Appendix — GHRH-R Agonist Alternatives

CJC-1295 (no DAC) + Ipamorelin as a Tesamorelin Substitute

Tesamorelin is FDA-approved and carries the strongest clinical evidence base for visceral and ectopic fat reduction in this protocol. However, it requires a physician prescription and its cost (typically USD 500–1,500/month) may be prohibitive. The combination of CJC-1295 (no DAC) and Ipamorelin activates the same downstream GH/IGF-1 signalling cascade through complementary, synergistic mechanisms, and may be considered as a substitution by clinicians where tesamorelin is inaccessible. The overall protocol structure — 3 thymopoietic weeks, 1 rapamycin clearance week, continuous daily base stack — is unchanged.

1. Mechanism of Action Comparison

Feature	Tesamorelin	CJC-1295 (no DAC)	Ipamorelin
Drug class	GHRH analogue (44 aa)	GHRH analogue (29 aa, 4 substitutions)	Ghrelin mimetic / GHS-R1a agonist
Primary receptor	GHRH-R (pituitary somatotroph)	GHRH-R (pituitary somatotroph)	GHS-R1a (pituitary + peripheral)
2nd messenger	cAMP → GH synthesis + release	cAMP → GH synthesis + release	Gq/11 → IP3/DAG → Ca^{2+} → GH release
Somatostatin feedback	Preserved	Preserved	Partially bypassed
GH pulse pattern	Physiological pulsatile	Physiological pulsatile	Pulsatile; additive with CJC-1295
Half-life	30–38 min (DPP-IV resistant)	~30 min	~2 hours
Peripheral GHS-R effects	None	None	Mild appetite stimulation; gut motility
Regulatory status	FDA-approved Rx (Egrifta SV)	Research peptide — no approved indication	Research peptide — no approved indication

Synergy rationale: CJC-1295 (no DAC) and ipamorelin act on separate receptors (GHRH-R and GHS-R1a) via distinct second-messenger cascades that converge at the pituitary somatotroph, producing a supra-additive GH pulse exceeding either agent alone.

2. Why Ipamorelin (Not GHRP-6 or GHRP-2)

Ipamorelin is the preferred ghrelin mimetic because it is highly selective for GH release with minimal cortisol and prolactin elevation. GHRP-6 and GHRP-2 cause significant cortisol and prolactin elevation — both suppress thymopoiesis.

Ghrelin Mimetic	GH Release	Cortisol	Prolactin	Appetite
GHRP-6	Strong	Significant ▲	Significant ▲	Marked ▲
GHRP-2	Strong	Significant ▲	Moderate ▲	Moderate
Ipamorelin	Strong	Minimal ✓	Minimal ✓	Mild

3. Dosing Substitution

Agent	Research Dose	Timing	Route / Note
Tesamorelin	0.5–2 mg (titrated; IGF-1 z-score 0→+1.5)	Nightly	SC; weeks 1–3 only
CJC-1295 no DAC	100–200 μg	Nightly 30–60 min pre-sleep	SC; combine with ipamorelin
Ipamorelin	100–300 μg	Nightly 30–60 min pre-sleep	SC; combine with CJC-1295 no DAC

Recommended combination: CJC-1295 no DAC 200 μg + Ipamorelin 200 μg, SC, combined in one injection, nightly 30–60 min pre-sleep, weeks 1–3 of each 4-week cycle. Paused in week 4 — identical rapamycin-window logic as tesamorelin. **Do NOT use CJC-1295 with DAC** (half-life ~7–8 days; causes continuous GH elevation, not physiological pulses — incompatible with week-4 pause architecture).

4. Side-Effect Profile Comparison

Side Effect	Tesamorelin	CJC-1295 no DAC	Ipamorelin
Injection site reactions	7.6% (Phase 3)	Similar (less data)	Mild, less common
Peripheral oedema	6.1% (Phase 3)	Similar	Milder
Arthralgia	Documented	Likely similar	Less common
Glucose / HbA1c rise	Modest (offset by imeglimin)	Possible	Generally minimal
Carpal tunnel	Documented (IGF-1 effect)	Possible at high IGF-1	Possible
Cortisol elevation	No	No	No ✓
Prolactin elevation	No	No	No ✓
Flushing at injection	No	Rare	Common (transient, benign)
Appetite stimulation	No	No	Mild

5. Protocol Compatibility Assessment

Criterion	Tesamorelin	CJC-1295 no DAC + Ipamorelin
GHRH-R activation	✓ Primary mechanism	✓ Via CJC-1295 component
Somatostatin feedback	✓ Preserved	Mostly ✓ (ipamorelin partially bypasses)
Physiological GH pulsatility	✓	✓ (nightly dosing)
TEC proliferation (IGF-1 signal)	✓	✓ (GH → liver IGF-1)
Visceral / thymic fat reduction	✓ Phase 3 RCT (n=806)	↑ Mechanistic inference; no Phase 3 RCT
Week-4 rapamycin pause logic	✓ Intact	✓ Identical logic applies
Melatonin somatostatin-suppression	✓ Enhances GH pulse	✓ Same benefit
IGF-1 z-score titration	✓	✓ Identical monitoring applies
Regulatory status	FDA-approved (Rx required)	Research peptides (unapproved)
Clinical evidence quality	Phase 3 RCT	Small human studies + animal data
Estimated monthly cost	USD 500–1,500	USD 50–150 (research suppliers)

6. Protocol Change — Weeks 1–3 Substitution

Parameter	Original (Tesamorelin)	Substituted (CJC-1295 no DAC + Ipamorelin)
Agent	Tesamorelin 0.5–2 mg SC nightly	CJC-1295 no DAC 200 μg + ipamorelin 200 μg SC nightly (combined injection)
Phase	Weeks 1–3 only (paused week 4)	Weeks 1–3 only (paused week 4) — unchanged
IGF-1 monitoring	Every 3 months; titrate to z-score 0→+1.5; ceiling +2.0	Identical monitoring and titration targets apply
Week-4 rapamycin	Tesamorelin paused; rapamycin 5 mg oral (Mon, fasted)	Peptides paused; rapamycin 5 mg oral (Mon, fasted) — unchanged
All other components	Unchanged (DHEA, imeglimin, Tα1, Zn/Cu, D3/K2, Ω-3, melatonin)	Unchanged

▲ **Evidence Grade Downgrade.** The protocol's primary clinical anchor is tesamorelin's Phase 3 RCT data (visceral fat reduction 10–18%, n=806). CJC-1295 no DAC + ipamorelin act through the same mechanistic pathway, but visceral fat reduction has not been tested in a Phase 3 trial. Tesamorelin: Phase 3 validated. CJC-1295 no DAC + ipamorelin: Mechanistic inference. This is a material limitation. Disclose to the patient and document in the clinical record.

7. Regulatory and Quality-Assurance Note — Research Peptides

CJC-1295 (no DAC) and ipamorelin are research peptides with no approved indication in any major regulatory jurisdiction. They are not subject to GMP lot-release testing, potency verification, or sterility assurance equivalent to pharmaceutical-grade products.

Risk Concern	Concern	Mitigation
Purity / potency	No mandatory third-party testing; batch-to-batch variability	Source from suppliers with CoA (HPLC ≥98%) and endotoxin data; cross-reference third-party lab panels
Sterility	Lyophilised powder reconstituted by user; no sterility assurance	Reconstitute aseptically; use 0.22 μm filter syringe; refrigerate; discard after 28 days
Legal status	Varies by jurisdiction; may be legal to purchase for research, illegal to administer without medical licence	Confirm jurisdiction-specific legal status before prescribing or purchasing
IGF-1 overshoot	Unknown dose–response variability vs pharmaceutical-grade compound	Check IGF-1 at day 7 of first cycle; adjust dose; mandatory ceiling z-score +2.0

This appendix is for clinician reference only. The primary protocol recommendation remains tesamorelin (FDA-approved, Phase 3 validated, pharmaceutical-grade). The CJC-1295 (no DAC) + ipamorelin substitution is provided for completeness where tesamorelin is inaccessible.