Beyond Topline Results for the Oral (Non-Peptide) GLP-1R Agonist TTP273 in Type 2 Diabetes: How Much and When?

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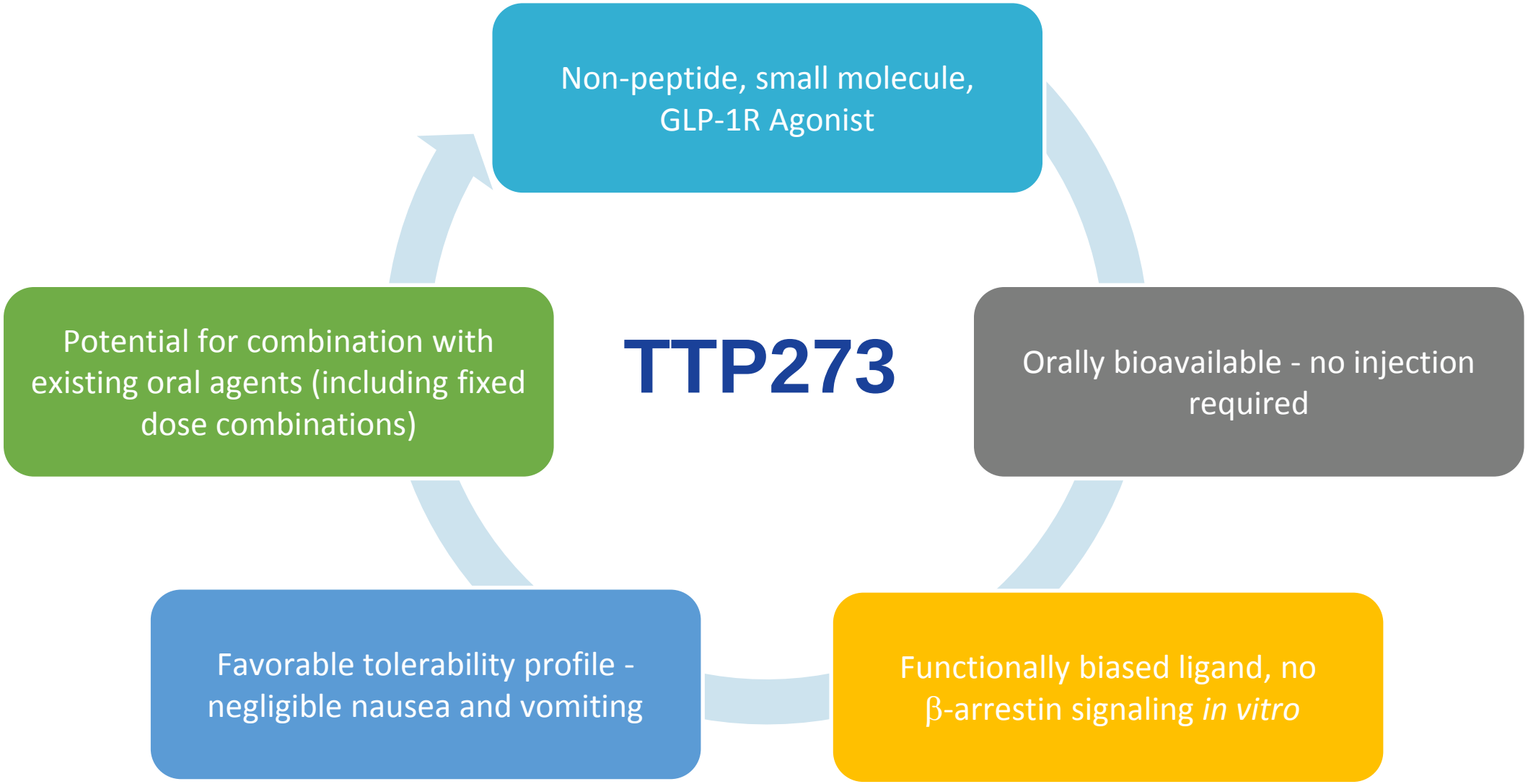
For a more detailed discussion of our risks, see the Risk Factors section in our prospectus filed with the SEC and our other filings with the SEC, including our most recent Quarterly Report on Form 10-Q. Undue reliance should not be placed on forward looking statements, which speak only as of the date hereof. All forward-looking statements contained herein are qualified in their entirety by the foregoing cautionary statements.

TTP273: Oral, Small Molecule GLP-1R Agonist



TTP273-201: LOGRA (aLlosteric Oral Glp1 Receptor Agonist) Study

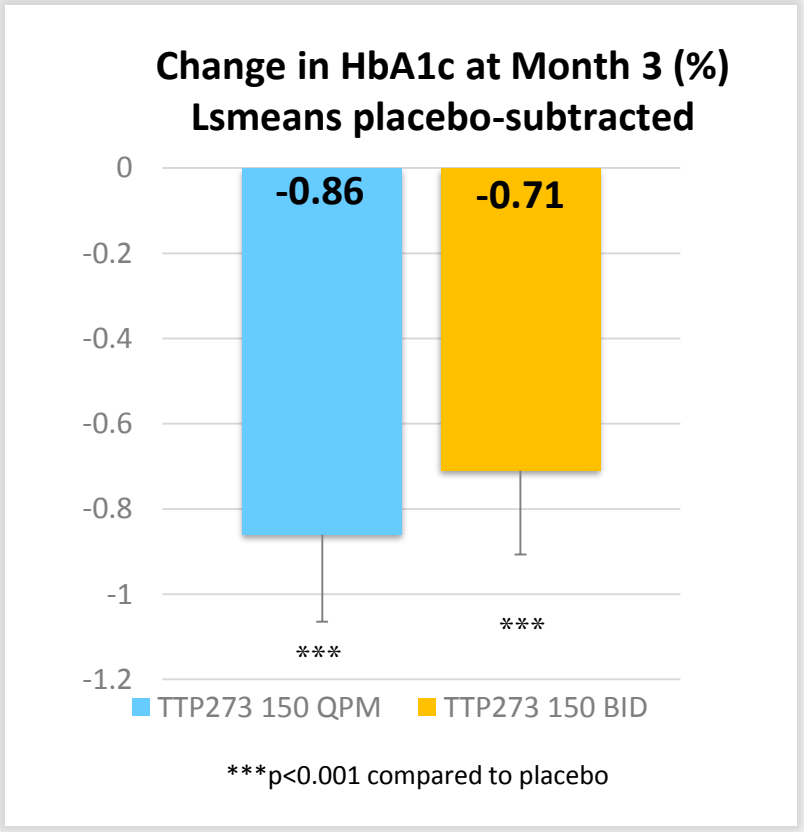
- 12 week randomized, double-blind, placebo-controlled, parallel group trial in type 2 diabetics on stable doses of metformin
- Arms:
  - TTP273 150mg dosed once daily in the evening (QPM)
  - TTP273 150mg dosed twice daily (BID)
  - PBO
- HbA1c (7.5-10%)
- Overweight to obese T2DM patients (BMI 25-45 kg/m^2)
- Patients are of generally stable health
- 30 US sites enrolled 174 patients
- Baseline characteristics: well balanced amongst groups
  - Mean age of 56 years, mean HbA1c of 8.6%, and mean BMI of 32 kg/m^2

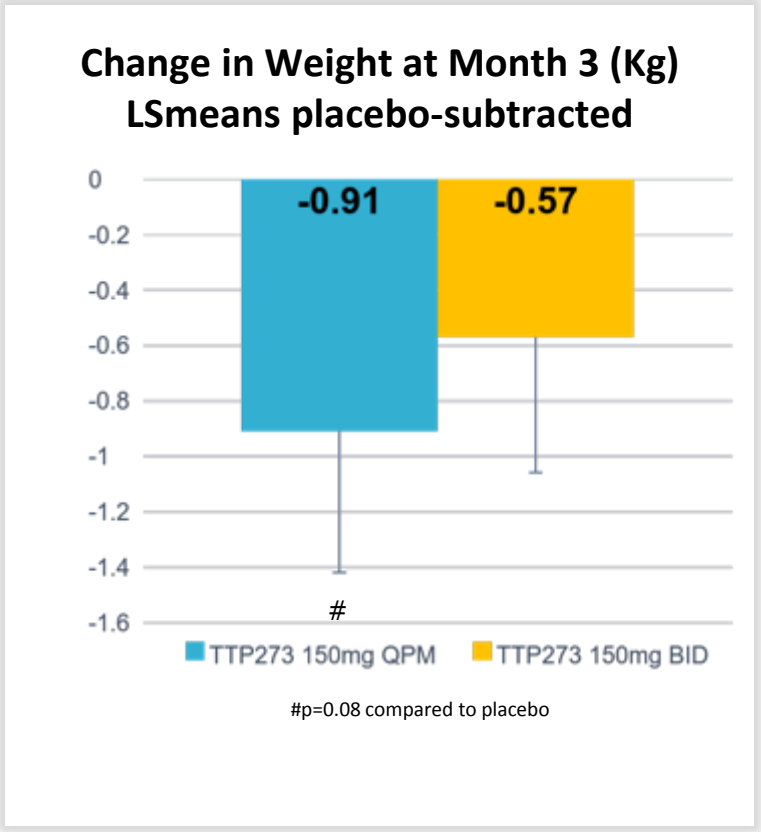
Study Goals:
- ✓ Competitive HbA1c reduction
- ✓ Weight loss
- ✓ Negligible GI side effects

logra

Topline Results Presented at ADA 2017

TTP273: Phase 2 Study Results Met Goals





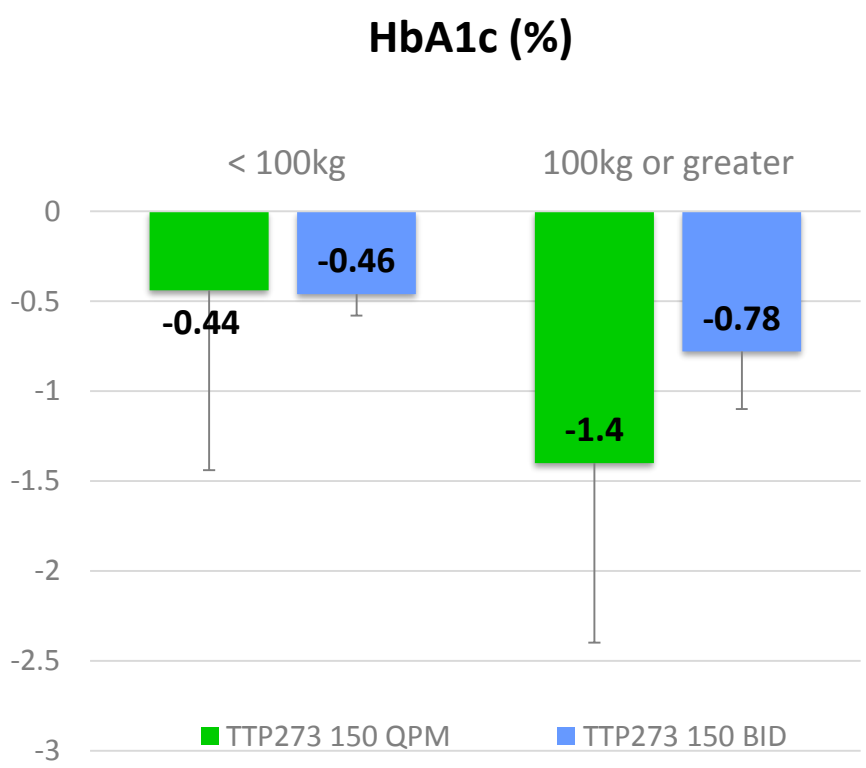
Safety Profile

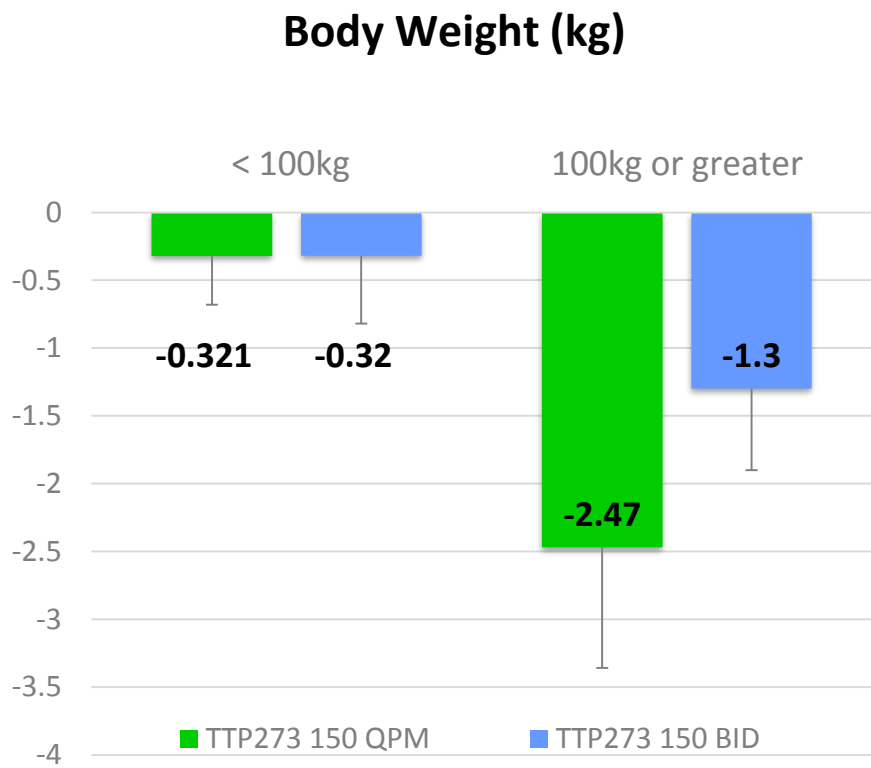
- Drug was well tolerated
- No incidences of vomiting in the TTP273 treated arms
- Nausea less than placebo: 7.3% in the Placebo arm, 3.4% in QPM arm and 5.0% in the BID arm

Topline Results Presented at ADA 2017

Analysis of Response by Subject Weight
(Protocol pre-planned analysis of subjects weighing 100kg or more)

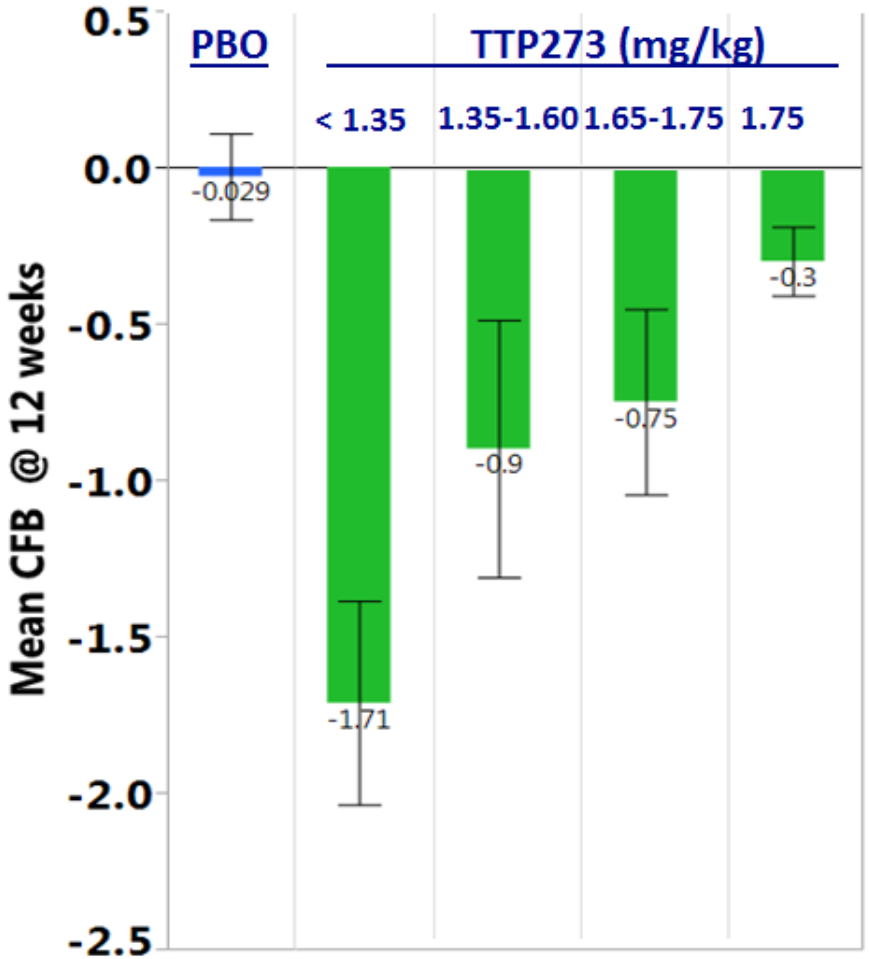
Placebo subtracted Change from Baseline at Week 12



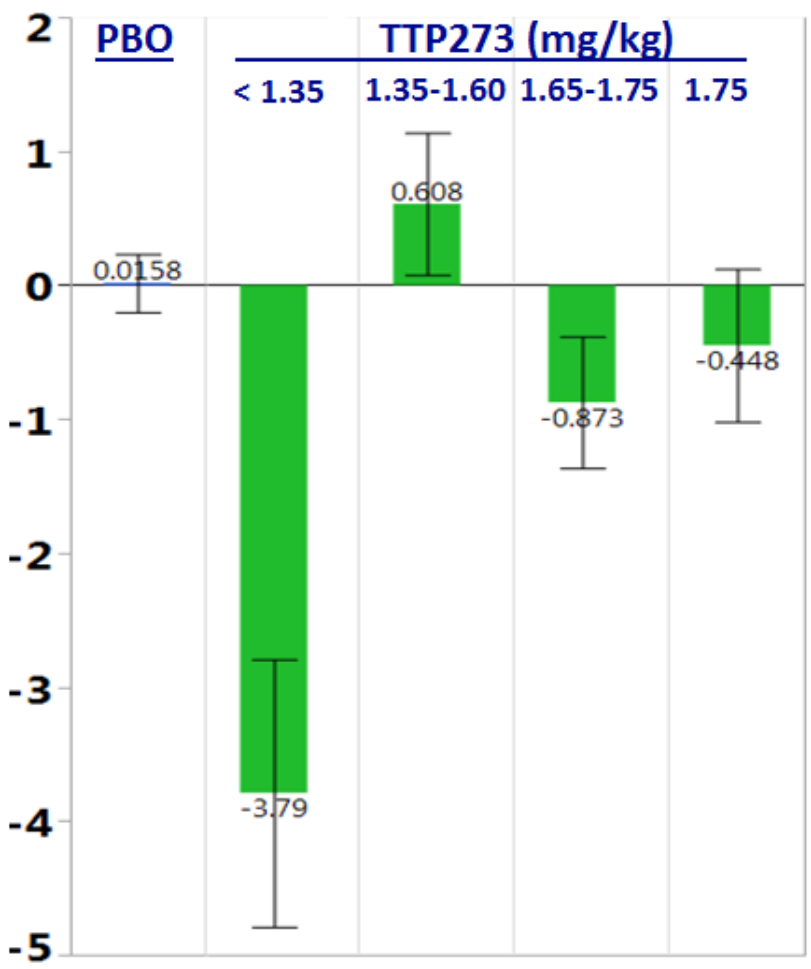


Focus on QPM versus PBO: Greatest efficacy with < 1.35 mg/kg

HbA1c (%)



Body Weight (kg)



Additional Analyses

- Confirmed when correlating TTP273 plasma concentration with efficacy
- GI AEs did not show an increased incidence rate with efficacy
- Trends are not dependent on age, sex, race, duration of diabetes

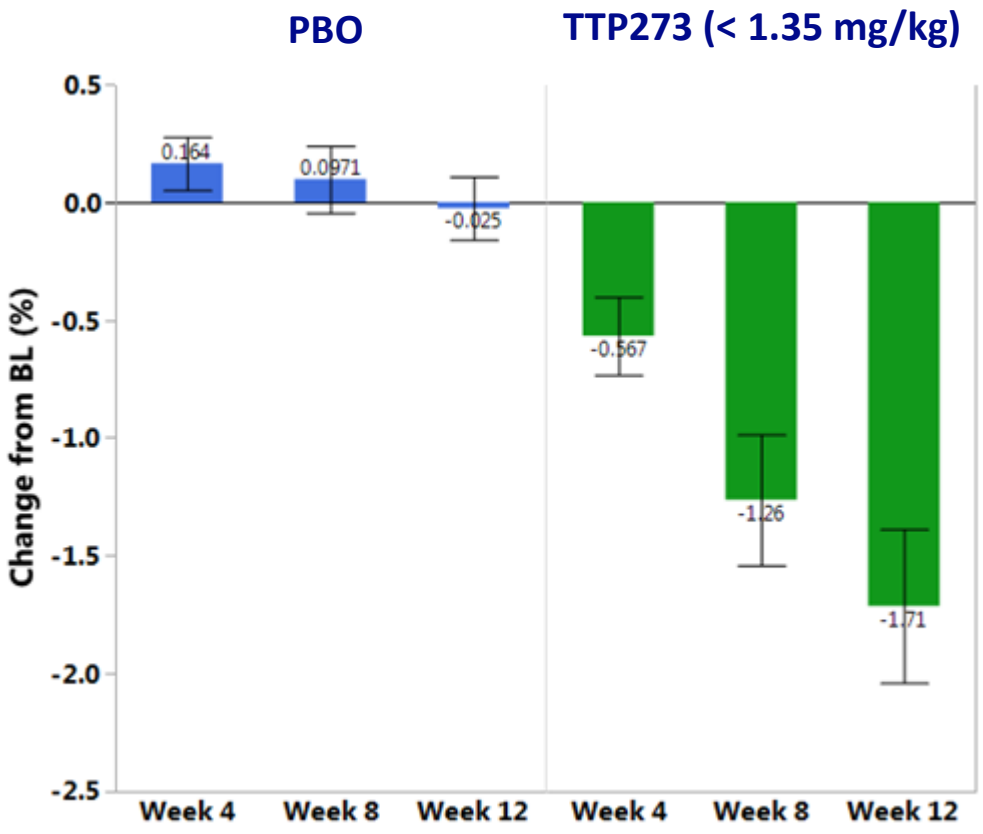
PBO

TTP273

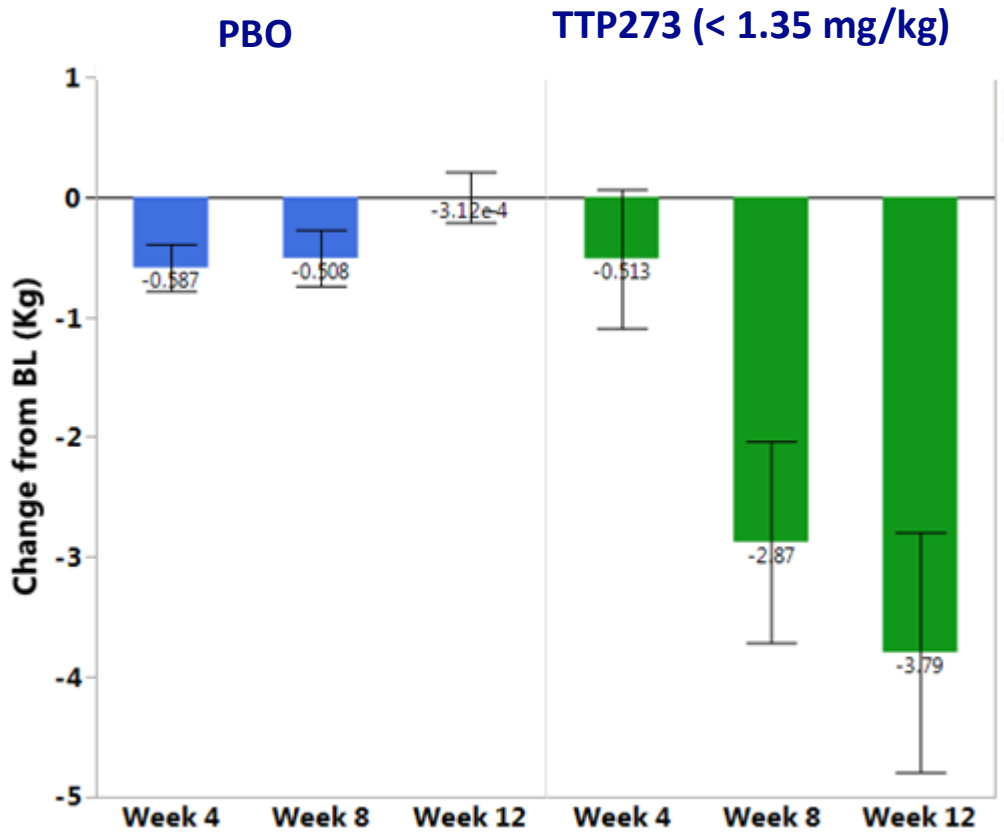
Focus on “less”: A1c and Weight (means*)

Trends over time are consistent with LOWER optimal dosing

HbA1c (%)



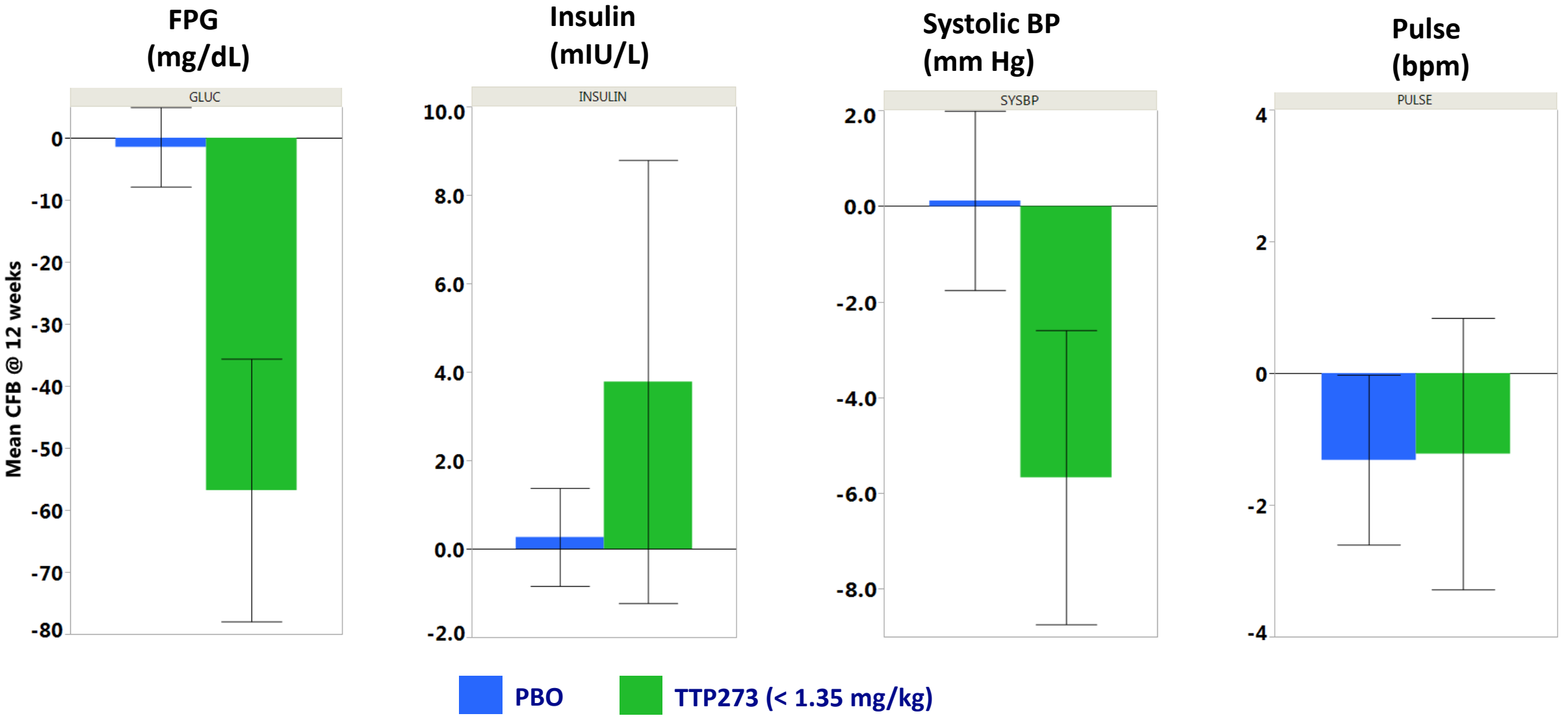
Weight (kg)



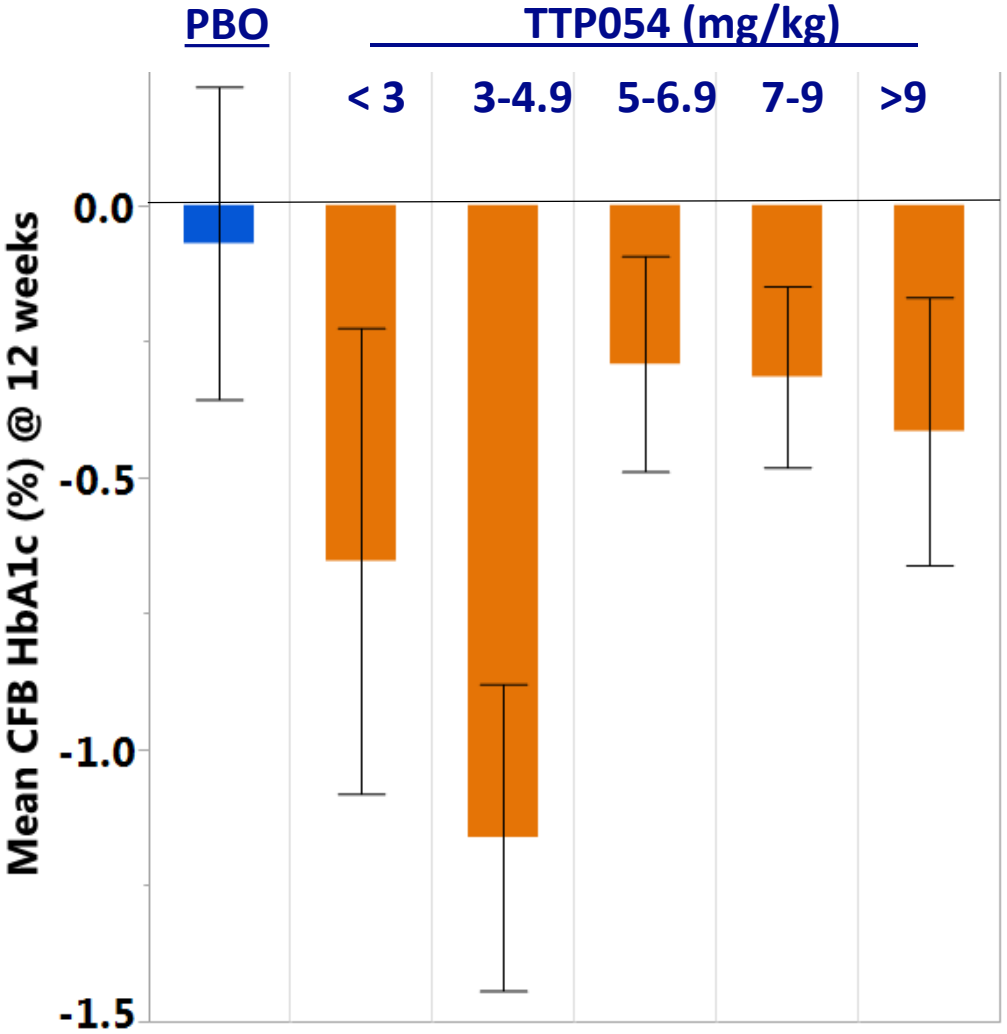
PBO TTP273 (< 1.35 mg/kg)

(*Medians are fully consistent with means)

Focus on “less”: Mean change from baseline at Week 12



Similar dose-response pattern observed in POC study in predecessor GLP-1R agonist (TTP054)



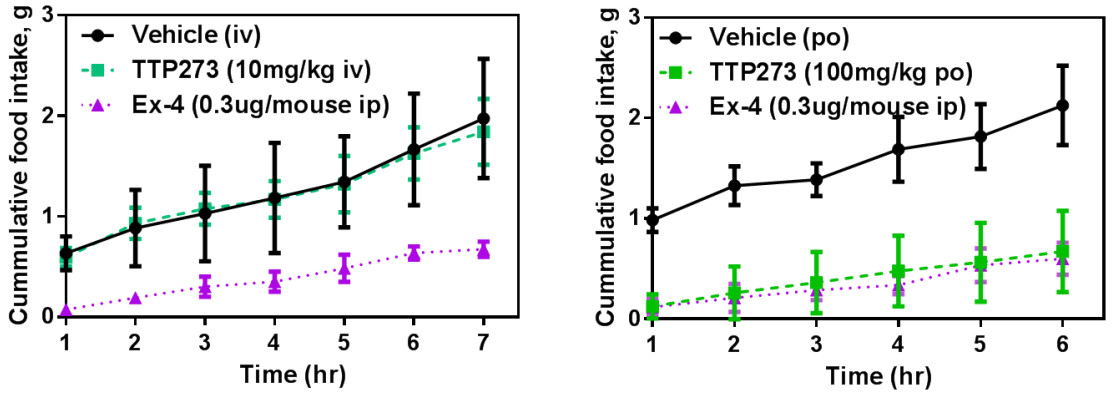
TTP054-201 POC Study

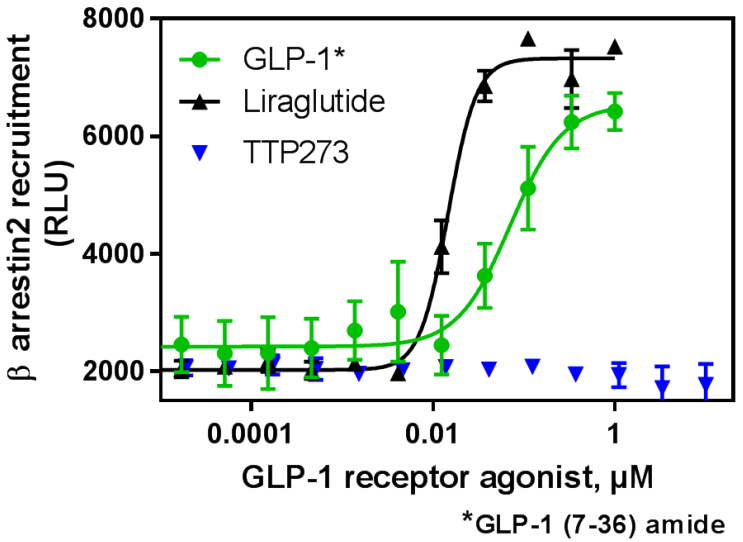
- 3 month, double-blind, placebo-controlled, parallel group trial in 184 type 2 diabetics on stable doses of metformin
- Target population: 8-11%
- Randomized to Arms: Placebo; TTP054 200mg, 400mg and 800mg QD

TTP273 is a small molecule agonist - not a peptide

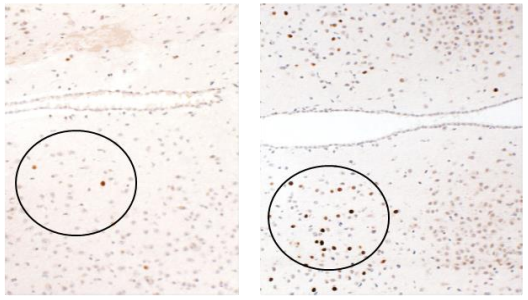
- Preclinical evidence:
  - TTP273 is functionally biased
  - Signaling occurs through the intestine
  - c-fos staining indicates vagal neuroendocrine signaling

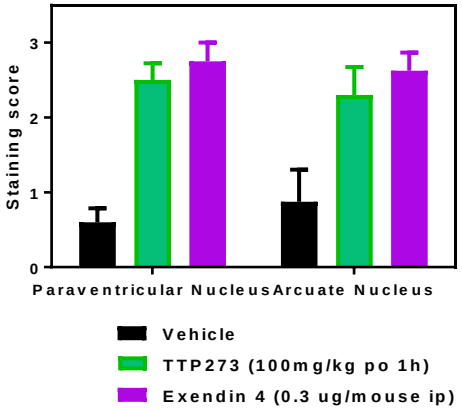
Food Intake: IV versus Oral





Paraventricular Nucleus





Preclinical Results Presented at ADA 2017

TTP273 is a small molecule agonist - not a peptide

- Preclinical evidence:
  - TTP273 is functionally biased
  - Signaling occurs through the intestine
  - c-fos staining indicates vagal neuroendocrine signaling

- Literature suggests
  - Long and short acting peptides have different profiles – precedence with peptides
  - Central effects desensitize more rapidly than peripheral effects
  - Biased ligands to other receptors exhibit different AE profiles

- As a stand alone small molecule GLP-1R agonist, optimal dosing likely differs from peptides

Relationships Between Gastric Emptying, Postprandial Glycemia, and Incretin Hormones

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CHRISTOPHER K. RAYNER, MBBS, PHD, FRACP
KAREN L. JONES, DIP APP SCI (NUCLEAR MEDICINE), PHD
MICHAEL HOROWITZ, MBBS, PHD, FRACP

DIABETES CARE, VOLUME 36, MAY 2013

Efpeglenatide: A Once Monthly GLP-1 RA in the Pipeline

Davies ML[1]*, Thiman ML[2] and Kugler AJ[1]

Austin J Endocrinol Diabetes - Volume 3 Issue 4 - 2016

Jenny Tong[1] and David D'Alessio[1,2]

Give the Receptor a Brake: Slowing Gastric Emptying by GLP-1

Molecular mechanisms underlying physiological and receptor pleiotropic effects mediated by GLP-1R activation

K Pabreja, M A Mohd, C Koole, D Wootten and S G B Furness

British Journal of Pharmacology (2014) **171** 1114–1128

Upper and/or lower gastrointestinal adverse events with glucagon-like peptide-1 receptor agonists: Incidence and consequences

Michael Horowitz MBBS, PhD[1] | Vanita R. Aroda MD[2] | Jenny Han MS[3] | Elise Hardy MD[4] | Chris K. Rayner MBBS, PhD[1]

Diabetes Obes Metab. 2017;19:672–681.
https://doi.org/10.1111/dom.12872

Rapid Tachyphylaxis of the Glucagon-Like Peptide 1–Induced Deceleration of Gastric Emptying in Humans

Michael A. Nauck,[1] Guido Kemmeries,[2] Jens J. Holst,[3] and Juris J. Meier[4]

Diabetes 60:1561–1565, 2011

Comparative Effects of Prolonged and Intermittent Stimulation of the Glucagon-Like Peptide 1 Receptor on Gastric Emptying and Glycemia

Diabetes Volume 63, February 2014

Mahesh M. Umapathysivam,[1] Michael Y. Lee,[1] Karen L. Jones,[2] Christopher E. Annink,[3] Caroline E. Cousins,[3] Laurence G. Trahair,[2] Chris K. Rayner,[2] Marianne J. Chapman,[1,3] Michael A. Nauck,[4] Michael Horowitz,[2] and Adam M. Deane[1,3]

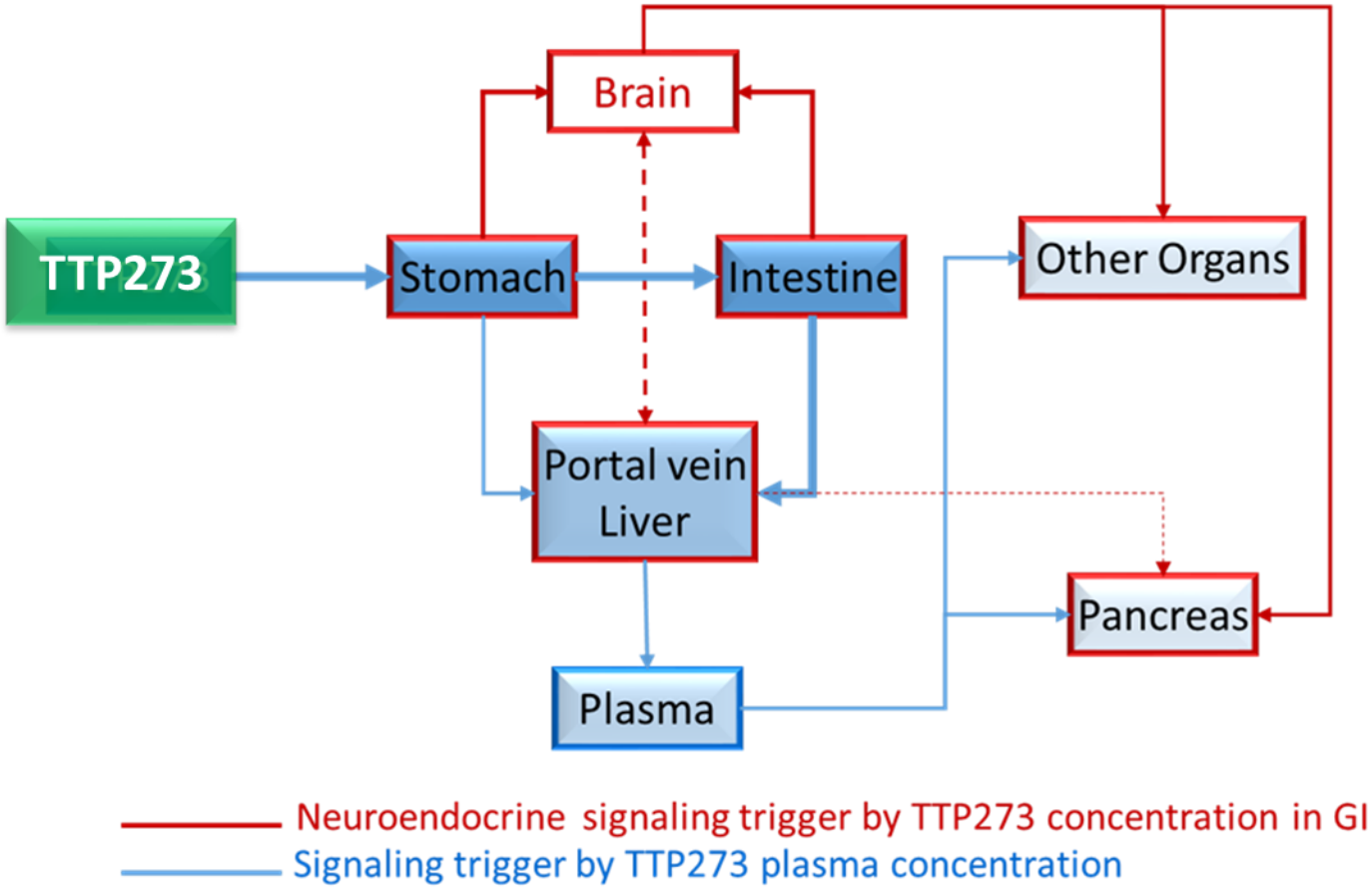
Biased agonism of the μ-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers

David G. Soergel[a,*], Ruth Ann Subach[a], Nancy Burnham[b], Michael W. Lark[a], Ian E. James[a], Brian M. Sadler[c], Franck Skobieranda[a], Jonathan D. Violin[a], Lynn R. Webster[d]

D.G. Soergel et al. / PAIN® 155 (2014) 1829–1835

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

At any given dose, the total efficacy will be the combination of these two pathways



Conclusions

- TTP273 has shown efficacy with negligible nausea and vomiting

- Concentration/effect analysis revealed an unexpected result: lower doses showed more pronounced effects for key efficacy endpoints
  - Observed with both vTv oral, GLP-1 agonists, TTP273 and TTP054

- Preclinical characteristics of TTP273 provide a potential scientific rationale for the observations:
  - TTP273 is functionally biased and does not activate β-arrestin
  - Neuro-enteroendocrine signaling may be a major contributor of TTP273 effect

- Additional clinical investigations using lower doses of TTP273 are necessary to determine the optimal efficacy of this promising investigational drug

Acknowledgements

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