Tirzepatide Reduces the Predicted Risk of Developing Type 2 Diabetes: Post hoc Analysis of the SURMOUNT-1 Trial

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BACKGROUND AND OBJECTIVE

■ Obesity is a chronic, progressive disease affecting around 41.5% of adults in the United States.
■ People with obesity have a higher risk of developing type 2 diabetes (T2D) compared with those without obesity.1

Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, demonstrated mean weight reductions of up to 22.5% among participants with overweight or obesity and without type 2 diabetes at 72 weeks of treatment in the Phase 3 SURMOUNT-1 trial.2

Surrogate endpoints include: weight loss, glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; mITT: modified intention-to-treat; MMRM: mixed model for repeated measures; PBO: placebo

CONCLUSIONS

■ Treatment with tirzepatide significantly reduced the 10-year predicted risk of developing type 2 diabetes compared with placebo in participants with obesity or overweight in the SURMOUNT-1 trial.

■ Most of the reduction in predicted risk of type 2 diabetes by tirzepatide was achieved by Week 24.

■ This study provides indirect evidence on the benefits of tirzepatide treatment for the prevention of type 2 diabetes.

■ As the predicted type 2 diabetes risk was calculated using the cardiometabolic disease staging risk engine, additional data from prospective randomized controlled trials are needed to further evaluate the effects of tirzepatide on type 2 diabetes risk reduction.

Methods

Study design and population

This was a post hoc analysis of SURMOUNT-1 data to compare change in predicted risk for T2D from baseline to 72 weeks between tirzepatide groups and placebo using the Cardiometabolic Disease Staging (CMDS) risk engine.

SURMOUNT-1 was a phase 3, randomized, double-blind, placebo-controlled study in participants with overweight or obesity without T2D, where a total of 2539 participants were randomized 1:1:1:1 to receive 5, 10, or 15 mg tirzepatide or placebo.

Efficacy analysis set included data from all randomized participants who had received at least one dose of the study intervention during the treatment period (N=2539). The analyses excluded data after study drug discontinuation.

The outcomes of post hoc analysis included:

-10-year predicted T2D risk scores at baseline, Week 24, and Week 72.

THE TIRZEPATIDE GROUPS HAD SIGNIFICANTLY GREATER CHANGE FROM BASELINE IN PREDICTED RISK OF DEVELOPING T2D COMPARED WITH PLACEBO AT WEEKS 24 AND 72

The effect of tirzepatide on the risk of developing T2D in people with overweight or obesity is unknown.

We assessed the impact of tirzepatide treatment on 10-year risk of developing type 2 diabetes (T2D) among people with overweight or obesity in the phase 3 SURMOUNT-1 trial through predictive modeling.

The outcomes of post hoc analysis included:

- 10-year predicted T2D risk scores at baseline, Week 24, and Week 72.

- Mean change of risk score from baseline to Week 24 and Week 72.

Demographic and baseline clinical characteristics were similar across treatment groups

The 10-year T2D risk scores were calculated using a validated robust tool, CMDS = a Bayesian logistic regression of T2D risk factors.

The 10-year T2D risk scores were calculated using a validated robust tool, CMDS = a Bayesian logistic regression of T2D risk factors.

Mean change in predicted risk score from baseline to Week 72 between tirzepatide groups and placebo using the Cardiometabolic Disease Staging (CMDS) risk engine.

RESULTS

- Median relative risk reductions for tirzepatide 5 mg, 10 mg, and 15 mg, and placebo groups were -48.8%, -54.9%, -57.2%, and -15.2% at Week 24 and -60.3%, -68.3%, -69.0%, and -10.8% at Week 72, respectively.

- *All comparisons of risk reductions from baseline between tirzepatide and PBO were statistically significant (p<0.001 for all).

- Difference in mean change in risk score between tirzepatide groups and placebo (95% CI) at Week 24 and Week 72:

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Week 24</th>
<th>Week 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZP 5 mg vs PBO</td>
<td>-10.4 (-11.4, -9.3)</td>
<td>-10.1 (-11.1, -9.0)</td>
</tr>
<tr>
<td>TZP 10 mg vs PBO</td>
<td>-14.0 (-15.4, -12.7)</td>
<td>-13.7 (-14.5, -12.9)</td>
</tr>
<tr>
<td>TZP 15 mg vs PBO</td>
<td>-16.6 (-17.8, -15.3)</td>
<td>-16.3 (-17.2, -15.5)</td>
</tr>
</tbody>
</table>

- **Statistical analysis**

Mean change in risk score from baseline to Week 24 and Week 72.

- **Demographic and baseline clinical characteristics were similar across treatment groups**

- **CONCLUSIONS**

- **Methods**

- **Study design and population**

- **CMDS risk engine**

- **Methods**

- **Statistical analysis**

Mean predicted CMDS risk scores at baseline, Week 24, and Week 72

At Weeks 24 and 72, the mean predicted CMDS risk scores for tirzepatide groups were lower than that for the placebo group.

**References**


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³University of Alabama at Birmingham, Birmingham, AL, US
BACKGROUND AND OBJECTIVE

Background

- Obesity is a chronic, progressive disease affecting around 41.9% of adults in the United States.¹

- People with obesity have a higher risk of developing type 2 diabetes (T2D) compared with those without obesity.²

- Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, demonstrated mean weight reductions of up to 22.5% among participants with overweight or obesity and without type 2 diabetes at 72 weeks of treatment in the Phase 3 SURMOUNT-1 trial.³ Tirzepatide is approved for T2D and is in development for obesity.

The effect of tirzepatide on the risk of developing T2D in people with overweight or obesity is unknown.

We assessed the impact of tirzepatide treatment on 10-year risk of developing T2D among people with overweight or obesity in the phase 3 SURMOUNT-1 trial through predictive modeling.
## Study design and population

- This study was a post hoc analysis of SURMOUNT-1 data to compare change in predicted risk for T2D from baseline to 72 weeks between tirzepatide groups and placebo using the Cardiometabolic Disease Staging (CMDS) risk engine.

- SURMOUNT-1 was a phase 3, randomized, double-blind, placebo-controlled study in participants with overweight or obesity without T2D, where a total of 2539 participants were randomized 1:1:1:1 to receive 5, 10, or 15 mg tirzepatide or placebo.

- Efficacy analysis set included data from all randomized participants who had received at least one dose of the study intervention during the treatment period (N=2539). The analyses excluded data after study drug discontinuation.

### Outcomes of post hoc analysis

- 10-year predicted T2D risk scores at baseline, Week 24, and Week 72.
- Mean change of risk score from baseline at Week 24, and Week 72.
METHODS

- **CMDS risk engine**
  - The 10-year T2D risk scores were calculated using a validated robust tool, CMDS.\(^4,5\)

- **Statistical analysis**
  - Mean risk scores and change from baseline to Weeks 24 and 72 were calculated using mixed model for repeated measures with treatment group and baseline risk score as the covariates.

### CMDS model inputs for calculating predicted 10-year T2D risk \(^4,5\)

A Bayesian logistic regression of T2D risk factors

- Age
- Sex
- Race
- Waist circumference
- Blood glucose
- SBP, DBP
- Triglycerides, HDL-C
Demographic and baseline clinical characteristics were similar across treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TZP 5 mg (N = 630)</th>
<th>TZP 10 mg (N = 636)</th>
<th>TZP 15 mg (N = 630)</th>
<th>Placebo (N = 643)</th>
<th>Total (N = 2539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.6 ± 12.7</td>
<td>44.7 ± 12.4</td>
<td>44.9 ± 12.3</td>
<td>44.4 ± 12.5</td>
<td>44.9 ± 12.5</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>426 (67.6)</td>
<td>427 (67.1)</td>
<td>425 (67.5)</td>
<td>436 (67.8)</td>
<td>1714 (67.5)</td>
</tr>
<tr>
<td>Race n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>447 (71.0)</td>
<td>452 (71.1)</td>
<td>443 (70.3)</td>
<td>450 (70.0)</td>
<td>1792 (70.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>68 (10.8)</td>
<td>71 (11.2)</td>
<td>66 (10.5)</td>
<td>71 (11.0)</td>
<td>276 (10.9)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>48 (7.6)</td>
<td>47 (7.4)</td>
<td>51 (8.1)</td>
<td>55 (8.6)</td>
<td>201 (7.9)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>56 (8.9)</td>
<td>58 (9.1)</td>
<td>59 (9.4)</td>
<td>58 (9.0)</td>
<td>231 (9.1)</td>
</tr>
<tr>
<td>*Others</td>
<td>11 (1.7)</td>
<td>8 (1.3)</td>
<td>11 (1.7)</td>
<td>9 (1.4)</td>
<td>39 (1.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37.4 ± 6.6</td>
<td>38.2 ± 7.0</td>
<td>38.1 ± 6.7</td>
<td>38.2 ± 6.9</td>
<td>38.0 ± 6.8</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>113.2 ± 14.3</td>
<td>114.8 ± 15.8</td>
<td>114.4 ± 15.6</td>
<td>114.0 ± 14.9</td>
<td>114.1 ± 15.2</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>123.6 ± 12.5</td>
<td>123.8 ± 12.8</td>
<td>123.0 ± 12.9</td>
<td>122.9 ± 12.8</td>
<td>123.3 ± 12.7</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>79.3 ± 8.1</td>
<td>79.9 ± 8.3</td>
<td>79.3 ± 8.2</td>
<td>79.6 ± 8.0</td>
<td>79.5 ± 8.2</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>97.6 ± 17.9</td>
<td>98.3 ± 18.3</td>
<td>98.2 ± 17.7</td>
<td>98.1 ± 18.3</td>
<td>98.1 ± 18.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 ± 0.4</td>
<td>5.6 ± 0.4</td>
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</tr>
<tr>
<td>Fasting serum glucose (mg/dL)</td>
<td>95.4 ± 9.7</td>
<td>95.5 ± 10.7</td>
<td>95.3 ± 10.3</td>
<td>95.7 ± 9.5</td>
<td>95.5 ± 10.1</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>149.5 ± 149.4</td>
<td>142.5 ± 86.2</td>
<td>142.9 ± 81.3</td>
<td>146.8 ± 82.0</td>
<td>145.4 ± 103.6</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mg/dL)</td>
<td>49.3 ± 13.3</td>
<td>49.2 ± 13.0</td>
<td>49.1 ± 12.8</td>
<td>48.3 ± 13.0</td>
<td>49.0 ± 13.1</td>
</tr>
</tbody>
</table>

Characteristics show mean ± SD, unless otherwise noted.
*Others: Native Hawaiian or Other Pacific Islander; Multiple N: Size of cohort; n: Size of sub-population
BMI: body mass index; DBP: diastolic blood pressure; eGFR: glomerular filtration rate, HbA1c: glycated hemoglobin; HDL: high-density lipoprotein, SBP: systolic blood pressure; SD: standard deviation; TZP: tirzepatide
At Weeks 24 and 72, the mean predicted CMDS risk scores for tirzepatide groups were lower than that for the placebo group.
The tirzepatide groups had significantly greater change from baseline in predicted risk of developing T2D compared with placebo at Weeks 24 and 72.

*All comparisons of risk reductions from baseline between tirzepatide dose groups and placebo were statistically significant (p<0.001 for all). Results were derived from MMRM where the covariates are baseline score, country, treatment, time point, and treatment*time point interaction.

| Difference in mean change in risk score between tirzepatide groups and placebo (95% CI) |
|---------------------------------|-----------------|-----------------|
| TZP vs PBO                      | Week 24         | Week 72         |
| TZP 5 mg                        | -8.9 (-9.9, -7.8) | -11.7 (-13.0, -10.3) |
| TZP 10 mg                       | -10.1 (-11.1, -9.0) | -13.7 (-15.0, -12.3) |
| TZP 15 mg                       | -10.4 (-11.4, -9.3) | -14.0 (-15.4, -12.7) |

Median relative risk reductions for tirzepatide 5 mg, 10 mg, 15 mg, and placebo groups were -48.8%, -54.9%, -57.2%, and -15.2% at Week 24 and -60.3%, -68.3%, -69.0%, and -10.8% at Week 72, respectively.

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CI: confidence interval; MMRM: mixed model for repeated measures; PBO: placebo; T2D: type 2 diabetes; TZP: tirzepatide
CONCLUSIONS

- Treatment with tirzepatide significantly reduced the 10-year predicted risk of developing type 2 diabetes compared with placebo in participants with obesity or overweight in the SURMOUNT-1 trial.

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REFERENCES

ABBREVIATIONS

BMI: Body mass index; CI: Confidence interval; SBP: Systolic blood pressure; CMDS: Cardiometabolic Disease Staging risk engine; DBP: Diastolic blood pressure; PBO – Placebo; HbA1c: Glycated hemoglobin; HDL-C: High-density lipoprotein cholesterol; mITT: Modified intention-to-treat; MMRM: Mixed model for repeated measures; SD: Standard deviation; T2D: Type 2 diabetes; TZP: Tirzepatide
Disclosures
ERH, LMN, HK, FW, NNA, and AS are employees and stockholders of Eli Lilly and Company. HW is an employee of Tech Data Service. WTG is an employee of University of Alabama at Birmingham, Birmingham, AL, and served as a consultant on advisory boards for Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Pfizer, Fractyl Health, Alnylam Pharmaceuticals, Inogen, and Merck, and as a site principal investigator for multi-centered clinical trials sponsored by his university and funded by Novo Nordisk, Eli Lilly and Company, Epitomee, Neurovalens, and Pfizer.

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