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 diabetes 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
- HbA1c 7.5-10% baseline HbA1c
- BMI 25-45 kg/m²
- Ages (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

<table>
<thead>
<tr>
<th>Patients with treatment-emergent adverse events (TEAEs), n (%)</th>
<th>Placebo</th>
<th>150 mg QPM TTP273</th>
<th>150 mg BID TTP273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects discontinued treatment due to AEs, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects discontinued treatment during the study, n (%)</td>
<td>25 (14)</td>
<td>14 (16)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Weight increased by ≥ 10% of body weight, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lack of efficacy, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Related withdrawal, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Results

Goal 1: HbA1c Reduction

- Change in HbA1c (% ILMeans ± Standard Error) Compared to Placebo:
  - Month 1: -0.87 ± 0.76
  - Month 2: -0.91 ± 0.76

Goal 2: Weight Loss

- Change in Weight (kg): ILMeans ± Standard Error
  - Month 1: -0.87 ± 0.64
  - Month 2: -0.87 ± 0.64

Goal 3: Negligible GI side effects


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 planned subgroup analysis suggests 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