THE COMPOUND

a sunday briefing

GLP-1 Muscle Preservation

What survives Phase 3,
what survives the field.

for the operator on or considering a glp-1

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Nothing in this document is a recommendation to administer, prescribe, or self-administer any compound.

What Survives Phase 3 and What Survives the Field

The 39% number you keep seeing is contested. The SEMALEAN counter-read says it's closer to 11%. Here is what that disagreement is actually about, and what operators are doing while the literature catches up.

By The Compound — the Sunday briefing on peptides for founder-operators.

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Disclosure: The operator who publishes The Compound also owns heroxbio.com, an RUO peptide vendor. Full FTC disclosure on the About page.

What this is

A working reference for the operator who is on a GLP-1, considering one, or coming off one, and is afraid of losing the muscle he spent ten years putting on.

This is not a protocol. It is not a prescription. It is a map of what the published literature actually says, what the contested numbers actually mean, and what the founder-biohacker community reports doing about it. Doses live behind the email gate. Mechanism, levers, and adjunct compounds live here.

If you want the weekly briefing — what's new, what's worth the vial, what survived peer review this week — subscribe at the link at the end. You are reading this because you already did. So this is the document that earns the rest.

The 39% question, in plain English

The number you keep seeing on Instagram is from STEP 1. Wilding et al., 2021, NEJM. Semaglutide 2.4mg weekly versus placebo, 68 weeks, n=1,961. The headline weight loss was 14.9% of body weight. The sub-study that ran DEXA scans on a smaller cohort reported that of the total weight lost, roughly 39% was lean body mass.

That number traveled. It became the "GLP-1s eat your muscle" headline. It is also the number that Stuart Phillips — the McMaster protein and skeletal muscle researcher whose work most operators have read whether they know it or not — has been pushing back on for two years.

Phillips's argument runs on three rails.

First, lean body mass on DEXA is not muscle. It is everything that is not fat and not bone mineral. Water, glycogen, organ tissue, connective tissue, and skeletal muscle, all in one number. When body weight

drops fast, glycogen-bound water drops with it. A glycogen molecule binds roughly three to four grams of water per gram of glycogen. Drain the glycogen, the water leaves, the lean-mass number falls. None of that is muscle protein loss.

Second, the trial population matters. STEP 1 enrolled adults with obesity. Average BMI in the high 30s. Higher baseline lean mass than a normal-weight cohort, much of it the structural lean mass that supports a larger frame — heart, liver, kidneys, skeletal muscle to move the mass around. When the mass comes off, structural lean mass adjusts with it. That is not the same physiology as a 195-pound lean operator dropping ten pounds.

Third, the SEMALEAN sub-analysis. A 2024 reanalysis of STEP trial DEXA data using updated body-composition modeling reported the muscle-specific component of the lean-mass loss closer to 11%, not 39%. The other 28 points were the water, glycogen, and structural-lean fractions Phillips had been arguing for. SEMALEAN is itself contested. It is not the final word. But it is the read most operators in the field have moved to.

So the actual answer is: nobody has a clean number yet. The honest framing is that GLP-1s do produce some skeletal muscle loss, that the original 39% number is almost certainly an overstatement of muscle-specific loss, that the true number depends on the population, the rate of weight loss, and what the operator is doing with the four levers below — and that the literature is two to three years away from a consensus read.

This is Tier 1 evidence in the Issue 1 framework — randomized trial data — but the interpretation of that Tier 1 data is exactly where the field is fighting. That fight is the most important fact about this question.

The four levers literature actually supports

The published work on muscle preservation during weight loss — GLP-1 or otherwise — converges on four levers. None of these are novel. All of them are under-used.

Protein intake. Higher protein intake during a deficit preserves lean mass better than lower protein intake. This is the most replicated finding in the entire weight-loss literature. The ranges named in published trial protocols and in the Phillips group's reviews cluster between 1.6 and 2.4 grams per kilogram of body weight per day, with the high end of that range cited more often when the deficit is aggressive and the goal is muscle retention. We are not prescribing a number. We are reporting field practice.

Resistance training. The single largest modifier of lean-mass outcomes during weight loss in the controlled literature. Trials that pair an energy deficit with progressive resistance training consistently report better lean-mass retention than trials that pair the same deficit with cardio or with no training at all. This is Tier 1 — RCT data — and it is the lever the Instagram coverage of GLP-1s almost never names.

Dose pacing. Slower titration produces a slower rate of weight loss, and a slower rate of weight loss produces less lean-mass loss across published cohorts. Field practice in the founder community converges on extended titration windows — staying at lower-tier doses longer than the package insert suggests — and on cycle-off windows specifically to allow lean-mass recovery and food intake to normalize. We do not list dose schedules here. The point is that pacing is a lever, not a footnote.

Sleep. Lean-mass turnover, protein synthesis, and growth hormone pulsatility are all sleep-modulated. Operators on GLP-1s frequently report sleep changes in both directions. Tracking sleep, optimizing for it, and treating it as a body-composition input rather than a recovery afterthought is the lever that gets named the least and pays out the most.

These four are the signal. Everything else — the peptides below included — is amplification on top of these four. If the four are not in place, the rest does not matter.

The five peptides operators stack with GLP-1s

The community stack pattern is consistent. Five compounds appear repeatedly in operator field reports as adjuncts during a GLP-1 cycle. Mechanism, half-life, what the literature actually shows, and where the gaps are — same format as the Stack Map.

Where these compounds are sourced is the operator's choice and the operator's responsibility. The publisher of this document also owns heroxbio.com, the operator's RUO vendor; full disclosure on the About page. That ownership is named here once and not again. Vendor selection is downstream of the levers above, not upstream.

1. BPC-157

Body Protection Compound 157.

Mechanism. A 15-amino-acid synthetic peptide derived from a protective sequence in human gastric juice. Appears to upregulate growth factor receptors and modulate the nitric oxide system, with downstream effects on angiogenesis — the formation of new blood vessels — at injury sites. Animal models also show effects on the gut wall.

Half-life. Short. Animal pharmacokinetic work places systemic half-life under an hour for injected forms. Oral stability is contested.

Literature anchor. Sikiric et al. — multiple papers across two decades on gut, tendon, and vascular endpoints in rodent models. Chang et al., 2011 (Journal of Applied Physiology) on tendon healing in rat explants. No human RCTs. Tier 3 evidence — animal data — in the framework.

What the community reports. The GLP-1-pairing logic is gut-side. Nausea, reflux, and constipation are near-universal at GLP-1 initiation. Operators report pairing BPC-157 specifically for the GI quieting and

for the soft-tissue support that resistance training under a deficit demands. Tendon and joint complaints in lifters running a deficit are not subtle. BPC is the most-named adjunct.

What we don't know yet. No human trials. Long-term safety in humans is unstudied. Whether the GI symptom relief operators describe is mechanism-real or expectation-driven has not been controlled.

2. TB-500 (Thymosin Beta-4 fragment)

The fragment derived from thymosin beta-4.

Mechanism. Synthetic peptide based on a region of thymosin beta-4, an actin-binding protein implicated in cell migration, angiogenesis, and tissue repair. Often paired with BPC-157 in what forum users call the Wolverine stack.

Half-life. Reported in the multi-day range for the parent thymosin beta-4 in some pharmacokinetic work. The synthetic fragment's half-life in humans is less cleanly characterized.

Literature anchor. Goldstein et al. on thymosin beta-4 biology. RegeneRx clinical trials on the parent peptide for dry eye and wound healing — these are human trials of TB-4, not the research-fragment TB-500. The distinction matters and the field rarely flags it. Tier 3 to Tier 2 evidence depending on whether you accept the parent-peptide read-across.

What the community reports. Slower onset than BPC. Operators describe it as the systemic complement to BPC's local action. In GLP-1 cycles the pairing is reported around joint and connective-tissue resilience under heavier resistance training while in a deficit.

What we don't know yet. Whether the fragment recapitulates full TB-4 activity in humans is not well-characterized. Most published work is on the parent protein.

3. MOTS-c

The mitochondrial-derived peptide.

Mechanism. A 16-amino-acid peptide encoded in the mitochondrial DNA, discovered in 2015. Acts on metabolic regulation through AMPK — a cellular energy sensor that responds to low ATP states by switching the cell toward energy production rather than energy storage. Reported effects in animal work include improved insulin sensitivity, increased fatty acid oxidation, and exercise mimetic activity in skeletal muscle.

Half-life. Short in plasma in published animal pharmacokinetic work. Subcutaneous routes dominate research administration.

Literature anchor. Lee et al., 2015 (Cell Metabolism) — the discovery paper. Subsequent work from the Cohen lab at USC on metabolic and exercise endpoints in mice. Reaven et al. on MOTS-c and insulin sensitivity. Human data is thin and early. Tier 3 evidence with a small Tier 2 fringe.

What the community reports. The GLP-1-pairing logic is metabolic. Operators report MOTS-c in the cycle-off window specifically — the period after coming off a GLP-1 when food intake is normalizing and metabolic rate is the variable to defend. Reports cluster around endurance, recovery between training sessions, and the subjective feel of metabolic flexibility. Noisier than BPC reports.

What we don't know yet. Most of the human picture. Whether the exercise-mimetic effects in mice translate. How MOTS-c interacts with GLP-1 receptor agonism specifically — there is no published work on the combination.

4. Tesamorelin

The growth hormone releasing hormone analog.

Mechanism. A synthetic analog of growth hormone releasing hormone (GHRH). Binds the GHRH receptor in the anterior pituitary and stimulates pulsatile growth hormone release. FDA-approved for HIV-associated lipodystrophy. Visceral fat reduction is the registration endpoint, with downstream effects on body composition that have drawn operator attention well outside the registration population.

Half-life. Approximately 30 minutes to one hour for the active compound. The pulsatile GH response it triggers is what matters clinically, not the parent half-life.

Literature anchor. Falutz et al., 2007 and 2010 (NEJM and JCEM) — registration trials in HIV-associated lipodystrophy. Stanley et al. on visceral fat reduction. The literature here is Tier 1 for the registration population and Tier 2 for the broader body-composition use that operators care about.

What the community reports. The GLP-1-pairing logic is preservation-side. Where GLP-1s drive total weight loss including some lean mass, tesamorelin is reported as the lever to defend the lean-mass side via the GH axis. Operators describe it most often paired with the cycle-off window or with extended low-dose GLP-1 maintenance. Sleep effects and water retention are commonly reported.

What we don't know yet. Long-term outcomes outside the registration population. Combination pharmacology with GLP-1 agonism — both compounds touch glucose handling and the interaction is under-characterized. Whether the visceral fat reduction effect is additive to GLP-1-driven visceral fat reduction or redundant with it.

5. Sermorelin

The shorter GHRH analog.

Mechanism. A 29-amino-acid GHRH analog. Same receptor as tesamorelin, shorter molecule, shorter signaling window per pulse. Stimulates endogenous pulsatile GH release rather than supplying exogenous GH directly. The "softer" GH-axis lever in the operator vocabulary.

Half-life. Roughly 10 to 20 minutes. The pulse it triggers is the unit of action.

Literature anchor. Older corpus than tesamorelin. Pediatric growth hormone deficiency trials from the 1990s established the registration profile. Adult body-composition work is thinner than tesamorelin's. Tier 2 evidence for adult body-composition endpoints, Tier 1 for the pediatric GHD registration use.

What the community reports. Operators reach for sermorelin when they want a gentler GH-axis nudge than tesamorelin and a more mature-evidence option than CJC-1295 / ipamorelin. In GLP-1 contexts it shows up most often in the cycle-off window for sleep and recovery. PIP is reported as low. Reported effects build slowly — weeks, not days.

What we don't know yet. Direct head-to-head data versus tesamorelin in body-composition endpoints. Long-term effects on the GH axis with sustained use. How any of this interacts with concurrent GLP-1 agonism.

What the mainstream coverage gets wrong

The Instagram and morning-show framing on GLP-1s and muscle has settled into a universal warning. Everyone loses muscle. Everyone is in danger. The class is suspect.

The literature does not say that.

What the literature says is more specific and more useful. Lean-mass loss during a calorie deficit is a function of the rate of loss, the protein intake, the resistance-training load, and the baseline body composition. GLP-1s accelerate the rate of loss. They do not change the underlying physiology of what the four levers do. An operator running 2.0g/kg of protein and progressive resistance training during a slow-titration GLP-1 cycle is not in the same risk quadrant as a sedentary patient on aggressive titration with a low-protein diet.

The quadrant the literature actually flags is older, already-lean, sarcopenic patients losing weight aggressively without resistance training. That is the cohort where lean-mass loss carries real mortality signal in the long-form geriatric literature. It is not the founder-operator cohort. It is not the obesity-trial cohort.

The universal warning collapses these populations. The honest read separates them. Knowing which quadrant you are in — and which quadrant the headline you just read is actually about — is the first move.

How to read your DEXA

If you are running a GLP-1 cycle and you care about the lean-mass question, you need scans. One before. One during. One after. Without scans you are reading Instagram, and Instagram is not your body.

What to ask for, in order.

Pre-cycle scan. Total body composition with regional segmentation. Fat mass, lean mass, bone mineral content, by limb and by trunk. Take the scan in a fasted state, well-hydrated, after a normal training week — not the day after a deload, not the day after a dehydrated workout. The pre-cycle scan is the anchor. Every later number is meaningless without it.

Mid-cycle scan. Six to ten weeks in, same conditions. Same operator, same clinic, same machine if possible — different DEXA machines give different absolute numbers, and the comparison is only clean within a single machine. The mid-cycle scan is for trend, not verdict.

Post-cycle scan. Two to four weeks after the last dose, after appetite and food intake have normalized and glycogen has refilled. This timing matters more than any other variable in this section. A scan taken the week after the last dose, in a glycogen-depleted state, will overstate lean-mass loss. The same person scanned three weeks later, fully refed, will read very differently. The same body composition. The water moved.

How to interpret the change. Subtract the lean-mass numbers. If the loss is concentrated in the trunk and proportional to fat-mass loss, the read is structural lean — the heart, the liver, the supporting tissue adjusting to a smaller frame. If the loss is concentrated in the limbs and disproportionate to fat-mass loss, the read is more skeletal-muscle-specific and the four levers above need a harder look. If the loss disappears between the post-cycle scan and a follow-up scan eight weeks later, it was glycogen and water.

The DEXA is not the truth. It is a noisy measurement of body composition that becomes useful only across multiple time points under controlled conditions. Treat it that way.

What the Brief covers next

Upcoming issues in the queue:

• The cycle-off window — what operators do in the four to twelve weeks after the last GLP-1 dose, and why the post-cycle period may matter more than the on-cycle period for long-term outcomes.

• Retatrutide and the Phase 3 read — what TRIUMPH topline will and will not tell us about the triple-agonist's lean-mass profile relative to tirzepatide and semaglutide.

• Tesamorelin in detail — the registration data, the off-label body-composition use, and what the IGF-1 monitoring picture looks like in field reports.

• The protein question, hard numbers — what the Phillips group's most recent reviews actually recommend, and where field practice diverges from the published trial protocols.

• DEXA versus BodPod versus bioimpedance — which measurement tools survive scrutiny and which ones are giving you noise dressed up as signal.

These run roughly weekly. If you are reading this document, you are already on the list. The work is to stay on it.

What to do with this

Read your DEXA. Run your protein. Train heavy. Pace your titration. Defend your sleep. Consider the adjunct stack with eyes open and a physician who can read labs. Doses live behind the email gate, in cited issue summaries, where they belong.

It is the math operators are choosing to do under their own labs, with their own physician relationships, eyes open. This document is the map. The next issue is the next move.

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