TTP273, an Orally-Available Glucagon-Like Peptide-1 (GLP-1) Agonist, Notably Reduces Glycemia in Subjects with Type 2 Diabetes Mellitus (T2DM)

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

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Employee of TransTech Pharma, LLC
Background

- GLP-1 Receptor Agonism: a validated target

- Currently marketed GLP-1 mimetics:
  - Injectable agents
  - Robust efficacy; notable gastrointestinal (GI) side effects

Expected Benefits of an Oral, Small Molecule, Non-Peptide GLP-1 Receptor Agonist

- More physiological than peptides: delivered at the site of secretion of native GLP-1 (intestine)
  - Efficacy contributions from gut (direct & indirect via neural signaling) & systemic

- Superior tolerability vs. peptide GLP-1 analogues
  - Low incidence of GI AEs

- No antibody formation

- Trend towards lowering of body weight, triglycerides, cholesterol and blood pressure
  - May reduce cardiovascular risk

- Ideal for combination with existing oral agents (including fixed-dose combinations)

- Convenience/Compliance
## 1st in Class: Oral, Small Molecule, Non-Peptide GLP-1R Agonists

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

- Randomized, placebo-controlled, investigator- and patient- blind, sponsor-open, multiple dose study (14 days)
  - TTP273 effects on safety, tolerability, PK, and PD
- Patients with T2DM on stable doses of metformin
- 3 week inpatient design
  - Inpatient Days -5 to 16; 23-point mean daily glucose and MMTT on Days -1 & 14
  - Isocaloric diets provided/encouraged
  - Subjects required to consume full menu Days -1 &14
- 10 cohorts; n=12 (9 active; 3 placebo) per cohort

- QD PO Dosing (6 Cohorts)
  - 25 mg QD
  - 50 mg QD
  - 75 mg QD
  - 100 mg QD
  - 150 mg QD
  - 450 mg QD

- Alternative PO Dosing Regimens (4 Cohorts)
  - 75 mg QPM
  - 25 mg BID
  - 75 mg BID
  - 150 mg BID
Disposition, Demography, & Pharmacokinetics

- 112 subjects randomized/dosed at a single site
  - N=108 completed; 4 withdrew
    - Two PBO (one AE [LFTs increased], one “other” [hyperglycemia])
    - Two actives (one AE [nausea; 75 mg QD], one “other” [death in family; 450 mg QD])

- Mean (±SD) baseline characteristics were relatively balanced amongst groups

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>All Placebo</th>
<th>All Active</th>
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<tbody>
<tr>
<td>Sample size</td>
<td>112</td>
<td>29</td>
<td>83</td>
</tr>
<tr>
<td>Gender; Male (%)</td>
<td>59 (53%)</td>
<td>16 (55%)</td>
<td>43 (52%)</td>
</tr>
<tr>
<td>Age in yrs; Mean ± SD (Min,Max)</td>
<td>58 ± 6 (43,70)</td>
<td>57 ± 6 (44,68)</td>
<td>58 ± 6 (43,70)</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.1 ± 0.7 (6.7,9.8)</td>
<td>8.4 ± 0.8 (7.3,9.8)</td>
<td>8.0 ± 0.7 (6.7,9.7)</td>
</tr>
<tr>
<td>BMI in kg/m²; Mean ± SD (Min,Max)</td>
<td>32 ± 4 (23,43)</td>
<td>31 ± 4 (23,39)</td>
<td>32 ± 4 (23,43)</td>
</tr>
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</table>

- Pharmacokinetics increased in linear, dose-responsive manner
  - Tmax ~2 hours
  - Half-life ~6 hours
Safety Summary

- All doses were safe and well tolerated
  - No SAEs
  - No hypoglycemia in any patient
  - Two discontinuations due to an AE
    - 1 placebo: elevated LFTs
    - 1 active (75 mg QD): nausea

- AEs were generally mild and similar in incidence between placebo and active dose groups

- Small number of GI AEs: mostly mild, resolved spontaneously with continued study drug administration, no dose response relationship
  - Minimal incidence of nausea (n=4 total of 112 randomized) and vomiting (n=1), with no dose response
  - Most common GI AE was diarrhea
    - No clear dose response
    - Often occurred on meal-challenge days when the timed consumption of meals was required
24-Hour Glucose Profile: QD Dosing Regimens

- Robust, dose responsive glucose lowering
- PD maximized at 150 QD
24-Hour Glucose Profile: Alternative Dosing Regimens

- Robust glucose lowering with evening regimens (QPM and BID)
TTP273-102 Mean Daily Glucose (MDG): Mean Change from Baseline (CFB) after 14-days of Treatment

**QD Regimens**

- Placebo (n=27)
- 25mg (n=9)
- 50mg (n=9)

**Alternative Regimens**

- Placebo (n=27)
- 25mg BID (n=9)
- 75mg QPM (n=7)
- 75mg BID (n=8)
- 150mg BID (n=8)

# P < 0.10 vs. placebo; * P < 0.05 vs. placebo; ** P < 0.01 vs. placebo
MDG at Baseline Influences Response to TTP273
TTP273-102 Fasting Plasma Glucose (FPG):
Mean Change from Baseline (CFB) after 14-days of Treatment

Mean FPG CFB (mg/dL): QD Regimens

- Placebo (n=27)
- 25mg (n=9)
- 50mg (n=9)
- 75mg (n=7)
- 100mg (n=9)
- 150mg (n=8)
- 450mg (n=7)

Mean FPG CFB (mg/dL): Alternative Regimens

- Placebo (n=27)
- 25mg BID (n=9)
- 75mg (n=7)
- 75mg QPM (n=7)
- 150mg BID (n=8)

# P < 0.10 vs. placebo; ** P < 0.01 vs. placebo
Changes in Secondary Parameters

- Study **not designed** to assess changes in secondary parameters
  - Strict dietary requirements, small sample size, and short duration
  - Yet, numerical, dose-responsive changes occurring in expected direction

- **Body weight:**
  - Trend for reduction (up to ~2 kg) in several active treatment groups vs. placebo (~0.6 kg)
  - Trend for correlation between mean daily glucose reduction and body weight reduction seen in active treatment groups (but not in placebo group)

- **Blood pressure:**
  - SBP: trend for reduction (up to ~8 mmHg) in several active treatment groups vs. placebo (~2 mmHg)
  - DBP: trend for reduction (up to ~5 mmHg) in several active treatment groups vs. placebo (~1 mmHg)

- **Triglycerides:**
  - Trend for reduction (up to ~50 mg/dL) in several active treatment groups vs. placebo (~30 mg/dL)
TTP273-102 Summary

- TTP273 demonstrated robust effects on postprandial & fasting glucose
  - Glucose reduction (40 mg/dL in MDG and FPG) appears more pronounced than TTP054
    - Consistent with the increased *in vitro* potency of TTP273 vs. TTP054
    - Assessments based on TTP054 shorter-term phase 1 studies; no head-to-head comparisons [Diabetes, 2013 ADA abstract (115-OR)]
  - Study likely underestimates maximum glycemic reduction
    - Subjects were required to consume isocaloric diets, thus any effect on food intake would not contribute to the PD response in this study
    - Notable placebo effect in the current study, that will likely wane with time (in contrast to active-treatment effects which generally do not wane)
- Secondary endpoints (BW, TG, blood pressure) tended to exhibit numerical, dose-responsive decreases despite the fact the study was not designed to assess such changes
- Negligible nausea/vomiting
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