**Rationale**

- Obesity is a major risk factor for obstructive sleep apnea (OSA), a common disease with increasing prevalence worldwide. 
- Weight loss is recommended for OSA treatment in people with obesity, but there are no current anti-obesity medications with demonstrated clinically meaningful improvement in OSA severity and symptomology.
- Tirzepatide (TZP) is a first-in-class GIP and GLP-1 single molecule receptor agonist approved for treatment of people with type 2 diabetes and under investigation for chronic weight management, OSA, and other obesity-related complications.
- TZP has demonstrated substantial reductions in body weight in people with obesity or without type 2 diabetes.

**Hypothesis:** TZP in people with OSA and obesity will yield important improvements in OSA severity as assessed by the apnea-hypopnea index (AHI).

**Study Design** (ClinicalTrials.gov Identifier: NCT05412004)

- Phase 3, 52-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of TZP at the maximum tolerated dose (MTD; 10 or 15 mg) versus placebo as an adjunct to diet and exercise in participants with moderate-to-severe OSA (AHI \( \geq 15 \) events/h) and obesity (BMI \( \geq 30 \) kg/m\(^2\)).
- 2 sub-studies with distinct participant populations in the trial explore cohorts on PAP and without PAP therapy.
- Estimated study completion date: March 29, 2024

**Endpoints**

**Key Inclusion Criteria**
- Adults aged \( \geq 18 \) years
- AHI \( \geq 15 \) events/h (CMS criteria), BMI \( \geq 30 \) kg/m\(^2\)
- At least 1 self-reported unsuccessful dietary effort to lose body weight

**Key Exclusion Criteria**
- Type 1 diabetes or Type 2 diabetes
- Prior or planned surgery for sleep apnea or major ear, nose, or throat surgery
- Active device treatment of OSA other than PAP
- Self-reported change in body weight >5 kg within 3 months prior to screening
- Prior or planned surgical or endoscopic treatment for obesity
- Known obesity hyperventilation syndrome

**Primary endpoint:** Change in AHI (assessed with polysomnography)

**Selected secondary endpoints:**
- FOSQ-based hierarchical combination of patient-reported outcomes
- Responder analysis of treatment efficacy
- Percent change in body weight
- Change in hsCRP concentration
- Change in systolic and diastolic blood pressure
- Lipids, fasting insulin, and other cardiometabolic indicators
- Hypoxic burden
- Actigraphy measures

**Baseline Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N=457)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49.7 (11.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>138 (30.2)</td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>37 (8.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>80 (17.5)</td>
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<tr>
<td>Black or African American</td>
<td>22 (4.8)</td>
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<tr>
<td>White</td>
<td>316 (69.3)</td>
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<tr>
<td>Multiple</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>166 (36.3)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>38.8 (6.4)</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>50.33 (28.43)</td>
</tr>
<tr>
<td>OSA Severity, n (%)</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</table>

**Statistical Considerations**

- Randomization within each ISA is stratified by country/geographic region, baseline AHI (moderate/severe), and gender
- A sample size of 206 per sub-study will provide at least 90% power to demonstrate superiority of TZP versus placebo for the primary endpoint at a 2-sided alpha level of 0.05, assuming 50% improvement compared to placebo, with a common SD of 50%, and up to 25% discontinuing investigational therapy in each arm
- For each sub-study, the superiority of TZP versus placebo will be evaluated against two estimands using data from patients who meet study eligibility criteria receiving at least one dose of study intervention
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    - Intercurrent event (ICE) of permanent discontinuation of study intervention will be considered as part of the treatment condition
  - **Efficacy estimand:** considers treatment condition to be randomized treatment
    - ICE of permanent discontinuation of study intervention will be handled using a hypothetical strategy assuming AHI after ICE is as if participants would remain on their randomly assigned treatment for 52 weeks

Abbreviations: AHl, apnea-hypopnea index; BMI, body mass index; FOSQ, Functional Outcomes of Sleep Questionnaire; hsCRP, high-sensitivity C-reactive protein; OSA, obstructive sleep apnea; PAP, positive airway pressure.
Tirzepatide for the Treatment of OSA: SURMOUNT-OSA Phase 3 Trial

Atul Malhotra¹, Josef Bednarik², Govinda Weerakkody², Julia P. Dunn², Terri Weaver³, Ron Grunstein⁴, Ingo Fietze⁵, Susan Redline⁶, Mathijs C. Bunck²

¹University of California, San Diego, USA
²Eli Lilly and Company, Indianapolis, USA
³University of Illinois Chicago, USA
⁴Woolcock Institute of Medical Research, Sydney, Australia
⁵Charité University Hospital Berlin, Germany
⁶Harvard Medical School, Boston, USA

SLEEP 2023; The 37th Annual Meeting of the Associated Professional Sleep Societies (APSS); Indianapolis, Indiana, USA; June 3rd – June 7th, 2023
■ Obesity is a major risk factor for obstructive sleep apnea (OSA), a common disease with increasing prevalence worldwide\(^1\)

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Hypothesis: TZP in people with OSA and obesity will yield important improvements in OSA severity as assessed by the apnea-hypopnea index (AHI)

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(ClinicalTrials.gov Identifier: NCT05412004)

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- Estimated study completion date: March 29, 2024

Abbreviations: AHI, apnea-hypopnea index; ISA, intervention-specific appendix; MTD, maximum-tolerated dose; OSA, obstructive sleep apnea; PAP, positive airway pressure; QW, once weekly; TZP, tirzepatide.
Eligibility Criteria

Key Inclusion Criteria

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Key Exclusion Criteria

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Abbreviations: AHI, apnea-hypopnea index; ISA, intervention-specific appendix; TZP, tirzepatide.
CONCLUSIONS

- SURMOUNT-OSA aims to determine whether TZP provides clinically meaningful improvement in obesity-related OSA by targeting an underlying etiology
  - ISA1: will assess the role of TZP as primary therapy
  - ISA2: will assess the role of TZP as an adjunctive therapy to PAP treatment

- Objective and subjective outcome measures should provide important guidance regarding optimal OSA management with weight management as principal component of the intervention

- SURMOUNT-OSA studies will bring important information on how TZP treatment impacts relevant cardio-metabolic indicators

- The studies employ wearable technology as HSAT/Actigraphy to investigate changes in sleep and activity, and MRI study addendum directly investigating effect of the treatment on upper airway patency

Abbreviations: HSAT, home sleep apnea test; ISA, intervention-specific appendix; OSA, obstructive sleep apnea; PAP, positive airway pressure; TZP, tirzepatide.
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