IASO AEGIS PROTOCOL

Version 17 — Master Evidence Review & Comprehensive Assessment

Theoretical protocol targeting ~4.3 cm aortic root dilation

Status: Phase 3 — Stabilization ACTIVE | Olmesartan 20 mg/day running | Phases 1 & 2 COMPLETE

I. Current Daily Stack — Version 17 Active Reference

> ***Permanent timing rules:*** *(1) QUERCETIN COPPER SEPARATION — Tue/Wed/Thu pulse days: Quercetin minimum 3h after morning GHK-Cu injection (Quercetin chelates copper, reducing LOXL-1 bioavailable Cu). (2) MT-1 PAUSE — pause MT-1 on Fisetin senolytic pulse days; anti-apoptotic MITF bias counterproductive to senolytic intent; resume next day. (3) EGCG MOVED TO EVENING — maximises temporal separation from morning GHK-Cu and midday Zn/Cu/Se copper sources while preserving SIRT1/AMPK benefit.*

10:00 AM — SubQ Peptides

Compound	Brand / Source	Dose	Schedule	Notes & Rationale
SubQ Peptides — Morning Injection Block				
GHK-Cu + KPV	*Custom/Research (combined solution)*	2.0 mg + 250 mcg	Mon–Fri (5/2)	**GHK-Cu:** LOXL-1 upregulation (copper-dependent amine oxidase). Collagen/elastin synthesis. TGF-β repair phenotype. Direct Cu cofactor delivery — GHK-Cu is itself a copper source (additive to Zn/Cu/Se 3-in-1), providing redundant Cu supply to LOXL-1. **KPV:** MC3R agonist; NF-κB suppression (third convergent route alongside Olmesartan AT1R and MT-1 cAMP/PKA); Gal-3 downstream modulation. Combined SubQ solution. PAUSE both during D+Q active window; resume Day 10 of LAG.
Retatrutide	*Custom/Research*	2.0 mg Mon / 2.0 mg Thu	Mon + Thu	Triple GLP-1/GIP/GCG agonist. PVAT reduction = direct structural aortic intervention — HELENA trial showed aortic diameter reduction correlated with visceral adipose tissue volume reduction in highest quartile at 12 weeks. GLP-1R on vascular endothelium: anti-inflammatory. At BP 108/66: maintained at 2.0 mg Mon/Thu (higher doses add BP-lowering risk). Food required Mon/Thu alongside AM Berberine.
MOTS-c	*Custom/Research*	5.0 mg	Tue + Fri	Mitochondrial-derived peptide: AMPK activation; insulin sensitivity; metabolic floor. 2×/week confirmed effective. Phase 2 complete; ongoing maintenance. Separate from Berberine dosing days.
MT-1 (Afamelanotide)	*Custom/Research — MC1R-selective ONLY. NOT MT-2*	0.5 mg	Every Other Day (EOD)	Foundation agent — continuous all phases. **Four-arm mechanism:** (1) NF-κB→MMP-2/9/13 suppression; Gal-3 transcription suppression — Gal-3 trend = MT-1 pharmacodynamic biomarker. (2) CD36↓ + ABCA1/ABCG1↑ (aortic wall oxLDL efflux axis). (3) MITF pathway: plausible anti-apoptotic bias — confirmed CNS/renal; VSMC evidence pending; stated as plausible only. (4) AMPK→TSC2+Raptor→mTORC1 suppressed — physiological upstream mTOR modulation without rapamycin CCN2/dissection risk. EOD justified by MC1R self-upregulation (receptor density increases with repeated dosing — positive feedback, no tachyphylaxis) and downstream cascade persistence. Annual dermatological review (MITF drives melanocyte activity). PAUSE on Fisetin pulse days.

10:00 AM — Oral Daily (7×/week)

Compound	Brand / Source	Dose	Schedule	Notes & Rationale
Oral Daily — All 7 Days				
Olmesartan	*Prescription — Generic*	10 mg AM + 10 mg PM = 20 mg total	Daily split AM/PM	AT1R inverse agonist with three-point conformation-resistant receptor contact (OH→Tyr113, COOH→Lys199/His256, tetrazole→Gln257) — blocks ground-state AND stretch-activated (mechanosensing) AT1R. Mechanosensing blockade is the critical pharmacological advantage: each heartbeat is a direct AT1R stretch signal at 4.3 cm. Simultaneously upregulates ACE2→Ang-(1-7)→Mas protective axis (confirmed OPG-KO mouse model — Ang-(1-7) is the actual mediator of olmesartan aortic protection). NEVER pause. Current 20 mg/day. Stepwise escalation: 30 mg (15+15) then 40 mg (20+20) only if standing systolic remains ≥100 mmHg at each step — monitor 2 weeks per dose change.
Grape Seed Extract Extra Strength	*Natural Factors GSE Extra Strength 100:1*	400 mg	Daily AM	OPC proanthocyanidin. Tixier 1984 (Biochem Pharmacol) — OPC class elastin-hydroxyproline binding applies to both pine bark and GSE equally. GSE 92–95% OPC vs pine bark 80–85% — higher concentration per dose. 400 mg GSE: SBP −13 mmHg (12-week RCT); eNOS +45% (human experiments); arterial stiffness improvement (PWV, Einc, distensibility). Correctly replaces Pycnogenol 100 mg with superior OPC load.
Active B Complex	*Natural Factors BioCoenzymated*	1 cap	Daily AM	Quatrefolic L-5-MTHF 400 mcg → DHFR → BH4 regeneration → eNOS coupling. Uncoupled eNOS produces superoxide not NO — direct aortic wall oxidative damage (mechanistically validated TAA driver). Methylcobalamin 500 mcg; P5P; R5P — all coenzymated active forms.
Taurine	*Organika Taurine*	1,000 mg AM + 1,000 mg PM	Daily split	Mitochondrial membrane osmoregulation; cardiac rhythm; mild antihypertensive; anti-inflammatory at 2g/day. 2g total.
Vitamin C	*Jamieson Vitamin C*	250 mg AM + 250 mg PM	Daily split	Prolyl/lysyl hydroxylase cofactor — collagen/elastin hydroxylation. 500 mg/day total. Supraphysiologic doses suppress H_2O_2 LOXL-1 redox signalling — 500 mg maintains cofactor function without this interference.
Magnesium Bis-Glycinate	*CanPrev*	200 mg AM + 200 mg PM	Daily split	VSMC relaxation; collagen hydroxylation cofactor; cardiac rhythm. 400 mg/day total. Serum Mg^{2+} on every bloodwork draw.

10:00 AM — 5/2 Staggered (Mon–Fri)

Compound	Brand / Source	Dose	Schedule	Notes & Rationale
5/2 Morning Stagger — Mon–Fri				
Citrus Bergamot AM	*Nutricost / Swanson (600 mg/cap)*	600 mg	Mon–Fri AM	AM half of 1200 mg/day total. HMG-CoA reductase inhibition (melitidin, brutieridin — structural HMG homology). LDL −38.6% at 1000 mg (Mollace et al. 237-patient RCT — clear dose-response). AMPK/SIRT1 activation. NF-κB inhibition. PM split maintains 24h coverage. SUSPEND during ATRA ON cycles (CYP3A4). 1200 mg/day justified by borderline-high LDL and ApoB <80 target.
Berberine AM	*PlantVital Berberine*	500 mg	Mon–Fri AM	AM half of 1000 mg/day total. Direct REV-ERBα agonist: Song et al. 2025 (Cardiovascular Research) TAAD model — BMAL1→REV-ERBα→c-MYC suppression→VSMC survival. AMPK; gut-liver bile acid axis (unique — not replicated by Bergamot); LDL-R upregulation. t½ 3–4h — AM/PM split sustains REV-ERBα agonism. SUSPEND during ATRA ON cycles. Food required Mon/Thu with Retatrutide.
Bamboo Silica	*Swanson Bamboo Silica*	300 mg	Mon–Fri	Orthosilicic acid: collagen type I synthesis stimulation; hydroxyproline incorporation in cross-links; connective tissue scaffold support. Confirm orthosilicic acid form (not silicon dioxide).
Curcumin Meriva	*Webber Naturals Curcumin Meriva*	500 mg	Mon–Fri	Primary MMP-9 transcription inhibitor. NF-κB suppression (independent of Olmesartan and MT-1 routes). Meriva phytosome: 500 mg ≈ 2g standard curcumin bioavailability. Retained ALL phases including LAG and ATRA ON cycles. No CYP3A4 interaction — NOT suspended during ATRA.
Quercetin Pulse	*Nutrawave Quercetin*	1,200 mg	Tue/Wed/Thu ONLY	Senomorphic/anti-MMP: p21 VSMC senescent cell pressure; TLR4 inhibition; Gal-3 suppression; MMP-9 via TLR4 route (distinct from Curcumin transcriptional route). COPPER SEPARATION RULE: minimum 3h after morning GHK-Cu on Tue/Wed/Thu. During D+Q cycles: switch to daily 1200 mg to maximise D+Q synergy; return to Tue/Wed/Thu pulse after LAG closes.

2:00 PM — Midday / Repair (Daily)

Compound	Brand / Source	Dose	Schedule	Notes & Rationale
Midday — 2:00 PM				
NMNH Complex	*California Gold Nutrition NMNH Complex*	1 cap	Daily	**Confirmed label doses:** NMNH 250 mg / CoQ10 100 mg / PQQ 20 mg / Ergothioneine 5 mg / TMG 25 mg (minor — Just Glow provides primary 500 mg TMG). NMNH 250 mg is in studied range for NAD+ repletion. NAD+→SIRT1→ACE2 upregulation→Ang-(1-7)/Mas protective axis. 2025 data: NAD+ precursors reduce Ang II-induced VSMC senescence via p-AMPK/KLF4 — direct VSMC relevance. CoQ10 100 mg here + 100 mg standalone bedtime = 200 mg/day total.
TMG	*Just Glow TMG*	500 mg	Daily	Primary TMG source (NMNH complex provides only 25 mg — insufficient as sole source). ApoB-safe methyl donor for NAD+/SIRT1 pathway. Betaine-homocysteine methyltransferase. Synergy with B Complex.
NAC	*Natural Factors NAC*	600 mg	Mon/Wed/Fri base; daily during D+Q window, Phase LAG, ATRA ON cycles	**Standard Mon/Wed/Fri:** preserves H_2O_2 LOXL-1 activation window on off-days (daily NAC chronically suppresses this signalling). **Exception windows requiring daily NAC:** D+Q active days (SASP-ROS buffering); full 28–35 day LAG; ATRA ON cycles (hepatic CYP26 conjugation support). Return to Mon/Wed/Fri when each exception closes.
Manganese Chelate	*Natural Factors*	~1.25 mg (split 2.5 mg tablet or alternate days)	Daily	MnSOD cofactor — primary mitochondrial matrix antioxidant enzyme (Mn-dependent superoxide scavenging at ETC source). Mn-dependent prolidase: collagen hydroxyproline recycling. Dose halved from 2.5 mg to prevent accumulation. Separate from zinc supplement.
Zinc Picolinate 3-in-1	*Herba Zinc Picolinate 3-in-1*	Zn 25 mg / Cu 2 mg / Se 200 mcg	Daily	**Cu: LOXL-1 catalytic cofactor** — copper-dependent amine oxidase; do not deplete. Cu tracking mandatory at every phase gate (additive with GHK-Cu). Ceruloplasmin at every gate draw. Se 200 mcg near tolerable UL — confirm sole dietary Se source.
D3 + K2	*Nutritionn D3+K2 (2 caps)*	5,000 IU D3 + 240 mcg K2 MK-7	Daily	MGP activation (K2 MK-7-dependent) — primary aortic calcification inhibitor. ACE2 transcriptional upregulation via VDREs (independent of SIRT1 — additive with Olmesartan-driven ACE2 upregulation). Target 25-OH D: 60–80 ng/mL. MK-7 confirmed in Nutritionn product.
TUDCA	*Generic TUDCA*	250 mg	Daily	ER stress reduction; hepatoprotective against combined peptide/supplement stack hepatic load; fat-soluble nutrient absorption support. Reduce to Mon/Wed/Fri once EGCG supply is exhausted.
Dill-Berry Extract	*Prepared fresh: European Anethum graveolens + mixed berries*	500 mL	Daily	**PRIMARY LOXL-1 activator.** Fhayli et al. 2020 (Biomolecules 10(2):173): LOXL-1 mRNA ×2, tropoelastin mRNA ×2, elastic lamella disruptions −33%, aortic stiffness reduced, LV hypertrophy reversed — ascending aorta aged mouse model. Prep: grind EUROPEAN dill seeds + ½ cup berries + 500 mL water; soak 24–48h refrigerated; filter. Berry anthocyanins add elastase inhibition and anti-calcification. PAUSE during D+Q active window; resume Day 7 of LAG.

10:00 PM — Bedtime / Shield Engine

Compound	Brand / Source	Dose	Schedule	Notes & Rationale
Bedtime — 10:00 PM (1–2h post-dinner)				
Olmesartan	*Prescription — Generic*	10 mg PM	Daily	PM half of 20 mg/day. Bedtime dosing optimises nocturnal BP control — aortic wall stress peaks during morning BP surge. NEVER pause.

Honokiol	*Econugenics HonoPure*	250 mg	5 days ON / 2 days OFF (NOT daily)	Direct rat aortic SMC evidence: MMP-2/MMP-9 inhibition via NF-κB/ERK1/2 blockade. TGF-β/Smad2/3 suppression. SIRT3 activation → VSMC mitochondrial integrity → contractile state maintenance. VCAM-1 suppression → prevents immune cell infiltration through endothelial barrier. NLRP3 inflammasome suppression. **GABAA positive allosteric modulator** — daily use risks GABAergic dependence (benzo-like withdrawal documented). 5/2 schedule mitigates this. **NOT paused during ATRA** (v16.2 error corrected — no CYP3A4 interaction; provides essential MMP-2/9 protection for newly synthesised uncrosslinked tropoelastin).
EGCG (Green Tea Extract)	*EBYSU Green Tea Extract*	500 mg	Mon–Fri EVENING (5/2) — moved from AM	**Retained — timing moved to evening.** SIRT1 activation (EGCG→AMPK→SIRT1) is the primary retention rationale. MMP-2/9 inhibition; anti-fibrotic (TGF-β). Copper chelation concern (EGCG catechin structure binds Cu) is mitigated by: (1) evening timing creates maximum separation from morning GHK-Cu SubQ; (2) separation from midday Zn/Cu/Se 3-in-1; (3) GHK-Cu + Zn/Cu/Se provide two independent Cu delivery pathways with temporal advantage. Monitor ceruloplasmin — if Cu trends low, consider reducing EGCG to 3/2 schedule.
Citrus Bergamot PM	*Nutricost / Swanson*	600 mg	Mon–Fri PM	PM half of 1200 mg/day total. 24h AMPK/SIRT1/eNOS coverage via AM/PM split. SUSPEND during ATRA ON cycles (CYP3A4 inhibition).
Berberine PM	*PlantVital Berberine*	500 mg	Mon–Fri PM	PM half of 1000 mg/day total. Sustained REV-ERBα agonism given t½ 3–4h. SUSPEND during ATRA ON cycles.
MT-1 (Afamelanotide)	*Custom/Research*	0.5 mg	Every Other Day (EOD)	Evening SubQ. SC depot absorption during overnight period. See full mechanism in morning peptide block. PAUSE on Fisetin pulse days.
Amino Stack	*Custom — 4 amino acids*	Gly 5g / Pro 3g / Val 2g / Lys 1.5g = 11.5g total	Nightly	**Ratios locked 5:3:2:1.5.** Glycine: primary collagen substrate + sleep architecture. Proline: collagen/elastin structural AA. **Valine: ESSENTIAL** — Val-Gly-Val-Pro-Gly (VPGVG) tropoelastin pentapeptide repeating motif. **Lysine: direct LOXL-1 substrate** — oxidised to allysine → desmosine/isodesmosine cross-links. Lysine is substrate; Cu-dependent LOXL-1 enzyme activity is the rate-limiting step. Circadian timing: collagen synthesis peaks in early sleep. PAUSE during D+Q active window; resume Day 21 of LAG.
CoQ10 (standalone)	*Generic Ubiquinol*	100 mg	Nightly	Standalone in addition to CoQ10 100 mg in NMNH Complex = 200 mg/day total. ETC overnight coverage. Ubiquinol form required (superior absorption vs ubiquinone).
Taurine	*Organika*	1,000 mg	Nightly	PM half of 2g/day split. Cardiac rhythm; nocturnal VSMC osmoregulation.
Vitamin C	*Jamieson*	250 mg	Nightly	PM half of 500 mg/day. Nightly collagen/elastin hydroxylation cofactor during peak circadian synthesis window.
Magnesium Bis-Glycinate	*CanPrev*	200 mg	Nightly	PM half of 400 mg/day. Nocturnal aortic VSMC relaxation; cardiac rhythm during sleep.
Melatonin	*Generic*	Start at 1 mg	Nightly PENDING	*PENDING:* ADAM17 inhibition → prevents ACE2 ectodomain shedding from endothelial surface. Circadian BMAL1 entrainment. START at 1 mg — monitor nocturnal BP 1 week before any increase. Additive hypotension risk with bedtime Olmesartan at BP 108/66.
Genistein	*Confirm supply*	40–60 mg	Nightly PENDING	*PENDING arrival.* ERβ agonism → SIRT1/ACE2 upregulation. Direct eNOS transcriptional upregulation 1.8–2.6-fold in primary human aortic endothelial cells at physiological concentrations — strongest direct human aortic endothelial evidence of any pending compound. RhoA suppression → endothelial barrier integrity. PKA mechanism independent of estrogen signalling.

II. Integrated Phase Architecture

Retrospective note: *Phase 1 (Olmesartan) should have been the first intervention — it is the pharmacological anchor without which all subsequent phases work against active AT1R-driven elastin destruction. SS-31 was initiated first only because Olmesartan was not yet prescribed. The numbering below reflects optimal biological order.*

Genetic context: *Canadian TAA genetic panel negative — no ACTA2, MYH11, MYLK, LOX, SMAD3, TGFBR1/2 confirmed. Negative LOX mutation = cross-linking machinery presumed intact → ATRA rationale STRENGTHENED (ATRA produces tropoelastin substrate that intact LOXL-1 can productively cross-link). LOX-TAA would be the contraindication for ATRA; its absence is permissive.*

#	Phase	Dose / Schedule	Duration	Rationale & Mechanism	Gate / Advance Criteria
1	**Foundation & Aortic Shield** **Olmesartan + Honokiol** **(ACTIVE — permanent foundation)**	Olmesartan 20 mg/day (10 AM + 10 PM) Honokiol 250 mg 5/2 bedtime	Permanent — never cycled off	**OLMESARTAN:** AT1R inverse agonism with three-point conformation-resistant receptor contact (OH→Tyr113, COOH→Lys199/His256, tetrazole→Gln257). Blocks ground-state AND mechanosensing stretch-activated AT1R — critical because each heartbeat is a direct AT1R stretch signal at 4.3 cm. Simultaneously upregulates ACE2→Ang-(1-7)→Mas (confirmed OPG-KO mouse model as primary aortic protective mechanism, not merely AT1R blockade). **HONOKIOL:** direct rat aortic SMC evidence for MMP-2/9 inhibition via NF-κB/ERK1/2. SIRT3 activation maintains VSMC mitochondrial integrity and contractile state. Not paused during any phase.	Current 20 mg/day. Escalation to 30 mg then 40 mg stepwise — only if standing systolic ≥100 mmHg at each step. Monitor BP 2 weeks after each dose change.
2	Cellular Reset Epitalon + MOTS-c (COMPLETE — repeat every 6 months)	Epitalon 1 mg/day SubQ × 10 consecutive days (bedtime only) MOTS-c 5 mg SubQ Tue+Fri × 4–6 weeks concurrent	Epitalon: 10 days only. MOTS-c: 4–6 weeks. Repeat both every 6 months.	**EPITALON (Khavinson 10-day protocol — NOT continuous):** TERT upregulation → telomere extension in vascular progenitor pool. Critical: when Phase 6 senolytic clearance removes senescent cells, progenitors must divide. Short telomeres → immediate re-senescence on first division → no structural gain (replacing zombie cells with new zombie cells). Epitalon prevents this. 10-day transcriptional trigger only — continuous use overstimulates without benefit. **MOTS-c concurrent:** AMPK provides ATP budget for energy-intensive TERT-mediated telomere extension.	All 10 Epitalon doses completed (hard gate). Bloodwork before advancing to senolytic phase: Gal-3 ≥20% reduction; IL-10 >20 pg/mL rise; HbA1c <5.4%; Fasting Insulin <6 µIU/mL.

3	Mitochondrial Sprint SS-31 Elamipretide (COMPLETE — repeat if indicated)	5 mg SubQ Mon–Fri	6–8 weeks per course	Cardiolipin binding → ETC supercomplex stabilisation → pathological ROS leak reduction. **NON-SCAVENGING mechanism** — critical: unlike antioxidants that suppress H_2O_2 LOXL-1 signalling, SS-31 reduces mitochondrial ROS without interfering with extracellular LOXL-1 redox activation. Post-treatment durability >6 months in vascular animal models. NMNH Complex concurrent is complementary (SS-31 stabilises cardiolipin structure; NAD+ fuels ETC substrate availability).	Completion of 6–8 week course. Durable mito-protection established.
4	Mitochondrial Biogenesis MOTS-c extended (COMPLETE — repeat with Phase 2)	5 mg SubQ Tue+Fri	4–6 weeks	AMPK-driven mitochondrial biogenesis following SS-31 stabilisation: creates new mitochondria to populate the stabilised cristae environment. Sequence logic: stabilise existing mitochondria (Phase 3) then expand healthy pool (Phase 4). Metabolic floor improvement prepares VSMC population for senolytic and regenerative phase demands.	Fasting insulin trending toward <6 µIU/mL. HbA1c <5.4%.
5	Bloodwork Confirmation Gate	No new agents — bloodwork only	Draw and confirm before advancing	Existing stack (MT-1 + KPV + Quercetin pulse + Olmesartan + Curcumin + Honokiol) has been suppressing Gal-3, NF-κB, MMP-9 throughout. Phase 5 confirms the inflammatory environment has been sufficiently calmed before introducing senolytic agents. Gal-3 trend from baseline = MT-1 pharmacodynamic biomarker.	ALL required before any senolytic cycle: • Gal-3 ≥20% reduction from baseline • IL-10 >20 pg/mL rise • sST2 trending <35 ng/mL • hs-CRP <1.0 mg/L • MMP-9 <900 ng/mL trending • HbA1c <5.4% + Fasting Insulin <6 µIU/mL
6	Senolytic Clearance Fisetin (Cycle 1) → D+Q (subsequent) MT-1 PAUSED on Fisetin days GHK-Cu/KPV + Dill-Berry + Amino Stack PAUSED during D+Q	Fisetin Cycle 1: 1500 mg/day × 3 consecutive days with fat D+Q subsequent: Dasatinib + Quercetin protocol (Quercetin switches to daily 1200 mg; NAC escalates to daily) Monthly Fisetin 1500 mg × 3 days continues as maintenance indefinitely	Fisetin Cycle 1: 3-day pulse; 2-week minimum recovery then resume normal stack. D+Q cycles: 3-day protocol then full 28–35 day LAG before ATRA. Monthly Fisetin maintenance: indefinite — no full LAG needed for routine pulses.	**FISETIN CYCLE 1** (Dasatinib pending): p16-positive senescent endothelial cells; CXCL12/SASP suppression; EndoMT prevention. 1500 mg with fat. MT-1 PAUSED on dosing days. **D+Q SUBSEQUENT CYCLES:** Dasatinib adds BCL-XL inhibition for VSMC senescent populations (unavailable from Fisetin or Quercetin alone). Strongest published VSMC vascular senolytic evidence (AHA ATVB 2025; NIH-backed AAA model 2024). During active D+Q window: PAUSE MT-1, GHK-Cu/KPV, Dill-Berry, Amino Stack. CONTINUE: Olmesartan (always), Honokiol, GSE, NAC (daily), NMNH Complex, Berberine, Curcumin, Zinc, D3+K2, TUDCA, Taurine, Vitamins, B Complex, Retatrutide, MOTS-c.	Phase 5 bloodwork gate must be met before any senolytic cycle. Fisetin: 2-week minimum recovery before resuming normal stack (not sufficient before ATRA — full LAG required for that). D+Q LAG gate: MMP-9 Day 14 post-final D+Q dose — HARD GATE. 28–35 days elapsed AND MMP-9 confirmed downward trend before proceeding to ATRA.
LAG	Post-Senolytic Vulnerability Window (D+Q cycles only)	Continue: Olmesartan, Honokiol, GSE, NAC (daily), Curcumin, Taurine, Vitamins Day 7+: Resume Dill-Berry Day 10+: Resume GHK-Cu + KPV Day 21–35: Resume Amino Stack + MT-1	28–35 days — BLOODWORK DRIVEN (not calendar-driven)	SASP burst from D+Q clearance: MMP-9 spikes days 3–7 post-final dose. Starting ATRA during elevated MMP-9 means synthesising new uncrosslinked tropoelastin into a proteolytically active ECM — monomers are destroyed before LOXL-1 can cross-link them. Active management: GHK-Cu + Dill-Berry resumed Day 10 to prime LOXL-1 — the cross-linking apparatus must be activated and waiting before ATRA initiates tropoelastin synthesis.	**HARD GATE:** MMP-9 at Day 14 post-final D+Q dose — confirmed downward trend required. 28–35 days elapsed AND MMP-9 gate met. Only then proceed to ATRA. For Fisetin-only cycles (no immediate ATRA): 2-week recovery sufficient to resume normal stack.
7	ATRA Regen Pulse VSMC Phenotype Restoration Honokiol CONTINUES (not paused) Berberine + Bergamot SUSPENDED during ON cycles NAC daily during ON cycles	ATRA 10 mg oral daily with 15g EVOO or avocado 14 days ON / 14 days OFF 3 complete cycles per course Annually or as imaging indicates	3 cycles = 12 weeks total per course. Annually thereafter.	RAR/RXR activation: ELN transcription↑; MMP-2/9 suppression; VSMC contractile phenotype restoration (α-SMA↑, SM22α↑, MHC↑); AT1R mRNA −50% (additive with Olmesartan — dual AT1R suppression); ABCA1/ABCG1↑ (foam cell reversal); CTGF suppression; AMPK→mTOR inhibition. **CYP26A1 kinetics:** autoinduction begins 24–48h; near-maximum day 7–10. 14-day ON: full transcriptional activation (days 1–5) + synthesis ramp (days 5–10) + consolidation (days 10–14). 14-day OFF: CYP26A1 normalises fully (requires 14–21 days — shorter OFF = progressive diminishing exposure across cycles). **14/14 LOCKED.** **HONOKIOL CONTINUES:** provides MMP-2/9 protection for newly synthesised uncrosslinked tropoelastin — most critical during ATRA ON cycles. No CYP3A4 interaction. **Genetic context:** negative LOX panel = intact cross-linking machinery = ATRA tropoelastin upregulation productively cross-linked.	Before each ON cycle: 2–3 weeks since last Fisetin pulse; MMP-9 settled. During ON cycles: • ALT/AST Day 7 and Day 14 — halt if >2× ULN • Fasting TG at end of each ON cycle • Serum retinol during course — no supplemental Vitamin A STOP immediately: persistent headache Day 5+; visual disturbance; pressure behind eyes (pseudotumor cerebri).
8	Quiet Window 6 Weeks Pre-Imaging	Maintain: Olmesartan, Taurine, Vitamins, B Complex, D3+K2, TUDCA, NAC Mon/Wed/Fri, GSE. Suspend: all peptides, phenolic stack, Retatrutide (optional for clean baseline). NEVER suspend Olmesartan.	6 weeks before September imaging scan	Newly synthesised tropoelastin requires weeks for full desmosine cross-link maturation and mechanical integration into existing lamellae. Imaging immediately after ATRA captures mid-process, not consolidated result. The quiet window allows passive elastin maturation — may be the most structurally productive period. Aerobic exercise (elliptical, 125–130 bpm, 30 min every other day) continues throughout — provides laminar shear stress → AT2R expression upregulation and progressive autonomic HR reduction.	September imaging: gated cardiac CTA preferred for consistent dimensional comparison. Full bloodwork: MMP-9, Gal-3, ApoB, hs-CRP, 25-OH D, Cu/Ceruloplasmin.

Cyclical rhythm (Year 2+): Phase 2 (Epitalon 10 days + MOTS-c) every 6 months. Monthly Fisetin 1500 mg × 3 days maintenance indefinitely. D+Q 1–2× per year when Dasatinib available. Phase 7 ATRA annually. Quiet Window before each major imaging. Olmesartan + Honokiol: permanent, never cycled off.

III. Compound Descriptions

IIIa. Peptides

Compound	Class	Primary Mechanism	Protocol Role, Evidence & Notes
SubQ Peptides — Active Protocol			
GHK-Cu (Copper Tripeptide-1)	Structural copper peptide	LOXL-1 upregulation (copper-dependent amine oxidase). Collagen/elastin synthesis via VSMC stimulation. TGF-β repair phenotype modulation. **GHK-Cu is itself a copper source** — additive to Zn/Cu/Se 3-in-1, providing two independent redundant Cu delivery pathways to LOXL-1.	Critical node in elastin synthesis chain: ATRA→ELN transcription → aminos→VPGVG substrate → Dill-Berry→LOXL-1 mRNA activation → GHK-Cu→Cu cofactor delivery → LOXL-1 enzyme → desmosine cross-links → mature elastic fiber. Without adequate Cu delivery, LOXL-1 is catalytically inactive and tropoelastin monomers remain structurally non-functional. Combined with KPV in same SubQ solution. PAUSE during D+Q active window; resume Day 10 of LAG.
KPV (Lys-Pro-Val)	Anti-inflammatory tripeptide	MC3R agonist: melanocortin anti-inflammatory. NF-κB suppression (third independent convergent route: Olmesartan AT1R, MT-1 cAMP/PKA, KPV MC3R). Gal-3 downstream modulation.	Continuous daily use — well-tolerated small tripeptide, no GABAergic concerns. Suppresses Gal-3 at effector level while MT-1 suppresses Gal-3 transcription upstream — dual-level coverage of the same target.
MT-1 (Afamelanotide) ***NOT MT-2***	Synthetic MC1R agonist (EMA-approved for EPP)	**ARM 1:** NF-κB→MMP-2/9/13 suppression; ↓Gal-3 transcription. Gal-3 trend = pharmacodynamic biomarker. **ARM 2:** CD36↓ + ABCA1/ABCG1↑ (aortic wall oxLDL efflux); eNOS/NO (FMD = independent aortic dilation predictor); SMAD3/PKA convergence. **ARM 3:** MITF — plausible anti-apoptotic bias; confirmed CNS/renal; VSMC evidence pending. **ARM 4:** AMPK→TSC2+Raptor→mTORC1 suppressed. Physiological upstream mTOR modulation without rapamycin CCN2/dissection risk.	Foundation — continuous all phases. True SC t½ 0.8–1.7h (Ugwu 1997 — the 15h figure is the Scenesse implant formulation, not the peptide). EOD justified by MC1R self-upregulation (receptor density increases with repeated dosing — positive feedback, no tachyphylaxis) and downstream cascade persistence (PKA→pCREB→MITF each with independent half-lives hours-days beyond plasma clearance). Annual dermatological review (MITF drives melanocyte activity — monitor naevi). MT-2 activates MC4R causing BP elevation/tachycardia — NOT interchangeable with MT-1.
Retatrutide	Triple GLP-1/GIP/GCG agonist	PVAT volume reduction: perivascular adipose tissue surrounding aorta secretes IL-6, IL-8, TNF-α that weaken elastin scaffolding and drive VSMC phenotype drift. GLP-1R on vascular endothelium: direct anti-inflammatory. GCG: adipose lipolysis. GIP: additive metabolic effects.	HELENA trial: aortic diameter reduction correlated with visceral adipose volume in highest weight-loss quartile — PVAT reduction is a structural aortic intervention, not merely metabolic. 2.0 mg Mon/Thu maintained at current BP 108/66. Hair thinning: GLP-1R follicle cycle effects + switch from daily dutasteride to finasteride-dominant 5α-reductase inhibition — both mechanisms contributing.
SS-31 (Elamipretide)	Mitochondrial cardiolipin-targeting peptide	Cardiolipin binding → ETC supercomplex stabilisation → pathological ROS leak reduction. NON-SCAVENGING — does not suppress extracellular H_2O_2 LOXL-1 redox signalling (unlike antioxidant supplements that impair LOXL-1 activation).	Phase 3 (COMPLETE). Post-treatment durability >6 months in vascular animal models — established protection persists into subsequent phases. NMNH concurrent is complementary: SS-31 stabilises cardiolipin structure; NAD+ fuels ETC substrate availability.
Phase-Specific Peptides			
Epitalon (Ala-Glu-Asp-Gly)	Pineal tetrapeptide telomerase activator	TERT upregulation → telomerase → telomere extension in vascular progenitor pool. Secondary: pineal melatonin pathway support; circadian resynchronisation.	Phase 2 (COMPLETE). Standard Khavinson protocol: 1 mg/day SubQ × 10 consecutive days, bedtime. NOT continuous — 10-day transcriptional trigger only; continuous use overstimulates regulatory pathways without benefit. Repeats every 6 months. Primary purpose: prevents post-senolytic progenitor collapse — progenitors with short telomeres re-senesce on first division after senolytic clearance (replacing senescent cells with new senescent cells = zero structural gain).
MOTS-c	Mitochondria-derived peptide (mdPEP)	AMPK activation in skeletal muscle via nuclear translocation. Insulin sensitivity improvement. Mitochondrial biogenesis. Provides ATP budget for TERT-mediated telomere extension (energy-intensive genomic repair requires metabolic support).	Phases 2 and 4 (COMPLETE for initial courses). 5 mg SubQ Tue+Fri. Separate from Berberine dosing days. Ongoing 2×/week maintenance. Repeat every 6 months concurrent with Epitalon.

IIIb. Supplements

Compound	Class	Primary Mechanism	Protocol Role, Evidence & Notes
Pharmacological Anchor			
Olmesartan **20 mg/day (10 AM + 10 PM)**	ARB — AT1R conformation-resistant inverse agonist	Three mechanisms: (1) Active-state AT1R inverse agonism — 3-point contact (OH→Tyr113, COOH→Lys199/His256, tetrazole→Gln257); blocks ground-state AND stretch-activated AT1R. (2) AT2R engagement via Ang II redirection → PP2A → ERK1/2 dephosphorylation → MMP-9 suppression. (3) ACE2 upregulation → Ang-(1-7) → Mas — confirmed as primary aortic protective mechanism in OPG-KO mouse model.	NEVER paused. Tanriverdi/Dogan 2024 Circulation: −0.48 mm/year aortic root on ARBs — but only losartan, irbesartan, telmisartan tested (pharmacologically inferior agents). TEDY trial (telmisartan, JAMA Cardiology 2020): no significant effect — confirms ARB selection matters. Weinberg 2003 (only human regression data): candesartan −3.5 mm, valsartan −4.9 mm at 1.5 years, BP barely changed — structural, not haemodynamic, mechanism. Olmesartan's pharmacological profile exceeds both tested agents.
eNOS / Endothelial Axis			

Grape Seed Extract Extra Strength 400 mg	OPC proanthocyanidin (same class as Pycnogenol)	OPC elastin-hydroxyproline binding (Tixier 1984 — OPC class; applies to pine bark and GSE equally). eNOS +45% (human experiments). SBP −13 mmHg (12-week RCT at 400 mg). Arterial stiffness improvement (PWV, Einc, distensibility). Elastase inhibition ('elastin shield').	Replaces Pycnogenol 100 mg. GSE 92–95% OPCs vs pine bark 80–85% — higher concentration per dose; at 400 mg GSE, OPC delivery substantially exceeds 100 mg Pycnogenol. The elastin-binding OPC mechanism is class-based, not source-specific. Natural Factors Extra Strength 100:1 (40,000 mg equivalent per cap). Does not interfere with LOXL-1 cross-linking.
Active B Complex (BioCoenzymated)	B-vitamin complex eNOS coupling support	Quatrefolic L-5-MTHF 400 mcg → DHFR → BH4 regeneration → eNOS coupled (produces NO not superoxide). eNOS uncoupling is a mechanistically validated TAA driver — produces superoxide that directly damages aortic wall. Methylcobalamin 500 mcg; P5P; R5P — all active coenzymated forms.	Quatrefolic bypasses MTHFR conversion — relevant for MTHFR variant carriers. Natural Factors BioCoenzymated confirmed correct formulation.
NAD+ / Mitochondrial Axis			
NMNH Complex (California Gold) NMNH 250 mg / CoQ10 100 mg PQQ 20 mg / Ergo 5 mg / TMG 25 mg	NAD+ precursor complex	NMNH 250 mg → NAD+ (confirmed label dose — 250 mg, not the incorrect 50 mg in v16.2). CoQ10 100 mg: ETC Complex I/III. PQQ 20 mg: mitochondrial biogenesis via PGC-1α. Ergothioneine 5 mg: selective mitochondrial antioxidant (does not suppress LOXL-1 redox signalling). TMG 25 mg (minor).	NMNH 250 mg in studied range for NAD+ repletion. NAD+→SIRT1→ACE2 upregulation→Ang-(1-7)/Mas protective axis — connects mitochondrial health directly to RAAS protective pathway. 2025: NAD+ precursors reduce Ang II-induced VSMC senescence via p-AMPK/KLF4 (direct VSMC relevance). Total CoQ10: 100 mg (complex) + 100 mg standalone bedtime = 200 mg/day.
Anti-inflammatory / MMP Suppression Axis			
Curcumin Meriva 500 mg	Polyphenol — phytosome	Primary MMP-9 transcription inhibitor. NF-κB suppression (independent route from Olmesartan and MT-1). Meriva phytosome: 500 mg ≈ 2g standard curcumin bioavailability.	Retained ALL phases including LAG and ATRA ON cycles. Three independent MMP-9 suppression routes in stack: Olmesartan (AT1R/NF-κB), MT-1 (cAMP/PKA/NF-κB), Curcumin (direct MMP-9 transcription). Redundancy ensures coverage if one pathway escapes. No CYP3A4 interaction — NOT suspended during ATRA.
Honokiol 250 mg (5/2)	Biphenol neolignan Magnolia officinalis	MMP-2/MMP-9 inhibition in rat aortic SMC via NF-κB/ERK1/2 blockade — direct aortic tissue evidence. TGF-β/Smad2/3 suppression. SIRT3 activation → VSMC mitochondrial integrity → contractile state maintenance. VCAM-1 suppression → prevents immune cell infiltration. NLRP3 inflammasome suppression.	5/2 NOT daily. GABAA positive allosteric modulator — daily use risks GABAergic dependence (benzo-like withdrawal documented in community). 5/2 provides mechanistic benefit while limiting dependence risk. **KEY CORRECTION from v16.2: Honokiol NOT paused during ATRA ON cycles.** No CYP3A4 interaction. During ATRA, newly synthesised uncrosslinked tropoelastin is maximally vulnerable to MMP degradation — Honokiol's MMP-2/9 protection is most critical exactly then.
EGCG 500 mg (Mon–Fri EVENING)	Catechin polyphenol SIRT1 activator	SIRT1 activation (EGCG→AMPK→SIRT1) — primary retention rationale. MMP-2/9 inhibition. Anti-fibrotic (TGF-β). Copper chelation: EGCG catechin structure binds Cu — concern mitigated by evening timing creating maximum separation from morning GHK-Cu SubQ and midday Zn/Cu/Se 3-in-1.	KEPT — timing moved to evening 5/2 (Mon–Fri bedtime) to resolve copper chelation timing conflict while preserving SIRT1/MMP benefit. GHK-Cu + Zn/Cu/Se provide two independent Cu delivery pathways with temporal advantage over EGCG. Monitor ceruloplasmin — if Cu trends lower, consider 3/2 schedule or further dose reduction.
Berberine 1000 mg/day (500 AM + 500 PM)	Alkaloid — direct REV-ERBα agonist	Direct REV-ERBα agonism: Song et al. 2025 (Cardiovascular Research) TAAD model — BMAL1→REV-ERBα→c-MYC suppression→VSMC survival. AMPK. Gut-liver bile acid axis (unique; not replicated by Bergamot). LDL-R upregulation. Microbiome SCFA production.	1000 mg/day via AM/PM split — sustained REV-ERBα agonism given t½ 3–4h. Not redundant with Bergamot — gut-liver axis is distinct. SUSPEND during ATRA ON cycles (CYP3A4 inhibition may increase ATRA plasma exposure). Resume during ATRA OFF cycles. Food required Mon/Thu with Retatrutide.
Quercetin Pulse 1200 mg Tue/Wed/Thu	Polyphenol — flavonol	Senomorphic: p21 VSMC senescent cell pressure; TLR4 inhibition; Gal-3 suppression; MMP-9 via TLR4 route (distinct from Curcumin transcriptional route). SIRT1 activation (secondary). Direct aortic aneurysm evidence in murine models.	3-on/4-off pulse. COPPER SEPARATION: min 3h from GHK-Cu on pulse days (quercetin chelates Cu → reduces LOXL-1 bioavailable copper). Not confirmed human VSMC senolytic without dasatinib. During D+Q cycles: daily 1200 mg to maximise D+Q synergy; return to Tue/Wed/Thu pulse after LAG closes.
Citrus Bergamot BPF 1200 mg/day (600 AM + 600 PM)	Standardised BPF HMG-CoA inhibitor + AMPK	Melitidin + brutieridin: HMG-CoA reductase inhibition (structural HMG homology — statin-like). LDL −38.6% at 1000 mg (Mollace et al. 237-patient RCT). AMPK/SIRT1 activation. NF-κB inhibition. Small dense LDL-3/4/5 reduction. Synergy with MT-1 dual-axis cholesterol management.	1200 mg/day (2 × 600 mg = nearest practical dose above 1000 mg evidence-base). ILEP Class IIa Level B. AM/PM split provides 24h coverage. SUSPEND during ATRA ON cycles (CYP3A4). Synergy with Olmesartan ACE2/Ang-(1-7) axis via AMPK/SIRT1/ACE2 pathway.
Structural Repair Axis			
Dill-Berry Extract 500 mL daily	Botanical preparation Primary LOXL-1 activator	LOXL-1 mRNA ×2; tropoelastin mRNA ×2; elastic lamella disruptions −33%; aortic stiffness reduced; LV hypertrophy reversed. Fhayli et al. 2020 (Biomolecules 10(2): 173) — ascending aorta aged mouse model. Active constituents: dill seed flavonoids/tannins; berry anthocyanins add elastase inhibition and anti-calcification.	Most directly relevant published paper for structural goals — only published evidence of non-pharmacological elastin neosynthesis in the ascending aorta. Preparation: grind EUROPEAN dill seeds (Anethum graveolens — NOT East Indian dill, different flavonoid profile) + ½ cup mixed berries + 500 mL water; soak 24–48h refrigerated; filter. PAUSE during D+Q active window (Day 0–7); resume Day 7+ of LAG.
Amino Stack 11.5g nightly Gly 5 / Pro 3 / Val 2 / Lys 1.5	Structural substrates 5:3:2:1.5 ratio LOCKED	Glycine: primary collagen substrate + sleep architecture (glycine receptor, brainstem). Proline: collagen/elastin structural AA. **Valine: ESSENTIAL** — Val-Gly-Val-Pro-Gly (VPGVG) tropoelastin pentapeptide repeating motif. **Lysine: direct LOXL-1 substrate** — oxidised to allysine → desmosine/isodesmosine cross-links.	Ratios locked — do not modify. Valine is irreplaceable for tropoelastin VPGVG structure. Lysine is the substrate; Cu-dependent LOXL-1 enzyme activity is the rate-limiting step (not substrate availability — Lysine increase would not accelerate cross-linking). Circadian timing: collagen synthesis peaks in early sleep phases — bedtime is optimal. PAUSE during D+Q active window; resume Day 21 of LAG (later than Dill-Berry and GHK-Cu — substrate provision is only useful once MMP environment has cleared).
Bamboo Silica 300 mg	Orthosilicic acid — mineral	Collagen type I synthesis stimulation; hydroxyproline incorporation in collagen cross-links; connective tissue scaffold support.	Retained. Confirm orthosilicic acid form (not silicon dioxide) for bioavailability. No aortic-specific RCT but mechanism is genuine and no interaction concerns.
Electrolyte / Cofactor / Hepatic Axis			
Zinc/Cu/Se 3-in-1 Zn 25 / Cu 2 / Se 200 mcg	Mineral complex	**Cu: LOXL-1 catalytic cofactor** — copper-dependent amine oxidase; Cu is the active site metal; depletion directly impairs elastin cross-linking. Zn/Cu-SOD. Selenoprotein P (cardiovascular protective).	Cu tracking MANDATORY at every phase gate — additive with GHK-Cu (which also delivers Cu SubQ). Ceruloplasmin at every phase gate draw. Se 200 mcg near tolerable UL — confirm sole dietary Se source. Separate from Quercetin on pulse days (chelation risk).

Manganese Chelate ~1.25 mg	Mineral — MnSOD cofactor	MnSOD: primary mitochondrial matrix antioxidant enzyme (Mn-dependent; scavenges superoxide at ETC source). Mn-dependent prolidase: collagen hydroxyproline recycling.	Dose halved from 2.5 mg — Mn accumulates with continuous use. Alternate days or split tablet. Separate from zinc supplement to avoid absorption competition.
Magnesium Bis-Glycinate 400 mg/ day	Chelated mineral	VSMC relaxation; collagen hydroxylation cofactor; cardiac rhythm and electrolyte balance.	Split 200 AM + 200 PM. Serum Mg^{2+} every bloodwork draw — Olmesartan K^{+}-sparing + Mg supplementation require electrolyte monitoring together.
D3 + K2: 5000 IU + 240 mcg MK-7	Fat-soluble vitamins	VDR signalling. **MGP activation (K2 MK-7-dependent)** — primary aortic calcification inhibitor. ACE2 transcriptional upregulation via VDREs (independent of SIRT1 — additive with Olmesartan-driven ACE2 upregulation).	Target 25-OH D: 60–80 ng/mL. MK-7 confirmed in Nutritionn product. Additive with ATRA Phase 7 RARα-driven MGP increase — dual calcification prevention during ATRA cycles.
NAC 600 mg	N-Acetyl Cysteine glutathione precursor	Glutathione precursor; hepatoprotective; Nrf2 activation. Antioxidant buffering during SASP burst clearance.	Mon/Wed/Fri standard: preserves H_2O_2 LOXL-1 activation window on off-days. Exception windows requiring daily NAC: D+Q active days; full Phase LAG; ATRA ON cycles (hepatic CYP26 conjugation support). Return to Mon/Wed/Fri when each exception closes.
TUDCA 250 mg	Bile acid — hepatoprotective	ER stress reduction; hepatoprotective against combined peptide/supplement stack hepatic load; fat-soluble nutrient absorption support.	Reduce to Mon/Wed/Fri once EGCG supply is exhausted (total hepatic load normalises).
TMG 500 mg	Methyl donor	Betaine-homocysteine methyltransferase; ApoB-safe methyl donor. Synergy with B Complex.	Primary TMG source — NMNH complex contains only 25 mg TMG (insufficient as sole source). Homocysteine recycling is cardiovascular protective.
Taurine 2g/day (1g AM + 1g PM)	Sulphonated amino acid	Mitochondrial membrane osmoregulation; cardiac rhythm; mild antihypertensive via renin-angiotensin modulation; anti-inflammatory at 2g/day.	Split AM/PM. 2g/day well within safety range.
Vitamin C 500 mg/day (250 AM + 250 PM)	Ascorbic acid	Prolyl/lysyl hydroxylase cofactor — collagen/elastin hydroxylation. Immune support.	500 mg/day: reduced from 1000 mg. Supraphysiologic doses suppress LOXL-1 adaptive H_2O_2 redox signalling. 500 mg maintains cofactor function without this interference.

IV. Optional Compounds Under Consideration

Compounds evaluated but not in active stack. Ranked from most to least actionable. Each entry explains conditions under which addition is justified.

Compound	Status	Mechanistic Case	Verdict & Conditions for Addition
High Priority — Pursue Now			
C21 (Buloxibutid) Vicore Pharma	Compassionate use enquiry recommended	Oral non-peptide AT2R agonist (pKi ~9.4; no AT1R affinity). Lange et al. 2018 (Hypertension): direct AT2R agonism alone produced −28% aortic diameter in elastase-induced rat AAA without AT1R involvement. FDA Fast Track. Phase IIb ASPIRE trial 2026.	PURSUE: Contact Vicore Pharma (info@vicorepharma.com, attention Jonathan Langley, Head of Global Medical Affairs). Reference Lange et al. 2018 Hypertension, state 4.3 cm thoracic aortic root diagnosis, request compassionate use or investigator-initiated aortic trial information. This is the largest pharmacological gap in the protocol — direct AT2R agonism cannot be replicated by supplements or olmesartan dose escalation.
Genistein 40–60 mg bedtime	PENDING — confirm supply	ERβ agonism → SIRT1/ACE2 upregulation. Direct eNOS transcriptional upregulation 1.8–2.6-fold in primary human aortic endothelial cells at physiological concentrations — strongest direct human aortic endothelial evidence of any pending compound. RhoA suppression → endothelial barrier integrity. PKA mechanism independent of estrogen signalling.	ADD when supply confirmed. 40–60 mg bedtime. No meaningful CYP3A4 interaction. ERβ agonism is distinct from MT-1 MC1R and Olmesartan PPARγ pathways — non-redundant.
Melatonin 1 mg bedtime (start)	PENDING — start cautiously	ADAM17 inhibition → prevents ACE2 ectodomain shedding from endothelial surface (ADAM17 cleaves ACE2, reducing protective Ang-(1-7) signalling at the cellular location where it is needed). Circadian BMAL1 entrainment.	START at 1 mg bedtime. Monitor nocturnal BP 1 week before any increase. Additive hypotension risk with bedtime Olmesartan at BP 108/66. 1 mg achieves melatonin receptor occupancy for ADAM17 and circadian effects — supraphysiological doses add hypotension risk without proportional mechanism benefit.
Consider If Specific Indication Arises			
Modified Citrus Pectin (MCP)	Consider if Gal-3 fails Phase 5 gate	TLR4 inhibition → ↓MMP-9. TGF-β signalling interference. Direct Gal-3 binding (PMC6893732) — distinct from MT-1 upstream NF-κB transcriptional suppression.	Add if Phase 5 bloodwork shows Gal-3 failing to trend ≥20% reduction despite adequate time on current stack. Would provide a fourth Gal-3 suppression route: MT-1 upstream + KPV MC3R + Quercetin TLR4 + MCP direct binding.
Urolithin A	Consider — mitophagy axis	Activates mitophagy (PINK1/Parkin) — selective clearance of damaged mitochondria. REV-ERBα activation (additive to Berberine). Mitochondrial biogenesis via mitophagy-driven turnover. Timeline Mitopure is standardised form.	Mitophagy pathway not covered by SS-31 (cardiolipin stabilisation) or NMNH/CoQ10/PQQ (ETC function/biogenesis). Urolithin A adds selective removal of irreparably damaged mitochondria — complementary quality control function. Consider after Phase 3 (SS-31 complete) when mitophagy-driven turnover becomes priority over acute stabilisation.
Icariside II (ICS-II from Icariin/ Epimedium)	Consider — bioavailability must be resolved	Mechanosensory VSMC phenotype restoration: integrin→FAK→MRTF-A→contractile gene expression. Bottom-up cytoskeletal approach complements ATRA's top-down nuclear approach (RAR/RXR). Non-overlapping entry points both converging on contractile phenotype. Equal to rapamycin as positive control in vascular remodelling without CCN2/ dissection risk.	Only add if standardised ICS-II phospholipid complex (bioavailability +342% in animal models) can be sourced. Standard icariin/ epimedium supplements produce highly variable plasma concentrations. Potential Phase 7 ATRA complement — attacking VSMC contractile phenotype from a different cellular address simultaneously.
Explicitly Excluded — Do Not Add			
Tesamorelin	EXCLUDED — sold kit	GHRH analogue: pulsatile GH; visceral fat reduction.	IGF-1 elevation is a wall stress signal — pro-growth signalling counterproductive in a wall requiring structural repair quiescence. Retatrutide addresses PVAT reduction (the structural benefit) without IGF-1 liability. Correctly excluded.

Ivabradine	EXCLUDED	HCN channel blockade: HR reduction without inotropy.	Appeared in external AI-generated planning document — was never part of this protocol. Similar BP concern to bisoprolol at BP 108/66. Aerobic exercise (elliptical 125–130 bpm, 30 min every other day) provides progressive HR management via autonomic adaptation.
Bisoprolol / Beta-blockers	EXCLUDED — BP too low; GP declined	HR reduction; dP/dt reduction — reduces mechanical strike intensity per heartbeat.	BP 108/66 on Olmesartan. Additive hypotension and bradycardia risk unacceptable. Reassess only if resting HR consistently >75 bpm after aerobic protocol established.
Pterostilbene	EXCLUDED — LDL elevation	SIRT1 activation; superior resveratrol bioavailability.	LDL elevation documented (Riche 2014: +17.1 mg/dL). SIRT1 covered four ways: NMNH/NAD+, Bergamot AMPK/SIRT1, Berberine REV-ERBα/SIRT1, EGCG AMPK/SIRT1. Adding fifth route at LDL cost counterproductive to ApoB <80 target.
Rapamycin	EXPLICITLY EXCLUDED — dissection risk	mTORC1 direct inhibition.	CCN2/VSMC adhesion impairment under active Ang II signalling promotes aortic dissection. MT-1 provides indirect upstream mTOR suppression via AMPK/TSC2/Raptor without this risk. Excluded categorically — the MT-1 AMPK pathway achieves the same mTOR suppression through physiological mechanisms.

V. Critical Synthesis — How This Protocol Targets Aortic Root Regression

5.1 The Disease Model — Five Simultaneous Failure Axes

TAA aortic root dilation is not a single-pathway disease. Five failure axes operate simultaneously — this is why every single-agent intervention in the published literature has produced at best modest slowing of progression. The benchmark: one patient ran telmisartan + rosuvastatin for 10 years and progressed from 4.2 cm to 6.2 cm requiring surgery. Standard of care is insufficient. This protocol exists because the standard of care is insufficient.

Axis 1 — ECM Degradation

MMP-2, MMP-9, MMP-13 continuously degrade elastin lamellae. Three independent suppression routes ensure that if one escapes, others maintain coverage: Olmesartan (AT1R/NF-κB→MMP-9), MT-1 (cAMP/PKA/NF-κB→MMP-2/9/13), Curcumin (direct MMP-9 transcription). Honokiol adds MMP-2/9 inhibition at aortic SMC level. GSE provides elastin shield — physical OPC-hydroxyproline binding protecting existing elastic fibers from elastase independently of MMP suppression.

Axis 2 — VSMC Phenotype Drift

VSMCs drift from contractile to synthetic/inflammatory under Ang II, mechanical stress, and oxLDL — becoming MMP-secreting rather than wall-maintaining. Olmesartan blocks the Ang II signal. MT-1 suppresses mTORC1 via AMPK/TSC2 (the kinase driving synthetic phenotype). Honokiol SIRT3 maintains mitochondrial integrity supporting contractile state. ATRA (Phase 7) directly reprograms surviving VSMCs to contractile phenotype via RAR/RXR→α-SMA/SM22α/MHC.

Axis 3 — Senescent Cell Burden

Senescent VSMCs and endothelial cells are primary SASP sources (IL-6, MMP-9, TGF-β) — destroying ECM from within while driving neighbouring cells toward senescence. Fisetin (Cycle 1): clears p16-positive senescent endothelial cells; prevents EndoMT. D+Q (subsequent cycles): clears p21-positive senescent VSMCs via dasatinib BCL-XL inhibition. Monthly Fisetin maintenance prevents re-accumulation indefinitely.

Axis 4 — Haemodynamic / Mechanical Stress

72 bpm = 103,680 mechanical strikes per day on the aortic root. Olmesartan's three-point mechanosensing blockade is the only pharmacological agent blocking stretch-activated AT1R directly. Aerobic exercise (elliptical, 125–130 bpm, 30 min every other day) provides laminar shear stress → AT2R expression upregulation and progressive autonomic HR reduction over months of consistent training.

Axis 5 — Endothelial Dysfunction and Cholesterol

FMD is an independent multivariate predictor of aortic dilation. MT-1 restores eNOS/NO via MC1R/cAMP. GSE eNOS upregulation via OPC. B Complex Quatrefolic supports BH4/eNOS coupling. MT-1 CD36 suppression + ABCA1/ABCG1 upregulation clears oxLDL from the aortic wall. Bergamot reduces systemic LDL supply. Dual-axis: wall-level cholesterol biology + systemic LDL supply — addressing what statins cannot reach.

5.2 The Elastin Synthesis Chain — Why Every Step Must Be Covered

The defining feature of this protocol is covering the entire elastin synthesis-to-cross-linking chain simultaneously:

- **ATRA (Phase 7):** initiates ELN gene transcription → tropoelastin mRNA produced
- **Amino Stack (Gly/Pro/Val/Lys nightly):** provides VPGVG substrate and Lysine (direct LOXL-1 oxidation substrate for cross-linking)
- **Dill-Berry Extract (daily):** activates LOXL-1 mRNA (~2×) — the cross-linking enzyme (Fhayli et al. 2020)
- **GHK-Cu (Mon–Fri SubQ) + Zn/Cu/Se (midday):** deliver copper cofactor via two independent routes — LOXL-1 is a copper-dependent amine oxidase and is catalytically inactive without Cu
- **LOXL-1 enzyme:** oxidises Lysine → allysine → desmosine/isodesmosine cross-links → mature elastic fiber integrated into lamellae

Without any single step, the chain fails. Most published protocols address one or two nodes. This protocol closes every gap. Negative LOX genetic panel confirms cross-linking machinery is intact — ATRA's tropoelastin upregulation can be productively cross-linked into functional lamellae.

5.3 Why Regression Is Mechanistically Plausible

Weinberg 2003 (AJH P-609 — only published human aortic root regression data): candesartan −3.5 mm, valsartan −4.9 mm over 1.5 years, BP barely changing. The mechanism was structural. If two pharmacologically inferior ARBs produced dimensional regression, the combination of olmesartan's superior mechanosensing blockade + ACE2/Ang-(1-7) upregulation + complete elastin synthesis chain + senolytic SASP source clearance + VSMC phenotypic reprogramming represents a substantially more mechanistically complete approach than what produced the Weinberg data.

> *The honest counter-reference: one patient ran telmisartan + rosuvastatin for 10 years — 4.2 cm to 6.2 cm, surgery. ARB monotherapy fails routinely. Each mechanism in this stack addresses a specific gap that ARB alone leaves open.*

Evidence: Fhayli 2020 (Biomolecules); HELENA trial; Lange et al. 2018 (Hypertension); Weinberg 2003 (AJH); TEDY 2020 (JAMA Cardiology); Tanriverdi/Dogan 2024 (Circulation); Song et al. 2025 (Cardiovascular Research); Frontiers 2025 PMC12852416; Mollace et al. BPF RCT; Khavinson Epitalon; Rinne 2018 ATVB + 2015 CVR; Ugwu 1997 MT-1 PK; NCT06133634 Fisetin; v16.2 Protocol Review