Thymosin α1 (Tα1) — Posology & Dosing Schedule Rationale

1. Why the 2-Hour Plasma Half-Life Does Not Drive the Dosing Interval

Thymosin α1 has a plasma $t_{½}$ of approximately 2 hours after SC injection. This appears to demand frequent dosing but is pharmacokinetically misleading. Tα1 does not act via sustained plasma concentration: its targets (dendritic cells, thymocytes, thymic epithelial cells) are activated through downstream transcriptional programs — Th1 polarisation via MAPK/NF-κB, MHC-II upregulation on APCs, and thymocyte differentiation cascades. These transcriptional effects persist for days to weeks after a single injection.

The peptide's mechanism is **pulse-triggered rather than concentration-sustained** — more analogous to LH/FSH pulses on gonadal receptors than a small-molecule drug requiring continuous tissue exposure. Full immune reconstitution typically requires 4–8 weeks of repeated dosing regardless of frequency, implying the downstream biology — not the PK — sets the therapeutic timescale.

2. Dosing Regimens Across Clinical Contexts

Setting	Dose	Schedule	Duration	Notes
Hepatitis B (approved)	1.6 mg SC	2×/week	52 weeks	Pivotal Zadaxin registration trials; reference posology for chronic immune support
Hepatitis C + IFN (approved)	1.6 mg SC	2×/week	26 weeks	Approved in 35+ countries; confirms twice-weekly as the regulatory standard
Sepsis (ETASS RCT)	1.6 mg SC	BID ×5d, then QD ×2d	7 days	Acute rescue; BID loading for rapid mHLA-DR restoration on monocytes
COVID-19 (moderate–severe)	1.6 mg SC	Daily ×5–7d	1–2 weeks	Adapted from sepsis model; front-loaded immune rescue, not chronic support
Oncology (adjunct)	1.6–6.4 mg SC	2×/week or daily	Cycle-dependent	Higher doses explored; no ceiling established in published trials
HIV (immune support)	1.6 mg SC	2×/week	Long-term	Extended use studied in small cohorts; consistent with hepatitis schedule
Longevity / thymic support (research)	1.0–1.6 mg SC	2×/week	Ongoing	Closest match to approved hepatitis posology; most defensible for chronic TEC support
Low-dose daily (research only)	300–500 µg SC	5-on/2-off	Ongoing	Similar weekly AUC; zero RCT support — PK extrapolation, not evidence-based

AUC = area under curve; mHLA-DR = monocyte HLA-DR; RCT = randomised controlled trial; TEC = thymic epithelial cell; BID = twice daily; QD = once daily.

3. Why Not Daily Dosing at 1.6 mg (Chronic)?

No RCT demonstrates that chronic daily Tα1 at 1.6 mg is harmful. However, three converging arguments favour the twice-weekly regimen for a months-to-year thymic-rebuilding objective:

a) Receptor saturation / tachyphylaxis (theoretical)

Daily 1.6 mg pulsing on a ~2-hour half-life receptor generates approximately 12× more receptor-engagement events per week than twice-weekly dosing. While no formal tachyphylaxis data exist for Tα1, cytokine-like peptides that trigger transcription factor activation (NF-κB, AP-1) can exhibit reduced sensitivity with continuous high-frequency stimulation. The 3–4 day inter-dose interval maintains receptor responsiveness by allowing time for re-sensitisation.

b) The randomised evidence base is entirely twice-weekly

The twice-weekly schedule was established in hepatitis B/C trials in the 1990s and carried into every subsequent approved indication. There is no head-to-head comparison of chronic daily vs. twice-weekly dosing for thymic or immune-maintenance endpoints. Claiming daily is superior would require evidence that does not exist.

c) The downstream biology does not require daily exposure

Key biological timescales: ETP → naive T cell (~3 weeks); DC activation half-life (~48–72 h); T-cell MHC-II upregulation duration per dose (~72 h). A 3–4 day inter-dose interval covers these windows without the injection burden, cost, or theoretical receptor-saturation risk of daily administration.

4. Daily Dosing (Sepsis/COVID) — A Different Clinical Objective

In sepsis and severe COVID-19, daily or BID dosing for 5–7 days is used because the window for immune reconstitution is narrow and immune paralysis is severe. The ETASS design (BID ×5d → QD ×2d) is a **rescue** rather than maintenance model: the goal is rapid mHLA-DR restoration, not TEC niche building.

> **Key distinction:** Acute immune rescue (sepsis/COVID) requires rapid receptor engagement over days. Thymic regeneration requires sustained receptor responsiveness over months. These objectives map to fundamentally different posological strategies. The daily sepsis schedule is **not** transferable to a chronic thymic-support protocol.

5. Implication for the Present Protocol

The **1.6 mg SC twice-weekly (Tuesday + Friday)** schedule is the most evidence-anchored choice for the chronic thymic-support context:

- Matches both approved indications (hepatitis B/C), providing 52-week twice-weekly efficacy data.
- Inter-dose spacing of 3–4 days aligns with the duration of MHC-II upregulation and Th1 polarisation per dose.
- Continuous across all 4 cycle weeks including the rapamycin week — safe because Tα1 acts via MAPK/NF-κB (mTOR-independent), not suppressed by rapamycin.
- Avoids cost, injection burden, and theoretical tachyphylaxis risk of daily dosing with no established efficacy benefit.

> **Alternative — low-dose daily (300–500 μg, 5-on/2-off):** Some practitioners use a lower daily dose to reduce per-injection cost and maintain similar weekly AUC. This regimen has zero RCT support — it is a pharmacokinetic extrapolation. It is not adopted in the present protocol.

Key References

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