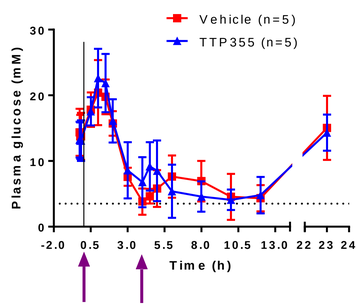


Normal counter-regulation

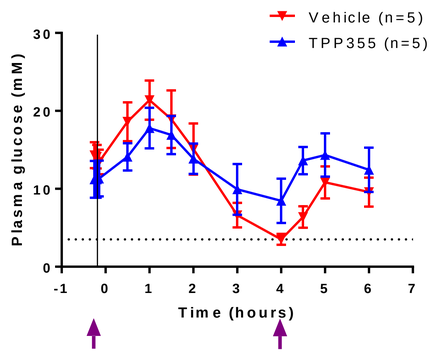


Ph2-3: Sub-Chronic Administration of TTP355 to Type 1 Minipigs - Improves Glycemic Control with Half of the Dose of Exogenous Insulin . No Hypoglycemia Was Observed

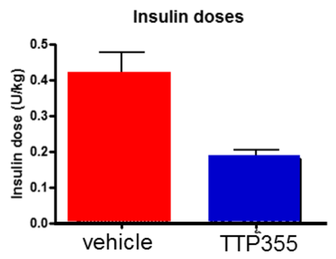
100mg for 7d. No hypoglycemia



200mg for 7d. Improved glycemic control

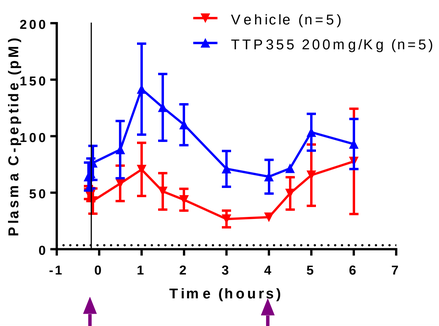


Half of exogenous insulin dose

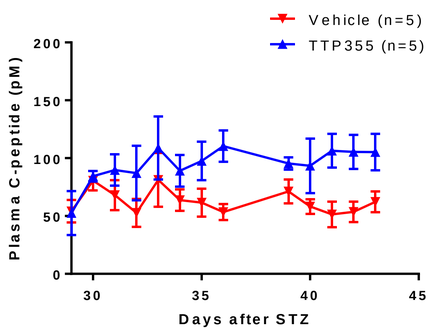


Better C-peptide Response with TTP355 Treatment- Indicative of Preservation and/or Improvement of Residual Beta-cell Function

Better C-peptide response to the meal

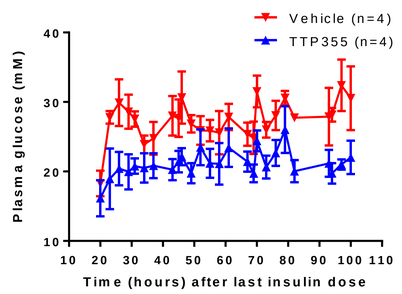


Preservation of β-cell function

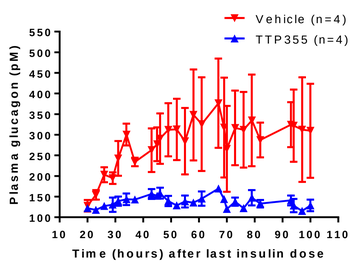


Ketoacidosis (KA) Induction: TTP355 Delayed/Prevented Increase in Glucose, Ketone Bodies and Glucagon after Discontinuation of Insulin

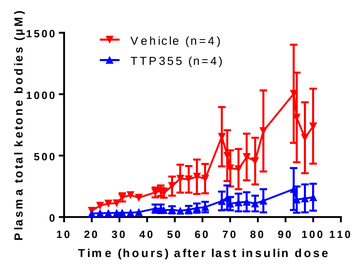
Lower plasma glucose



No increase in glucagon

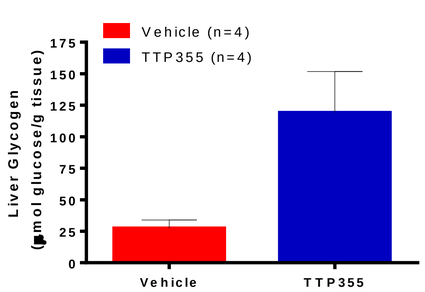


Delayed increase in ketone bodies

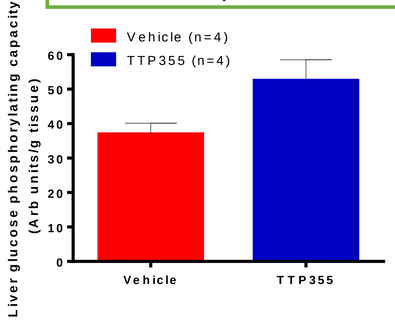


Adjunctive Treatment with TTP355 Normalizes GK Activity and Glycogen Content in the Liver, Confirming the Potential of TTP355 to Address Two Major Deficiencies in Diabetes

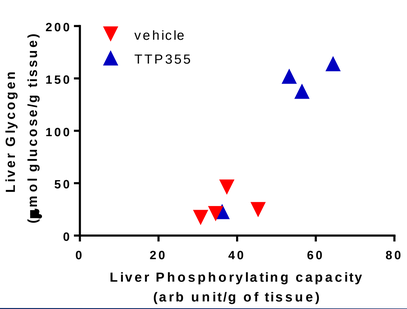
TTP355 increased/normalized glycogen content in the liver



TTP355 increased/normalized GK activity in the liver



Higher glycogen content correlates with higher GK activity



Conclusion

The results of this study suggest that selective activation of GK in the liver may offer an adjunctive therapy for type 1 diabetes with the potential to:

- Improve glycemic control;
- Reduce insulin dose;
- Reduce risk of hypoglycemia; and
- Reduce risk of ketoacidosis.

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