Thymic Rejuvenation Protocol

Tesamorelin · Thymosin α1 · Rapamycin · Imeglimin · DHEA

Evidence-based combinatorial strategy for thymic fat reversal and T-cell regeneration

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> **Research and informational use only.** This document describes a theoretical protocol derived from published primary literature. No clinical trial has tested this specific combination. All interventions require physician supervision, baseline cancer screening, and ongoing monitoring. Nothing herein constitutes medical advice.

Executive Summary

The thymus involutes progressively after the first decade of life, replacing functional thymic epithelial cells (TECs) with adipose tissue and reducing naive T-cell output. Partial reversal was demonstrated in the 9-subject TRIIM trial (Fahy et al., 2019) using recombinant human GH (Norditropin, 0.015 mg/kg/day SC), DHEA, and metformin. The present protocol replaces rhGH with tesamorelin (FDA-approved GHRH analogue; preserves pituitary feedback), replaces metformin with imeglimin (no GH-axis antagonism; direct TEC mitochondrial protection), adds thymosin α1 for direct T-cell maturation support, and integrates weekly rapamycin exclusively in the one-week tesamorelin-free window. The result is nine components and one repeating 4-week cycle with no conditional logic.

#	Component	Dose	Frequency	Phase
1	DHEA	25-50 mg	Daily	All phases
2	Imeglimin	500-1000 mg	Daily	All phases
3	Zinc + Copper	Zn 20-25 mg + Cu 2 mg	Daily	All phases
4	Vit D3 + K2	D3 3000-5000 IU + K2 150 mcg	Daily	All phases
5	Omega-3 (EPA+DHA)	2-3 g	Daily	All phases
6	Melatonin	0.3 mg	Bedtime	All phases
7	Tesamorelin	0.5-2 mg SC (titrated to IGF-1 z-score)	Nightly	Weeks 1-3 of 4
8	Thymosin α1	1.6 mg SC	2x/week	All weeks
9	Rapamycin	5 mg oral	1x/week (Mon)	Week 4 only

Background: Thymic Aging and the Case for Intervention

The thymus is the primary lymphoid organ generating naive T lymphocytes. Thymopoietic output peaks in the first decade then declines ~3% per year. By the sixth decade, >70% of functional thymic parenchyma has been replaced by adipose tissue. The downstream consequences are clinically significant: reduced TCR diversity, contraction of the naive T-cell compartment, expansion of terminally differentiated effector memory cells, and declining vaccine responsiveness — all hallmarks of immunosenescence.

The TRIIM Trial: Proof of Concept

Fahy et al. (2019, *Aging Cell*) demonstrated in 9 healthy men (51-65 years) that a one-year protocol of recombinant human GH (Norditropin, 0.015 mg/kg/day SC) + DHEA + metformin produced: (i) reduced thymic adipose on MRI; (ii) increased sjTREC (marker of recent thymic emigrants); (iii) increased naive CD4+/CD8+ T cells; (iv) mean epigenetic age reversal of 2.5 years (Horvath clock). Underpowered (n=9, no control arm), it nonetheless provided the first mechanistic framework for pharmacological thymic rejuvenation.

Rationale for Protocol Modifications

• **rhGH → Tesamorelin:** rhGH bypasses the hypothalamic-pituitary axis and produces non-pulsatile IGF-1 elevation with documented risks (oedema, insulin resistance). Tesamorelin preserves somatostatin feedback, produces physiological GH pulses, and directly reduces visceral/ectopic fat (FDA Phase 3 validated, n=806).

• **Metformin → Imeglimin:** Metformin suppresses GH secretion via STAT3 inhibition and upregulates IGFBP-2, reducing free IGF-1 — antagonising the protocol's primary signal. Imeglimin achieves metabolic control through mitochondrial respiratory chain rebalancing with no GH-axis antagonism.

• **Thymosin α1 added:** While tesamorelin rebuilds the TEC niche, thymosin α1 supports T-cell maturation via a complementary, non-redundant mechanism on thymocyte differentiation and MHC-II expression.

• **Rapamycin in clearance week only:** mTORC1 is essential for TEC proliferation. Continuous rapamycin causes thymic atrophy. By administering rapamycin only during the tesamorelin-free week, senescent stromal cell clearance occurs without antagonising TEC mTOR signalling during the three thymopoietic weeks.

Daily Base Stack (All Phases, Year-Round)

Six components taken every day regardless of cycle phase, providing foundational TEC support, anti-inflammaging activity, and metabolic buffering throughout.

Component	Dose	Timing	Rationale
DHEA	25-50 mg	Morning	Androgen receptor on TECs; insulin sensitisation; original TRIIM component
Imeglimin	500-1000 mg	With dinner	Mitochondrial ROS reduction in TECs; GSIS enhancement; no GH-axis antagonism
Zinc + Copper	Zn 20-25 mg + Cu 2 mg	Morning	Thymulin cofactor; copper mandatory to prevent depletion from zinc supplementation
Vit D3 + K2	D3 3000-5000 IU + K2 150 mcg	With fat, morning	VDR signalling on TECs; K2 (MK-7) prevents vascular Ca misdeposition
Omega-3 (EPA+DHA)	2-3 g	With meals	NF-kB / NLRP3 inflammasome suppression in thymic stroma
Melatonin	0.3 mg	30 min before sleep	MT1/MT2 receptors on TECs; somatostatin suppression enhances tesamorelin GH pulse

■ **Zinc-Copper Safety:** Long-term zinc above 20 mg/day without copper supplement causes copper-deficiency anaemia and neurological effects. The 2 mg/day copper co-supplement is **mandatory** whenever zinc is taken at these doses.

The 4-Week Repeating Cycle

Every 4-week cycle is structurally identical. No conditional scheduling. The daily base stack runs uninterrupted throughout all weeks.

Week	Phase	Active (beyond daily base)	Rationale
1	THYMOPOIESIS	Tesamorelin 0.5-2 mg SC nightly Thymosin α1 1.6 mg SC (Tue+Fri)	IGF-1-driven TEC proliferation + T-cell maturation
2	THYMOPOIESIS	Tesamorelin 0.5-2 mg SC nightly Thymosin α1 1.6 mg SC (Tue+Fri)	Sustained; the ~3-week thymocyte maturation cycle spans weeks 1-3
3	THYMOPOIESIS	Tesamorelin 0.5-2 mg SC nightly Thymosin α1 1.6 mg SC (Tue+Fri)	Sustained GH pulse; minimum meaningful thymopoietic window
4	CLEARANCE	Tesamorelin PAUSED Thymosin α1 1.6 mg SC (Tue+Fri) Rapamycin 5 mg oral (Mon, fasted)	mTOR inhibition with no active IGF-1 signal; autophagy + senescent stromal cell clearance

• **Why 3 thymopoietic weeks?** The ETP-to-naive-T-cell journey takes ~3 weeks. Two weeks would be below the minimum biologically meaningful thymopoietic window.

• **Why rapamycin only in week 4?** IGF-1 activates TECs via PI3K/Akt/mTORC1. Concurrent rapamycin would directly block this. Pausing tesamorelin eliminates the antagonism while preserving the senolytic benefit.

• **Why thymosin α1 continuous?** It acts via MAPK/NF-kB (mTOR-independent), making it safe alongside rapamycin. Continuous dosing maximises T-cell maturation support.

• **Annual tesamorelin exposure:** 3/4 × 365 ≈ 274 days/year.

• **Rapamycin frequency:** ~13 doses/year — consistent with published intermittent longevity-dosing regimens; avoids continuous immunosuppression.

Component Deep-Dives

1. Tesamorelin (GHRH Analogue)

Full-length (44 aa) synthetic GHRH analogue with N-terminal trans-3-hexenoic acid modification conferring DPP-IV resistance (~30-38 min half-life). Activates pituitary somatotrophs with preserved somatostatin feedback, producing physiological GH pulses. Primary FDA-validated effect: visceral fat reduction 10-18% over 26-52 weeks (Phase 3, n=806). Directly targets ectopic adipogenesis driving thymic involution. FDA-approved as Egrifta (2010) and Egrifta SV (2025) for HIV-associated lipodystrophy.

Parameter	Detail
Starting dose	0.5 mg SC nightly — titrate up by IGF-1 z-score (see titration table below)
Maximum dose	2 mg SC nightly (HIV lipodystrophy approved dose; reached only if z-score permits)
Schedule	Weeks 1-3 of every 4-week cycle; paused week 4 (rapamycin week)
Week-4 break rationale	Required to allow rapamycin without antagonising TEC mTORC1. NOT driven by receptor desensitisation — no GHRH-R tachyphylaxis observed in 52-week Phase 3 data.
Common AEs	Injection-site pruritus (~7.6%); peripheral oedema (~6.1%); arthralgia; nausea
Glucose effect	Modest glucose/HbA1c increase; offset by imeglimin GSIS enhancement
IGF-1 monitoring	Every 3 months; target z-score 0 to +1.5; hard ceiling z-score +2.0
Contraindications	Active malignancy; pituitary tumour; pregnancy; hypersensitivity

IGF-1 Z-Score Titration (Day-7 of Cycle 1 and every 3 months)

IGF-1 Z-Score	Action
< 0 (below age-mean)	Increase by 0.5 mg at next cycle start (e.g. 0.5 → 1.0 mg)
0 to +1.5 (target zone)	Maintain current dose — optimal range achieved
+1.5 to +2.0 (approach ceiling)	Maintain or reduce by 0.5 mg; recheck at 6 weeks
> +2.0 (above ceiling)	Reduce dose by 0.5 mg immediately; do not escalate further

■ **Day-7 IGF-1 draw (Cycle 1):** Obtain serum IGF-1 on Day 7 of the first cycle before proceeding. If z-score > +2.0, reduce dose to 0.5 mg. If z-score < 0, confirm compliance and consider escalation at the start of Cycle 2.

2. Thymosin α1 (Thymic Peptide)

28-amino-acid N-terminally acetylated peptide derived from prothymosin α. Supports thymocyte maturation, upregulates MHC-II expression on TECs, and activates dendritic cells via TLR2/4 and MAPK/NF-kB pathways. Approved in multiple countries for hepatitis B/C and as a cancer adjunct immunotherapy. Acts via mTOR-independent pathways — safe alongside rapamycin.

Parameter	Detail
Dose/schedule	1.6 mg SC — Tuesday and Friday every week (including week 4)
Half-life	~2 hours; negligible accumulation
Mechanism	MAPK/NF-kB; TLR2/TLR4 activation; MHC-II upregulation on TECs
Why continuous?	mTOR-independent → no antagonism with week-4 rapamycin; maximises maturation support
Safety profile	Excellent — no serious AEs in clinical trials; mild injection-site reactions
Contraindications	Organ transplant recipients on immunosuppression (may counteract)

3. Rapamycin / Sirolimus (mTORC1 Inhibitor)

Macrolide lactone that binds FKBP12, allosterically inhibiting mTORC1. At intermittent low doses (~5 mg/week), primary effects are autophagy induction, senescent cell clearance, and extension of healthspan in animal models. Continuous dosing causes thymic atrophy — hence administration is strictly confined to the tesamorelin-free week.

Parameter	Detail
Dose/schedule	5 mg oral — Monday of week 4 only (fasted, ≥10 h after last meal)
Annual exposure	~13 doses/year — intermittent, not continuous immunosuppression
Primary targets	mTORC1 → autophagy; senescent stromal cell clearance in thymus
Why week 4 only?	TEC proliferation requires mTORC1 (IGF-1/PI3K/Akt/mTOR). Concurrent use with tesamorelin would block TEC regeneration.
Common AEs	Mouth ulcers; mild dyslipidaemia; transient WBC reduction at higher doses
Drug interactions	CYP3A4 substrate — avoid grapefruit; caution with azole antifungals
Contraindications	Active infection; pregnancy; hypersensitivity to sirolimus

4. Imeglimin (Mitochondrial Amplifier)

First-in-class tetrahydrotriazine compound approved in Japan (Twymeeg, 2021) for type 2 diabetes. Rebalances mitochondrial respiratory chain complex I/III, reduces mitochondrial ROS, and enhances glucose-stimulated insulin secretion (GSIS) without GH-axis antagonism. Its ROS-reduction mechanism is directly relevant to aged TEC biology where oxidative stress is a primary driver of dysfunction.

Parameter	Detail
Dose/schedule	500-1000 mg with dinner, daily
Mechanism	Mitochondrial ETC rebalancing; ROS reduction; GSIS enhancement
GH-axis effect	None — no STAT3 inhibition, no IGFBP-2 upregulation (unlike metformin)
Approval status	Japan (2021); not yet FDA-approved; sourced as research compound
Safety profile	Generally well tolerated; mild GI effects; no hypoglycaemia as monotherapy
Evidence gap	No human trial in thymic rejuvenation context; mechanistic rationale only

■ **Imeglimin Evidence Gap:** Imeglimin's role in this protocol is mechanistically justified but not clinically validated in the thymic rejuvenation context. Physician oversight and periodic metabolic monitoring are essential.

5. DHEA (Dehydroepiandrosterone)

Adrenal steroid precursor to androgens and oestrogens. Serum levels decline ~80% between age 25 and 75. TECs express androgen receptors; androgen signalling promotes TEC survival and thymic architecture. DHEA was a component of the original TRIIM trial at 50 mg/day. Additionally provides mild insulin-sensitising effects.

Parameter	Detail
Dose/schedule	25-50 mg oral, morning, daily
Monitoring	DHEA-S, testosterone, oestradiol at baseline and 6 months
Sex-specific notes	Men: androgenic AEs (acne, hair); Women: virilisation risk — start at 25 mg
Contraindications	Hormone-sensitive cancers (prostate, breast, ovarian); polycythaemia

Monitoring and Safety

All monitoring should be supervised by a physician familiar with GH-axis pharmacology, immunology, and metabolic medicine. The schedule below represents minimum recommended frequency; clinical judgment may require more frequent assessment.

Timepoint	Tests / Actions
Baseline (before starting)	Full metabolic panel; CBC; IGF-1 with z-score; HbA1c; fasting glucose; DHEA-S; testosterone; oestradiol; PSA (men >45); thyroid panel; MRI thymus (optional but ideal)
Day 7, Cycle 1	Serum IGF-1 (z-score) — primary tesamorelin dose titration signal
Monthly (months 1-3)	Fasting glucose; HbA1c; CBC; metabolic panel
Every 3 months	IGF-1 z-score; DHEA-S; testosterone; lipid panel
Every 6 months	Full panel repeat; PSA (men); echocardiogram if oedema present
Annually	MRI thymus (ideal); epigenetic clock assay (optional); sjTREC (research labs)
Stop criteria	IGF-1 z-score > +2.0 persistently; active malignancy detected; significant oedema unresponsive to dose reduction; active serious infection (pause rapamycin + thymosin α1)

Drug Interactions

Interaction	Severity	Management
Tesamorelin + Insulin / Oral antidiabetics	Moderate	Tesamorelin raises glucose; adjust antidiabetic dose if needed; imeglimin partially compensates
Rapamycin + CYP3A4 inhibitors (azoles, grapefruit, clarithromycin)	Significant	Markedly elevated rapamycin levels → toxicity. Avoid combination; grapefruit absolutely contraindicated.
Rapamycin + CYP3A4 inducers (rifampicin, carbamazepine, St John's Wort)	Significant	Reduced rapamycin efficacy. Avoid or recheck trough levels.
DHEA + Anticoagulants (warfarin)	Moderate	DHEA may potentiate anticoagulant effect. Monitor INR closely.
DHEA + Hormone-sensitive medications	Moderate	Androgenic effects may interact with aromatase inhibitors, anti-androgens.
Thymosin α1 + Immunosuppressants	Moderate	Opposing mechanism — thymosin α1 stimulates immunity; may counteract transplant immunosuppression.
Imeglimin + Other antidiabetics	Low-Moderate	Additive glucose-lowering; monitor for hypoglycaemia if combined with insulin or sulfonylureas.

Limitations and Evidence Quality

• **No combination trial exists.** The full 9-component protocol has never been tested in any clinical trial. Evidence for each component is extrapolated from separate studies.

• **TRIIM trial was underpowered.** n=9, no control arm, no randomisation. The epigenetic age reversal finding requires replication in a larger controlled trial.

• **Tesamorelin dose extrapolation.** The 0.5 mg starting dose and IGF-1 z-score titration approach is a conservative physician adaptation — not from a thymic rejuvenation trial. Optimal dosing for this indication is unknown.

• **Imeglimin lacks Western regulatory approval and thymic evidence.** Used as a mechanistically-justified metformin replacement. Long-term safety data outside Japan is limited.

• **Rapamycin longevity dosing is extrapolated from animal models.** The intermittent 5 mg/week human longevity dosing regimen is observational and lacks RCT data.

• **Thymosin α1 thymic data is limited.** Evidence comes primarily from oncology and infectious disease contexts, not from thymic rejuvenation trials.

• **Individual variation is substantial.** GH pulsatility, IGF-1 sensitivity, rapamycin clearance (CYP3A4 polymorphisms), and baseline thymic reserve vary widely between individuals.

• **Long-term oncogenic risk is unknown.** Sustained IGF-1 elevation, even within the target z-score range, has theoretical pro-proliferative effects. Regular cancer screening is mandatory throughout the protocol.

> **Important:** This document is a research synthesis, not a clinical guideline. All decisions about initiating, adjusting, or stopping this protocol must be made by a qualified physician who has reviewed the individual patient's full medical history, current medications, and baseline investigations.

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