

GLP-1 weight loss: Is muscle loss inevitable?

Written by The Life Science Feed Editorial Team · Published 1 October 2026 · Edited by Mara Voss

Rapid weight loss on a GLP-1 drug comes with a cost rarely discussed alongside the headline numbers: a substantial share of what patients lose is muscle, not fat. A phase 2 trial in press with *The Lancet* tested whether blocking myostatin, a protein that actively suppresses muscle growth, could protect lean mass during semaglutide-driven weight loss without blunting the weight loss itself.¹

KEY TAKEAWAYS

- **The Pivot:** Trevogrumab, an anti-myostatin antibody, cuts lean mass loss from semaglutide roughly in half and preserves up to 72% of thigh muscle volume, with a safety profile close to placebo when used alone.
- **The Data:** Semaglutide alone reduced lean mass by 6.6-7.3% depending on trial part; adding trevogrumab cut that loss to 2.1-3.9%, and switching to trevogrumab after stopping semaglutide moved patients to net lean-mass gain (+0.4%) instead of continued loss (-2.4%).
- **The Action:** Watch this as a candidate adjunct specifically for patients at higher sarcopenia risk starting aggressive GLP-1 weight loss, not the triple-combination regimen, which carried a materially higher rate of serious adverse events and discontinuation.

Trevogrumab blocks GDF8, more commonly known as myostatin, a negative regulator of muscle mass. Regeneron, which sponsored the trial and manufactures trevogrumab, also tested it alongside garetosmab, an antibody against a related growth factor, ActA, to see whether blocking both pathways compounded the benefit.¹

The two-part trial enrolled 975 adults with obesity. Part A randomised 599 participants to 26 weeks of semaglutide plus placebo, trevogrumab at 200mg or 400mg, or the triple combination of semaglutide, trevogrumab 400mg and garetosmab, followed by a 26-week semaglutide withdrawal period. Part B randomised 376 participants to 52 weeks of semaglutide plus placebo or lower-dose trevogrumab, 25mg or 75mg. Lean mass was measured by DXA scan and, in a substudy, skeletal muscle volume specifically by MRI.¹

The Numbers

Semaglutide alone cut lean mass by 6.6% over 26 weeks in Part A. Adding trevogrumab roughly halved that loss, to about 3.4% at 200mg and 3.9% at 400mg. The triple combination with garetosmab preserved lean mass further still, to around 2.1% loss, the best result in the trial on that single measure.¹

The withdrawal-period finding is arguably the more clinically interesting result. Patients who stopped semaglutide and switched to placebo for 26 weeks still sat at -2.4% lean mass from baseline at week 52. Patients who switched to trevogrumab 400mg instead saw lean mass rise to +0.4% above baseline, a 2.8 percentage-point swing that suggests

the drug can help rebuild lean mass lost during the weight-loss phase, not just slow its loss.

Part B, testing lower doses over a full year, found semaglutide alone cut lean mass 7.3% by week 52. Trevogrumab 75mg improved on that by 3.1 percentage points, a statistically significant difference; the 25mg dose trended the same direction but did not reach significance. An MRI substudy measuring thigh muscle volume directly found trevogrumab preserved 69% to 72% of the muscle volume otherwise lost, a larger relative effect than the DXA lean-mass numbers alone suggest.

Safety diverged sharply by arm. Trevogrumab alone, at every dose tested, had a safety profile close to placebo. The triple combination with garetosmab did not: serious adverse events hit 9% against 0.7% to 1.3% for trevogrumab-alone arms, discontinuation reached 32% against 4.6% to 10.6%, and muscle spasms affected 41% of patients on the triple combination against roughly 5% to 8% elsewhere. Two deaths occurred during the trial, both in the triple-combination arm; no causal link to treatment has been established.

The stark safety divergence observed with the triple combination arm, particularly the higher rates of serious adverse events, discontinuations, and muscle spasms, raises significant concerns regarding the clinical viability of simultaneously targeting both myostatin and ActA pathways. While the individual blockade of myostatin with trevogrumab demonstrated a favorable safety profile comparable to placebo, the addition of garetosmab clearly introduced substantial tolerability issues. This suggests a potential ceiling for the combined inhibition of these growth factors, or perhaps an undesirable off-target effect of garetosmab that warrants further investigation. The two deaths in the triple-combination arm, though not causally linked, underscore the need for extreme caution when considering multi-pathway interventions in this context.

Clinical Implications and Future Directions

The findings from this Regeneron-sponsored trial suggest that mitigating muscle loss during GLP-1 induced weight loss is a clinically achievable goal, with trevogrumab demonstrating a promising safety and efficacy profile in preserving lean mass. The ability of trevogrumab to not only slow lean mass loss but also potentially rebuild it during a semaglutide withdrawal period is particularly noteworthy, offering a potential strategy for optimizing body composition in patients undergoing significant weight reduction. This could translate to improved functional outcomes, reduced sarcopenia risk, and enhanced metabolic health in the long term, especially for older adults or those with pre-existing muscle weakness.

However, several limitations warrant consideration. The trial primarily focused on a 26-week or 52-week intervention period, which, while substantial, may not fully capture the long-term effects of trevogrumab on muscle mass and function in the context of chronic GLP-1 agonist use. Furthermore, while DXA scans and MRI substudies provided robust measures of lean mass and muscle volume, direct measures of muscle strength and physical function were not primary endpoints. Future studies should incorporate these functional assessments to fully understand the clinical benefit of lean mass preservation. The generalizability of these findings to diverse patient populations, including those with different comorbidities or varying degrees of obesity, also requires further exploration.

The significant safety concerns associated with the triple combination arm effectively rule out the simultaneous blockade

of both myostatin and ActA with the tested agents in their current formulations. This highlights the importance of carefully evaluating the risk-benefit profile of multi-target therapies, even when individual components appear safe. Future research should focus on optimizing the dose and regimen of trevogrumab as a monotherapy or in combination with other agents that do not introduce similar safety liabilities. Exploring different myostatin inhibitors or alternative strategies to enhance muscle anabolism during weight loss will also be crucial.

Ultimately, these results pave the way for a more nuanced approach to obesity management, moving beyond simply weight reduction to focus on improving body composition. Clinicians managing patients on GLP-1 agonists, particularly those at risk of significant muscle loss, should be aware of emerging strategies like myostatin inhibition. While trevogrumab is not yet clinically available, these data provide a strong rationale for its continued development and underscore the potential for pharmacologic interventions to address a critical unmet need in obesity care.

CLINICAL IMPLICATIONS

The safety data here draw a clean line most coverage of this trial will be tempted to blur: trevogrumab alone looks genuinely safe at every dose tested, and the triple combination with garetosmab does not. A 32% discontinuation rate and 9% serious-adverse-event rate in that arm, against single digits everywhere else, is not a rounding difference, it is a different risk profile, and the numerically larger lean-mass benefit it bought does not obviously justify it on its own.

The subgroup finding on sarcopenia risk is the detail worth carrying into practice ahead of any approval. Older patients, and those meeting imaging criteria for low lean mass, lost more muscle on semaglutide alone and gained more from trevogrumab, and in that specific group trevogrumab alone matched the triple combination's benefit without its toxicity. That is the population a myostatin inhibitor is built for, not GLP-1 patients broadly.

The withdrawal-phase result deserves more attention than a single secondary finding usually gets. Weight regain after stopping a GLP-1 drug is already a well-documented problem, and the concern has always been that regained mass skews toward fat. A drug that lets patients rebuild lean mass specifically during that vulnerable window, rather than simply slowing its loss during active treatment, addresses a different and arguably more consequential part of the GLP-1 lifecycle.

Regeneron funded and will develop trevogrumab, and the company has an obvious commercial incentive to pair it with GLP-1 therapy broadly. The data support a narrower claim than that: a real, well-tolerated benefit as an adjunct for patients with elevated sarcopenia risk undergoing rapid weight loss, pending confirmation in a larger trial and, ideally, evidence that preserved muscle translates into preserved physical function.

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REFERENCES

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