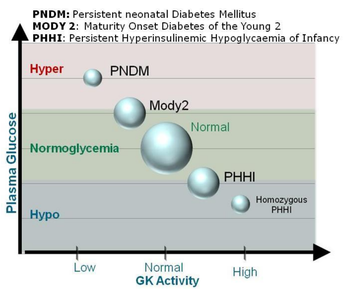
The Importance of Tissue Selectivity and Preservation of the Physiological Regulation when Targeting Key Metabolic Regulators as Glucokinase

vTv Therapeutics

Introduction

Previously identified GKAs evaluated in the clinic for the treatment of Type 2 diabetes demonstrate improved glucose control; however, these GKAs also show increased incidence of hypoglycemia and hyperlipidemia and an apparent lack of durability. These liabilities have been correlated to hyper-stimulation of the ß-cells (as could be predicted by the phenotype of patients with GK-activating mutations) and/or the accumulation of lipids in the liver (consistent with the disruption of GK and GKRP interaction by these activators). Thus, liver selective GKAs that do not activate GK in ß-cells or affect the GK-GKRP interaction are expected to demonstrate a superior profile.

Rational



Human GK Loss and gain of Function Mutations Correlate with HYPER and HYPOglycemia respectively

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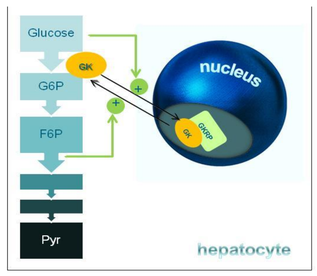


Human GKRP Loss of Function Mutations Correlate with Increased Plasma Lipids

Hypothesis

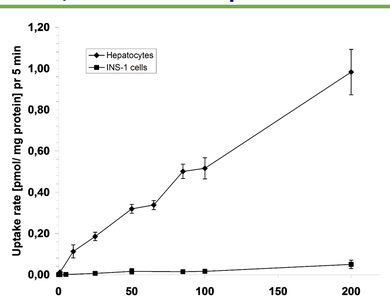
Liver selective GKAs that do not activate GK in ß-cells or affect the GK-GKRP interaction are expected to demonstrate a superior profile.

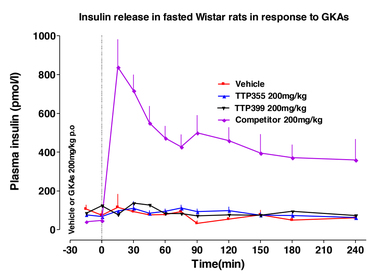
Results

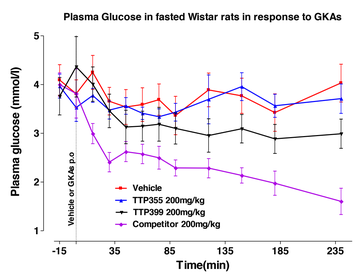
TTP399 is a liver-selective GKA that does not disrupt the interaction between GK and GKRP and has shown normalization of glycemic control in animal models and in Type 2 diabetic subjects. These results came about without inducing hypoglycemia or dyslipidemia and without increasing glycogen or TG in the liver.

1. TTP399 Liver Selectivity Protects Against the Severe and Prolonged Hypoglycemia seen with Dual Acting GKAs

Differential Uptake into Rat Hepatocytes Compared to a Rat β-cell Line → Does not Affect Insulin Secretion in contrast with dual acting GKAs → No hypoglycemia ,compare to dual acting GKAs → No hypoglycemia in the clinic after 6wks of treatment. *(T2 Diabetics on metformin)*





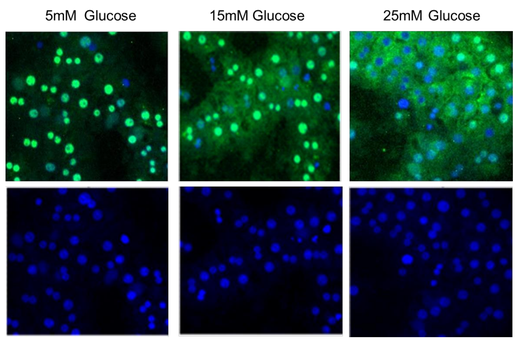


	Placebo	TTP399	Rescue medication /treatment change
Severe hypoglycemia	0	0	
Documented severe hypoglycemia	0	0	
Asymptomatic hypoglycemia (measure BG≤ 70 mg/dL / ≤ 3.9 mmol/L)	4/61	5/90	No
Probable symptomatic hypoglycemia	0	0	
Relative hypoglycemia (symptomatic)	1/61	0/90	No

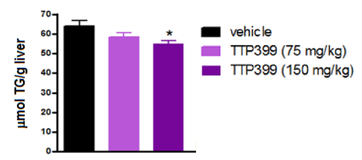
Data from the continuous glucose monitoring confirmed that the frequency of hypoglycemic events was not different between placebo and the treated groups

2. TTP399 Does not Interfere with the Interaction between GK and GKRP and does not Increase Plasma or Hepatic Lipids

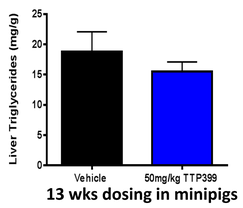
Normal regulation of GK by GKRP → NO increase in Hepatic or Plasma TGs → NO Liver Toxicity in animals* → No increase in plasma lipids or LFTs in the clinic after 6wks of treatment *(T2 Diabetics on metformin)*



Fresh isolated rat hepatocytes [TTP399] 1µM



4 wks dosing in ob/ob mice

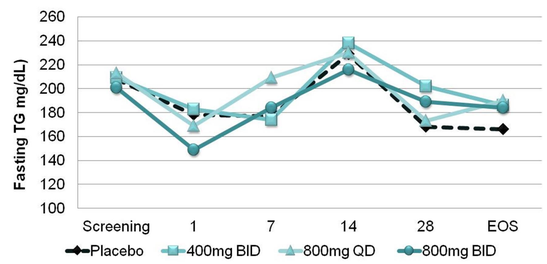


13 wks dosing in minipigs

	Change from Day 1 (CFB), following 39 weeks of dosing							
	ALT (U/L)		AST (U/L)		GGT (U/L)		Total Billirubin (mg/dL)	
TTP399 dose (mg/kg)	Female	Male	Female	Male	Female	Male	Female	Male
0	4.5	13.5	12.8	26.2	-7.6	-6.6	-0.02	0.03
25	1.5	-2.2	36	20.8	-5.7	0.2	0	-0.03
100	1.4	-0.8	-6.5	24.2	-29.8	-11	0	0
200	-1.4	5	7	11.3	-10.9	-14.7	-0.02	0

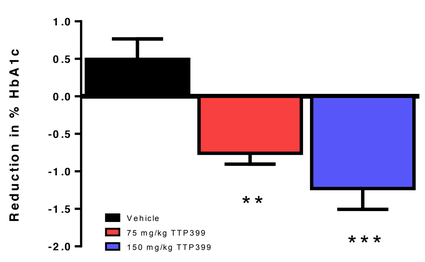
39 wks of dosing in minipigs

*at TTP399 plasma concentrations 100-fold therapeutic exposure in humans

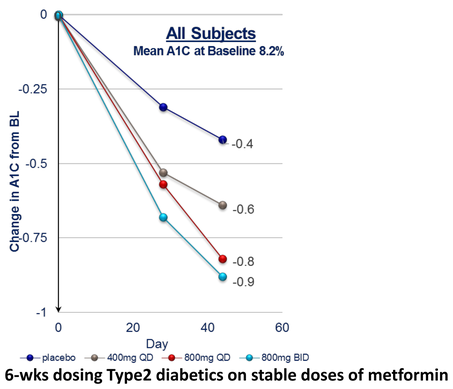


	400-mg BID (29)	800-mg QD (31)	800-mg BID (30)	Placebo (30)
Elevated LFTs	0	0	0	0

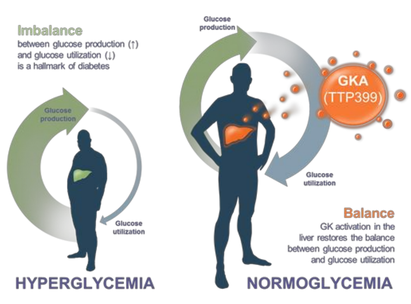
3. TTP399 Significantly Improved Glycemic Control in ob/ob mice and Humans after only 6 weeks of treatment



4 wks dosing in ob/ob mice



6-wks dosing Type2 diabetics on stable doses of metformin



Conclusion

These results indicate that TTP399 has a superior profile compared to other GKAs and demonstrate the importance of tissue selectivity and preservation of the physiological regulation when targeting key metabolic regulators such as GK

Carmen Valcarce (on behalf of the GKA discovery and development teams @ vTv Therapeutics LLC, High Point, NC and Novo Nordisk, Målov, DK)

agata TYPE 2 DIABETES STUDY