Poster Board No.: 171

Tirzepatide for the Treatment of OSA: SURMOUNT-OSA Phase 3 Trial

Atul Malhotra[1], Josef Bednarik[2], Govinda Weerakkody[2], Julia P. Dunn[2], Terri Weaver[3], Ron Grunstein[4], Ingo Fietze[5], Susan Redline[6], Mathijs C. Bunck[2]

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

RATIONALE

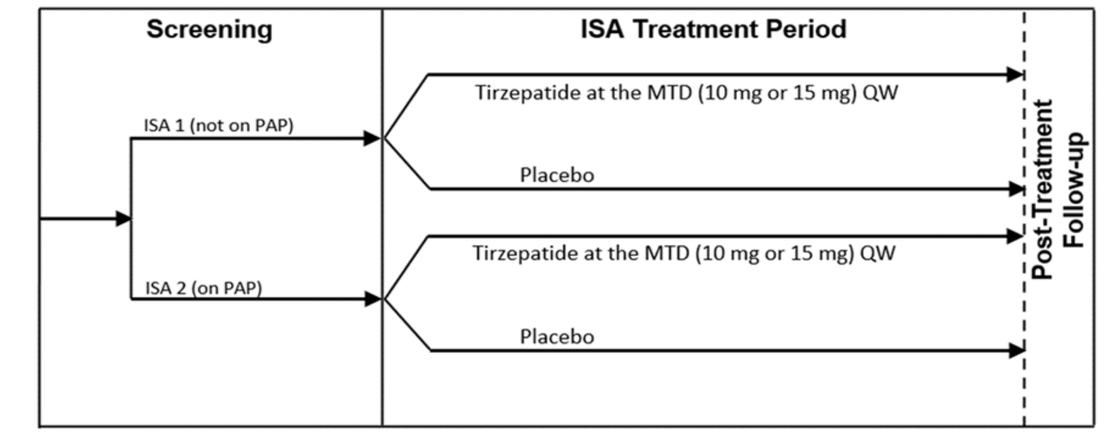
- Obesity is a major risk factor for obstructive sleep apnea (OSA), a common disease with increasing prevalence worldwide[1]
- Weight loss is recommended for OSA treatment in people with obesity or overweight, but there are no current anti-obesity medications with demonstrated clinically meaningful improvement 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 with or without type 2 diabetes[2-7]

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

1. Young T, et al. Am J Respir Crit Care Med. 2002;165:1217-1239. 2. Rosenstock J, et al. Lancet. 2021;398:143-155. 3. Frías J, et al. N Engl J Med. 2021;385:503-515. 4. Ludvik B, et al. Lancet. 2021;398:583-598. 5. Del Prato S, et al. Lancet. 2021;398:1811-1824. 6. Dahl D, et al. JAMA. 2022;327:534-545. 7. Jastreboff AM, et al. N Engl J Med. 2022;387:205-216.

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 ≥15 events/h) and obesity (BMI ≥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



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; MTD, maximum-tolerated dose; PAP, positive airway pressure; QW, once weekly.

Eligibility Criteria

Key Inclusion Criteria

- Adults aged ≥18 years
- AHI ≥15 events/h (CMS criteria), BMI ≥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 hypoventilation syndrome

Endpoints

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

Parameter Mean (standard deviation) or n(%)	Total (N=457)
Age, y	49.7 (11.4)
Female, n (%)	138 (30.2)
Race/Ethnicity, n (%)	
American Indian or Alaska Native	37 (8.1)
Asian	80 (17.5)
Black or African American	22 (4.8)
White	316 (69.3)
Multiple	1 (0.2)
Hispanic or Latino	166 (36.3)
BMI, kg/m^2	38.8 (6.4)
AHI, events/h	50.33 (28.43)
OSA Severity, n (%)	
Moderate (AHI 15-30 events/h)	147 (32.7)
Severe (AHI >30 events/h)	297 (66.0)
Not yet available	7

Abbreviations: AHI, 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.

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 aligned to two estimands using data from patients who meet study eligibility criteria receiving at least one dose of study intervention
  - **Treatment regimen estimand:** considers treatment condition to be randomized treatment with allowance for potential dose interruptions and modifications regardless of adherence to study intervention
    - 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
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Disclosures: AM is funded by the NIH and reports income related to medical education from Zoll, Livanova, Eli Lilly and Company, and Jazz; ResMed provided a philanthropic donation to UCSD. **TW** declares consultant/advisory boards: Bayer AG, Eli Lilly and Company, Idorsia Alliance for Sleep, and Alkermes Orexin Advisory Board; royalty fee for use FOSQ: Alkermes Inc, Axsome, Bayer AG, Bioproject Deutschland GmbH, Eli Lilly and Company, Harmony Biosciences, Ignis Therapeutics (Shanghai) Ltd, Inspire Medical Systems, Jazz, LIvaNova, Nyxoah, Philips Respironics Inc, ResMed, Signant Health, Signifier Medical Technologies, Stratevi, Syneos, Vallis Bioscience Inc, Verily Life Sciences. **RG** declares consultancy with Eli Lilly and Company. **IF** declares consultant: Eli Lilly and Company, Idorsia, ResMed, Stada; speaker: Idorsia, Hennig; research grants: ResMed, Löwenstein. **SR** reports grants from NIH during the conduct of the study; grants and personal fees from Jazz, personal fees from Eli Lilly and Company, personal fees from Apnimed Inc, outside the submitted work; and is the first incumbent of an endowed professorship donated to the Harvard Medical School by Dr Farrell, the founder and Board Chairman of ResMed, through a charitable remainder trust instrument, with annual support equivalent to the endowment payout provided to the Harvard Medical School during Dr Farrell's lifetime by the ResMed Company through an irrevocable gift agreement. **JB, GW, JPD, and MCB** are employees and shareholders of Eli Lilly and Company.

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SLEEP 2023; The 37th Annual Meeting of the Associated Professional Sleep Societies (APSS); Indianapolis, Indiana, USA; June 3rd – June 7th, 2023

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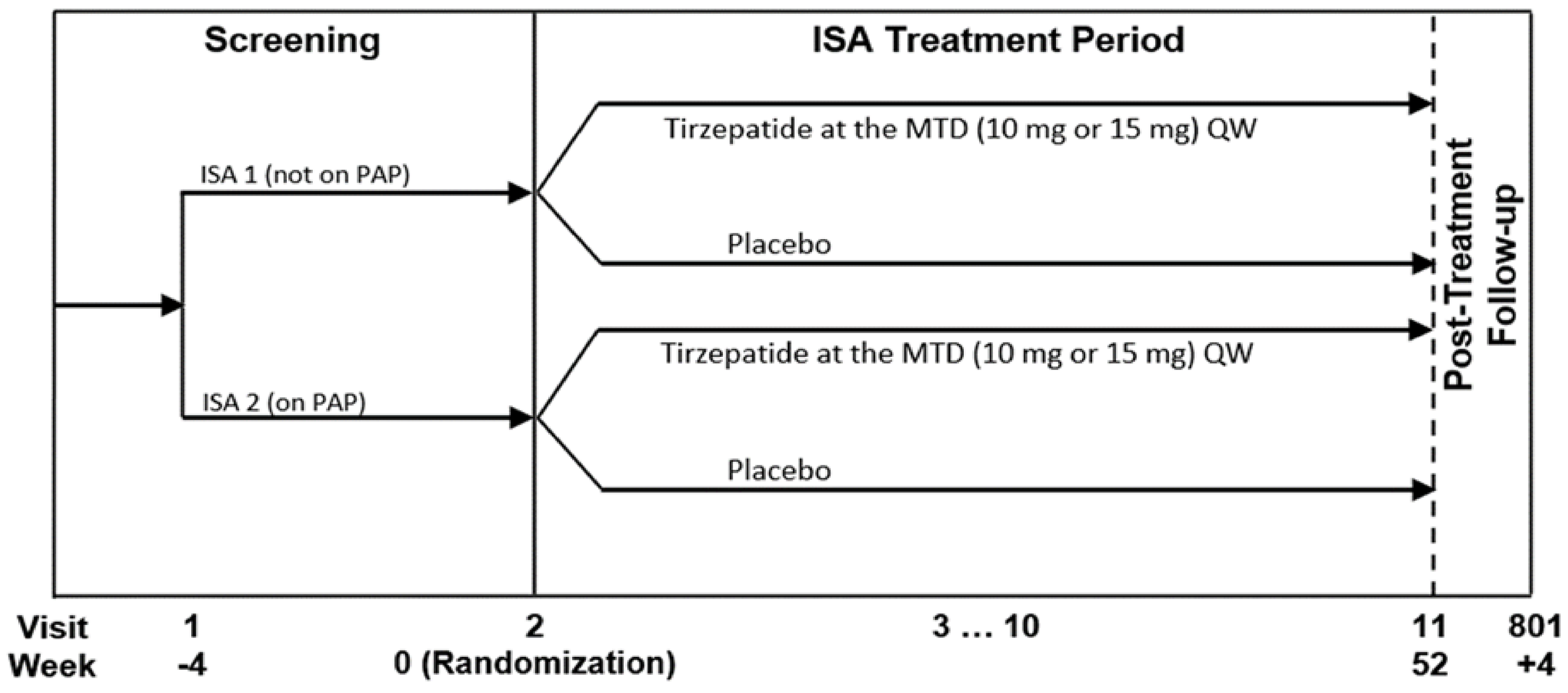

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