TTP273, Investigational Oral (Non-Peptide) GLP-1R Agonist: Improved Glycemic Control without Nausea and Vomiting in Phase 2

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Introduction

GLP-1R is a well validated target for the treatment of Type 2 diabetes, with multiple marketed injectable GLP-1 analogues/mimetics that provide glycemic control and weight loss. Their widespread use may be hindered by the route of administration and by the high incidence of gastrointestinal side effects.

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. TTP273 has been well tolerated in studies to date with low incidences of GI related adverse events and is orally bioavailable. Results from a phase 2a proof of concept study are reported here.

Aim

The goals of this 12 week, randomized, double-blind, placebo- controlled, parallel group trial in type 2 diabetics on stable doses of metformin were to prove:

1. HbA1c reduction
2. Weight loss
3. Negligible GI side effects

LOGRA Study Design

- 174 T2DM patients randomized
- 7.5-10% baseline HbA1c
- BMI 25-45 kg/m^2
- Arms (1:1:1)
  - Placebo
  - TTP273 150mg once daily (QPM)
  - TTP273 150mg twice daily (BID)
- **Primary endpoint:** Change from baseline in HbA1c at 12 weeks

Disposition of Patients

	Placebo	150 mg QPM TTP273	150 mg BID TTP273
Subjects randomized (N=174)	55	59	60
Subjects completed Treatment Period (N=137)	42 (76%)	46 (78%)	49 (82%)
Subjects discontinued during treatment (N=37; 21%)	13 (24%)	13 (22%)	11 (18%)
Adverse event	1	1	5
Withdrawal by subject	5	2	3
Lost to follow-up	3	4	1
Lack of efficacy	1	1	2
Protocol Deviation	1	1	0
Other	2	4	0

Demography – Baseline Characteristics

	Placebo (n=55)	150 mg QPM TTP273 (n=59)	150 mg BID TTP273 (n=60)
Age (years): Mean	58	57	56
Gender: males; females (% males)	28; 27 (51%)	33; 26 (56%)	31; 29 (52%)
Ethnicity: Not Hispanic or Latino, n (%)	31 (56%)	32 (54%)	33 (55%)
Race: White, n (%)	40 (73%)	42 (71%)	42 (70%)
Weight (kg): Mean	90.0	90.2	92.5
BMI (kg/m2): Mean	32	32	33
Baseline HbA1c: Mean (Median)	8.56 (8.5)	8.61 (8.4)	8.48 (8.25)

Safety Overview: No Overall Safety Issues

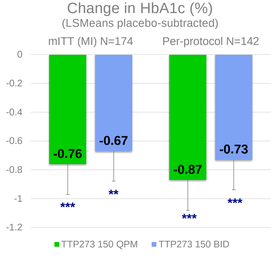
	Placebo (n=55)	150 mg QPM TTP273 (n=59)	150 mg BID TTP273 (n=60)
Subjects with any Treatment-emergent adverse event (TEAE), n (%)	24 (44%)	23 (39%)	30 (50%)
Subjects with any Serious AE[1], n (%)	1	2	2
Subjects with any related TEAE, n (%)	6 (11%)	6 (10%)	11 (18%)
Subjects with TEAE leading to discontinuation of study (**related** TEAE[2]), n (%)	0	0	4 (7%)
Subjects meeting Hy's Law	0	0	0
Subjects with AST or ALT > 3*ULN and BILI > 1.5 ULN	0	0	0
Subjects with severe hypoglycemia[3]	0	0	0
Subjects with ICH E14 criteria: QTc >480 msec, n	0	0	1
Subjects with ICH E14 criteria: QTc change > 60 msec	0	0	0

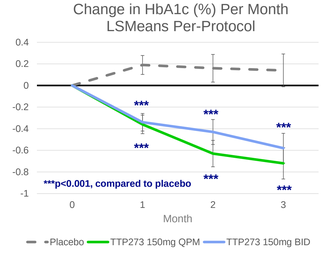
[1]SAEs Not Considered Related to Study Drug 1) Inguinal Hernia Strangulated 2) Dehydration 3) Syncope 4) Depression 5) Peritonsillar Abscess
[2]Related TEAEs leading to discontinuation of study were in the 150mg BID dose group and resolved without sequalae. The TEAE and severity are as follows: 1) Dizziness, Headache, Somnolence and Decreased appetite (mild & moderate) 2) Diarrhoea (mild) 3) Hepatic enzyme increase (moderate) 4) Fatigue (mild).
[3]Three AEs of hypoglycemia occurred in the study with N=1 (150mg BID) documented symptomatic hypoglycemia, N=1 (150mg QPM) asymptomatic hypoglycemia, N=1 (PBO) probable symptomatic hypoglycemia

Given the issues observed with GLP-1 analogues, lipase and amylase levels were monitored at every visit. An AE of amylase increase was reported in one placebo and AEs of lipase increased were reported in 3 subjects (N=1 PBO; N=2 150mg QPM). All of the AEs of elevated amylase and/or lipase were transient in nature and resolved upon retest without any change in study drug.

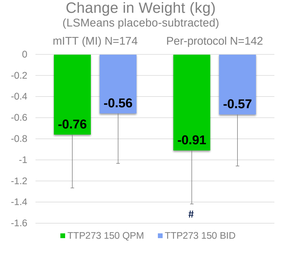
Results

Goal 1: HbA1c Reduction ✓





Goal 2: Weight Loss ✓

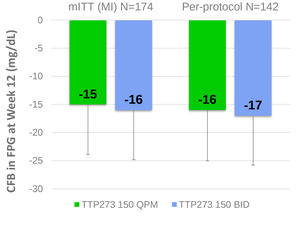


Goal 3: Negligible GI side effects ✓

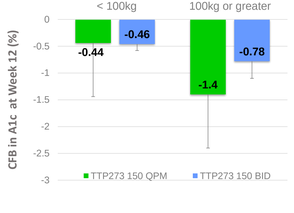
GI Adverse Events, n (%) (All Causality)	Placebo (n=55)	150 mg QPM TTP273 (n=59)	150 mg BID TTP273 (n=60)
Gastrointestinal disorders	7 (13)	9 (15)	12 (20)
Diarrhea	1 (1.8)	2 (3.4)	7 (11.7)
Nausea	4 (7.3)	2 (3.4)	3 (5.0)
Vomiting	1 (1.8)	0	0

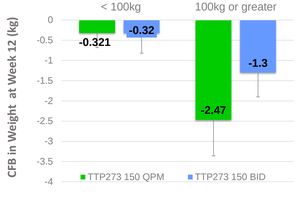
- Incidences of Diarrhea were mild-moderate
- Occurring mostly during the first month of treatment
- All resolving either on continued treatment or shortly after the last dose
- All patients completed the study except for one in the BID study arm

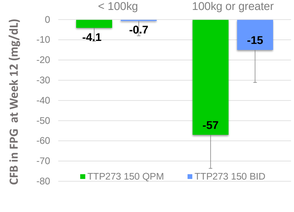
Change in Fasting Plasma Glucose



Protocol Pre-planned analysis in **subjects weighing 100 kg or more** demonstrated **better efficacy** in this group







The modified intent to treat analysis set (mITT) includes randomized subjects who receive at least one dose of randomized study medication (N=174). The per protocol set includes all FAS subjects who do not have significant protocol violations, where a significant violation is one that has the potential to affect the analysis conclusions (N=142). The safety population includes all subjects who received at least one dose of study medication (N=174). ANCOVA adjusted for baseline HbA1c. Multiple imputation used for missing data. ***p<0.001, **p<0.01, *p<0.05, #p=0.08 compared to placebo. CFB= Change from Baseline.

Conclusions

- This phase 2a study confirms the potential of TTP273 as a treatment for Type 2 diabetes that could potentially expand the use of the GLP-1 therapeutic class.
- A preplanned subgroup analysis suggest that better efficacy is achieved with lower doses or a once daily dose regimen.
- Further studies are needed to determine the optimal dose/dose regimen and/or target population
- See poster **168-LB** for additional data

		TTP273	GLP-1 Analogues
Tolerability	No significant gastrointestinal side effects	✓	X
Convenience	Oral Small molecule	✓	X
	Ideal for co-formulation with existing OADs	✓	X
	No need for medical device or sophisticated formulations	✓	X
Benefits	Lowers blood glucose	✓	✓
	Decreases HbA_{1c} levels	✓	✓
	Weight loss	✓	✓