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Maintenance of weight reduction in obesity: what does the SURMOUNT-MAINTAIN actually resolve?

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MAIN TEXT

The central challenge in obesity pharmacotherapy has shifted from inducing weight loss to maintaining it. What treatment ultimately targets is not the number on the scale but the organ and tissue dysfunction that excess adiposity produces, which is the basis on which clinical obesity is now defined^[1]. That incretin-based agents produce 15 to 21% weight loss is beyond dispute; whether that benefit persists after the drug is stopped is a separate and far less reassuring question. A systematic review and meta-analysis reported a pooled mean regain of approximately 9.7 kg after discontinuation of semaglutide or tirzepatide^[2], and nonlinear modelling indicates that about 60% of the weight lost returns within one year, the extrapolated trajectory then levelling off at an estimated 75.3% [95% confidence interval (CI): 68.9 to 81.6] of the weight lost^[3]. Discontinuation is itself common: among 125,474 United States adults with overweight or obesity, 64.8% of those without type 2 diabetes and 46.5% of those with type 2 diabetes stopped therapy within the first year, with gastrointestinal adverse events, smaller weight loss and, in those with type 2 diabetes, lower income each associated with stopping^[4]. Against this backdrop, the SURMOUNT-MAINTAIN is a methodologically careful and clinically relevant trial, the first dedicated randomised controlled study to test not whether tirzepatide should be continued, but whether the maintenance dose can be attenuated rather than withdrawn during the maintenance phase^[5].

In the SURMOUNT-MAINTAIN, after a 60-week open-label weight-loss period followed by a 52-week double-blind maintenance phase, the primary endpoint, that is the percentage change in body weight from baseline at week 112, was reached with a reduction of 21.9% with the maximum tolerated dose, 16.6% with 5 mg, and 9.9% with placebo^[5]. Only 8% of participants on the maximum tolerated dose and 25% on



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5 mg required rescue tirzepatide for regain of at least half of the weight they had lost, compared with 67% on placebo^[5]. This finding is consistent with what is already known from SURMOUNT-4 and the STEP 1 trial extension: discontinuing incretin-based pharmacotherapy is followed by pronounced weight regain and partial reversal of cardiometabolic benefit^[6,7]. A potential limitation arises from the selected study population. Randomisation at week 60 was open only to participants who had tolerated at least 10 mg tirzepatide by week 48 and who had achieved at least 5% weight reduction from baseline; a body weight plateau, defined as less than 5% body weight change between weeks 48 and 60, was one of three stratification factors at randomisation rather than an eligibility criterion^[5,8]. Randomisation occurred in 378 of the 441 enrolled participants^[5]. The cohort is therefore enriched for tolerability and for response, since those who could not tolerate at least the 10 mg dose or who lost less than 5% never reached randomisation. Therefore, findings from the SURMOUNT-MAINTAIN may better apply to good responders who tolerated titration to the maximum tolerated dose. In routine practice, patients discontinue treatment far more often than the 9% non-completion rate observed during the maintenance phase of this trial^[4,5].

The rescue protocol further stimulates some additional reflections. From week 84, that is 24 weeks after randomisation, participants could receive rescue tirzepatide if they regained more than 50% of their lost weight. Rescue therapy was given to 8% of the maximum tolerated dose group, 25% of the 5 mg group, and 67% of the placebo group^[5]. The handling of these participants warrants clarification. They were not excluded: all randomly allocated participants were retained in the primary analysis, with no further benefit attributed to the assigned treatment once rescue was initiated, in accordance with the protocol^[5]. Although the primary, modified treatment regimen estimand assumes that these participants derive no further benefit from their assigned treatment, the fact that two-thirds of the placebo arm crossed over to active drug means that the untreated natural history after discontinuation remains to be determined, and that the separation between continued treatment and withdrawal is unlikely to be smaller than reported. A further point of discussion is that the 5 mg dose is not shown to be sufficient, only superior to placebo. Dose reduction is framed as an attractive alternative to discontinuation. Yet, the gap between the maximum tolerated dose and 5 mg is clinically meaningful, a 21.9% reduction against 16.6%, as is the difference in the proportion regaining at least half of their lost weight, 8% against 25%, a threefold increase^[5]. The message is therefore not that 5 mg suffices, but that 5 mg is a compromise carrying a measurable cost. In the absence of a pre-specified non-inferiority analysis, and of validated predictors of who will succeed at the lower dose, the individualised, patient-centred care that the trial advocates remains not fully elucidated.

What would justify de-escalation deserves precise statement. Weight is a surrogate for the outcomes that treatment targets, so a reduced maintenance dose is defensible only if cardiometabolic benefit is preserved out of proportion to weight: glycaemic control, blood pressure, lipids, hepatic endpoints and, ultimately, major adverse cardiovascular events should be retained to a greater extent than body weight itself. If benefit is instead lost in proportion to the weight regained, the lower dose offers no metabolic advantage and its justification is economic alone. The post hoc analysis of SURMOUNT-4 points towards proportionality: after withdrawal, cardiometabolic improvement reversed in graded fashion, most markedly in those who regained the most weight^[9]. Maintenance trials should therefore report the retention of each cardiometabolic and complication-related endpoint alongside the retention of weight.

Reading the dose reduction agenda in context, it is worth asking why a dedicated dose reduction trial appears at this particular moment. One interpretation is that this reflects an emerging need for lower-cost maintenance strategies capable of preserving clinically meaningful weight loss over the long term. The acquisition cost of injectable incretin therapy at the maximum tolerated dose, sustained indefinitely across the very large populations that meet treatment criteria, is unsustainable for most health systems and for most patients paying out of pocket. Whether a lower dose is also a cheaper dose is, however, a matter of pricing

and reimbursement rather than of pharmacology. Incretin therapies are commonly priced per pen or per pack, and reimbursement is negotiated per treatment course, so halving the maintenance dose does not halve the cost, and in some settings it may not reduce it at all. We therefore offer the economic reading as a hypothesis rather than a conclusion. Where a lower maintenance dose does cost meaningfully less, a demonstration that it can hold most of the benefit is what would make lifelong therapy financially conceivable. Seen in that light, SURMOUNT-MAINTAIN does not only answer a clinical question, but it may prepare the policy ground for a tiered model of care in which induction is delivered at high dose and maintenance at a reduced one. Dose reduction is only one route to maintenance. Switching to an older and less costly agent, extending the dosing interval, transition to an oral agent, amylin-based combinations now in development, and sustained dietary and physical activity change are all plausible alternatives, none yet compared with continued incretin therapy in a randomised maintenance design. Cost pressure may also ease independently of dose: semaglutide patents began to expire during 2026 in countries carrying close to half of the global obesity burden, and production-cost analyses indicate that generic injectable semaglutide could be supplied at a fraction of current prices^[10]. This can be of potential importance for many health systems worldwide.

Questions of duration and surrogate endpoints compound the above reflections. Fifty-two weeks of maintenance is a short period for a chronic disease, and body weight and cardiometabolic parameters are surrogate outcomes. The trial was neither designed for, nor can it answer, the question of cardiovascular morbidity and mortality under long-term reduced-dose therapy. The 2026 European Association for the Study of Obesity (EASO) framework makes explicit that obesity management should move beyond total body weight loss to match therapy to the presence and severity of obesity-related complications^[11]. The relevant question for the coming decade is whether a given strategy preserves remission of diabetes, regression of hepatic fibrosis, and reduction of cardiovascular events. The composition of regained weight is as relevant as its magnitude. Approximately a quarter of the weight lost on incretin-based therapy is lean mass^[12], and body composition after cessation has not been characterised^[3]; should regain prove disproportionately adipose, a return to baseline weight would leave an adverse fat-to-lean ratio relative to pre-treatment. The SURMOUNT-MAINTAIN does not engage with this agenda, and that is its most important conceptual gap.

In conclusion, the SURMOUNT-MAINTAIN usefully moves the debate beyond the simple choice of whether to continue or stop treatment, towards the more refined question of which dose to continue. Future maintenance trials should move beyond continuation *vs.* withdrawal and determine who can be maintained at lower doses, who requires full-dose therapy, and whether oral agents can provide a scalable long-term strategy. The task for the field is to define maintenance success by the preservation of target organ benefit, and to generate the affordable, durable, complication-oriented evidence that such a definition demands.

DECLARATIONS

Authors' contributions

Conceptualised and designed the commentary: Janez A, Rizzo M

Conducted the literature search and interpretation: Janez A, El-Tanani M, Rangraze IR

Drafted the original manuscript: Janez A

Critically revised the manuscript for important intellectual content: El-Tanani M, Rangraze IR, Rizzo M

Supervised the work: Rizzo M

All authors contributed to the development of the manuscript, reviewed and approved the final version, and agreed to be accountable for all aspects of the work.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tools NotebookLM (Google, web version, accessed October 2026) and Gemini 3.1 Pro (Google, version 3.1 Pro, released 2026-02-19) were used solely to support literature searches, while Grammarly (Grammarly Inc., web version, accessed October 2026) and ChatGPT (OpenAI, GPT-5.6, released 2026-07-09) were used solely for grammar correction and language refinement. These AI tools did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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REFERENCES

1. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. 2025;13:221-62. [DOI PubMed PMC](#)
2. Berg S, Stickle H, Rose SJ, Nemec EC. Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: a systematic review and meta-analysis. *Obes Rev*. 2025;26:e13929. [DOI PubMed](#)
3. Budini B, Luo S, Tam M, et al. Trajectory of weight regain after cessation of GLP-1 receptor agonists: a systematic review and nonlinear meta-regression. *EClinicalMedicine*. 2026;93:103796. [DOI PubMed PMC](#)
4. Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw Open*. 2025;8:e2457349. [DOI PubMed PMC](#)
5. Horn DB, Aronne LJ, Wharton S, et al. Tirzepatide for maintenance of bodyweight reduction in people with obesity in the USA (SURMOUNT-MAINTAIN): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2026;407:2305-18. [DOI PubMed](#)
6. Aronne LJ, Sattar N, Horn DB, et al. ; SURMOUNT-4 Investigators. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA*. 2024;331:38-48.[PMCID:PMC10714284 DOI:10.1001/jama.2023. 24945 PMID:38078870].
7. Wilding JPH, Batterham RL, Davies M, et al. ; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24:1553-64. [DOI PubMed PMC](#)
8. Horn DB, Aronne LJ, Wharton S, et al. Tirzepatide for the maintenance of body weight reduction: rationale, design, and baseline characteristics of SURMOUNT-MAINTAIN. *Obesity*. 2025;33:1873-85. [DOI PubMed PMC](#)
9. Horn DB, Linetzky B, Davies MJ, et al. Cardiometabolic parameter change by weight regain on tirzepatide withdrawal in adults with obesity: a post Hoc analysis of the SURMOUNT-4 trial. *JAMA Intern Med*. 2026;186:157-67. [DOI PubMed PMC](#)
10. Levi J, Cross S, Ramesh N, Venter F, Hill A. How low could semaglutide prices fall? An analysis of production cost and implications for global access. *Obesity*. 2026;34:1545-50. [DOI PubMed PMC](#)
11. Ciudin A, Baker JL, Belančić A, et al. Framework for the pharmacological treatment of obesity and its complications from the European Association for the Study of Obesity (EASO): 2026 update. *Nat Med*. 2026;32:1962-6. [DOI PubMed](#)
12. Karakasis P, Patoulas D, Fragakis N, Mantzoros CS. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: systematic review and network meta-analysis. *Metabolism*. 2025;164:156113. [DOI PubMed](#)

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