TTP054, a Novel, Orally-Available Glucagon-Like Peptide-1 (GLP-1) Agonist, Lowers HbA$_{1c}$ in Subjects with Type 2 Diabetes Mellitus (T2DM)

STEPHANIE GUSTAVSON, IMOGENE GRIMES, CARMEN VALCARCE, AARON BURSTEIN, ADNAN MJALLI

TransTech Pharma, LLC
High Point, NC
Presenter Disclosure Information

The American Diabetes Association requires the following disclosure to the participants:

Stephanie Gustavson, PhD, MSCI

Employee of TransTech Pharma, LLC
**1st in Class: Oral, Small Molecule, Non-Peptide GLP-1R Agonists**

<table>
<thead>
<tr>
<th>Overview</th>
<th><strong>TTP054 (First Generation)</strong></th>
<th><strong>TTP273 (Second Generation)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Achieved POC for Program</strong></td>
<td><strong>HbA$_1c$ reduction with no GI side effect signal</strong></td>
<td><strong>Achieved POM</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Glucose reduction with no GI side effect signal</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>More potent than TTP054</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Appears more efficacious (based on short-term glucose lowering) than TTP054</strong></td>
</tr>
<tr>
<td>Clinical Status</td>
<td><strong>Phase 2: 3 months in patients with T2DM</strong></td>
<td><strong>Phase 1: 14 days in patients with T2DM</strong></td>
</tr>
<tr>
<td></td>
<td><strong>TTP054-201 (#156 Oral)</strong></td>
<td><strong>TTP273-102 (#155 Oral)</strong></td>
</tr>
</tbody>
</table>
TTP054-201 Primary Study Objective

- To evaluate the efficacy and safety of TTP054 administered once daily for 12 weeks in adults with type 2 diabetes mellitus (T2DM) on stable doses of metformin
Study Design

For a detailed study design, please refer to the diagram above. The diagram outlines the protocol, including screening visits, wash-out periods, randomization, and visits at various timepoints. Key points to note include:

- Continue stable Metformin
- Blinded Study Medication (TTP054 or Matching Placebo)
- Treatment Phase
- Screen Visit
- Wash-Out
- Visit (V2)
- Run-In
- Visit (V3)
- Day 1
- Visit (V4)
- Randomization
- 3-13 weeks for majority of subjects

Additional notes:
- Those on stable doses of metformin alone prior to V1 may combine V2 & V3
- 2-wk Run-In to test compliance with dosing
Statistical Analysis:

- **Enrichment strategies** (*FDA guidance; December 2012*)
  - Enrolled broad population to understand safety (Baseline HbA$_1c$ 6.5-11%)
  - Utilize enrichment strategy to evaluate magnitude of drug effects
    - Primary efficacy analysis (ITT principle):
      - Protocol Target Population (Baseline HbA$_1c$ 8-11%)
    - Standard methodology: ANCOVA, MMRM, MI, LOCF, and OC

- Meta-analysis of 5 OAD Classes
  - SUs, meglitinides, metformin, TZDs, AGI

- When baseline HbA$_1c$ < 8%, HbA$_1c$ reduction of 0.1-0.2% in active vs. control

*Bloomgarden et al, 2006. Diabetes Care 29:2137-9*
### Subject Disposition
All Subjects Dosed

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Placebo</th>
<th>200 mg</th>
<th>400 mg</th>
<th>800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Randomized &amp; Dosed</td>
<td>50</td>
<td>27</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Withdrawn for any reason</td>
<td>17 (33%)</td>
<td>5 (19%)</td>
<td>10 (20%)</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>8**</td>
<td>0</td>
<td>2*</td>
<td>3</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Adverse events</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Moved away/family emergency</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Medication/visit compliance/other</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Subject 1075 had baseline HbA$_1c$ = 11.2%; Subject 1052 had screening HbA$_1c$ = 10.8; day 14 HbA$_1c$ = 11.2
** 4 subjects withdrew prior to day 28; no post baseline HbA$_1c$ data
## Treatment-Emergent AEs of Special Interest

### All Subjects Dosed

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>AE Preferred Term</th>
<th>Placebo (n=50)</th>
<th>200 mg (n=27)</th>
<th>400 mg (n=51)</th>
<th>800 mg (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects with any AE</td>
<td>20 (40%)</td>
<td>10 (37%)</td>
<td>14 (27%)</td>
<td>25 (45%)</td>
<td></td>
</tr>
<tr>
<td>Total Number of Events</td>
<td>56</td>
<td>27</td>
<td>28</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>5 (10%)</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
<td>9 (16%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders (Related)</td>
<td>4 (8%)</td>
<td>1 (4%)</td>
<td>1 (2%)</td>
<td>5 (9%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

- SAEs considered treatment-related: 2 LFT elevations, both in 800 mg cohort
  - Both had other potential contributing factors, and both resolved
  - Neither had concerning symptoms or increases in bilirubin

- No major LFT concern
  - No increase in median LFT values over time in any dose group
  - No LFT signal in any other clinical study or in any toxicology study
HbA$_{1c}$ at Baseline Influences Response to TTP054
Baseline HbA$_{1c}$ 11% or less

**PLACEBO**

Change from baseline in A1c to Day 84 vs. Baseline A1c

$p=0.545$

**TTP054**

Change from baseline in A1c to day 84 vs. Baseline A1c

$P<0.0001$
# Demography: Protocol Target Population

**Baseline HbA\textsubscript{1c} 8-11\%**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
<th>Placebo (n=31)</th>
<th>200 mg (n=19)</th>
<th>400 mg (n=28)</th>
<th>800 mg (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male (number)</td>
<td>21</td>
<td>15</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Female (number)</td>
<td>10</td>
<td>4</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Race</td>
<td>White/Black/Other (number)</td>
<td>27/2/2</td>
<td>16/3/0</td>
<td>25/3/0</td>
<td>24/9/2</td>
</tr>
<tr>
<td>Age</td>
<td>Mean (Range)</td>
<td>52 (30-67)</td>
<td>55 (42-70)</td>
<td>54 (26-69)</td>
<td>57 (32-69)</td>
</tr>
<tr>
<td>Weight</td>
<td>Mean (Range)</td>
<td>84 (53-125)</td>
<td>83 (59-143)</td>
<td>82 (45-117)</td>
<td>87 (48-132)</td>
</tr>
<tr>
<td>Baseline HbA\textsubscript{1c} (%)</td>
<td>Mean (SD)</td>
<td>9.2 (0.8)</td>
<td>9.1 (0.9)</td>
<td>9.0 (0.9)</td>
<td>8.8 (0.8)</td>
</tr>
<tr>
<td>Metformin</td>
<td>Monotherapy (number)</td>
<td>25</td>
<td>13</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Plus OAD (number)</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Completers</td>
<td>Completer (Dropout)</td>
<td>20 (11)</td>
<td>15 (4)</td>
<td>21 (7)</td>
<td>28 (7)</td>
</tr>
</tbody>
</table>
Primary Analysis: LSMean (Baseline-Adjusted) Change in $\text{HbA}_{1c}$
Protocol Target Population (LOCF; ITT)
Subjects with Baseline $\text{HbA}_{1c}$ 8-11%

- All groups show statistically significant placebo-corrected, reductions in $\text{HbA}_{1c}$
- No statistically significant difference between doses
LSMean (Baseline-Adjusted) Change in FPG
Protocol Target Population (LOCF; ITT)
Subjects with Baseline HbA$_{1c}$ 8-11%

- All groups show statistically significant placebo-corrected, reductions in FPG
- No statistically significant difference between doses
LSMean (Baseline-Adjusted) Change in Bodyweight
Protocol Target Population (LOCF; ITT)
Subjects with Baseline HbA$_{1c}$ 8-11%

- Dose-responsive trend (non-significant) for reduction in body weight (endpoint not adequately powered)

- When OAD-washout patients were excluded (blue bars):
  - More pronounced weight loss observed
  - Significant for 800 mg group (p<0.05)
TTP054-201 Summary

- Oral GLP-1R agonist TTP054 demonstrated Proof of Concept
  - Significant HbA$_{1c}$ lowering at all doses tested
    - Same conclusions whether target population used vs. full protocol population
  - Trend for BW reduction (significant for metformin-monotherapy patients)
  - Negligible GI side effects

- Magnitude of HbA$_{1c}$ reduction was similar to that predicted from a previously disclosed 4-week study [Diabetes, 2013 ADA abstract (115-OR)]
  - 1% placebo-adjusted decrease in HbA$_{1c}$ was predicted from the results of the 400 mg dose
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