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

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 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.

TTP273 does not signal through β-arrestin.

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

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

TTP273 does not signal through β-arrestin.

Advisory clinical investigation is needed to confirm that for TTP273, less is more.

Conclusions

• Concentration/effect analysis revealed an unexpected result: lower doses showed more pronounced effects for key efficacy endpoints.

• TTP273 effect is mediated by two different types of GLP-1R agonist analogues due to lower GLP-1 analogues, but 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.

• The survival advantage observed on TTP054 suggests that the effect on A1c was greater at lower doses or less frequent dosing.

Similar dose-response pattern observed on TTP054.

TTP273 is a 12-week, multicenter, double-blind, placebo-controlled, randomized trial of 174 patients with T2DM (ADA 2017 poster # 1220-P). Topline results were presented previously (158-CRF-2016). Concentration/effect analysis of the data show a similar trend where a lower dose shows more effect.

The observation based on mg/kg dose is confirmed when correlating TTP273 plasma concentration with efficacy.

Reduced HbA1c was observed across all dose levels in TTP054, may indicate that the effect on A1c was greater at lower doses or less frequent dosing.

For additional details.

Importance of Neuro-enteroendocrine Signaling

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

Additional clinical investigation is needed to confirm that for TTP273, less is more.