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

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TTP273: Oral, Small Molecule GLP-1R Agonist

Non-peptide, small molecule, GLP-1R Agonist

Orally bioavailable - no injection required

Functionally biased ligand, no β-arrestin signaling in vitro

Favorable tolerability profile - negligible nausea and vomiting

Potential for combination with existing oral agents (including fixed dose combinations)
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/m²)

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/m²

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

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

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**Change in HbA1c at Month 3 (%)**
- Lsmeans placebo-subtracted
  - TTP273 150 QPM: -0.86
  - TTP273 150 BID: -0.71

- ***p<0.001 compared to placebo

**Change in Weight at Month 3 (Kg)**
- Lsmeans placebo-subtracted
  - TTP273 150 QPM: -0.91
  - TTP273 150 BID: -0.57

- #p=0.08 compared to placebo

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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

HbA1c (%)

-0.44  -0.46
-1.4  -0.78

Body Weight (kg)

-0.321  -0.32
-2.47  -1.3

< 100kg  100kg or greater

TTP273 150 QPM  TTP273 150 BID
Focus on QPM versus PBO: Greatest efficacy with < 1.35 mg/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
Focus on “less”: A1c and Weight (means*)
Trends over time are consistent with LOWER optimal dosing

HbA1c (%)

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>TTP273 (&lt; 1.35 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>0.06</td>
<td>-0.025</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.067</td>
<td>-0.125</td>
</tr>
<tr>
<td>Week 12</td>
<td>-1.26</td>
<td>-1.71</td>
</tr>
</tbody>
</table>

Weight (kg)

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>-0.487</td>
<td>-0.088</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.963</td>
<td>-0.513</td>
</tr>
<tr>
<td>Week 12</td>
<td>-2.87</td>
<td>-3.79</td>
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</tbody>
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(*Medians are fully consistent with means)
Focus on “less”: Mean change from baseline at Week 12

- **FPG (mg/dL)**
  - Mean change from baseline at Week 12

- **Insulin (mIU/L)**
  - Same as FPG, showing mean change from baseline at Week 12

- **Systolic BP (mm Hg)**
  - Same as FPG, showing mean change from baseline at Week 12

- **Pulse (bpm)**
  - Same as FPG, showing mean change from baseline at Week 12

Legend:
- **PBO**
- **TTP273 (< 1.35 mg/kg)**
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

Preclinical Results Presented at ADA 2017
TTP273 is a small molecule agonist - not a peptide

- Preclinical evidence:
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  - 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
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

- vTv discovery and development teams
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