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ORIGINAL RESEARCH

Clinical OBESITY WILEY

Time to weight plateau with tirzepatide treatment in the SURMOUNT-1 and SURMOUNT-4 clinical trials

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Summary

The rate of weight reduction during obesity treatment declines over time and eventually reaches a weight plateau. We investigated factors associated with time to weight plateau (TTWP) in tirzepatide-treated participants with obesity or overweight in a post-hoc analysis of SURMOUNT-1 and SURMOUNT-4 trials. Participants adherent to tirzepatide treatment and achieving ≥5% weight loss by primary endpoint (week 72 SURMOUNT-1; week 88 SURMOUNT-4) were included. Weight plateau was defined as a weight change <5% over a 12-week interval and all subsequent 12-week intervals. TTWP was time from randomization to the start of the first 12-week interval. Association between baseline characteristics and TTWP was assessed. Overall, 1438 participants in SURMOUNT-1 and 259 in SURMOUNT-4 were included. Across BMI categories (overweight, class I, II, and III), median TTWP in SURMOUNT-1 was 24.3, 26.0, 36.1, and 36.1 weeks, respectively (p <.05, class II and III vs. overweight). By week 72, 90.2%, 88.9%, 87.6%, and 87.8% of participants in SURMOUNT-1 had reached a weight plateau across respective BMI categories [Correction added on 22 January 2025, after first online publication: The "72%" has been changed to "72" in this version.]. Higher doses of tirzepatide (10/15 mg), younger age, and female sex were more likely to reach a weight plateau later. Results in SURMOUNT-4 were similar. In this post-hoc analysis, most participants reached a weight plateau by week 72. Higher doses of tirzepatide, younger age, and female sex were associated with a longer TTWP. Further research into modifiers of weight reduction phases with tirzepatide may inform treatment decisions for its use in chronic weight management. *Clinical Trial Registration*: ClinicalTrials.gov, identifiers NCT04184622 (SURMOUNT-1) and NCT04660643 (SURMOUNT-4), available at http://www.clinicaltrials.gov/

KEYWORDS
obesity, tirzepatide, weight plateau

What is already known?

- During a weight reduction intervention, weight loss slows over time, and a weight plateau can be observed.
- Defining the drivers of a pharmacologically induced weight plateau can provide opportunity to modify the course of an intervention and individualize treatment.
- Tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist demonstrated significantly greater weight reduction compared with placebo in people with obesity or overweight in the SURMOUNT trials.

What does this study add?

- In this exploratory analysis, the majority of participants treated with tirzepatide reached a weight plateau by week 72 regardless of baseline BMI category.
- Across the four BMI categories of overweight, class I, class II, and class III obesity, the median time to weight plateau was 24.3, 26.0, 36.1, and 36.1 weeks, respectively.
- Multivariate analysis showed that higher doses of tirzepatide (10 and 15 mg), younger age, and female sex were associated with a longer time to weight plateau, while BMI and waist circumference had no association.
- These findings provide insight into potential factors contributing to time to weight plateau with tirzepatide treatment in people with obesity and overweight.

1 | INTRODUCTION

The goal of treating obesity is to improve long-term health outcomes including quality of life and to prevent disease and premature death by achieving and maintaining weight reduction based on individualized health needs. During successful obesity treatment, two phases of weight reduction are often observed: an initial weight-loss phase followed by a weight-maintenance phase. The transition from weight loss to weight maintenance—the weight plateau—represents a stage of complex physiology. Both changes in appetite with weight loss, secondary to an increase in the hunger hormone, ghrelin, combined with decreases in satiety hormones (hormonal adaptation),[1] and decreases in energy expenditure during which energy homeostasis shifts from negative to neutral balance (metabolic adaptation), play a role.[2]

Inevitably, the weight response, and with that the time it takes to reach a weight plateau, varies between individuals and can potentially be influenced by individual intrinsic (e.g., genetics, age) and extrinsic (e.g., concomitant medications) characteristics and by the type of weight reduction intervention.[3] Understanding these potential contributors to a weight plateau during a weight reduction intervention could inform clinical decision-making and provide additional opportunities to achieve individualized weight reduction targets, as well as offer scientific insights into the biological response to weight reduction.

Tirzepatide is a once-weekly GIP/GLP-1 receptor agonist approved for chronic weight management in adults with overweight and adiposity-related complications or obesity and for glycemic control in adults with type 2 diabetes.[4,5] Tirzepatide demonstrated consistent weight-reduction efficacy in the SURMOUNT programme for chronic weight management, with mean weight reduction of up to 26% achieved.[6–9] While most participants achieved clinically meaningful weight reduction in the SURMOUNT trials, there was variable response to tirzepatide treatment, with weight reduction ranging from <5% to >30% by the end of the treatment period. It is unknown why this degree of heterogeneity of weight reduction occurs with tirzepatide treatment or with other weight reduction interventions.[3] Individual characteristics including age, sex, body mass index (BMI), and race have previously been implicated in the observed response to weight reduction intervention.[10]

Research to define factors influencing treatment response could ultimately support clinical approaches focused on personalized treatment targets as opposed to the current 'wait-and-see' approach with weight reduction interventions. A relevant factor is the time to near complete treatment response, which for weight reduction interventions is the time when the weight plateau is reached.

This post-hoc analysis is an exploratory effort utilizing data from SURMOUNT-1[6] and SURMOUNT-4[9] to identify factors that may influence the time to reach the weight plateau with tirzepatide treatment in people with obesity or overweight and at least one adiposity-related complication, without type 2 diabetes.

2 | MATERIALS AND METHODS

2.1 | Study design of the phase 3 trials

SURMOUNT-1 and -4 were phase 3, double-blind, randomized, placebo-controlled trials evaluating the efficacy and safety of tirzepatide in adults with obesity or overweight and at least one adiposity-related complication, who did not have diabetes.[11] The primary study period of SURMOUNT-1 included a 2-week screening period followed

by randomization (1:1:1:1) to 72 weeks of treatment with tirzepatide 5, 10, or 15 mg, or placebo. SURMOUNT-4 included a 2-week screening period, followed by 36 weeks of open-label tirzepatide treatment to achieve a maximum tolerated dose (MTD) of 10 or 15 mg, followed by randomization to a 52-week treatment period of either continuing tirzepatide treatment or switching to placebo.

We utilized data from the SURMOUNT-1 and -4 clinical trials; the 72-week SURMOUNT-1 trial was the primary focus of the current post-hoc analysis, while the 88-week SURMOUNT-4 trial data was used to evaluate consistency of the primary findings due to its longer duration. The SURMOUNT-2 and -3 trials were not included in the present analyses due to aspects of the study design that were expected to affect the time to weight plateau (type 2 diabetes population in SURMOUNT-2 and a 12-week lead-in on an intensive lifestyle modification programme in SURMOUNT-3).[11]

2.2 | Participants

This post-hoc analysis included data from participants treated with tirzepatide who received at least 75% of the study doses and achieved at least 5% weight loss. Data after discontinuation of study drug was excluded (efficacy analysis set). For SURMOUNT-1, participants were to have reached their assigned dose by week 24, have no dose reduction by week 72, and have a weight measurement at week 72. For SURMOUNT-4, participants were to have reached their MTD dose by week 24, have no dose reduction by week 88, and have a weight measurement at week 88. Overall, 1438 participants in SURMOUNT-1 and 259 participants in SURMOUNT-4 were included (75.8% and 77.3% of all tirzepatide-treated participants, respectively).

2.3 | Weight plateau definition

In SURMOUNT-1, a weight plateau was defined as a weight change of less than 5% over a 12-week interval and all subsequent 12-week intervals. Applicable intervals were weeks 24–36, weeks 36–48, weeks 48–60, and weeks 60–72. The time to reach this weight plateau was defined as the time from randomization to the start of the first 12-week interval with the respective weight change. The same definitions were applied to SURMOUNT-4 except that it included one 16-week interval (secondary to the study design); the applicable intervals for assessing weight plateau were weeks 24–36, weeks 36–52, weeks 52–64, weeks 64–76, and weeks 76–88.

2.4 | Statistical analysis

2.4.1 | Time to weight plateau by baseline body weight category

To determine if the time to a weight plateau varied with baseline BMI, we conducted a descriptive analysis of time to weight plateau by baseline body weight category. Tirzepatide treatment arms were pooled for the analysis and categorized by baseline BMI as follows:

- ≥27–<30 kg/m^2 (Overweight)
- ≥30–<35 kg/m^2 (Class I obesity)
- ≥35–<40 kg/m^2 (Class II obesity) and
- ≥40 kg/m^2 (Class III obesity).

2.4.2 | Baseline characteristics by time to weight plateau category

Participants were classified by the time that they reached a weight plateau: 24 weeks (early), between 36 and 60 weeks (intermediate), 72 weeks (later; SURMOUNT-4 only), or not reached by end of study. Baseline characteristics were then summarized descriptively by time-to-weight plateau categories.

2.4.3 | Baseline characteristics associated with time to weight plateau

Multivariate linear regression models were used to assess baseline characteristics associated with the time to a weight plateau among participants in SURMOUNT-1 who reached weight plateau (Table S1). Independent variables in each model included tirzepatide dose, age, sex, race, and one anthropometric measure as shown in Table 1. Multivariate regression analysis was not performed for SURMOUNT-4 because tirzepatide dose could not be assessed with the MTD being 15 mg for 93% of participants at randomization.

Two-sided *p*-values of <.05 were considered statistically significant.

3 | RESULTS

For SURMOUNT-1, 1438 (75.8%) tirzepatide-treated participants met specified criteria for analysis and were included. Table S1 shows baseline characteristics by BMI category in SURMOUNT-1. Overall, the mean age was 45.3 years, 67% were female, mean weight was 105.0 kg, and mean BMI was 38.1 kg/m^2. The mean BMI by category at baseline was 28.7, 32.7, 37.4, and 46.1 kg/m^2 in the overweight, class I, II, and III obesity categories, respectively. BMI steadily declined in each of the BMI categories during the treatment period, such that at week 72, mean BMI was 23.7, 26.0, 29.3, and 36.2 kg/m^2, respectively (Figure 1). Similar results were observed in SURMOUNT-4: the mean BMI by category at baseline was 29.1, 32.8, 37.4, and 45.3 kg/m^2 in the overweight, class I, II, and III obesity categories, respectively, and decreased to 24.4, 24.8, 27.7, and 32.4 kg/m^2, respectively, by week 88 (Figure S1 in Supplementary Appendix).

In SURMOUNT-1 percent body weight reduction was greatest in the first 24 weeks of treatment and similar across BMI groups: mean

TABLE 1 Model variables in multivariate regression analysis based on SURMOUNT-1 data.

	Model 1	Model 2	Model 3
Independent variables	Tirzepatide dose	Tirzepatide dose	Tirzepatide dose
	Age	Age	Age
	Sex	Sex	Sex
	Race	Race	Race
Anthropometric measure	BMI category (<30, ≥30–<35, ≥35–<40, ≥40 kg/m^2)	Waist circumference (cm)	Waist circumference category (<median, ≥median)

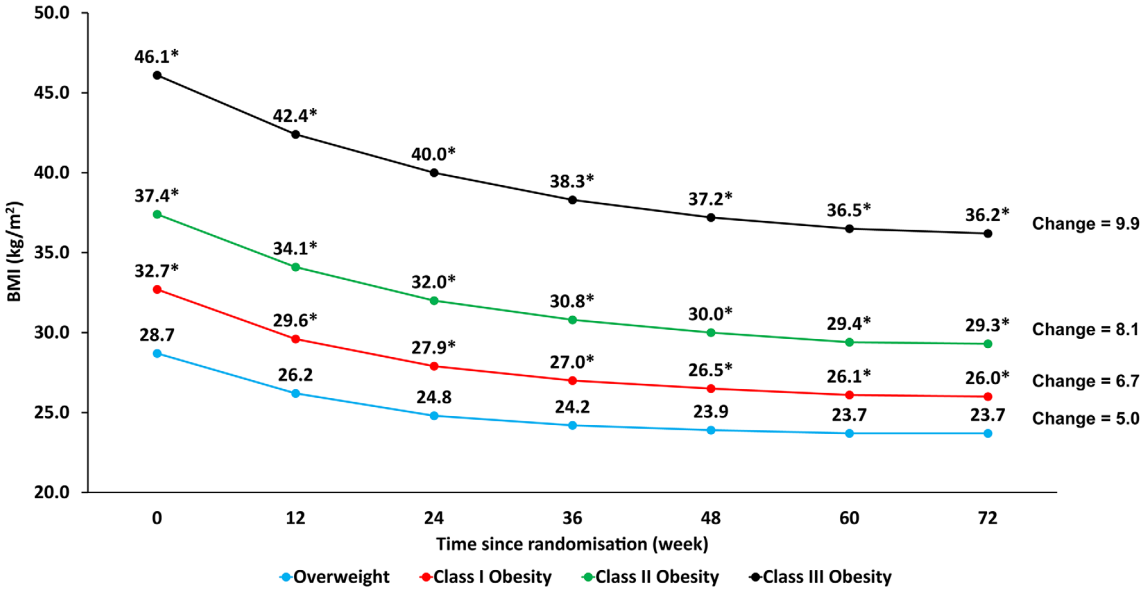

FIGURE 1 Mean BMI over time by baseline BMI category in SURMOUNT-1. *p <.05 for comparison of mean BMI of the given BMI category versus BMI category ≥27–<30 kg/m^2 (overweight) based on analysis of variance (ANOVA) model. BMI, body mass index.

weight change across the four BMI categories from baseline to week 24 was −13.4%, −14.5%, −14.3%, and−13.3%. However, between weeks 24 and 72, additional weight loss was significantly greater in the higher BMI categories compared to the overweight category (Figure 2A; −7.0%, −8.8%, and −9.7% for class I, II, and III, respectively, versus −4.6% for the overweight category; p < .05 for all comparisons to overweight category). Across the four BMI categories, the median time to weight plateau was 24.3, 26.0, 36.1, and 36.1 weeks, respectively (p < .05 for class II vs. overweight and class III vs. overweight categories). The proportion of participants who had reached weight plateau by week 72 in SURMOUNT 1 was 90.2%, 88.9%, 87.6%, and 87.8% across the four BMI categories, respectively (Figure 2B).

3.1 | Baseline characteristics by time to weight plateau category

Table 2 shows the baseline characteristics by time to weight plateau category (early [24 weeks], intermediate [36–60 weeks], or not reached at week 72) in SURMOUNT-1. Participants receiving higher doses of tirzepatide, of female sex, or White race were more likely to reach a weight plateau later. Participants with comorbidities at baseline (prediabetes, hypertension, and dyslipidemia) or of Asian race, were more likely to reach a weight plateau earlier. The average percent weight loss at the time of a plateau and at week 72, was higher when the weight plateau was reached later. Results in SURMOUNT-4 were similar (Supplementary Table S2).

3.2 | Baseline characteristics associated with time to weight plateau in SURMOUNT-1

Across the 3 models, higher doses of tirzepatide, younger age, and female sex were associated with a longer time to weight plateau (p <.05; Figure 3). Mean time to weight plateau was 4.4 and 6.7 weeks longer with tirzepatide 10 and 15 mg, respectively, compared with tirzepatide 5 mg; 0.9 weeks longer with every 10-year decrease in age; and 4.2 weeks longer in females vs. males.

Race was significantly associated with time-to-weight plateau in models 2 and 3, with a mean time-to-weight plateau of approximately 2.6 weeks longer in White versus Asian participants.

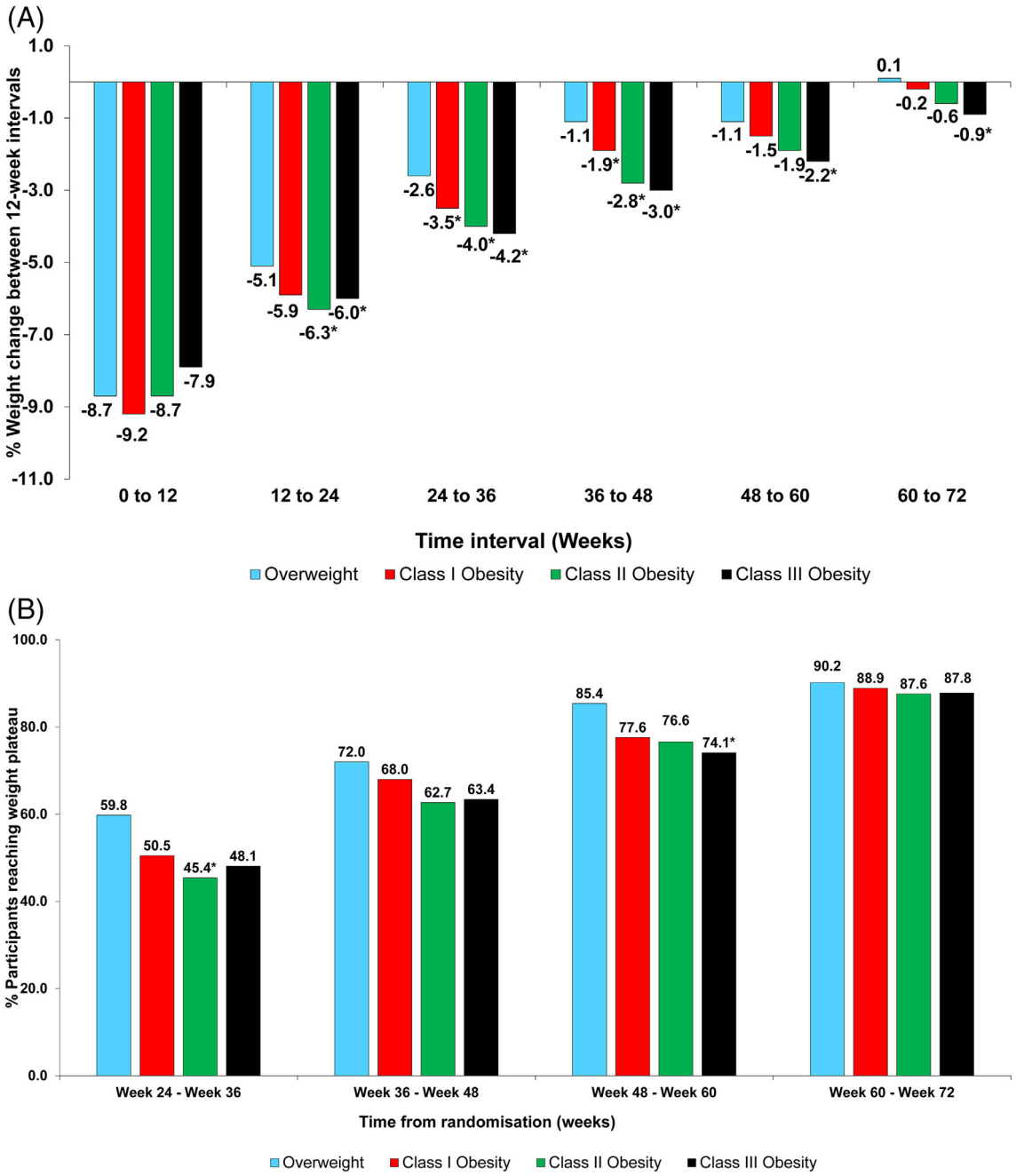

FIGURE 2 Panel (A) shows the percent weight change over 12-week intervals by BMI category. Panel (B) shows the proportion of participants reaching <5% weight plateau in SURMOUNT-1. *p <.05 for comparison with BMI category ≥27–<30 kg/m^2 (overweight).

None of the anthropometric measures (BMI category, waist circumference, and waist circumference category) were associated with time to weight plateau. However, their inclusion in the model slightly modified race association.

4 | DISCUSSION

In this exploratory post-hoc analysis, factors were identified that assist in explaining variable treatment responses to tirzepatide by utilizing the time when the weight plateau is reached in people with overweight and at least one adiposity-related complication or obesity. In general, a longer time to weight plateau was associated with greater weight reduction. While the mean percent of weight decrease early on was similar across BMI categories, after 24 weeks of treatment the mean percent of weight loss between groups separated such that, the overweight group had the least additional mean percent of weight loss while the amount increased with higher BMI categories lending to class 3 obesity having over double additional weight loss as seen in the overweight group. The modelled analysis demonstrated

TABLE 2 Baseline characteristics by time to weight plateau category in SURMOUNT-1.

	Time to weight plateau category			
	24 weeks ($N = 702$)	36–60 weeks ($N = 567$)	Not reached ($N = 169$)	*p*-value[b]
Age, years	46.4 (12.2)	44.6 (12.0)	43.0 (12.5)	<.001
Female, *n* (%)	414 (59.0)	433 (76.4)	120 (71.0)	<.001
Race, *n* (%)				<.05
Asian	100 (14.2)	49 (8.6)	13 (7.7)	
Black or African American	47 (6.7)	34 (6.0)	15 (8.9)	
White	469 (66.8)	421 (74.3)	125 (74.0)	
Weight, kg	106.2 (22.9)	103.6 (21.8)	104.9 (21.2)	NS
BMI, kg/m^2	38.0 (7.2)	38.1 (6.5)	38.1 (6.3)	NS
BMI category, *n* (%)				NS
<30	49 (7.0)	25 (4.4)	8 (4.7)	
≥30–<35	246 (35.0)	187 (33.0)	54 (32.0)	
≥35–<40	186 (26.5)	173 (30.5)	51 (30.2)	
≥40	221 (31.5)	182 (32.1)	56 (33.1)	
Prediabetes[a], *n* (%)	311 (44.3)	217 (38.3)	52 (30.8)	<.05
Hypertension, *n* (%)	253 (36.0)	171 (30.2)	48 (28.4)	<.05
Dyslipidemia, *n* (%)	247 (35.2)	148 (26.1)	41 (24.3)	<.001
Duration of obesity, years	14.9 (11.0)	15.2 (11.0)	13.7 (11.1)	NS
Tirzepatide 5 mg, *n* (%)	311 (44.3)	140 (24.7)	46 (27.2)	<.05
Tirzepatide 10 mg, *n* (%)	222 (31.6)	196 (34.6)	55 (32.5)	NS
Tirzepatide 15 mg, *n* (%)	169 (24.1)	231 (40.7)	68 (40.2)	NS
Percent change in body weight at plateau	12.1 (5.1)	24.3 (8.0)	-	<.05
Percent change in body weight at week 72	15.4 (6.9)	26.3 (8.4)	25.9 (12.4)	<.05

Note: Data shown as *n* (%) represent the percent of people within the respective weight plateau category with the specified parameter. Data are mean (standard deviation) unless otherwise stated.

Abbreviations: BMI, body mass index; NS, not significant.

[a]Prediabetes was defined in accordance with 2019 American Diabetes Association Standards of Medical Care in Diabetes as fasting glucose 100–125 mg/dL (5.6–6.9 mmol/L) during oral glucose tolerance test (OGTT), 2-h glucose 140–199 mg/dL (7.8–11.0 mmol/L) during OGTT and HbA1c 5.7%–6.4% (38.8–46.5 mmol/mol).

[b]*p*-value <.05 for a given group versus 24 weeks group based on Chi-square test for categorical variable or ANOVA for continuous variable.

that higher doses of tirzepatide, female sex, or White race were associated with later weight plateau while prediabetes and Asian race, were associated with an earlier weight plateau. The available anthropometric measures, which were limited to BMI and waist circumference, were no longer associated with time to weight plateau in the modelled analyses.

BMI and BMI classification are commonly used clinical tools. In the current study, the mean BMI decrease was similar across all the BMI classes in the first 12 weeks, but this pattern did not continue. After week 24, in both SURMOUNT-1 and SURMOUNT-4, the BMI in the overweight category demonstrated a shorter time to weight plateau as after week 24 the mean BMI decreases were ≤1 kg/m^2. In contrast, the mean BMI decrease increased progressively across the obesity classes contributing to a mean BMI decrease for class 3 obesity after week 24 of 3.7 kg/m^2 and 6 kg/m^2 in SURMOUNT-1 and SURMOUNT-4, respectively. These findings are consistent with a trend seen in a sub-group analysis of the SURPASS programme in people from East Asia with type 2 diabetes.[12] In Asian participants with a baseline BMI <25 kg/m^2 (mean ∼ 23.9 kg/m^2) treated with tirzepatide, the mean BMI decreased by ∼1 kg/m^2 between week 24 and week 52 irrespective of the tirzepatide dose, while for those with a baseline BMI ≥25 kg/m^2 (mean ∼ 29.1 kg/m^2) a weight plateau was less evident within the same time interval, particularly for participants on the highest tirzepatide dose of 15 mg.[12] This data suggests that across trials with tirzepatide treatment, weight reduction is lower in those with overweight compared to those with more advanced obesity. Combined, these data suggest a potential physiological response to tirzepatide treatment such that trajectory of weight loss and long-term weight reduction is proportional to the baseline degree of obesity.

Although in our univariate analyses, the baseline BMI category was associated with BMI decrease overtime in both SURMOUNT-1 and SURMOUNT-4, BMI was not associated with the time to weight plateau in SURMOUNT-1 in the multivariate analyses. This may be due to BMI's limited physiologic relevance. We attempted to address this hypothesis in models 2 and 3 by incorporating waist

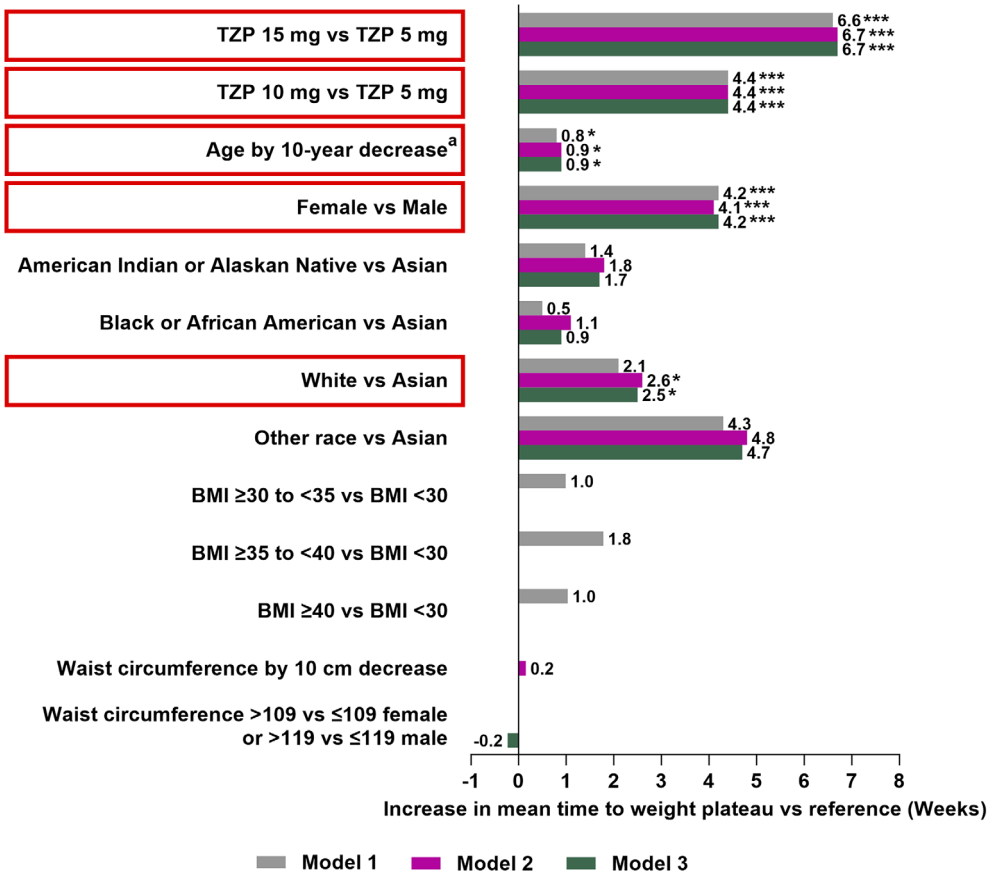

FIGURE 3 Average increase in mean time to weight plateau between subgroups in SURMOUNT-1. ***p <.001, *p <.05. [a]Age comparison of older versus younger by 10 years. TZP, tirzepatide.

circumference as an indirect measure of visceral adiposity. However, waist circumference did not demonstrate significance in the modelling for time to weight plateau. We suggest that future research use more precise individual measures of body adiposity to investigate a relationship to time to weight plateau which may allow better understanding of the effect of tirzepatide on different phenotypes of obesity.[13]

The weight plateau is often a retrospective clinical observation. It defines the transition from negative energy balance to neutral energy balance and ideally, the beginning of a state of long-term weight reduction maintenance. The transition includes physiologic adaptations[2] including changes in resting energy requirements and a shift in neuroendocrine hormones that increase hunger and decrease satiety. Due to the strength of these physiologic adaptations, some individuals will transition from a negative to a positive energy balance with a limited weight plateau and a trajectory of weight regain soon after reaching a weight nadir.[14] The intake side of energy balance is more easily observable. In contrast, only translational research methods can quantify adaptive thermogenesis, increased muscle efficiency, changes in the autonomic nervous system, and hormones and adipokines relevant to energy expenditure which also contribute to the challenge of long-term weight reduction maintenance and weight regain for many.[15–17] The current study could not define which of these contribute to the variations in weight plateau with tirzepatide treatment because such measurements of energy homeostasis were not obtained in the included studies.

While the existence of a weight plateau is recognized, there is no clear consensus as to its exact definition. We utilized a working definition, identifying a weight plateau in participants who had an initial weight reduction of at least 5%, as a weight change of less than 5% over 12 weeks that was maintained to the end of the study. There is no established definition of body weight plateau, whereas clinically meaningful body weight reduction is considered ≥5%.[18] On the other hand, 1%–2% change in body weight is within normal physiological fluctuation.[19] We found that higher doses of tirzepatide, younger age, and female sex were consistently associated with a longer time to weight plateau, while race was an inconsistent factor. It is possible that alternate definitions of weight plateau could result in additional (or differing) associations. It is important to note that the current lack of an agreed definition of weight plateau limits opportunity for coalescing evidence. Before future research can provide reproducible evidence to support the weight plateau as an opportunity for treatment decision-making, an accepted definition of weight plateau will be necessary. The ongoing SURMOUNT-MAINTAIN study will offer further insights into understanding the weight plateau and successful weight reduction maintenance with tirzepatide treatment (NCT06047548).

The findings in the current study are exploratory and should be interpreted as such. Future studies investigating more physiologic relevant modifiers of energy balance and reliable biomarkers to shifts in energy balance are needed. The current work does add to the understanding of the weight loss plateau as a physiological phase of

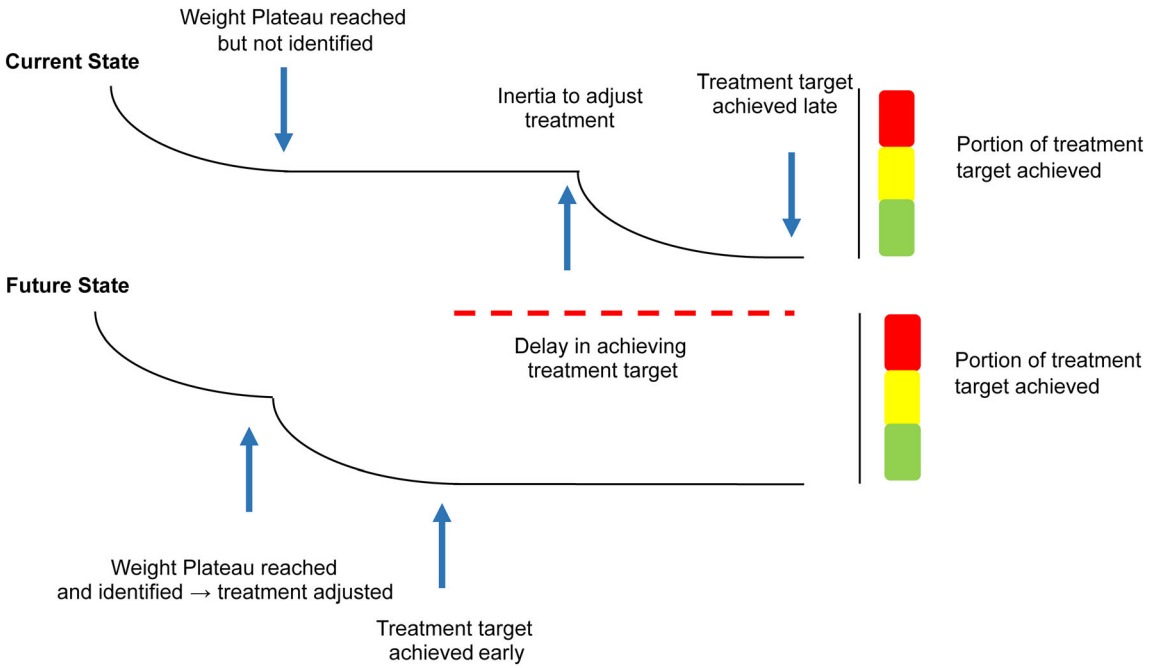

FIGURE 4 Current and future state of obesity treatment.

intentional weight reduction. The potential to modify the onset of the weight plateau and to support maintaining negative or neutral energy balance could improve weight reduction interventions and allow for personalized treatment targets, such as more defined weight loss targets based on specific health conditions or risk factors, in order to optimize health outcomes.[20] Physiologic biomarkers are commonly used in chronic disease management, such as the measuring of HbA1c with diabetes mellitus or thyroid stimulating hormone with autoimmune thyroid dysfunction, to monitor the effect of treatment, support informed treatment adjustments, and allow timely achievement of treatment targets. The appropriate application of these biomarkers includes understanding the time to plateau of the treatment effect to prevent excessive treatment adjustments. Currently for treatment of people with overweight or obesity, body weight is the primary biomarker and identifying the plateau of the treatment effect is often made retrospectively. With this retrospective identification of the weight plateau, treatment decisions to support patients achieving treatment targets is often delayed thus hampered by inertia. Although the correlation between biomarkers and the weight plateau were not included in this analysis, this a promising area for future research. As the modern era of obesity care advances, identification of known or novel biomarkers could inform treatment personalization to optimize success and limit inertia within chronic obesity management (Figure 4).

Another reason to highlight the weight plateau is that it can contribute to negative clinical experience as it is often mistakenly interpreted as the end of the intervention's benefit or even as loss of treatment effect. Importantly, the SURMOUNT-4 study demonstrated that compared to withdrawal of tirzepatide, continued treatment with tirzepatide after initial weight reduction promoted maintenance of this initial weight reduction as well as additional weight reduction.[9] Similar findings have been reported for other obesity management medications and for lifestyle interventions.[2,21,22] Informing clinicians and patients to expectations over the course of treatment can improve patient experience. In the current study, the weight loss at the time of weight plateau was slightly lower than end-of-study weight reduction; as such the degree of weight reduction at the weight plateau could be used to predict longer-term weight reduction from treatment and support decisions to modify treatment if necessary.

Interpretation of current findings should take into account specific limitations. The current analyses focused on participants who achieved a weight plateau and did not have a magnitude of weight variation of 5% or greater, so the findings may not be generalizable to those with greater weight variation. The sample size of some of the subgroups including the overweight group and multiple racial groups, was small, thus potentially affecting comparative analysis. In SURMOUNT-1, it could not be determined who reached a weight plateau at week 72 due to the 72-week primary study period. While SURMOUNT-4 provided more data up to 88 weeks, additional follow-up time may still be necessary given that ~12% of participants had not reached weight plateau at the end of the study period. Data from participants of the SURMOUNT-1 trial (NCT04184622) who had prediabetes at baseline and enrolled in an additional 2-year treatment period with tirzepatide as well as the ongoing SURMOUNT-MAINTAIN trial, may allow further exploration of the weight plateau. Due to limited information, the time to weight plateau event could not be observed as would normally be done for time-to-event variables (e.g., death, disease progression) but rather was defined according to the study schedule.

5 | CONCLUSIONS

The current work aimed to elevate the importance of understanding the weight plateau and explore its physiologic drivers with tirzepatide treatment. The exploratory findings provide insights to develop further research to investigate heterogeneity of the weight reduction response and the weight plateau with tirzepatide treatment in people with overweight and obesity. In the current study, higher doses of tirzepatide, younger age, and female sex were associated with a longer time to weight plateau. Further research into the modifiers of the phases of weight reduction including maintenance of the weight reduced state with tirzepatide may assist in informing treatment decisions for its use in chronic weight management.

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CONFLICT OF INTEREST STATEMENT

Deborah Horn participated on advisory boards for Amgen, Eli Lilly and Company, and Novo Nordisk and received consulting fees from Amgen, Eli Lilly and Company, Gelesis, and Novo Nordisk. She served as an unpaid member of the World Obesity Clinical Care Committee, The Obesity Society Annual Program Committee, and The Obesity Society Clinical Science Section Committee. Scott Kahan participated on advisory boards and received consulting fees from Boehringer, Carmot, Currax, Eli Lilly and Company, Novo Nordisk, Pfizer, and Vivus. He served on the board of directors for The Obesity Society and Obesity Action Coalition and had roles in committee leadership for the American Diabetes Association and the Endocrine Society. Rachel Batterham participated on advisory boards, received honoraria, and/or received consulting fees from Eli Lilly and Company, Epitomee Medical Ltd., Gila Therapeutics Ltd., International Medical Press, Medscape, Novo Nordisk, and ViiV Healthcare. She served in unpaid leadership positions including the Royal College of Physicians (RCP) special advisor on obesity; Chair of RCP Advisory Group on nutrition, weight and health; Member of RCP Advisory Group on health inequalities; Council member of British Obesity and Metabolic Surgery Society; Member of National Bariatric Surgery Registry; Trustee for the Association for the Study of Obesity; Co-chair of NHS England clinical advisory group on specialist weight management; Obesity Health Alliance Strategy Group; Co-chair of International Federation for the Surgery for Obesity and Metabolic Diseases European Chapter; Committee member of NICE Weight Management Advisory Group; Chair and founding member of Obesity Empowerment Network UK; and Clinical Committee member of the European Society for Endocrinology. Sylvia Gonsahn-Bollie received consulting fees and was a grant recipient from the Black Physicians Healthcare Network. She participated on an advisory board for Novo Nordisk. She received travel fees and speaker honoraria from the Obesity Medicine Association. She served in unpaid leadership roles for the Obesity Medicine Association, National Wellness Institute, and Black Physicians Healthcare Network. Rachel Batterham, Dachuang Cao, Clare Lee, Madhumita Murphy, Sylvia Gonsahn-Bollie, Farai Chigutsa, Adam Stefanski, and Julia P Dunn are employees and shareholders of Eli Lilly and Company.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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