Is Less More? Learning to dose the investigational oral, non-peptide GLP-1R Agonist, TTP273 in Type 2 Diabetics

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Introduction

TTP273 is an investigational oral (non-peptide) GLP-1 receptor agonist that has been shown to significantly lower blood glucose with trends toward reduction in weight in preclinical and phase 1 studies as well as a phase 2 proof of concept study in Type 2 Diabetics (T2DM) (ADA 2017 poster # 1220-P).

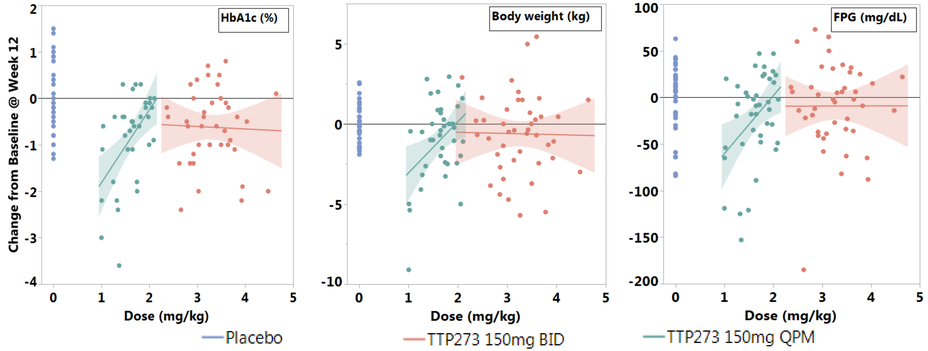
Subsequent concentration/effect analysis in the phase 2 study revealed an unexpected result: **lower** doses showed **more** pronounced effects for key efficacy endpoints. Similar findings observed in the phase 2 study with our predecessor GLP-1 agonist (TTP054) prompted additional analysis to examine how much and when to dose an orally bioavailable GLP-1 receptor agonist.

TTP273-201 Study Topline Results

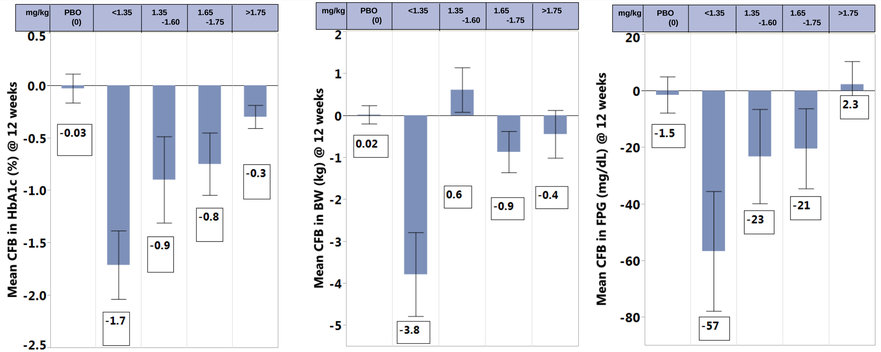
Visit poster **1220-P** for additional details

TTP273-201 is a 12-week, multi-center phase 2, double-blind, placebo-controlled, randomized study of 174 patients with T2DM on stable doses of metformin who were randomized to either placebo or TTP273 (150 mg once (QPM) or twice (BID) daily). Baseline characteristics were well balanced amongst groups with an overall mean age of 57 years, mean HbA1c of 8.6% and mean BMI of 32 kg/m^2. TTP273 was well tolerated with no severe hypoglycemia AEs. The most common TEAE was diarrhea, mostly mild in intensity, with only one subject discontinued due to mild diarrhea (150 mg BID). Less nausea was observed in active groups than placebo and the only incidence of vomiting occurred with placebo dosing. Once daily dosing of TTP273 (150 mg QPM) demonstrated placebo-subtracted decrease from baseline of 0.9% in HbA1c and 0.9 kg in weight.

Beyond Topline Results: More Efficacy With Lower mg/kg Dose



Focus on QPM versus PBO: Greatest efficacy with < 1.35 mg/kg*



**The observation based on mg/kg dose is confirmed when correlating TTP273 plasma concentration with efficacy.*
Note: GI adverse events did not show an increased incidence rate with efficacy. 1 AE of diarrhea and 1 AE of nausea was reported for patients who received <1.35 mg/kg, further confirming topline results that TTP273 improves glycemic control without nausea and vomiting.

Similar dose-response pattern observed on TTP054-201

TTP054-201 is a 12-week, multi-center, phase 2, double-blind, placebo-controlled, randomized study of 187 patients with T2DM on stable doses of metformin who were randomized to either placebo or 200, 400 or 800mg QD of TTP054. Topline results were presented previously. (156-OR, ADA 2014). Concentration/effect analysis of the data show a similar trend where a lower dose shows more effect.

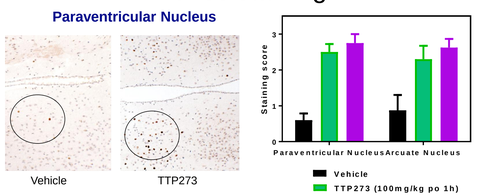
Dose (mg/kg)	Placebo	<3	3-4.9	5-6.9	7-9	>9
HbA1c CFB @ Week 12	-0.07	-0.65	-1.16	-0.9	-0.32	-0.42

Note: The limited clinical data in the public domain for efpeglenatide, a GLP-1 analogue showing reduced β-arrestin recruitment and less GLP1R internalization[1], may indicate that the effect on A1c was greater at lower doses or less frequent dosing[2].

[1]Choi et al. ADA 76th Scientific Sessions, New Orleans, Louisiana, USA; June 10-14, 2016; [2]Davies et al. Austin J Endocrinol Diabetes. 2016; 3(4): 1053.

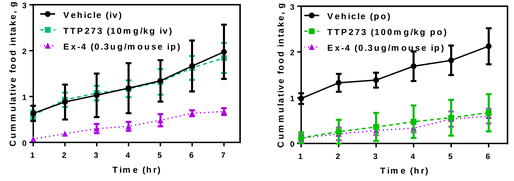
Preclinical Findings Reinforce Importance of Neuro-Enteroendocrine Signaling

c-fos staining



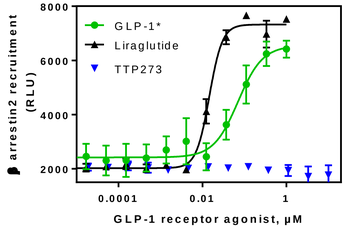
Food intake and c-fos staining 1 hour post dose suggest signaling through vagus nerve, as only negligible amounts of compound are present in the brain.

Food Intake: IV versus Oral



***ONLY** animals dosed **orally** with TTP273 showed reduction in food intake.*

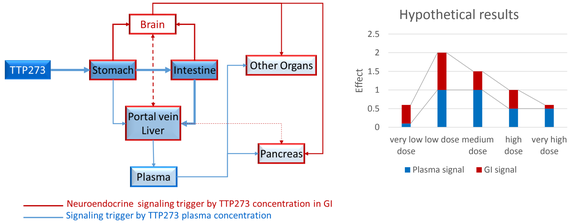
TTP273 does not signal through β-arrestin



Acknowledgment: In vitro β-arrestin recruitment assays were conducted in collaboration with Dr. Patricia McDonald at The Scripps Research Institute

Hypothesis: Oral Administration of High Concentrations of TTP273 May Alter the Signaling Dynamic

- ❑ TTP273 effect is mediated by two different types of signaling (based on preclinical evidence)
- ❑ Concentrations of TTP273 at any given dose will be different at the GI/portal vein and plasma (driven by oral bioavailability)
- ❑ The two signaling mechanisms may have different tolerance/desensitization thresholds (e.g. GLP-1 effects on gastric emptying)
- ❑ The tolerance/desensitization pattern may be different for TTP273 compared to injectable GLP-1 analogues due to the distinct signaling pattern (i.e. TTP273 does not signal through β-arrestin)
- ❑ At any given dose, the total efficacy will be the combination of these two pathways



Conclusions

- ➢ Concentration/effect analysis revealed an unexpected result: **lower** doses showed **more** pronounced effects for key efficacy endpoints
- ➢ The characteristics of TTP273 provide a potential scientific rationale for the observations described herein
  - TTP273 is functionally biased and does not activate β-arrestin
  - Neuro-enteroendocrine signaling may be a major contributor of TTP273 effect
- ➢ Additional clinical investigation is needed to confirm that for TTP273, less is more.