Oral Small Molecule GLP-1 Receptor (GLP-1R) Agonists for Type 2 Diabetes (T2DM) with Negligible Nausea and Vomiting

Introduction

GLP-1R is a well validated target for the treatment of T2DM, with multiple marketed injectable GLP-1 analogues/mimetics that provide glycemic control and weight loss in T2DM patients.

Although the peptides targeting GLP-1 receptor are generally safe, the use of these agents are limited by two major factors: 1) all are injectable and 2) the primary side effects of nausea and vomiting make this treatment approach intolerable for some patients.

TTP054 and TTP273 are oral small molecule (non-peptide) GLP-1R agonists that are delivered near the site of secretion of GLP-1 (the gut) and have clinically demonstrated efficacy by improving glycemic control and reducing body weight with superior tolerability than the peptide GLP1 analogues/mimetics.

Phase 1b (TTP273 and TTP054) and Phase 2 (TTP054) Studies

Study Design:

- Type 2 Diabetic Subjects on Stable Doses of Metformin

Baseline Characteristics were relatively balanced amongst groups in each study

<table>
<thead>
<tr>
<th>Baseline Parameter</th>
<th>TTP054-108</th>
<th>TTP054-102</th>
<th>Placebo</th>
<th>TTP273 Phase 2</th>
<th>TTP273 Phase 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>12/23</td>
<td>13/22</td>
<td>15/25</td>
<td>9/11</td>
<td>9/10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>71 (18)</td>
<td>65 (17)</td>
<td>63 (14)</td>
<td>64 (16)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean (SD)</td>
<td>27.7 (4.7)</td>
<td>26.1 (4.4)</td>
<td>29.2 (4.5)</td>
<td>28.5 (4.6)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Mean (SD)</td>
<td>8.5 (1.1)</td>
<td>8.6 (1.2)</td>
<td>8.6 (1.3)</td>
<td>8.6 (1.3)</td>
</tr>
</tbody>
</table>

Safety Results:

TTP054 and TTP273 have Comparable Safety Profiles:
- Negligible Nausea and Vomiting and No Evidence of Hypoglycemia

Efficacy Results:

TTP273 Shows Greater Improvement in Glycemic Control than TTP054 in Phase 1b studies

TTP273 Seems To Have A Better Effect on Body Weight Loss than with TTP054 in a Phase 1b study

TTP054 showed significant reduction in A1c in a 3 month study

TTP273 is expected to be more efficacious based on better Phase 1 results and in vitro potency

Conclusion

With a superior safety and convenience profile, TTP273 could provide an alternative to current GLP-1r therapies and expand the use of this therapeutic class

Jennifer L R Freeman, Stephanie Gustafson, Imogene Dunn, Aaron Burstein, and Carmen Valcarce, vTv Therapeutics, High Point, NC