

SURMOUNT-OSA - Study 2

Participants on PAP Therapy

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Tirzepatide



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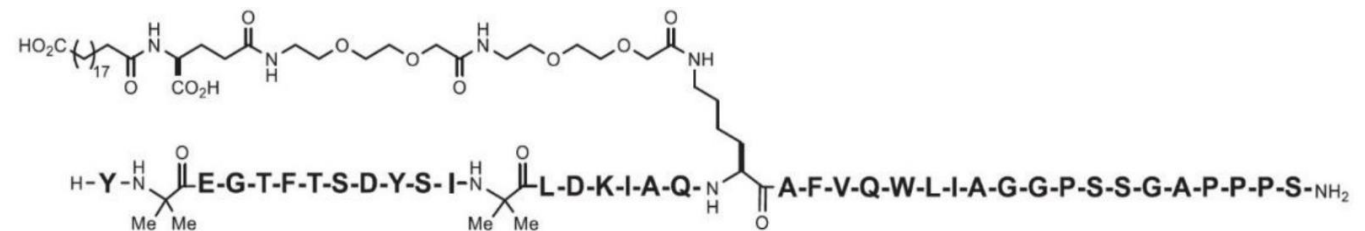
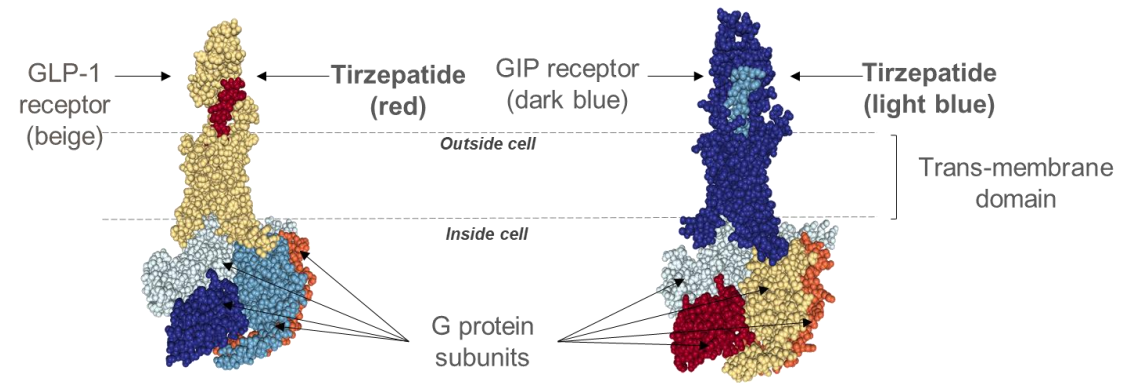


Summary

Tirzepatide: Molecular Structure and Properties



- Tirzepatide is a long-acting GIP receptor and GLP-1 receptor agonist¹
- Its amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life¹
- Mean half-life of approximately 5 days (116.7 h), enabling once-weekly dosing¹
- Its plasma concentrations in patients with renal and hepatic impairment do not differ from those in healthy people²



GIP=Glucose-Dependent Insulinotropic Polypeptide; GIPR=Glucose-Dependent Insulinotropic Polypeptide Receptor; GLP-1R=Glucagon-Like Peptide-1 Receptor.

1. Coskun T, et al. *Mol Metab.* 2018;18:3-14. 2. Urva S, et al. *Diabetes.* 2020;69(1):Abstract 971-P.

Study Design



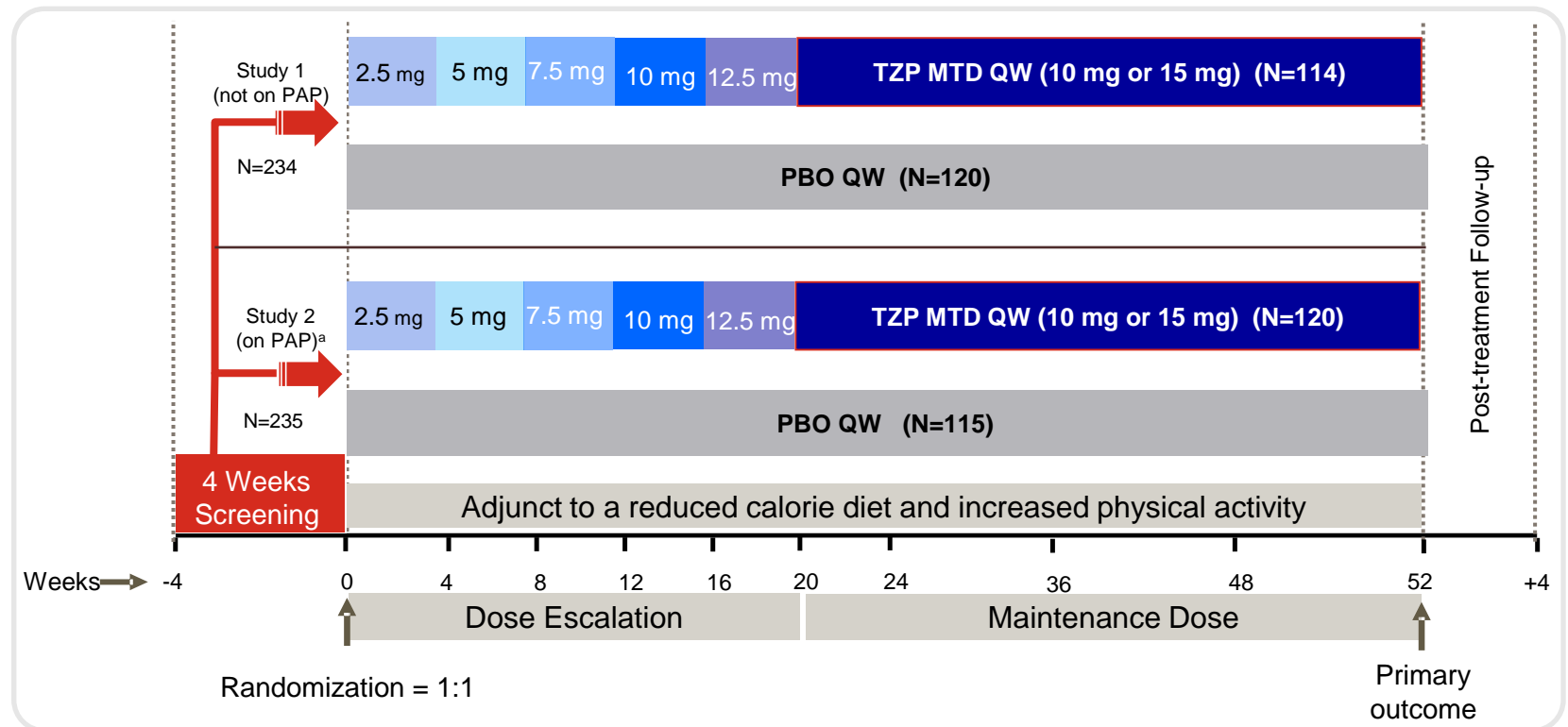
Phase 3, 52-week, randomized, double-blind, placebo-controlled master protocol to evaluate the efficacy and safety of TZP at the MTD (10 or 15 mg) vs. placebo as an adjunct to diet and exercise in participants with moderate-to-severe OSA (AHI ≥ 15 events/hour) and obesity (BMI ≥ 30 kg/m²) without T2D¹⁻³

Hypothesis:

TZP in people with OSA and obesity will yield important improvements in OSA severity as assessed by the AHI^{1,2}



US, Australia, Brazil, China, Czechia, Germany, Japan, Mexico and Taiwan³



^aParticipants in Study 2 were instructed to suspend PAP therapy for 7 days prior to PSG and PRO assessments at baseline, week 20, and week 52.

AHI=Apnea-Hypopnea Index; BMI=Body Mass Index; MTD=Maximum Tolerated Dose; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure; PBO=Placebo; PRO=Patient Reported Outcomes; PSG=Polysomnography; QW=Once Weekly; R=Randomization; T2D=Type 2 Diabetes; TZP=Tirzepatide.

1. Malhotra A, et al. *Contemp Clin Trials*. 2024;141:107516. 2. <https://clinicaltrials.gov/study/NCT05412004> (Accessed April 15, 2024). 3. Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Key Inclusion and Exclusion Criteria of Participants



AHI=Apnea-Hypopnea Index; BMI=Body Mass Index; BW=Body Weight; CMS=Centers for Medicare and Medicaid Services; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure; T1DM=Type 1 Diabetes Mellitus; T2DM=Type 2 Diabetes Mellitus.

1. Malhotra A, et al. *Contemp Clin Trials*. 2024;141:107516. 2. Malhotra A, et al. Poster presented at: APSS 2023. Poster: 171.

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Participant Disposition

SURMOUNT-OSA Study 2: Participants on PAP Therapy



Study 2 (N=235)

TZP (n=120)

PBO (n=115)

90.0% (108) stayed on treatment throughout the study
94.2% (113) completed the study period

73.9% (85) stayed on treatment throughout the study
77.4% (89) completed the study period

10.0% (12) discontinued study treatment

3.3% (4) AEs
3.3% (4) withdrawal by participants
1.7% (2) assigned treatment by mistake
0.8% (1) physician decision
0.8% (1) other

5.8% (7) discontinued study

3.3% (4) withdrawal by participants
1.7% (2) other
0.8% (1) AEs

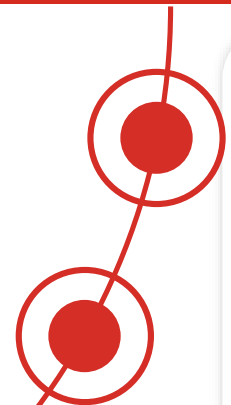
26.1% (30) discontinued study treatment

13.0% (15) withdrawal by participants
7.0% (8) AEs
3.5% (4) assigned treatment by mistake
0.9% (1) non-adherence to treatment
0.9% (1) screening failure
0.9% (1) other

22.6% (26) discontinued study

12.2% (14) withdrawal by participants
4.3% (5) AEs
2.6% (3) assigned treatment by mistake
2.6% (3) other
0.9% (1) screening failure

SURMOUNT-OSA Endpoints



Primary Endpoint^{1,2}

Change in AHI from baseline to Week 52

Key Secondary Endpoints^{1,2}

From baseline to Week 52:

- Percentage change in AHI
- Percentage of participants with clinically meaningful change in AHI^a
- Percentage of participants with OSA remission or mild nonsymptomatic OSA^b
- Change in SASHB
- Percentage change in body weight
- Change in inflammatory status (hsCRP)
- Change in PROMIS Short Form Sleep-Related Impairment 8a^c
- Change in PROMIS Short Form Sleep Disturbance 8b^c

From baseline to Week 48^d:

- Change in systolic BP

Graphical Testing Scheme 

^a%Participants with $\geq 50\%$ reduction in AHI.

^bPercent of participants with AHI < 5 or AHI 5-14 without excessive sleepiness measured by Epworth Sleepiness Scale ≤ 10 .

^cPROMIS type 1 error-controlled endpoints from both studies were pooled and tested using a distinct graphical testing scheme to provide relevant power for analysis.

^dBP was assessed at Week 48 because PAP suspension at Week 52 may confound BP measurement.

AHI=Apnea-Hypopnea Index; BP=Blood Pressure; hsCRP=High-Sensitivity C-reactive Protein; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure; PROMIS=Patient-Reported Outcomes Measurement Information System; SASHB=Sleep Apnea Specific Hypoxic Burden.

1. Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print). 2. <https://clinicaltrials.gov/study/NCT05412004> (Accessed April 17, 2024).

Baseline Characteristics

SURMOUNT-OA Study 2: Participants on PAP Therapy



Parameters	Total (N=235)	TZP (N=120)	PBO (N=115)	Parameters	Total (N=235)	TZP (N=120)	PBO (N=115)
Age (years)	51.7 ± 11.0	50.8 ± 10.7	52.7 ± 11.3	AHI, events/hour	49.5 ± 26.7	46.1 ± 22.4	53.1 ± 30.2
<50 years	99 (42.1)	54 (45.0)	45 (39.1)	OSA severity ^b , n (%)			
≥50 years	136 (57.9)	66 (55.0)	70 (60.9)	No Apnea	-	-	-
Female, n (%)	65 (27.7)	33 (27.5)	32 (27.8)	Mild (≥5 to <15 AHI events/hour)	2 (0.9)	0	2 (1.8)
Race/ethnicity, n (%)				Moderate (≥15 to <30 AHI events/hour)	72 (30.9)	37 (32.5)	35 (29.4)
Black or African American	11 (4.7)	8 (6.7)	3 (2.6)	Severe (≥30 AHI events/hour)	159 (68.2)	84 (70.6)	75 (65.8)
American Indian or Alaska Native	19 (8.1)	10 (8.3)	9 (7.9)	Missing	2	1	1
Asian	33 (14.1)	17 (14.2)	16 (14.0)	ESS	10.2 ± 4.5	10.8 ± 4.6	9.5 ± 4.4
White	171 (73.1)	85 (70.8)	86 (75.4)	SASHB, %min/hour ^c	137.0 (97.5)	132.2 (83.4)	142.1 (112.5)
Multiple	-	-	-	PROMIS Sleep-Related Impairment T-Score	55.2 ± 8.9	55.3 ± 8.4	55.0 ± 9.5
Hispanic or Latino	98 (41.9)	51 (44.7)	47 (39.2)	PROMIS Sleep Disturbance T-Score	55.9 ± 7.6	56.0 ± 7.6	55.7 ± 7.6
Body Weight, kg	115.5 ± 22.0	115.8 ± 21.5	115.1 ± 22.7	Hypertension, n (%)	182 (77.4)	91 (75.8)	91 (79.1)
Mean BMI ^a , kg/m ²	38.7 ± 6.0	38.6 ± 6.1	38.7 ± 6.0	Systolic BP (mmHg)	130.5 (13.5)	130.5 (14.3)	130.5 (12.8)
BMI category, n (%) ^a				Diastolic BP (mmHg)	81.8 (8.5)	83.2 (8.2)	80.5 (8.6)
<35	66 (28.3)	33 (27.7)	33 (28.9)	hsCRP (mg/L)	2.8 (125.8)	3.0 (124.3)	2.7 (127.5)
≥35 to <40	88 (37.8)	47 (39.5)	41 (36.0)	HbA1c (%)	5.63 ± 0.41	5.62 ± 0.37	5.65 ± 0.44
≥40	79 (33.9)	39 (32.8)	40 (35.1)	Prediabetes n (%)	133 (56.6)	69 (57.5)	64 (55.7)
Waist circumference, cm	121.2 ± 15.7	122.6 ± 16.6	119.8 ± 14.8	Dyslipidemia n (%)	197 (83.4)	100 (83.3)	97 (84.3)

Note: Data are mean±SD unless otherwise stated.

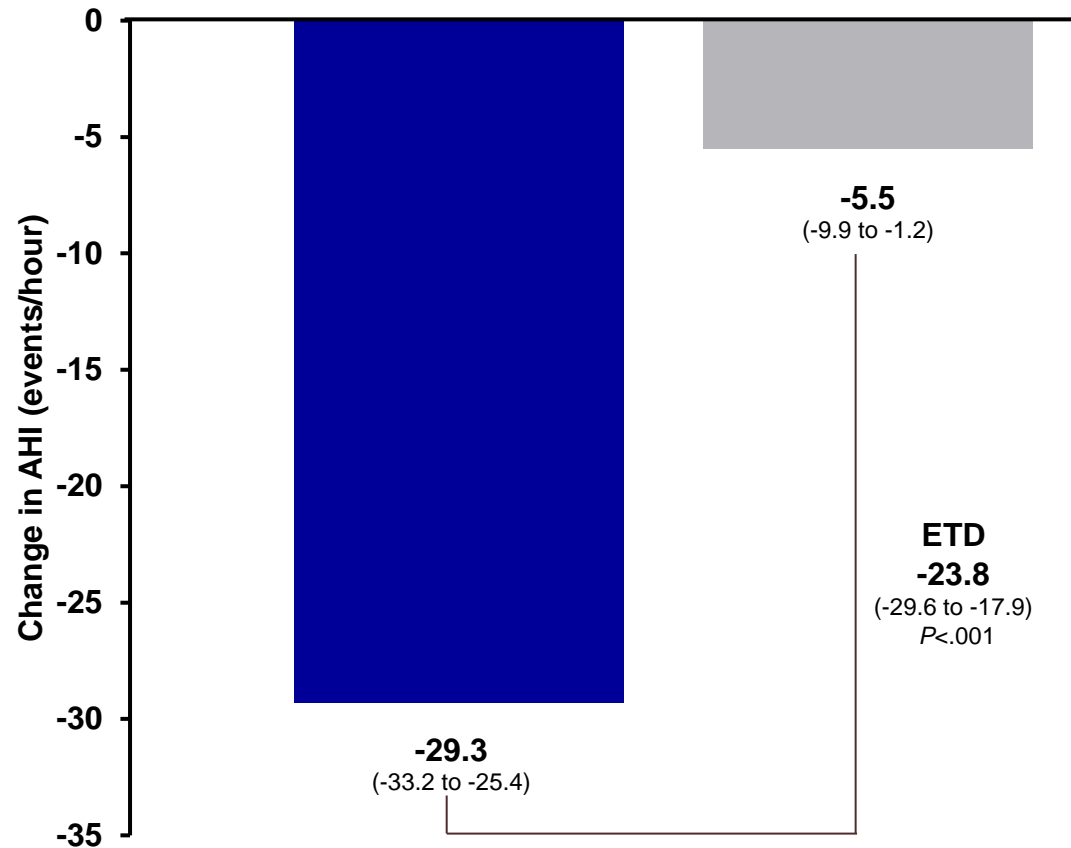
Footnotes, abbreviations and references are available in speaker notes section.

Primary Endpoint - Change in AHI

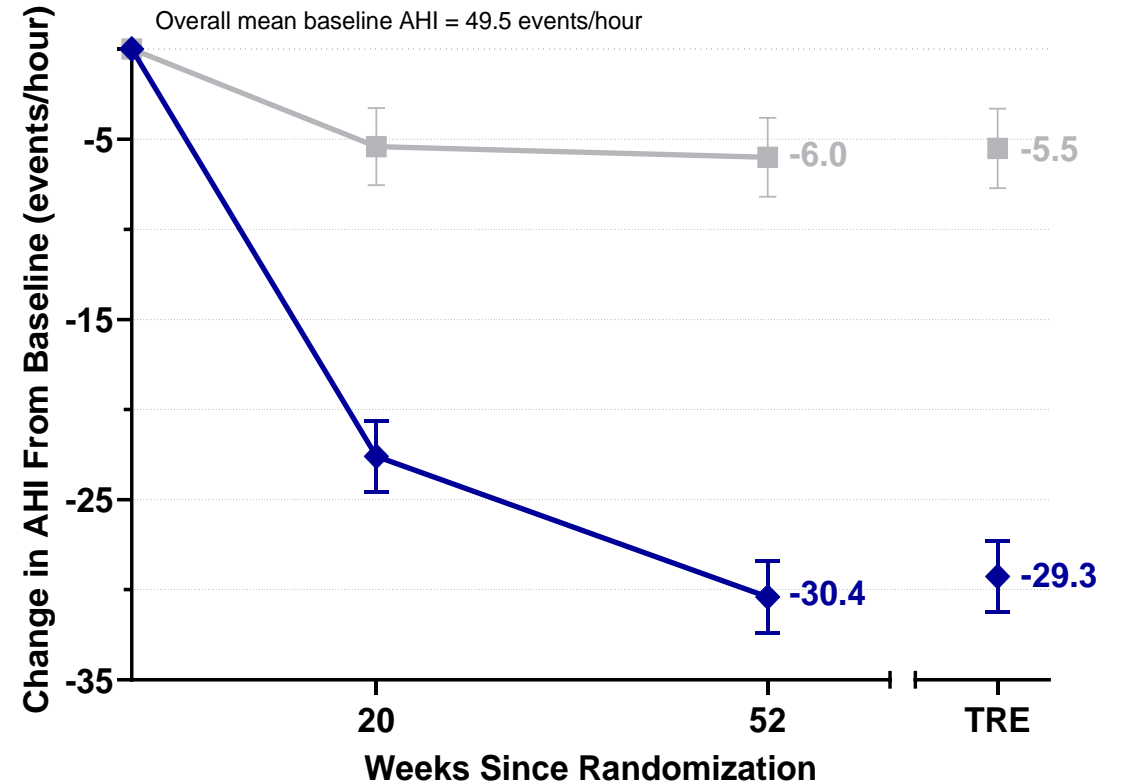
SURMOUNT-OA Study 2: Participants on PAP Therapy



Change From Baseline in AHI at Week 52 (TRE)



Change in AHI by Visit (Efficacy Estimand)



■ TZPa^a N=120 ■ PBO N=115

^aTZP MTD is a maximum tolerated dose of 10 mg or 15 mg once weekly. The starting dose of 2.5 mg TZP was increased by 2.5 mg every 4 weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD.

Note: Data are least-squares means (95% confidence interval) or n (%), unless otherwise stated. Changes are from baseline to Week 52.

AHI=Apnea-Hypopnea Index; ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

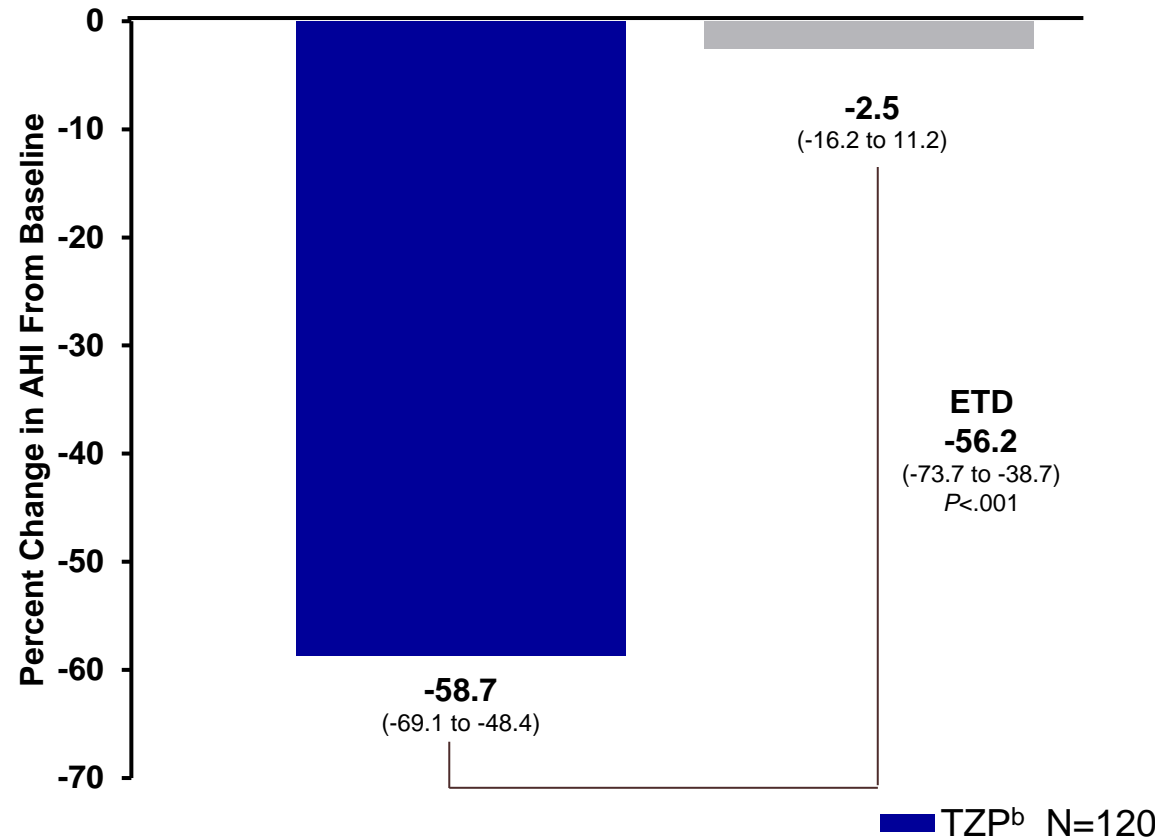
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Change in Sleep Disordered Breathing-Related Endpoints

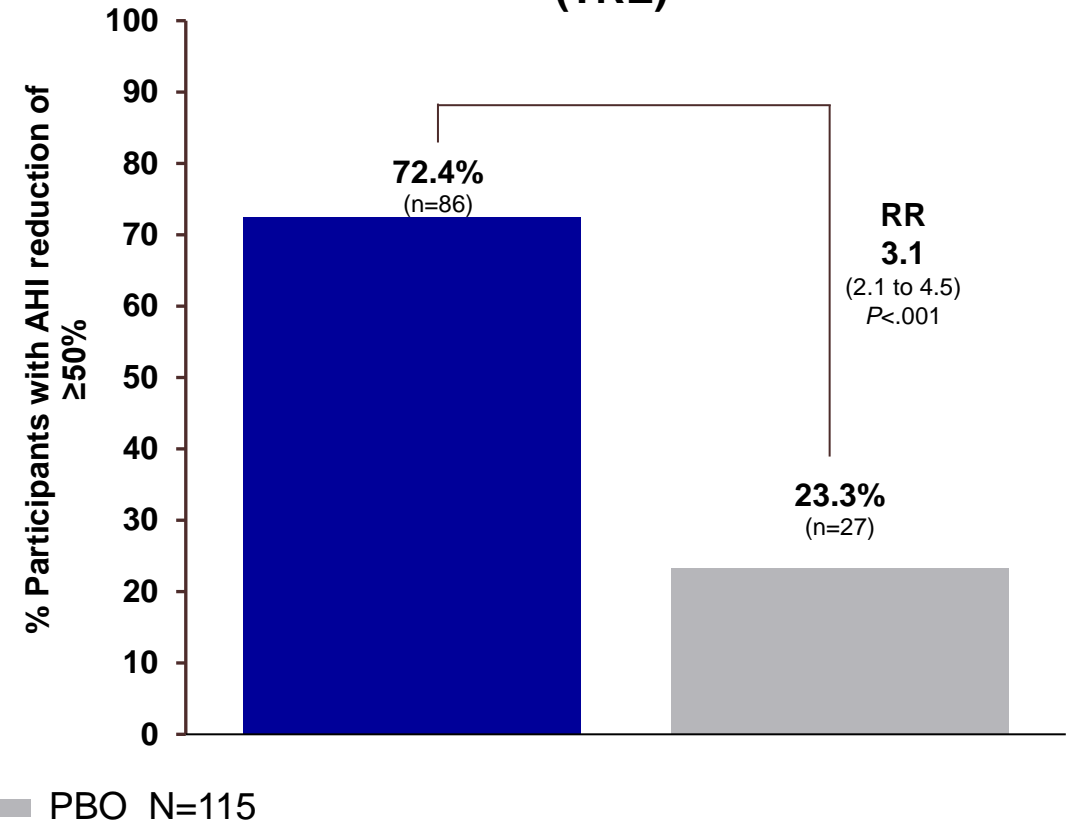


SURMOUNT-OA Study 2: Participants on PAP Therapy (1 of 2)

Percent Change From Baseline in AHI at Week 52 (TRE)



Participants with AHI Reduction of ≥50% at Week 52^a (TRE)



Percent change in AHI at 52 weeks and participants with AHI reduction of ≥50% at 52 weeks were key secondary endpoints.

^aRRs are calculated using g-computation methods from logistic regression. P-values for categorical endpoints are based on logistic regression model.

^bTZP MTD is a maximum tolerated dose of 10 mg or 15 mg once weekly. The starting dose of 2.5 mg TZP was increased by 2.5 mg every 4 weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD.

Note: Data are least-squares means (95% confidence interval) or n (%), unless otherwise stated. Changes are from baseline to Week 52.

AHI=Apnea-Hypopnea Index; ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; RR=Relative Risk; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

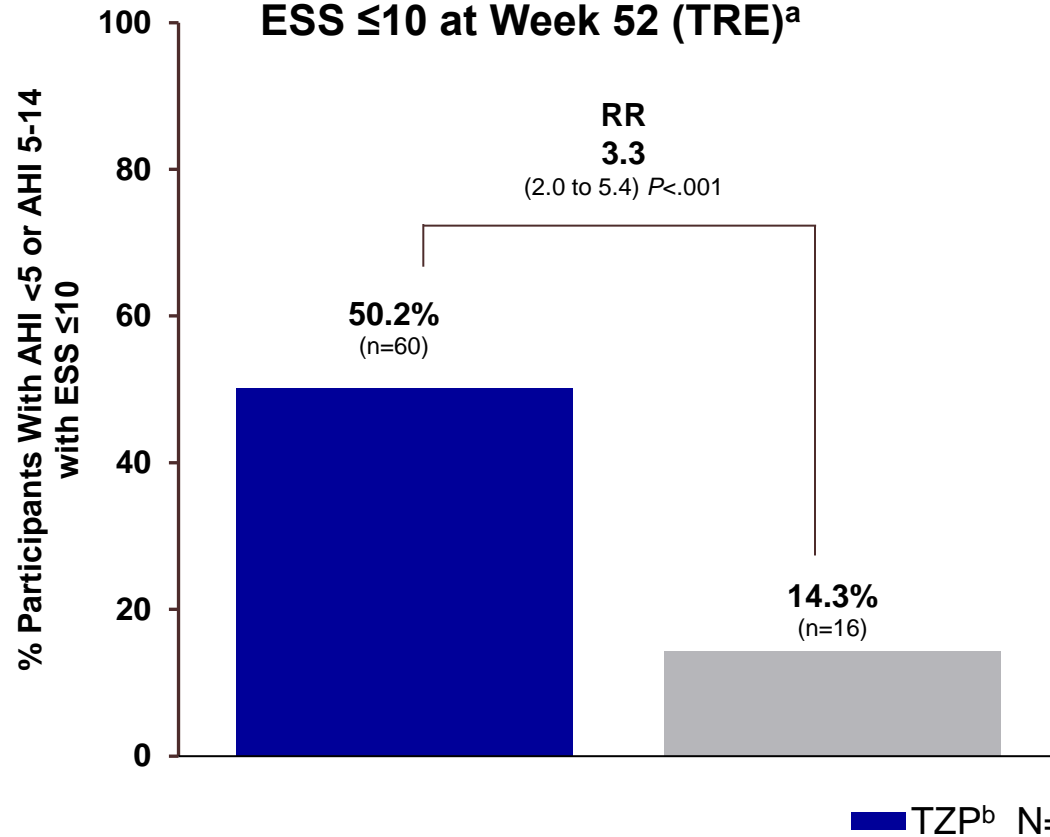
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Change in Sleep Disordered Breathing-Related Endpoints

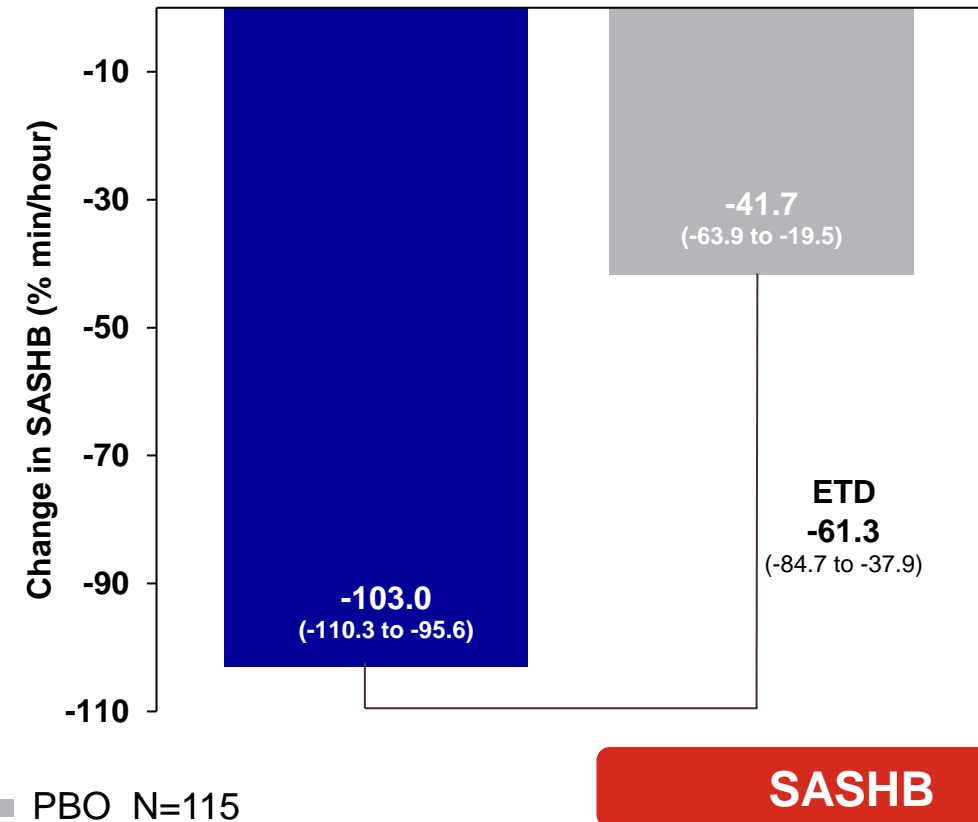


SURMOUNT-OA Study 2: Participants on PAP Therapy (2 of 2)

Participants With AHI <5 or AHI 5-14 With ESS ≤10 at Week 52 (TRE)^a



Change From Baseline in SASHB at Week 52 (TRE)



SASHB

Percent of participants with AHI <5 or AHI 5-14 with ESS ≤10 at Week 52 and change in SASHB at Week 52 were key secondary endpoints.

^aRRs are calculated using g-computation methods from logistic regression. *P*-values for categorical endpoints are based on logistic regression model.

^bTZP MTD is a maximum tolerated dose of 10 mg or 15 mg once weekly. The starting dose of 2.5 mg TZP was increased by 2.5 mg every 4 weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD.

Note: Data are least-squares means (95% confidence interval) or n (%), unless otherwise stated. Changes are from baseline to Week 52.

AHI=Apnea-Hypopnea Index; ESS=Epworth Sleepiness Scale; ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; RR=Relative Risk; SASHB=Sleep Apnea Specific Hypoxic Burden; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.

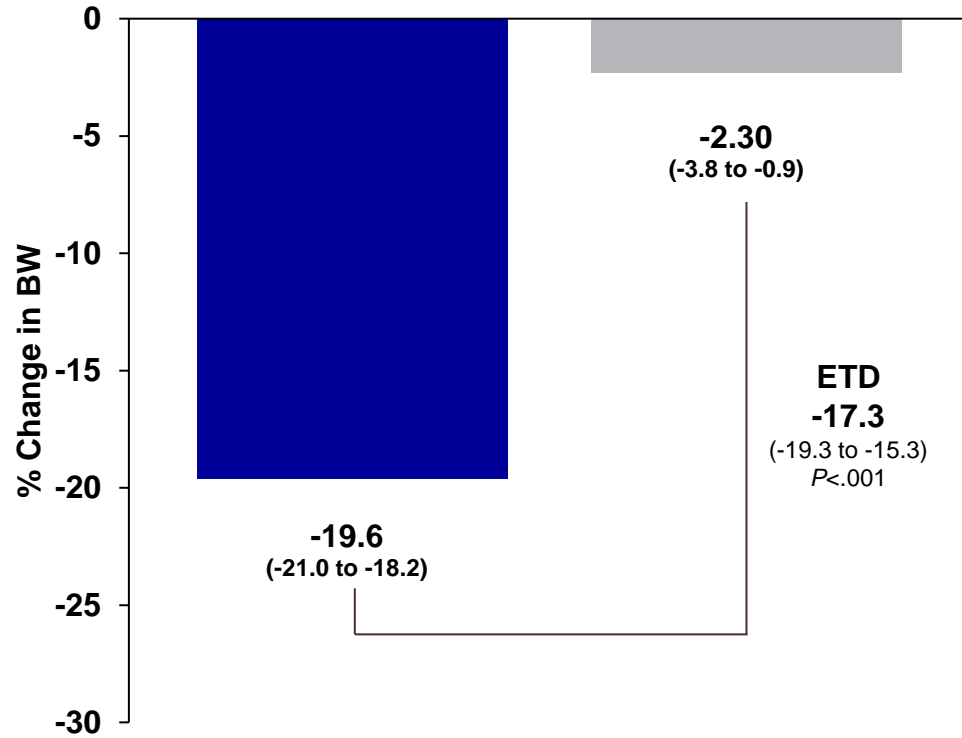
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Change in BW

SURMOUNT-OSA Study 2: Participants on PAP Therapy

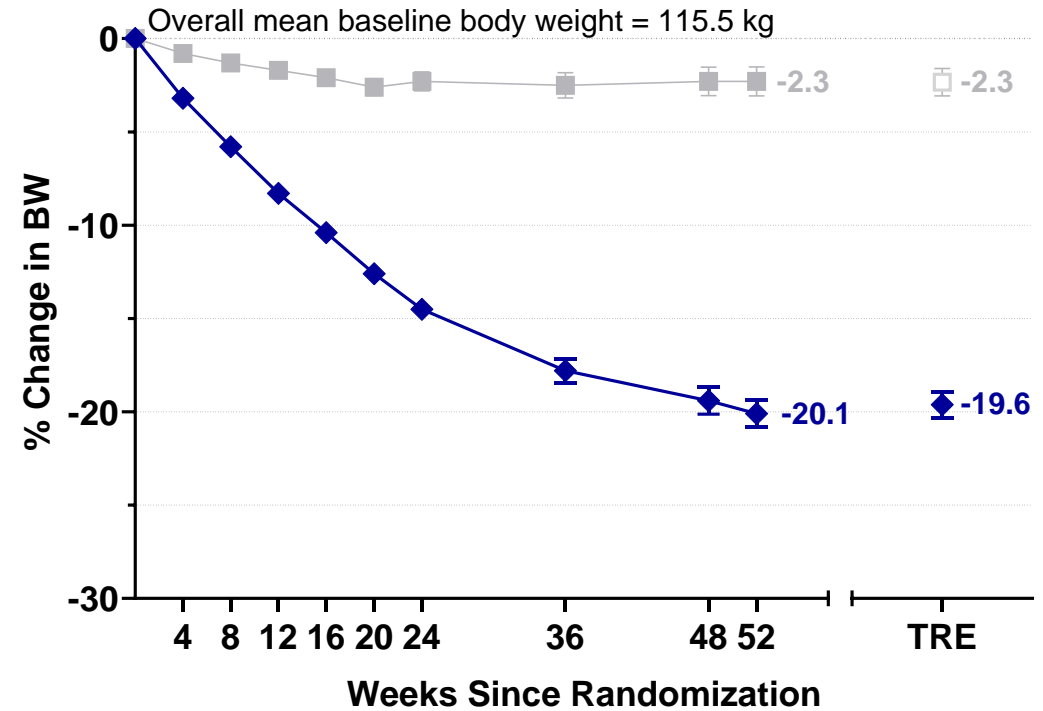


Percent Change in BW (TRE)



■ TZPa^a N=120 ■ PBO N=115

Percent Change in BW by Visit (Efficacy Estimand)



Percent change in BW at Week 52 was a key secondary endpoint.

^aTZP MTD is a maximum tolerated dose of 10 mg or 15 mg once weekly. The starting dose of 2.5 mg TZP was increased by 2.5 mg every 4 weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD.

Note: Data are least-squares means (95% confidence interval) or n (%), unless otherwise stated. Changes are from baseline to Week 52.

AHI=Apnea-Hypopnea Index; BW=Body Weight; ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.

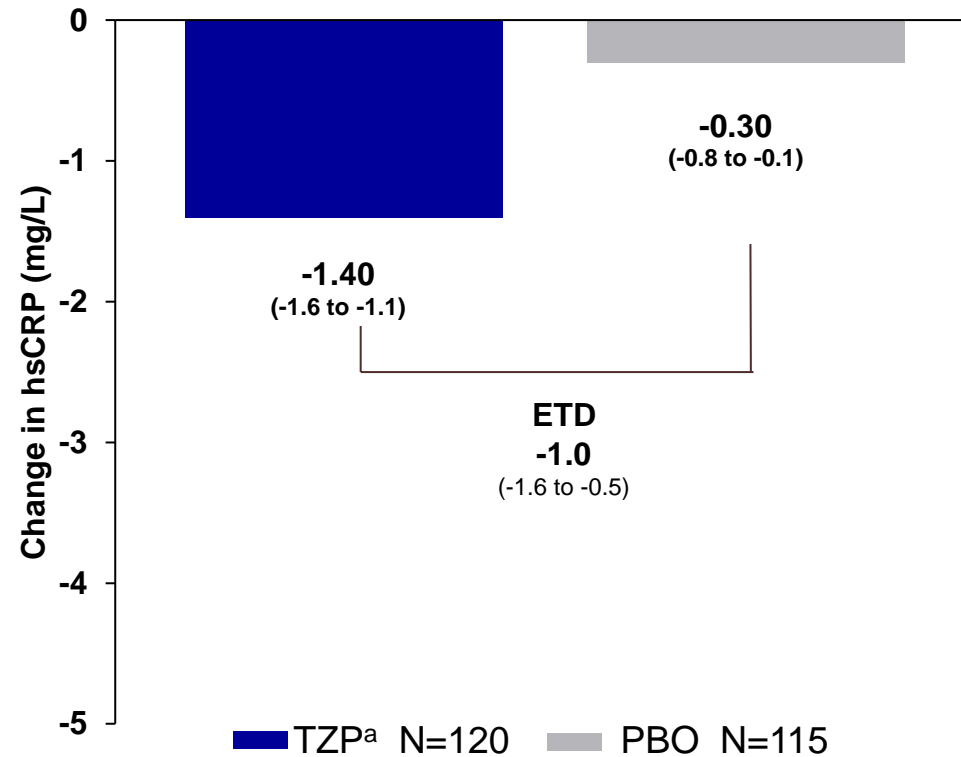
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Change in hsCRP

SURMOUNT-OSA Study 2: Participants on PAP Therapy



Change From Baseline in hsCRP at Week 52 (TRE)



Change in hsCRP was a key secondary endpoint.

^aTZP MTD is a maximum tolerated dose of 10 mg or 15 mg once weekly. The starting dose of 2.5 mg TZP was increased by 2.5 mg every 4 weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD.

Note: Data are least-squares means (95% confidence interval) or n (%), unless otherwise stated. Changes are from baseline to Week 52.

ETD=Estimated Treatment Difference; hsCRP=High-Sensitivity C-reactive Protein; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.

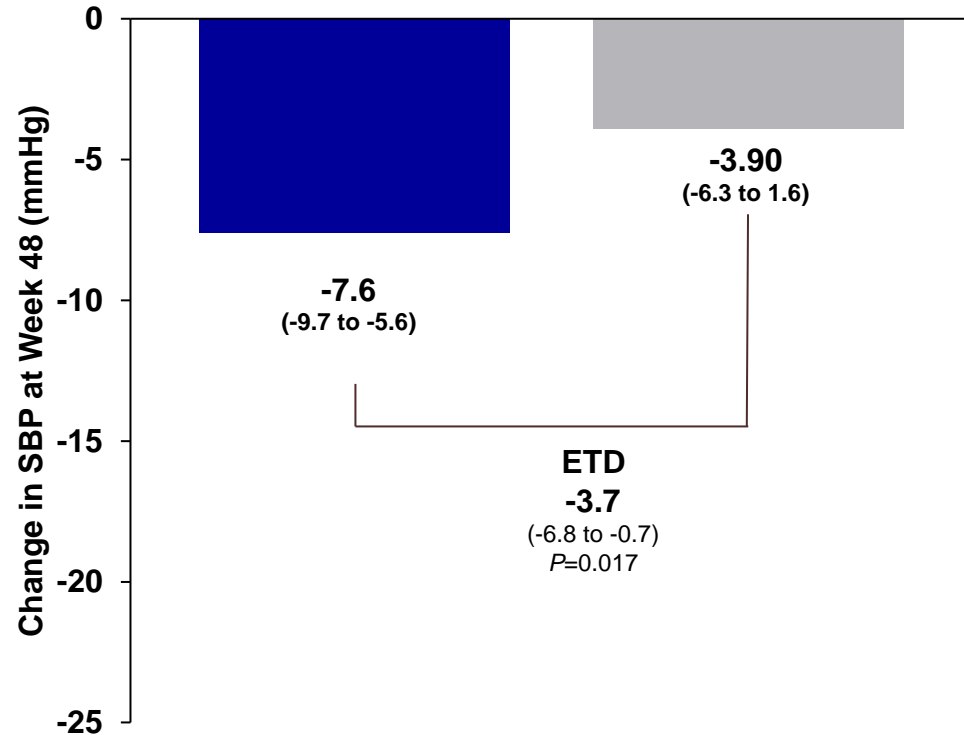
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Change in BP

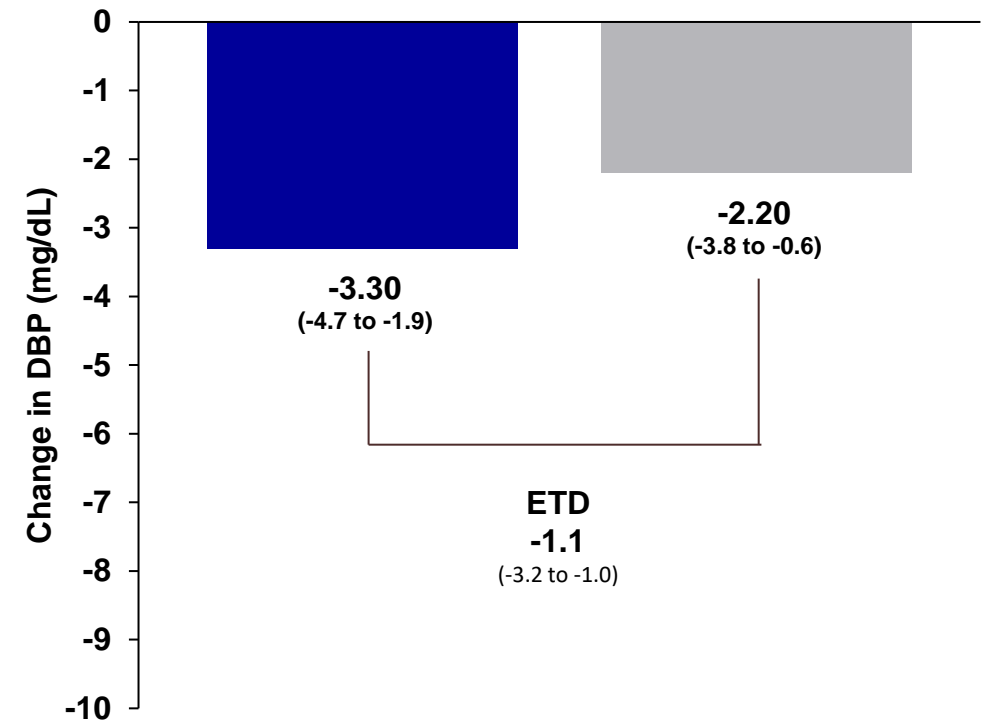
SURMOUNT-OSA Study 2: Participants on PAP Therapy



Change From Baseline in SBP at Week 48^a (TRE)



Change From Baseline in DBP at Week 48^{a,b} (TRE)



■ TZP^c N=120 ■ PBO N=115

SBP was a key secondary endpoint and DBP was an additional secondary endpoint.^b

^aBP was assessed at Week 48 because PAP suspension at Week 52 may confound BP measurement.

^bConfidence intervals for any endpoint that is not part of the primary or key secondary endpoints, have not been adjusted for multiplicity and should not be used to make inferences.

^cTZP MTD is a maximum tolerated dose of 10 mg or 15 mg once weekly. The starting dose of 2.5 mg TZP was increased by 2.5 mg every 4 weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD.

Note: Data are least-squares means (95% confidence interval) or n (%), unless otherwise stated.

BP=Blood Pressure; DBP=Diastolic Blood Pressure; ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; SBP=Systolic Blood Pressure; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.

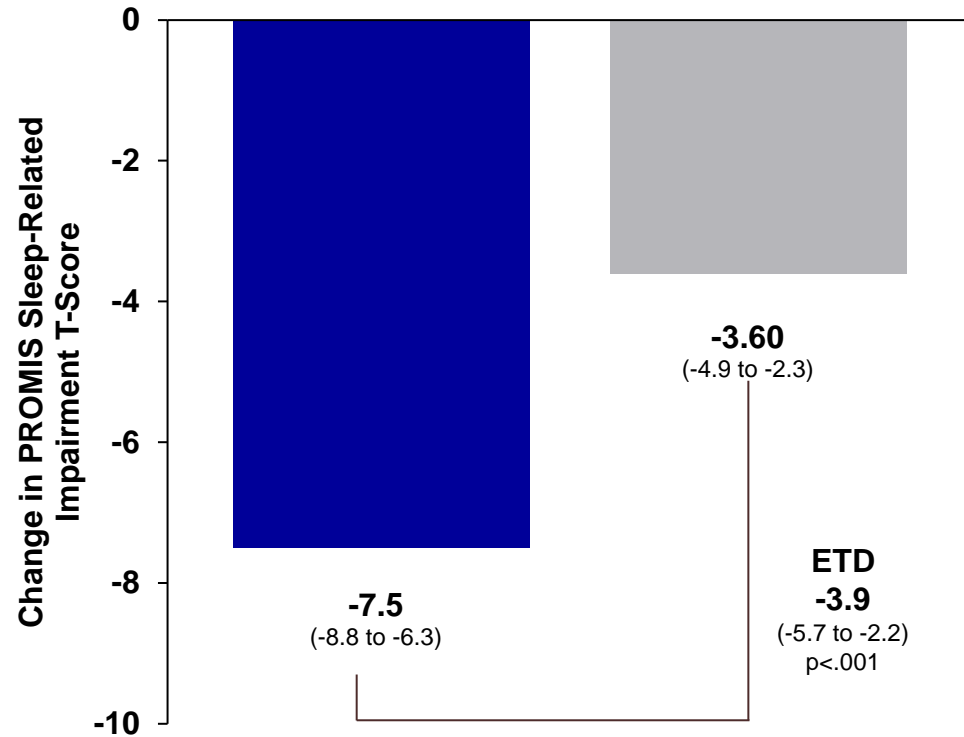
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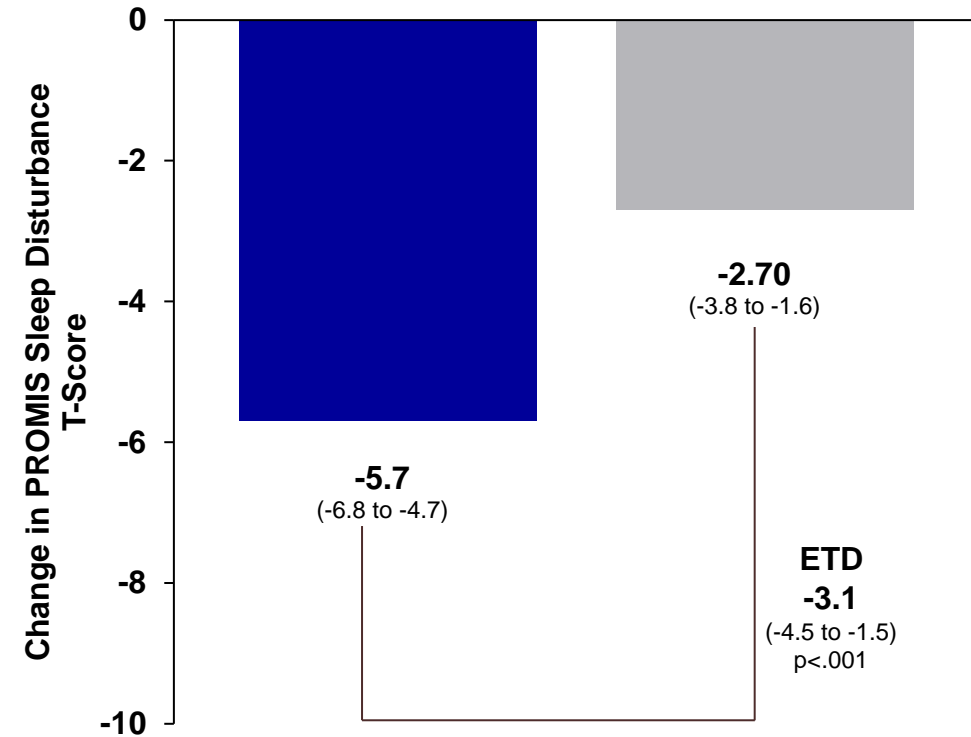
Pooled Study 1 and Study 2 Patient-Reported Outcomes



Change in PROMIS Sleep-Related Impairment T-Score From Baseline to Week 52



Change in PROMIS Sleep Disturbance T-Score From Baseline to Week 52



■ TZP^a N=234 ■ PBO N=233

Graphical testing scheme

Study 1 PROs

Study 2 PROs

Footnotes, abbreviations and references are available in speaker notes section.
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Adverse Events

SURMOUNT-OSA Study 2: Participants on PAP Therapy



AEs	TZP (N=119)	PBO (N=114)
Participants with ≥1 treatment-emergent AEs	99 (83.2)	83 (72.8)
SAEs	7 (5.9)	12 (10.5)
AEs leading to discontinuation of TZP or PBO or placebo	4 (3.4)	8 (7.0)
AEs occurring in ≥5% of participants in any treatment group		
Diarrhea	26 (21.8)	10 (8.8)
Nausea	26 (21.8)	6 (5.3)
Vomiting	11 (9.2)	1 (0.9)
Constipation	18 (15.1)	5 (4.4)
Eructation	10 (8.4)	1 (0.9)
GERD	6 (5.0)	0 (0.0)
Injection site reaction	6 (5.0)	0 (0.0)
Abdominal pain	5 (4.2)	2 (1.8)
URTI	5 (4.2)	8 (7.0)
COVID-19	8 (6.7)	11 (9.6)
Nasopharyngitis	15 (12.6)	12 (10.5)
Dyspepsia	11 (9.2)	1 (0.9)
Gastroenteritis	8 (6.7)	1 (0.9)
Upper Abdominal Pain	7 (5.9)	2 (1.8)
Influenza	3 (2.5)	3 (2.6)
Arthralgia	4 (3.4)	5 (4.4)
Bronchitis	3 (2.5)	7 (6.1)
Hypertension	2(1.7)	2 (1.8)

No cases of death reported.

AE=Adverse Event; GERD=Gastro-esophageal Reflux Disorder; PAP=Positive Airway Pressure; PBO=Placebo; SAE=Serious Adverse Event; TZP=Tirzepatide; URTI=Upper Respiratory Tract Infection.

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

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Other Adverse Events of Special Interest

SURMOUNT-OSA Study 2: Participants on PAP Therapy



AEs of Special Interest	TZP (N=114)	PBO (N=120)
Severe hypoglycemia	0 (0.0)	0 (0.0)
Adjudication-confirmed MACE	0 (0.0)	1 (0.9)
Treatment-emergent arrhythmias and cardiac conduction disorders	6 (5.0)	2 (1.8)
Severe or serious GI events ^a	4 (3.4)	0 (0.0)
Severe or serious acute renal events	1 (0.8)	0 (0.0)
Adjudication-confirmed acute pancreatitis	2 (1.7)	0 (0.0)
Severe or serious major depressive disorder/suicidal behavior and ideation events	0 (0.0)	2 (1.8)

In Study 2, there were no cases reported of severe or serious hepatic events, C-cell hyperplasia and thyroid malignancies or severe or serious allergic/hypersensitivity reactions including injection site reactions and antidrug antibody formation.






^a3 participants had diarrhea; 2 had nausea and 1 had acute pancreatitis.

AE=Adverse Event; GI= Gastrointestinal; MACE=Major Adverse Cardiac Event; PAP=Positive Airway Pressure; PBO=Placebo; TZP=Tirzepatide.

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

SURMOUNT-OSA Summary



-  SURMOUNT-OSA included two Phase 3 double-blind, randomized, placebo-controlled studies: Study 1 - participants not on PAP therapy; n=234; Study 2 - participants on PAP therapy; n=235
-  Adults with moderate-to-severe OSA and obesity demonstrated a significant and clinically relevant^a decrease in AHI with TZP treatment compared to PBO
-  TZP demonstrated significant improvement in AHI, BW, sleep-related patient-reported outcomes^b, hsCRP, SBP and SASHB in participants with moderate-severe OSA and obesity
-  The safety and tolerability profile of TZP in participants with moderate-to-severe OSA and obesity was consistent with the safety profile of TZP reported in previous trials
-  The most frequent adverse events were gastrointestinal-related and were mild to moderate

^aAccording to the AASM, a clinically significant threshold for AHI is defined as ≥ 15 events/hour.

^bIncludes pooled analysis of PROMIS Sleep-Related Impairment and PROMIS Sleep Disturbance.

AASM=American Academy of Sleep Medicine; AHI=Apnea-Hypopnea Index; BW=Body Weight; hsCRP=High-Sensitivity C-reactive Protein; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure; SASHB=Sleep Apnea Specific Hypoxic Burden; SBP=Systolic Blood Pressure; TZP=Tirzepatide.

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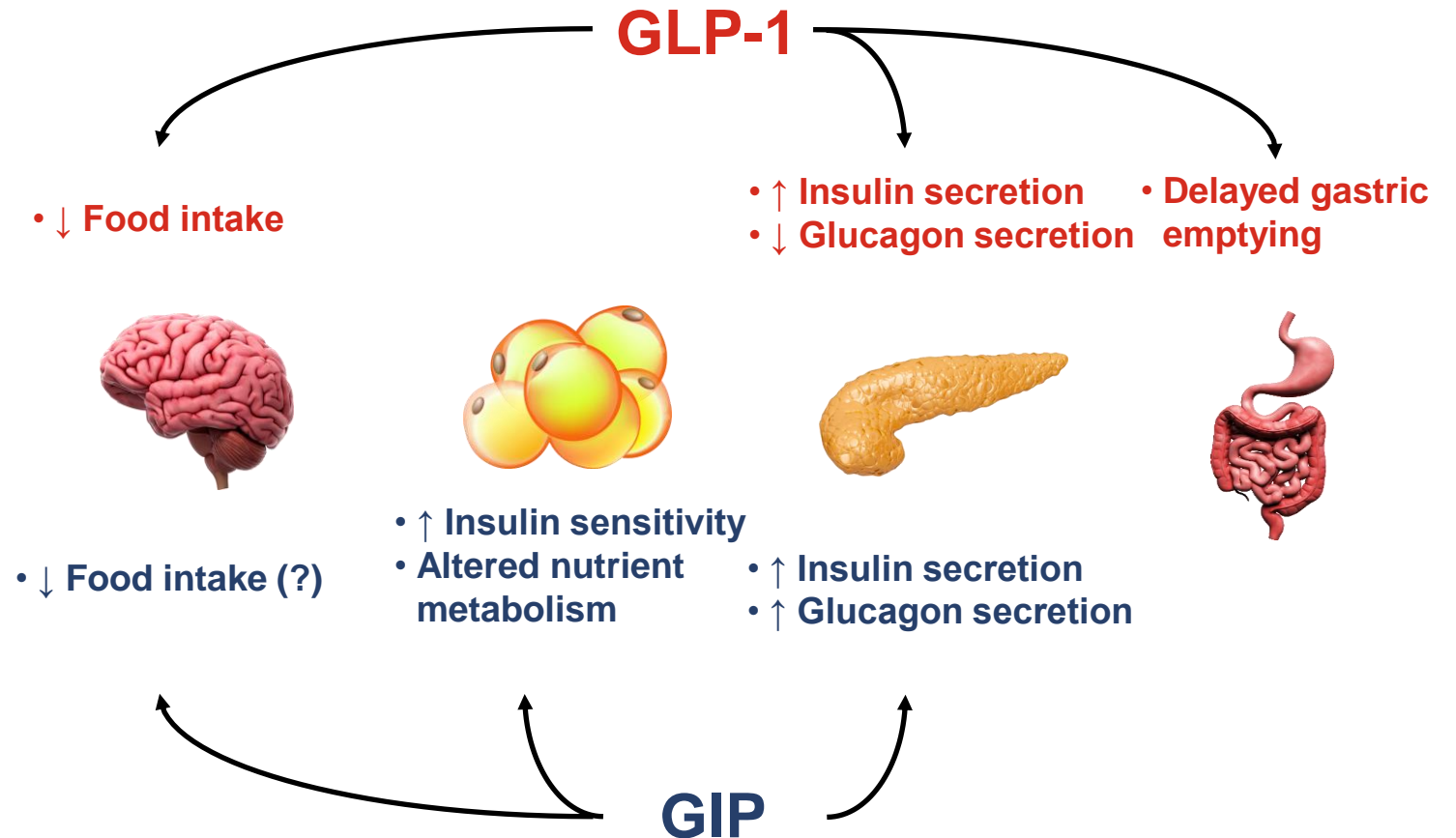
Backup

Lilly

GIP and GLP-1 Receptor Agonist: Potential Mechanism of Action



- GLP-1 has suggested direct actions in the CNS, islets, and stomach^{1,2}
- GIP has shown potential actions in research in the CNS (preclinical), adipose tissue (clinical and preclinical), and islets (clinical and preclinical)²⁻⁴
- A single-molecule GIP/GLP-1 receptor agonist may enable therapeutic actions that are improved over the sum of GIP and GLP-1 single-receptor agonism^{5,6}



CNS=Central Nervous System; GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1=Glucagon-Like Peptide-1.

1. Müller TD, et al. *Mol Metab.* 2019;30:72-130. 2. Seino Y, et al. *J Diabetes Investig.* 2010;1(1-2):8-23. 3. Fukuda M. *Diabetes.* 2021;70(8):dbi210001. 4. Nauck MA, et al. *Diabetes Obes Metab.* 2021;23(3):5-29. 5. Samms RJ, et al. *Trends Endocrinol Metab.* 2020;31(6):410-421. 6. Bastin M, et al. *Diabetes Metab Syndr Obes.* 2019;12:1973-1985.

Tirzepatide: Mechanism of Action



CNS

Appetite, feeding behavior



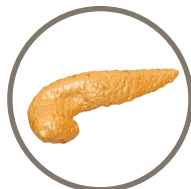
Liver

Liver fat content



Pancreas

Insulin secretion, glucagon regulation



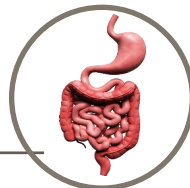
Cardiovascular

Lipid regulation



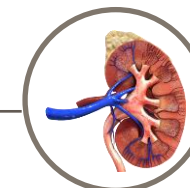
GI tract

Delayed gastric emptying



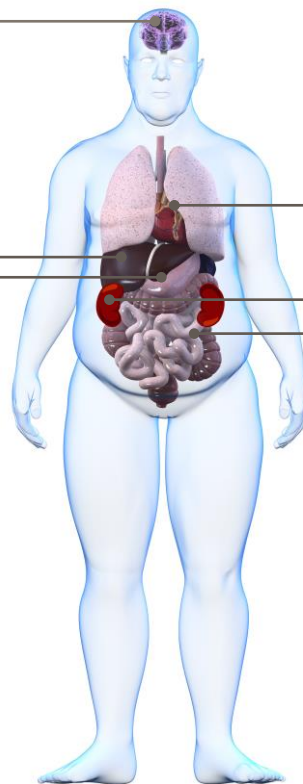
Kidney

Proteinuria and renal function



Systemic Effects

Insulin sensitivity



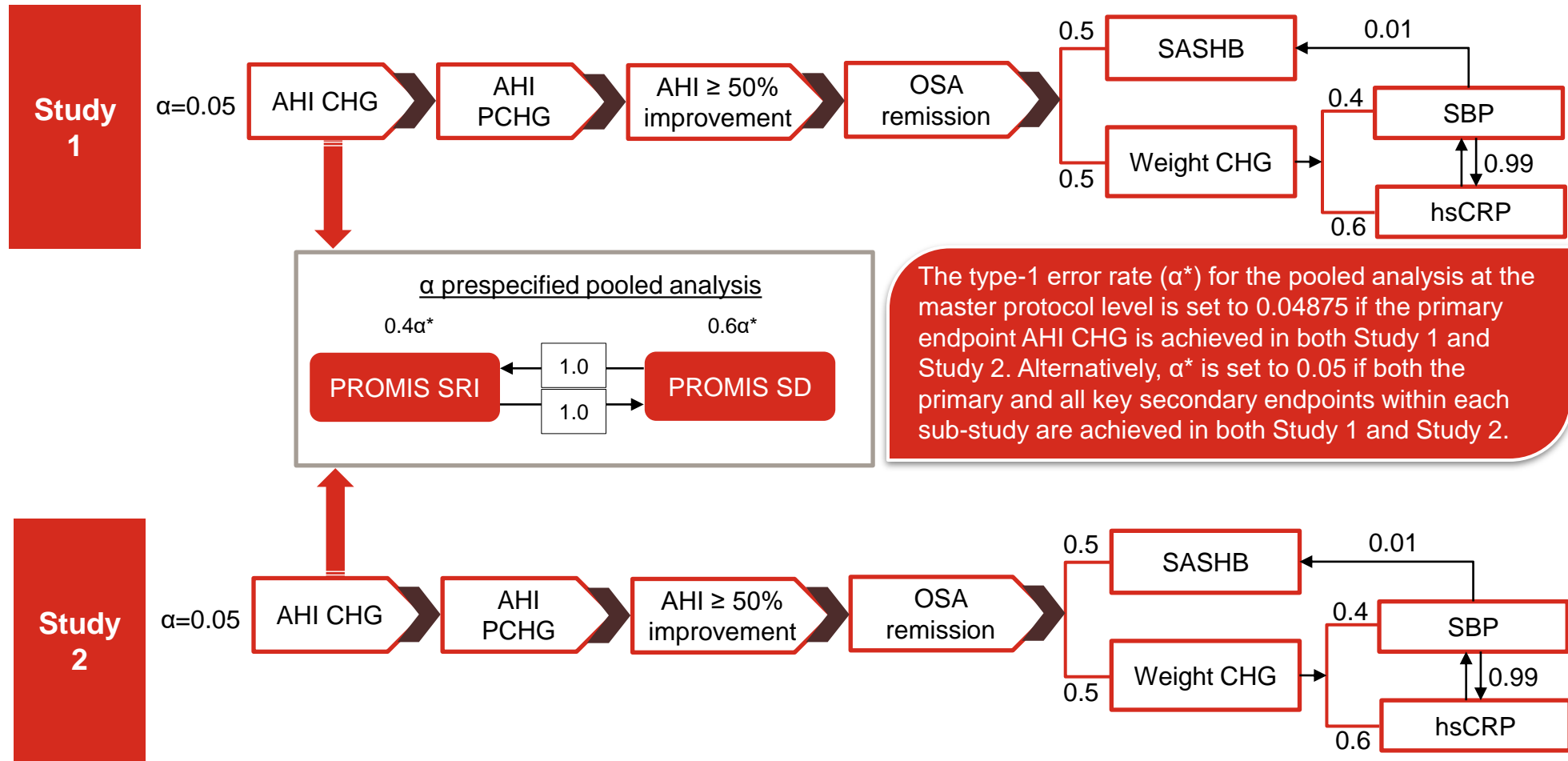
CNS=Central Nervous System; GI=Gastrointestinal.

1. Heise T, et al. Oral presentation at: ADA 2022. Abstract 338-OR. 2. Heise T, et al. *Lancet Diabetes Endocrinol.* 2022;10(6):418-429. 3. Gastaldelli A, et al. *Lancet Diabetes Endocrinol.* 2022;10(6):393-406. 4. Samms RJ, et al. *Trends Endocrinol Metab.* 2020;31(6):410-421. 5. Patel H, et al. Oral presentation at: 58th EASD. Abstract 568.

SURMOUNT-OSA Endpoints



Pre-specified Multiplicity Control for SURMOUNT-OSA Master Protocol



The type-1 error rate (α^*) for the pooled analysis at the master protocol level is set to 0.04875 if the primary endpoint AHI CHG is achieved in both Study 1 and Study 2. Alternatively, α^* is set to 0.05 if both the primary and all key secondary endpoints within each sub-study are achieved in both Study 1 and Study 2.

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

^a%Part
^bPerce
^cPROM
^dBP wa
AHI=Ap
Airway P

1. Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print). 2. <https://clinicaltrials.gov/study/NCT05412004> (Accessed April 17, 2024).

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Change in Sleep Disordered Breathing-Related Endpoints

SURMOUNT-OA Study 2: Participants on PAP Therapy (2 of 2)



% Participants With AHI <5 or AHI 5-14 with ESS ≤10

Percent
RRs are
TZP MT
Participa
Note: Data

AHI=Apnea-Hypopnea Index; ESS=Epworth Sleepiness Scale; ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; RR=Relative Risk; SASHB=Sleep Apnea Specific Hypoxic Burden; TRE=Treatment-Regimen Estimand; TZP=Tirzepatide.
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

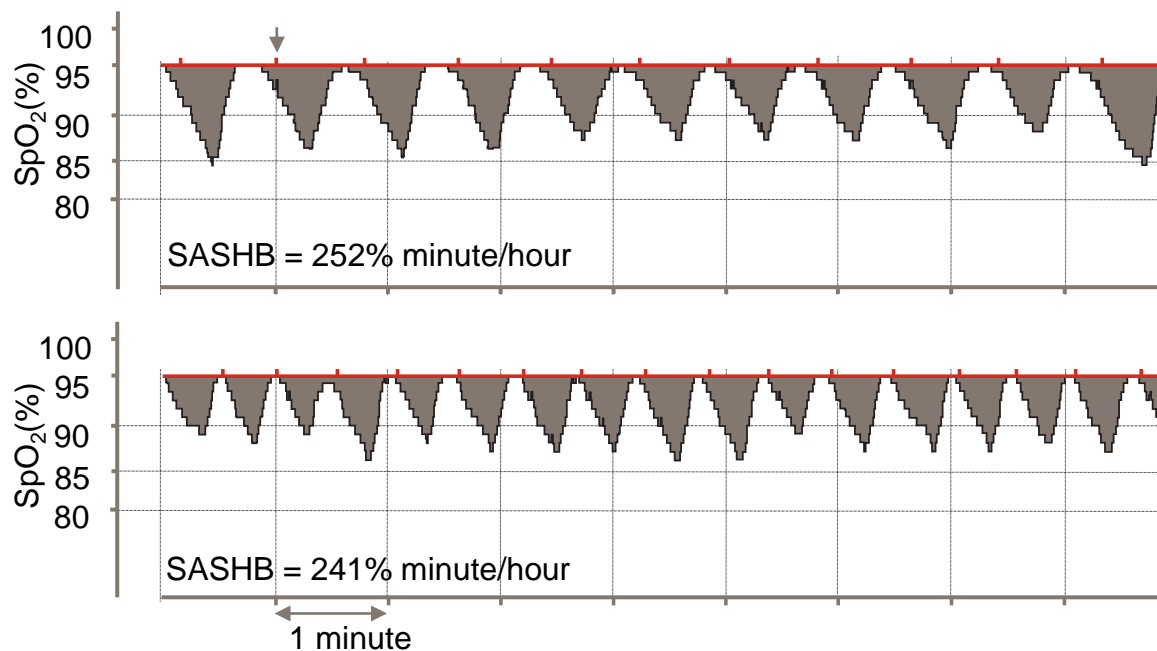
Sleep Apnea-Specific Hypoxic Burden (SASHB)



- Area under the curve below the pre-event SpO₂ baseline
 - Expressed as %minutes/hour
- (SASHB of 50%min/h = 5% reduction in SpO₂ below baseline for 10 min every hour of sleep)

Cardiovascular outcomes are more strongly and consistently (across cohorts) associated with a quantitative measure of SASHB than the usual measure of respiratory event frequency (AHI)

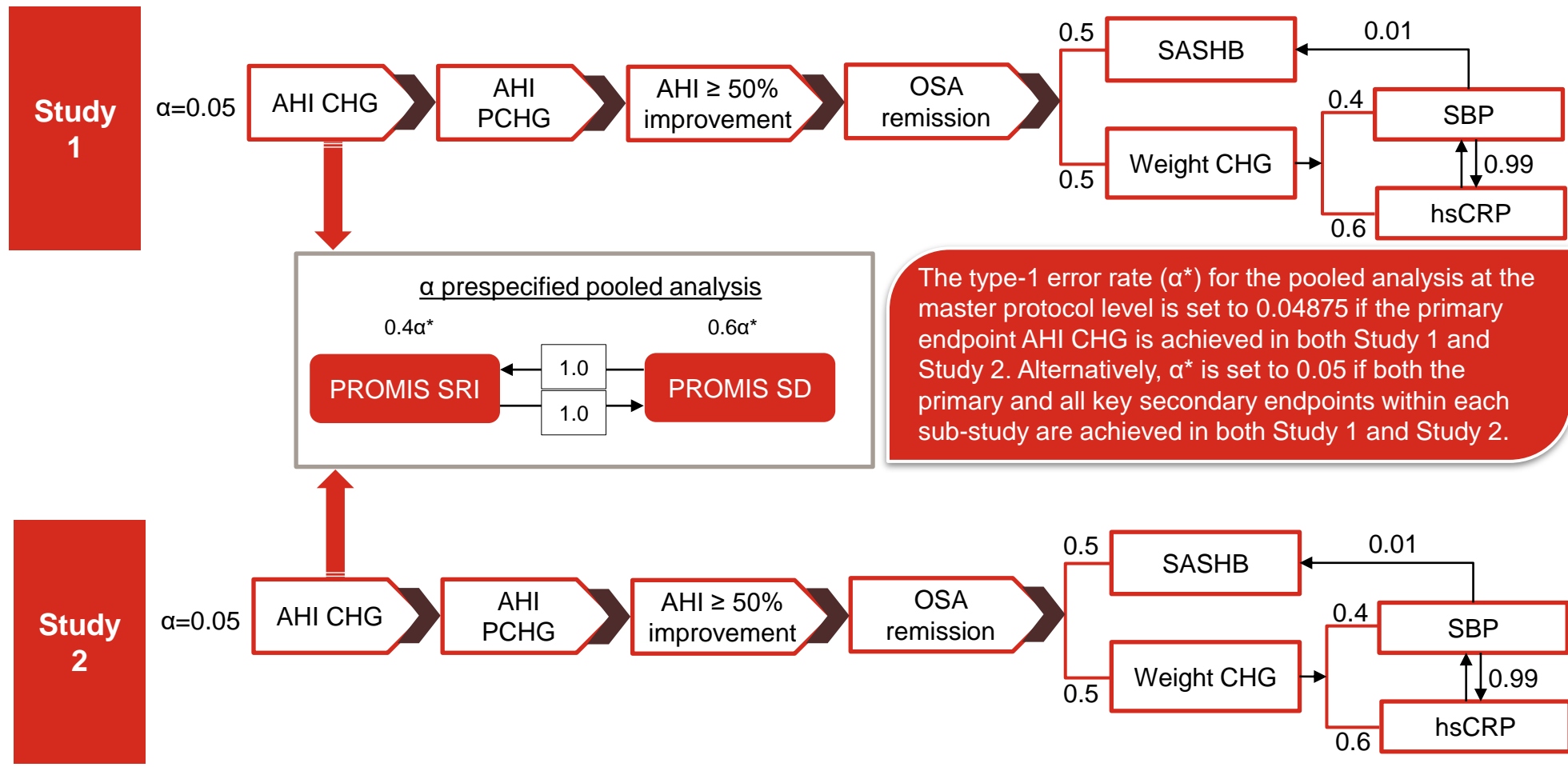
Azarbarzin A, et al. *Chest*. 2020;158(2):739-750.





Pre-specified Multiplicity Control for SURMOUNT-OSA Master Protocol

Change in PROMIS Sleep-Related



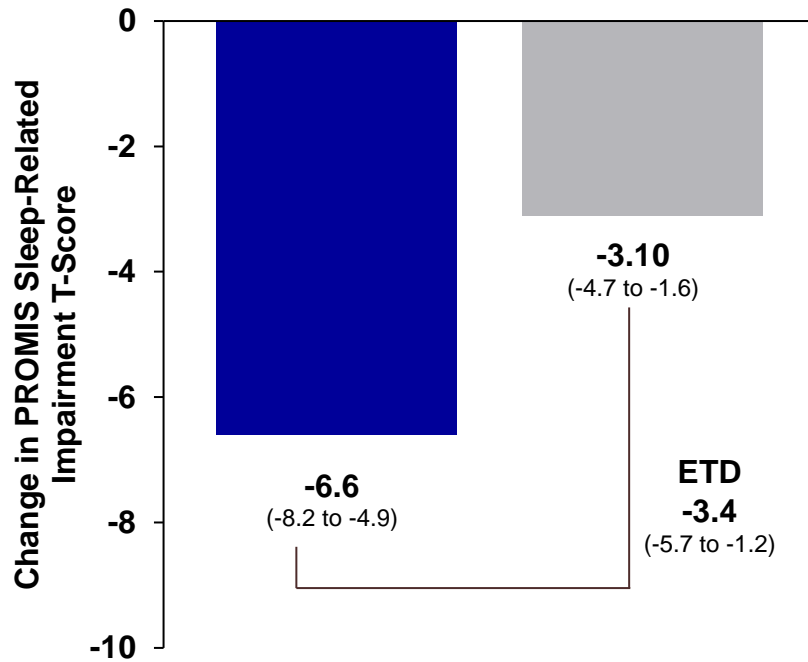
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Footnotes:
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

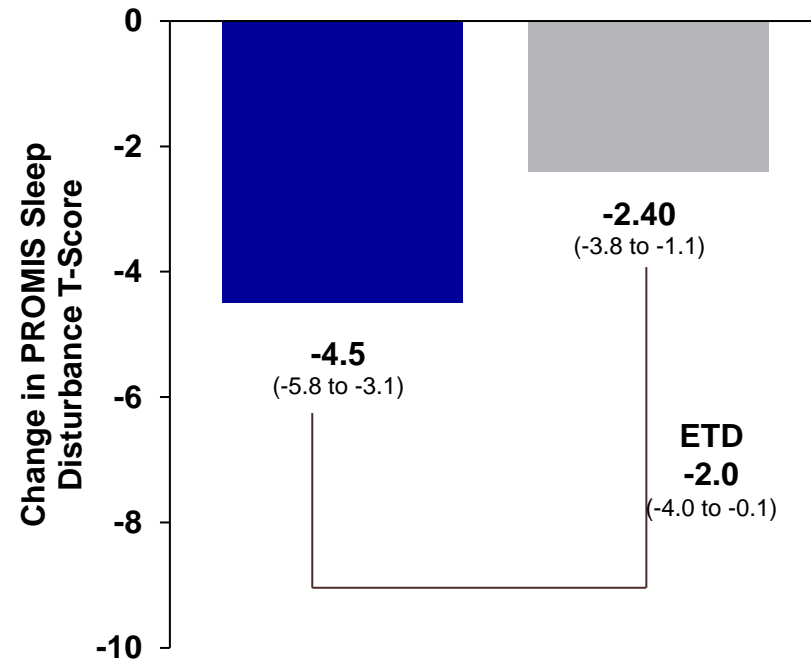
Pooled Study 1 and Study 2 Patient-Reported Outcomes

Study 1 Patient-Reported Outcomes

Change in PROMIS Sleep-Related Impairment T-Score from Baseline to Week 52



Change in PROMIS Sleep Disturbance T-Score from Baseline to Week 52



■ TZP N=114 ■ PBO N=120

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Footnotes, abbreviations and references are available in speaker notes section.

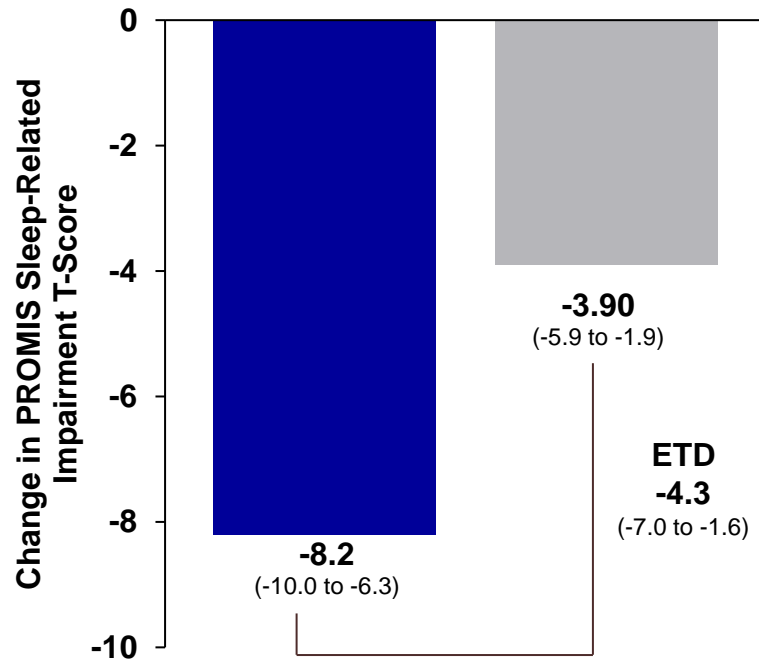
ETD=Estimated Treatment Difference; MTD=Maximum Tolerated Dose; PAP=Positive Airway Pressure; PBO=Placebo; PROMIS=Patient-Reported Outcomes Measurement Information System; TZP=Tirzepatide.

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

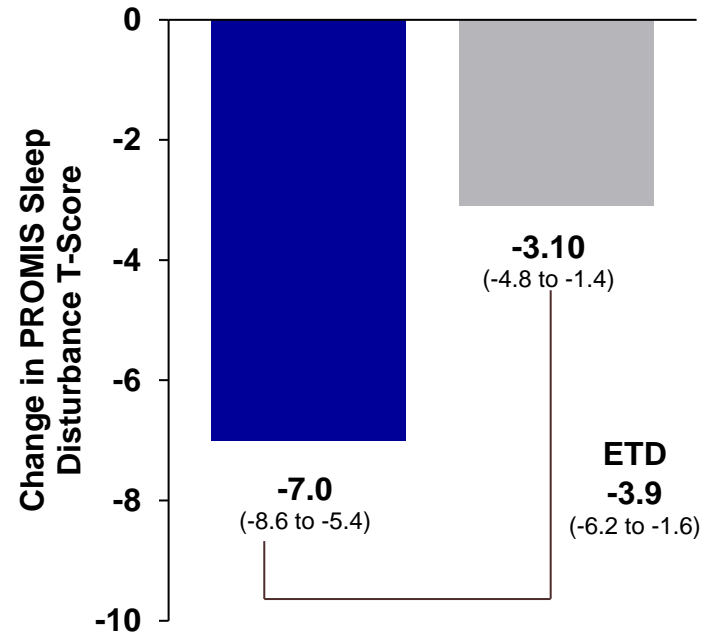
Pooled Study 1 and Study 2 Patient-Reported Outcomes

Study 2 Patient-Reported Outcomes

Change in PROMIS Sleep-Related Impairment T-Score from Baseline to Week 52



Change in PROMIS Sleep Disturbance T-Score from Baseline to Week 52



■ TZP N=114 ■ PBO N=120

Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

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Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).