Longitudinal Bone Growth Protocol

A Multi-Axis Pharmacological Framework for Growth Plate Optimization

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Theoretical research compilation — for physician consultation and academic reference only

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1.0 Overview

1.1 What This Protocol Addresses

This protocol is built on one foundational premise: that the limiting factor in longitudinal bone growth is not any single signaling deficit but a convergence of simultaneous constraints acting across multiple independent axes. No compound in this stack duplicates the mechanism of any other. Each was selected because it addresses a bottleneck that removing all others still leaves unresolved. The result is a protocol where the simultaneous removal of all six major rate-limiting constraints produces a growth-favorable environment that no single intervention or simpler combination can replicate.

The six axes addressed are: insufficient anabolic drive at the growth plate, constitutive FGFR3-mediated suppression of chondrocyte proliferation, inadequate reinforcement of the downstream MAPK axis that FGFR3 activates, epigenetic silencing of the Runx2 gene program that executes hypertrophic differentiation, insufficient Wnt/β-catenin activation of the transcriptional machinery that Runx2 de-repression requires, and unchecked ERα-mediated progression of the progenitor senescence program that terminates the treatment window. Every known major regulatory brake on growth plate output is addressed. Nothing relevant is left unaccounted for.

1.2 Who This Protocol Is For

This protocol is designed for individuals with documented open growth plates who are pursuing maximal longitudinal bone growth within their biological window. A baseline bone age X-ray is the first step before initiating any component — the remaining treatment window determines the urgency and approach for everything that follows. Without confirmed plate status, the protocol cannot be responsibly started.

All compounds described here are either FDA-approved medications being applied outside their labeled indications or research chemicals without clinical approval. Every element requires physician supervision. This document is compiled with research reference, not a clinical recommendation. It serves as a foundation for informed discussion between an individual and a physician knowledgeable in endocrinology and growth physiology.

2.0 Theoretical Foundation

2.1 The Growth Plate — Biology and Architecture

The growth plate, or physis, is the cartilaginous disc sitting between the epiphysis and metaphysis of each long bone. All longitudinal skeletal growth after birth occurs here. The plate is organized into three functionally distinct zones that operate as a coordinated pipeline.

The resting zone (sometimes called the reserve or stem cell zone) contains a population of slowly cycling chondrocyte progenitors anchored near the epiphysis. These cells have stem-like properties and are the source of all cells that subsequently enter active growth. Their preservation and proliferative capacity determine how long the growth window can remain open. The proliferative zone sits below the resting zone and is where rapid mitotic activity occurs, producing the columns of daughter chondrocytes that extend the bone longitudinally. Column formation here is the direct cellular mechanism of height gain. Finally, the hypertrophic zone, deepest in the plate, is where chondrocytes enlarge dramatically, secrete a specialized collagen X matrix, and undergo apoptosis or transdifferentiation; the process by which the cartilaginous matrix is vascularized and replaced by trabecular bone.

Growth velocity is determined by three variables working together: the rate at which resting zone progenitors enter and populate the proliferative zone, the speed of chondrocyte column production in the proliferative zone, and the efficiency of the transition through the hypertrophic zone into new bone. This protocol addresses each of these variables through the six mechanistic layers described in section five.

2.2 Key Signaling Pathways

The IHH/PTHrP feedback loop is the master regulator of column progression rate. Indian Hedgehog, secreted by pre-hypertrophic chondrocytes, travels retrograde to the resting zone where it stimulates PTHrP production. PTHrP feeds forward to keep proliferating chondrocytes in a cycling state and delays their entry into the hypertrophic program. This loop prevents premature plate exhaustion by balancing the rate of column production with the preservation of the progenitor pool.

FGF18, secreted by perichondrial fibroblasts surrounding the growth plate, activates FGFR3 on proliferative zone chondrocytes and constitutively brakes their mitotic activity through RAS/RAF/MEK/ERK MAPK signaling, STAT1-mediated direct mitosis suppression, and a paradoxically differentiation-promoting PI3K/AKT arm. This system acts as a biological governor. CNP, produced locally by growth plate chondrocytes, activates NPR-B and counters the MAPK arm of FGFR3 signaling through cGMP/PKG-mediated RAF inhibition, an endogenous brake on the brake.

Wnt/β-catenin signaling governs chondrocyte identity and differentiation across zones. In the resting zone it maintains progenitor characteristics. In the proliferative-to-hypertrophic transition, nuclear β-catenin drives TCF/LEF-mediated transcription of Sox9 and Runx2, the master transcription factors of chondrocyte identity and hypertrophic differentiation respectively. HDAC4 and HDAC5 maintain Class IIa co-repressor complexes at Runx2 gene loci in the proliferative zone, silencing its expression until the proper differentiation signal arrives. This is the chromatin-level gate that controls when Runx2-driven differentiation begins.

2.3 Growth Plate Closure and the Treatment Window

Growth plate closure is not a passive event. It is actively driven by estrogen acting through ERα. ERα activation in resting zone progenitors initiates a senescence program: cells lose their stem-like properties, exhaust their proliferative capacity, and the progenitor pool progressively shrinks until it can no longer sustain column production. When the resting zone is depleted, the proliferative and hypertrophic zones follow, and the cartilaginous plate is eventually replaced entirely by bone bridge formation. The plate is fused and growth is permanently ended.

The clinical evidence for estrogen's role as the closure driver is unambiguous. Males with estrogen deficiency or ERα insensitivity continue growing well into adulthood and reach extraordinary stature. Historically, physicians administered high-dose exogenous estrogen specifically to accelerate plate closure and halt excessive growth in tall pediatric patients; an intervention that works precisely because ERα activation directly drives the senescence cascade. This protocol inverts that logic: by limiting ERα activation while simultaneously amplifying the proliferative and differentiation signals upstream, the window is extended and the output during that window is maximized.

Importantly, pharmacological extension of an open plate is fundamentally different from reopening a closed one. Once the progenitor pool is exhausted and bone bridge formation is complete, as of right now no pharmacological intervention can restore what is structurally gone. The protocol operates on the assumption of viable plates, confirmed by bone age imaging before initiation.

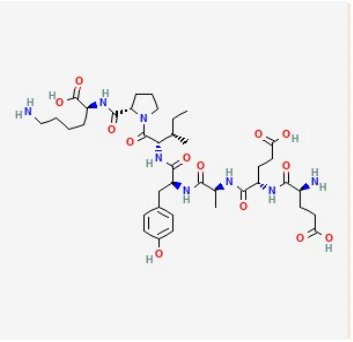
3.0 The Primary Compound Stack

Each compound is described below with its mechanism and the rationale for its selection over alternatives in its mechanistic class. Where a superior alternative exists but a different compound was chosen, the reasoning is explicit.

3.1 Recombinant Human Growth Hormone (Somatropin)

Recombinant Human Growth Hormone

GH RECEPTOR AGONIST — ANABOLIC FOUNDATION



Minimum Dose	0.44 mg/kg/week
Route	Subcutaneous injection, fasted morning
Administration	Pre-lyophilized pharmaceutical kits reconstituted with bacteriostatic water

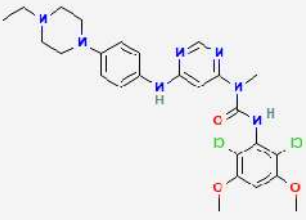
Growth hormone's effect on longitudinal bone growth operates through two arms that are both necessary for maximum output. Directly, GH binds GH receptors on resting zone progenitor chondrocytes and drives their proliferation through JAK2-STAT5b signaling, stimulating local IGF-1 production within the plate itself. Indirectly, and more significantly at the doses used in this protocol, GH drives hepatic IGF-1 production at scale, elevating systemic concentrations that act on IGF-1R at the growth plate, activating PI3K/AKT/mTORC1 signaling across the entire proliferative zone. This systemic IGF-1 elevation is the foundational anabolic signal that every other compound in the stack is built upon. Without it, the downstream interventions are amplifying a system that is not operating anywhere near its maximum input.

The minimum dose of 0.44 mg/kg/week is weight-based. Individual optimization beyond this minimum should be guided by IGF-1 response on bloodwork and physician guidance. Raw somatropin API is available at significantly lower per-gram cost through synthesis suppliers, but formulating injectable-grade somatropin from API powder requires pharmaceutical freeze-drying equipment that is not easily accessible in standard research settings. Pre-lyophilized kits are the most practical and reliable format for this compound, and its accessibility doesn't allow this to be an issue.

3.2 Infigratinib (BGJ398)

Infigratinib (BGJ398)

PAN-FGFR INHIBITOR — FGFR3 DEREPRESSION



Dose Range	5–20 mg/day, split BID
Route	Oral solution, formulated from raw API
Class	Non-covalent pan-FGFR1/2/3 inhibitor with ~60× selectivity over FGFR4

Infigratinib occupies the ATP-binding cleft of FGFR1, FGFR2, and FGFR3, preventing phosphorylation-mediated activation. The relevant target here is FGFR3, through which FGF18 exerts constitutive suppression of growth plate chondrocyte proliferation via three converging cascades: RAS/RAF/MEK/ERK MAPK signaling suppressing mitosis, STAT1-mediated direct inhibition of chondrocyte division, and a PI3K/AKT arm that, when activated through the FGFR3 route rather than the IGF-1R route, promotes premature differentiation rather than proliferative expansion. Blocking FGFR3 removes all three simultaneously.

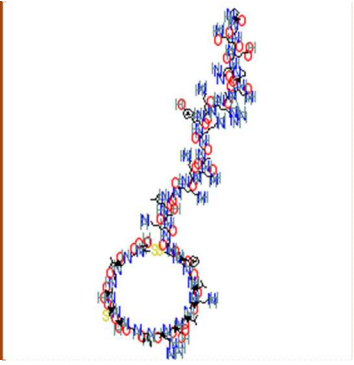
Clinical validation comes from the PROPEL clinical program in achondroplasia (a condition where gain-of-function FGFR3 mutations constitutively activate these suppressive cascades) where FGFR inhibition produced significant increases in growth velocity. The biological rationale here is identical: wild-type FGFR3 still actively suppresses proliferative output on a normal growth plate. Removing that constraint shifts the plate's operating setpoint.

On the question of infigratinib versus TYRA-300 (dabogratinib): TYRA-300 was initially considered given its more precise FGFR3 selectivity, which avoids FGFR1 off-target effects entirely. The practical conclusion is that infigratinib inhibits FGFR3 just as effectively, at approximately one-tenth of the cost per gram. The tradeoff is FGFR1 off-target activity, hyperphosphatemia through disruption of FGF23 signaling, and increased risk of central serous retinopathy. These liabilities are not ignored; they are managed directly through dedicated ancillaries described in section eight. For this application, infigratinib with appropriate ancillary support produces an equivalent net FGFR3 outcome at a fraction of the cost. The justification for this choice is explicit rather than assumed.

3.3 Vosoritide (BMN 111)

Vosoritide (BMN 111)

CNP ANALOG — NPR-B AGONIST — CONVERGENT MAPK REINFORCEMENT



Dose	15 mcg/kg/day
Route	Subcutaneous injection, formulated from raw API
Class	Modified CNP analog engineered for NEP resistance; FDA-approved (Voxzogo) at this dose for achondroplasia

Vosoritide is a modified C-type natriuretic peptide analog engineered with resistance to neutral endopeptidase cleavage, significantly extending its half-life compared to the endogenous CNP peptide. It activates NPR-B, a transmembrane guanylyl cyclase expressed on growth plate chondrocytes, elevating intracellular cGMP and activating protein kinase G. PKG phosphorylates and inhibits RAF kinase, a central node in the MAPK cascade downstream of FGFR3 activation. This provides a mechanistically independent, downstream block on the same suppressive axis that infigratinib addresses at the receptor level.

The relationship between vosoritide and infigratinib is one of convergent redundancy rather than true redundancy. Infigratinib prevents FGFR3 from initiating MAPK signaling. Vosoritide suppresses MAPK at RAF regardless of what the receptor is doing. The practical consequence: even if compensatory upstream signaling partially overcomes FGFR3 blockade, vosoritide's independent downstream inhibition

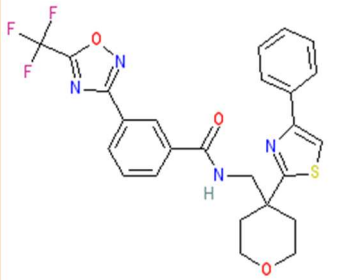
ensures that MAPK suppressive output is reduced at a second chokepoint. This two-point attack substantially reduces the probability that the growth plate can restore suppressive MAPK signaling through compensatory mechanisms.

The dose of 15 mcg/kg/day mirrors the FDA-approved weight-based dosing from the Voxzogo prescribing information, the only rigorously validated human dose for this compound, making it the most defensible reference point available.

3.4 TMP269

TMP269

SELECTIVE CLASS IIA HDAC INHIBITOR — EPIGENETIC CHROMATIN OPENING



Dose Range	5–20 mg/day
Route	Oral solution, formulated from raw API
Class	Selective HDAC 4/5/7/9 inhibitor; >30× selectivity over Class I HDACs; discovered alongside TMP195 (Lobera et al., Nature Chemical Biology, 2013)

TMP269 selectively inhibits Class IIa histone deacetylases (specifically HDAC 4, 5, 7, and 9) with greater than 30-fold selectivity over Class I HDACs. This selectivity is mechanistically critical. Class IIa HDACs maintain co-repressor complexes at Runx2 gene loci in the proliferative zone, keeping the chromatin compacted and Runx2 transcription silenced. Class I HDACs perform overlapping silencing functions at Sox9 gene loci; pan-HDAC inhibitors like vorinostat de-repress both, creating Sox9/Runx2 antagonism in the hypertrophic zone that partially cancels the benefit. TMP269's Class IIa selectivity de-represses Runx2 without simultaneously elevating Sox9 to antagonistic levels, preserving the directional drive toward hypertrophic differentiation.

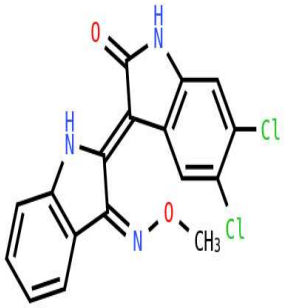
The specific selectivity mechanism derives from a structural difference at the HDAC active site: a tyrosine residue in Class IIa HDACs replaces the histidine present in Class I, creating a distinct binding pocket geometry that TMP269's scaffold occupies preferentially. This is not pharmacological subtlety; it is the mechanistic basis for why a selective Class IIa inhibitor produces fundamentally different chromatin outcomes than a pan-inhibitor at the same dose.

A uniquely valuable interaction with the physical training component of this protocol: resistance training activates CaMKII through calcium signaling, which phosphorylates HDAC4 and HDAC5 at specific serine residues and drives their nuclear export, the same functional outcome TMP269 achieves pharmacologically. Training therefore acts as a co-stimulant for the same epigenetic axis this compound targets. Taking TMP269 around the training window converts the transient Runx2 chromatin opening that exercise initiates into a sustained state, amplifying and extending what the mechanical signal alone produces.

3.5 KY19382

KY19382

WNT PATHWAY ACTIVATOR — CXXC5-DVL INHIBITOR



Dose Range	5–20 mg/day
Route	Oral solution, formulated from raw API
Class	Small molecule inhibitor of the CXXC5-Dishevelled protein interaction; canonical Wnt/β-catenin activator

KY19382 inhibits the protein-protein interaction between CXXC5 and Dishevelled (Dvl). CXXC5 is an endogenous negative regulator of Wnt signaling that binds Dvl and facilitates formation of the β-catenin destruction complex, targeting β-catenin for proteasomal degradation and keeping the Wnt pathway tonically suppressed. By blocking this interaction, KY19382 prevents Dvl sequestration, disrupts destruction complex assembly, and permits β-catenin to accumulate in the cytoplasm and translocate to the nucleus. There, β-catenin associates with TCF/LEF transcription factors and drives expression of Sox9 and Runx2, which directly activates the growth plate's differentiation program.

Among available Wnt pathway activators, KY19382 represents the most precisely targeted approach for the growth plate application. WAY-316606, an alternative that inhibits SFRP1 to free endogenous Wnt ligands from extracellular sequestration, operates upstream at the ligand-availability level, its effects depend on ambient Wnt ligand concentrations in the growth plate microenvironment and activate signaling broadly across any tissue expressing those ligands. KY19382's intracellular target, by contrast, is active specifically wherever CXXC5 and Dvl are co-expressed, without dependence on extracellular ligand availability. The CXXC5/Dvl axis is well-characterized in growth plate chondrocyte and osteoblast-lineage biology, making it the more directly validated intervention point. PTH analogs such as teriparatide and abaloparatide, sometimes considered for adjacent growth plate effects through PTH1R, have their entire clinical evidence base built on bone density outcomes in osteoporotic populations (NOT longitudinal growth) and carry black box osteosarcoma warnings that make their risk-benefit profile inappropriate for this application. KY19382 targets the validated transcriptional driver of plate differentiation directly.

The synergy with TMP269 is the most structurally elegant relationship in the protocol: KY19382 activates the transcriptional machinery that writes the hypertrophic differentiation program into Runx2 gene targets, while TMP269 has opened the chromatin at those same targets to allow that writing to be expressed. The two compounds address the same gene from orthogonal angles; one from the signaling side, one from the epigenetic side, with neither capable of fully achieving the outcome nor the other enables.

4.0 Supporting Hormones and Androgens

The following compounds are not primary growth plate signaling interventions but are necessary to establish and maintain the endocrine environment in which the five primary compounds can function. Their inclusion is required for the protocol to operate safely and effectively.

4.1 Testosterone

Testosterone at a minimum replacement dose provides the androgenic foundation for normal tissue anabolism and metabolic function during what is an otherwise demanding physiological protocol. Anavar is suppressive, it meaningfully suppresses endogenous LH and FSH through negative feedback on the hypothalamic-pituitary axis, reducing the body's own testosterone production in proportion to dose and duration. For individuals who are not already on exogenous testosterone, oxandrolone use in this protocol requires exogenous testosterone replacement to maintain adequate testosterone levels during and after the protocol. Whether this is used at a physiological replacement dose or a supraphysiological level is an individual decision; both are valid approaches that carry different risk and benefit profiles, and that decision belongs with the individual and their physician. What is not acceptable is running oxandrolone without addressing the suppression it causes.

4.2 Anastrozole

Anastrozole inhibits aromatase (CYP19A1), the enzyme responsible for testosterone-to-estradiol conversion, reducing circulating E2 by approximately 70 percent at standard doses. Within this protocol its function is the preservation of the treatment window. Estradiol acting through ERα drives the senescence program in resting zone progenitors that terminates the growth plate. By maintaining E2 in the 20 to 40 pg/mL range (confirmed by LC-MS/MS blood testing) anastrozole limits the cumulative ERα activation load on the progenitor pool. The target range reflects a specific biological tradeoff: below 20 pg/mL, ERβ signaling that provides mild proliferative zone support is also impaired; above 50 pg/mL, ERα-mediated senescence accelerates enough to meaningfully shorten the window regardless of the five upstream interventions.

Dose is titrated to bloodwork rather than fixed. The correct dose is the one that produces E2 within target range at the individual's actual aromatization rate, which varies substantially based on body composition, testosterone dose, and genetics.

4.3 Oxandrolone (Anavar)

Oxandrolone is a DHT-derived anabolic steroid with a unique combination of properties that make it the most appropriate androgen for this protocol: zero aromatization, direct AR agonism, clinical evidence specifically for growth velocity in pediatric populations, and a favorable anabolic-to-androgenic ratio. Its primary mechanism at the growth plate is induction of local IGF-1 through AR signaling in chondrocytes and periosteal cells, a signal that is distinct from and additive to the systemic IGF-1 elevation produced by rHGH.

The clinical evidence from Turner syndrome and constitutional delay of growth and puberty is the direct validation for including this compound. These are patient populations where oxandrolone's effect on height velocity has been specifically studied; the mechanism being exploited here is the same. Dosing is

derived from this clinical literature: 0.0625 to 0.2 mg/kg/day, with the range reflecting the spectrum of studied protocols from conservative (Turner syndrome) to more aggressive (CDGP) applications.

On the question of whether another DHT derivative would serve better: several androgens have higher AR binding affinity than oxandrolone, including stanolone (pure DHT), which sits at the reference 1:1 anabolic-to-androgenic ratio. Higher androgenic potency at peripheral tissues is specifically what makes these alternatives inferior for this goal. Oxandrolone's dramatically skewed anabolic-to-androgenic ratio means it provides the AR stimulation relevant to local growth plate IGF-1 production while contributing less androgenic signal to bone age advancement, a critical consideration, since androgenic acceleration of bone maturation shortens the window the protocol is trying to extend. Clinical data specifically confirms that oxandrolone produces growth velocity increases with relatively modest bone age advancement per unit of anabolic effect. No other DHT derivative shares this validated property in the pediatric growth context.

5.0 Mechanistic Synergy — The Integrated Architecture

The most important property of this protocol is not the potency of any individual compound but the complete non-redundancy of the stack. Each of the six primary axes is addressed by a compound that occupies a mechanism with no meaningful overlap with any other. What follows describes how each layer interacts with and depends on the others, the architecture as a system rather than a list.

Layer I — Proliferative Drive

rHGH provides the foundational anabolic input. At minimum 0.44 mg/kg/week, the hepatic IGF-1 production it drives saturates IGF-1R/PI3K/AKT/mTORC1 signaling across the proliferative zone and maximizes the intrinsic rate of chondrocyte proliferation. Without this layer, the downstream interventions address a growth plate that is not operating at its maximum unsuppressed potential. With it, Layers II through V are amplifying a system that is already operating at its anabolic ceiling.

Layer II — FGFR3 Derepression

FGFR3 is the constitutive governor of growth plate proliferation, active in wild-type growth plates as well as pathological ones. Infigratinib eliminates FGFR3 receptor signaling entirely, preventing FGF18 from initiating the RAS/RAF/MEK/ERK, STAT1, and PI3K/AKT suppressive cascades. The removal of this governor shifts the plate's operating setpoint, the same rHGH-driven anabolic input from Layer I now produces a larger proliferative output because the biological brake has been released.

Layer III — Convergent MAPK Reinforcement

Vosoritide addresses the same downstream MAPK cascade as infigratinib, but through an entirely independent mechanism and at a different point in the pathway. While infigratinib eliminates FGFR3's ability to initiate RAS/RAF/MEK/ERK signaling at the receptor, vosoritide activates NPR-B/cGMP/PKG to inhibit RAF kinase activity downstream of any remaining MAPK activation. The convergence of two independent mechanisms on the same suppressive cascade dramatically reduces the probability that compensatory upstream signaling through either mechanism alone can restore pathway activity. This is the most complete pharmacological suppression of the FGFR3/MAPK growth brake achievable with currently available compounds.

Layer IV — Epigenetic Chromatin Opening

TMP269 addresses a constraint that signaling-level interventions cannot reach: the chromatin state of the growth plate differentiation gene program. Even with FGFR3 suppressed and MAPK inhibited, the transcriptional output of the hypertrophic differentiation program is gated by Class IIa HDAC repressor complexes at Runx2 loci. TMP269's selective HDAC 4/5/7/9 inhibition de-represses these loci, allowing

H3K27ac marks to accumulate and Runx2 transcription to proceed. This layer converts the growth-favorable signaling environment created by Layers I through III into actual gene expression at the executors of the hypertrophic differentiation program. Resistance training amplifies this layer at no additional pharmacological cost, the CaMKII-mediated HDAC4/5 nuclear export produced by exercise is mechanistically identical to what TMP269 achieves pharmacologically.

Layer V — Wnt-Driven Transcriptional Activation

KY19382 activates canonical Wnt/β-catenin signaling to drive nuclear β-catenin accumulation and TCF/LEF-mediated transcription of Sox9 and Runx2. This layer is orthogonally complementary to Layer IV: KY19382 activates the transcriptional machinery that writes the hypertrophic differentiation program, while TMP269 has already opened the chromatin at those gene targets to allow the transcription to proceed. Neither layer can fully deliver its intended outcome without the other. Together they provide simultaneous chromatin accessibility and transcription factor activation at the same genetic targets, a degree of transcriptional de-repression that neither intervention achieves alone.

Layer VI — Window Preservation via ERα Suppression

Anastrozole is the temporal anchor of the protocol. It does not accelerate the rate of growth plate output; it preserves the window within which all five preceding layers can operate. By maintaining E2 at 20 to 40 pg/mL, it limits the cumulative ERα activation that drives resting zone progenitor senescence and ultimately closes the plate. This layer makes the protocol viable for longer, meaning more time for Layers I through V to produce their cumulative effect. It is the reason the protocol can sustain its output rather than delivering a short burst before the window closes.

This master synergy map below summarizes these relationships across all six layers simultaneously.

Compound	Primary Target	Signaling Layer	Downstream Action	Key Synergy
rHGH	GHR → JAK2/STAT5b	I — Proliferative Drive	Hepatic IGF-1 → IGF-1R/PI3K/AKT/mTORC1 across proliferative zone	Foundation layer. Saturates the anabolic signal environment that all downstream interventions amplify
Infigratinib	FGFR1/2/3 ATP-binding cleft	II — FGFR3 Derepression	Eliminates FGF18-driven RAS/RAF/MEK/ERK, STAT1, and PI3K/AKT suppression of chondrocyte mitosis	Vosoritide independently blocks MAPK downstream; both address the same suppressive axis from orthogonal entry points
Vosoritide (BMN 111)	NPR-B → cGMP → PKG	III — Convergent MAPK Reinforcement	PKG phosphorylates and inhibits RAF kinase — independent downstream block of FGFR3 cascade	Dual coverage of MAPK suppression with infigratinib; active regardless of FGFR3 receptor occupancy
TMP269	HDAC 4/5/7/9 (Class IIa)	IV — Epigenetic Chromatin Opening	H3K27ac accumulation at Runx2 loci; chromatin opens for hypertrophic differentiation transcription	Exercise-driven CaMKII amplifies the same HDAC4/5 nuclear export. Training is a free co-stimulant; opens the chromatin that Layer V writes to
KY19382	CXXC5-Dvl protein interaction	V — Wnt Transcriptional Activation	β-catenin nuclear accumulation → TCF/LEF → Sox9 + Runx2 gene expression	Drives Runx2 transcription into the chromatinally-accessible state created by Layer IV (TMP269)
Anastrozole	CYP19A1 (aromatase)	VI — Window Preservation	Reduces E2 from physiological 30–80 to protocol target 20–40 pg/mL; limits ERα-mediated progenitor senescence	Preserves the viable treatment window for all five upstream layers, the temporal anchor of the protocol

6.0 Dosing and Administration

6.1 Dosing Table

Weight-based dosing is applied where clinical literature supports it. For the three research oral compounds (infigratinib, TMP269, KY19382), established human weight-based dosing does not exist; conservative research starting ranges are provided with the understanding that individual titration guided by bloodwork and physician assessment governs the final applied dose.

Compound	Dose	Timing	Rationale
rHGH	Min. 0.44 mg/kg/week SC	Fasted AM	Fasted state maximizes hepatic GHR responsiveness and avoids insulin interference. Dose is weight-based; no upper range is formally established for this application.
Infigratinib	5–20 mg/day oral (split BID)	AM meal + PM meal	Split dosing bridges the 8 to 9 hour half-life, maintaining continuous FGFR3 inhibition. A single daily dose produces a trough window of unblocked receptor activity.
Vosoritide	15 mcg/kg/day SC	45–60 min pre-sleep	Peptide half-life of approximately 30 to 40 minutes means timing is pharmacologically meaningful. Pre-sleep injection aligns NPR-B stimulation with the N3 growth window.
TMP269	5–20 mg/day oral	1 hr pre-training or early evening	CaMKII activated by resistance training independently exports HDAC4/5 from the nucleus. Taking TMP269 before training compounds pharmacological and mechanical de-repression of Runx2.
KY19382	5–20 mg/day oral	AM with meal	Once daily. Wnt/β-catenin transcriptional effects operate on a slower timescale than receptor signaling, making consistency more critical than precise timing.
Oxandrolone	0.0625–0.2 mg/kg/day oral	Split BID, pre-training and pre-sleep	Consistent with the 9 to 10 hour half-life. Range is derived from pediatric clinical literature (Turner syndrome and CDGP studies). Pre-training dose maximizes local IGF-1 during CaMK-active window; pre-sleep maintains AR occupancy through the growth window.
Anastrozole	Titrated to bloodwork	2–3× per week	Target E2: 20–40 pg/mL by LC-MS/MS. Below 20 pg/mL removes beneficial ERβ support; above 50 pg/mL accelerates ERα-mediated plate senescence.

6.2 Timing Rationale — Two Non-Obvious Decisions

Most timing decisions in this protocol follow straightforward pharmacokinetic logic. Two deserve explicit justification because they deviate from standard or labeled protocols in ways that require understanding rather than assumption.

Infigratinib is split into two equal doses rather than administered as a single daily dose. The compound's half-life of approximately 8 to 9 hours means that once-daily dosing produces near-zero plasma concentrations before the next dose is due, a multi-hour window each day during which FGFR3 is completely unblocked. For a systemic disease like cancer, this trough window is acceptable. For the purpose of continuous growth plate FGFR3 inhibition, it represents a significant period of unsuppressed receptor activity during which the braking signal can recover. BID dosing eliminates this trough.

Vosoritide is administered 45 to 60 minutes before sleep rather than in the morning as specified in the FDA-approved Voxzogo prescribing information. The clinical morning protocol was designed around patient adherence, not mechanistic optimization. With a parent peptide half-life of approximately 30 to 40 minutes, the biological window of elevated NPR-B activation is short and timing is pharmacodynamically meaningful. Growth plate cellular activity (proliferative zone mitosis, hypertrophic zone differentiation, matrix synthesis) peaks during N3 slow-wave sleep, coinciding with the largest endogenous GH pulse of the day. Pre-sleep injection times the NPR-B/cGMP signal to the growth window rather than to the waking hours when growth plate activity is at its lowest.

7.0 Form and Administration

All five primary research compounds are sourced as raw API powder and require preparation before administration. Detailed step-by-step preparation instructions (for BMN 111, Infigratinib, TMP269, and KY19382) can be provided in the form of companion formulation documents, just send me a message on discord and I will send them to you. The table below summarizes the administrative form and key considerations for each compound without duplicating the formulation process itself.

Compound	Form Sourced As	Administration Notes
rHGH (Somatropin)	Pre-lyophilized kit	Reconstituted into an injectable subcutaneous solution.
Vosoritide (BMN 111)	Raw API powder	Formulated into an injectable subcutaneous solution.
Infigratinib	Raw API powder	Formulated into oral solution.
TMP269	Raw API powder	Formulated into oral solution.
KY19382	Raw API powder	Formulated into oral solution. Note: KY19382 is a deep red powder — this is a structural property of the molecule, not an impurity. Confirmed by my sources COA.
Oxandrolone	Oral tablet (pharmaceutical)	Sourced as commercially manufactured tablets.
Anastrozole	Oral tablet (pharmaceutical)	Sourced as commercially manufactured tablets.

8.0 Side Effects, Ancillaries, and Sleep

This protocol combines compounds with distinct and overlapping side effect profiles. The ancillary compounds described here are not optional additions for comfort. Several address genuine risks that, if unmanaged, would necessitate reduction or discontinuation of primary compounds. Understanding why each ancillary is necessary requires first understanding which side effects it is preventing or managing.

8.1 Side Effects by Compound

The primary side effect liabilities introduced by each compound and the mechanism responsible:

Compound	Primary Side Effect Liabilities
rHGH	Water and sodium retention (IGF-1-mediated renal sodium reabsorption); insulin resistance; elevated IOP; possible carpal tunnel at high doses
Infigratinib	Hyperphosphatemia (FGFR1 inhibition disrupts FGF23 phosphate regulation); central serous retinopathy (FGFR1 at RPE); stomatitis/mouth sores; GI effects including nausea
Vosoritide	Injection site reactions; transient hypotension (NPR-B vasodilation); minor GI effects
TMP269	Mild immunomodulatory effects (Class IIa HDACs play roles in immune cell function); no significant reported liabilities at research doses
KY19382	No significant adverse profile established at research doses; Wnt pathway effects in other tissues are theoretically possible but not documented
Oxandrolone	HDL suppression; LDL elevation; hepatotoxicity (C17-alpha alkylated); HPTA suppression (requires TRT); mild androgenic effects
Anastrozole	E2 suppression below target (if overdosed), removes beneficial ERβ support, joint discomfort, mood effects; lipid profile changes

8.2 Non-Negotiable Ancillaries

These are required while running the protocol. Each addresses a direct, documented consequence of the primary compounds that, if unmanaged, would necessitate protocol modification.

Compound	Dose / Frequency	Rationale
Anastrozole	Titrated to bloodwork 2–3× per week	E2 management: the most mechanistically critical ancillary. Maintains the 20 to 40 pg/mL target that balances ERα suppression for window preservation against ERβ preservation for proliferative support.
Eplerenone	25 mg BID oral	Aldosterone antagonism serves two functions: primary prevention of central serous retinopathy through reduction of choroidal fluid accumulation secondary to FGFR1 inhibition by infigratinib, and secondary diuretic effect managing rHGH-related sodium retention. Both functions are active simultaneously.
HCTZ	12.5–25 mg oral AM	Thiazide diuretic addressing rHGH-induced sodium and water retention. Notably, HCTZ causes potassium waste while eplerenone causes potassium retention, the combination is pharmacologically complementary, and potassium balance remains manageable. Monitor serum potassium.
Sevelamer carbonate	As directed by physician based on phosphate levels	Binds dietary phosphate in the GI tract to prevent absorption. Required when infigratinib's FGFR1 inhibition produces hyperphosphatemia through disruption of FGF23-mediated phosphate excretion. Baseline phosphate and interval monitoring determines whether and at what dose sevelamer is needed.
Zeaxanthin + Lutein	4 mg + 20 mg daily	Macular carotenoids supporting RPE integrity and antioxidant defense at the retinal pigment epithelium. Provides targeted RPE support against the FGFR1 liability from infigratinib, complementing eplerenone's fluid management approach with direct antioxidant support.

8.3 Cardiovascular and Protective

These compounds address the cardiovascular load introduced by the combination of supraphysiological rHGH, testosterone, and oxandrolone. They are not emergency interventions; they are routinely co-administered to maintain cardiovascular health throughout the protocol.

Compound	Dose / Frequency	Rationale
Telmisartan	20–40 mg oral daily	AT1R blocker with unique PPAR-gamma partial agonism. Manages testosterone and rHGH-driven blood pressure elevation through renin-angiotensin system blockade while contributing mild insulin-sensitizing and cardiovascular-protective effects through PPAR-gamma. Preferred over older ARBs for this application.
Tadalafil (Cialis)	5–10 mg oral daily or as needed	PDE5 inhibitor producing sustained NO-mediated vasodilation. Addresses androgenic vasoconstriction, maintains vascular health, and has documented effects on growth plate biology through cGMP elevation that partially overlaps with vosoritide's NPR-B mechanism. The cardiovascular benefit is the primary rationale here.
Nebivolol	2.5–5 mg oral daily or as needed	Third-generation beta-1 selective blocker with the unique addition of beta-3 agonism driving eNOS activation and nitric oxide release, a vasodilatory property absent from older beta-blockers. Manages stimulant-driven or protocol-related tachycardia without impairing exercise capacity through beta-2 sparing. Superior to propranolol for active individuals.

8.4 Insulin Sensitivity and Hypertension

rHGH at therapeutic doses causes meaningful insulin resistance through direct counter-regulatory mechanisms, growth hormone is a physiological antagonist of insulin action. At the doses relevant to this protocol, fasting glucose and post-prandial glucose management require active attention. The standard tools for AMPK-mediated insulin sensitization, including metformin and berberine, both activate AMPK through Complex I inhibition and consequently inhibit mTORC1, the same downstream signaling node that rHGH/IGF-1 activates for growth plate anabolic effects. Using these compounds risk partially blunting the protocol's primary growth-promoting signal.

Imeglimin (approved in Japan as Twymeeg) represents the mechanistically superior alternative. It improves mitochondrial function through ATP synthase alpha-subunit modulation rather than Complex I inhibition, restoring mitochondrial efficiency without the same AMP:ATP ratio elevation that drives AMPK-mediated mTORC1 suppression. Additionally, imeglimin enhances glucose-stimulated insulin secretion from pancreatic beta cells; directly beneficial when rHGH is reducing peripheral insulin sensitivity. For individuals where glucose management becomes necessary during the protocol, imeglimin is the preferred intervention.

Blood pressure elevation from testosterone and oxandrolone is addressed primarily through telmisartan in the cardiovascular section. If additional blood pressure management is needed, the protocol already has eplerenone (aldosterone blockade) and HCTZ (thiazide diuresis) in place, which provide a multi-mechanism antihypertensive foundation. Dietary sodium management and adequate cardiovascular conditioning further support blood pressure control throughout the protocol.

8.5 On Hand

These are compounds that should be available but are not necessarily taken daily. They address contingencies that may arise during the protocol.

Compound	Dose / Frequency	Rationale
Ezetimibe	10 mg oral daily (if needed)	NPC1L1 inhibitor reduces intestinal cholesterol absorption. Oxandrolone suppresses HDL and can elevate LDL through hepatic lipid metabolism effects. Ezetimibe is a clean, well-tolerated intervention if lipid panel monitoring shows concerning LDL elevation.
Anti-nausea agents (e.g., ondansetron)	As needed	FGFR inhibitors including infigratinib produce GI effects including nausea, particularly during the initial weeks of use. A 5-HT3 antagonist antiemetic should be available before initiating infigratinib.
Imeglimin or alternative insulin sensitizer	As directed by physician	If fasting glucose trends upward on bloodwork, an insulin sensitizer without mTORC1 liability should be initiated promptly rather than reactively.

8.6 N3 NREM Sleep — Maximizing the Growth Window

N3 slow-wave sleep is the physiological state during which restorative processes are most active. It is the phase associated with the largest endogenous growth hormone pulse of the day, the deepest reduction in cortisol, and the highest level of growth plate cellular activity. Even when the rHGH dose is fixed and the pharmacological interventions are consistent, the duration and quality of N3 sleep directly determines how much growth-relevant biological work is done during each 24-hour cycle. This is not a peripheral consideration; it is a meaningful variable in the protocol's daily output.

Dexmedetomidine, an alpha-2A adrenergic receptor agonist originally developed for procedural sedation, reduces norepinephrine release from the locus coeruleus, the brain's primary arousal nucleus. This produces a sleep state that is qualitatively different from that produced by sedatives: rather than inducing unconsciousness through GABAergic or histaminergic suppression, it quiets the arousal system and allows the natural delta oscillation architecture of N3 to emerge. The result is deeper, more restorative sleep with enhanced slow-wave activity. Orexin receptor antagonists (including lemborexant and daridorexant, both FDA-approved) remove the active wake-stabilizing orexin/hypocretin signal rather than forcing sedation, producing sleep architecture closer to natural than traditional sleep aids allow. The combination of dexmedetomidine (NPE suppression) with an orexin antagonist (wake drive removal) addresses N3 quality from two independent mechanisms and represents the most complete pharmacological approach to sleep architecture optimization that is currently accessible. Specific dosing for these compounds is outside the scope of this protocol document and should be established with a physician.

9.0 Monitoring Schedule

Baseline values for all parameters below should be established before initiating any compound. Abnormal findings at baseline or during the protocol should be addressed with a physician before continuing. Bone age imaging is the most important single data point, as it determines whether the protocol is viable and how much time remains in the window.

Parameter	Frequency	Target and Notes
E2 (LC-MS/MS)	Every 4–6 weeks	Target: 20 to 40 pg/mL. LC-MS/MS is specified over standard immunoassay due to superior accuracy at suppressed ranges. Adjust anastrozole to maintain target. Below 20 pg/mL, reduce dose. Above 50 pg/mL, increase dose or add endoxifen.
Serum phosphate	Every 4–6 weeks	Monitors FGFR1-mediated hyperphosphatemia from infigratinib. Initiate sevelamer if phosphate rises above 5.5 mg/dL. Values above 7 mg/dL warrant dose reduction discussion with physician.
Potassium	Every 4–6 weeks	Eplerenone retains potassium; HCTZ wastes it. The combination typically remains balanced but must be verified. Target: 3.5 to 5.0 mEq/L.
Fasting glucose	Every 6–8 weeks	rHGH at therapeutic doses causes meaningful insulin resistance. Fasting glucose should remain below 100 mg/dL. Upward trend indicates need for dietary adjustment or consideration of imeglimin.
ALT / AST	Every 6–8 weeks	Baseline and ongoing. Oxandrolone is C17-alpha alkylated; hepatic monitoring is standard. Infigratinib at low doses carries minimal hepatic liability but should still be tracked.
CBC	Every 6–8 weeks	Baseline values establish reference for tracking any shifts in red cell indices or platelet counts from FGFR inhibition and the broader anabolic environment.
OCT (Optical Coherence Tomography)	Every 8–12 weeks	CSR surveillance for infigratinib FGFR1 retinal liability. Baseline OCT before initiating infigratinib is required. Subretinal fluid on OCT: hold infigratinib and reassess eplerenone dose.
Bone age X-ray	Baseline, then every 6 months	Left-hand radiograph read by radiologist. The single most important metric, as plate status determines remaining protocol window. Establishes trajectory for monitoring closure progression.
IGF-1	Every 8–12 weeks	Reflects the downstream effect of rHGH dosing. Supraphysiological levels are expected and intended; monitoring provides context for any metabolic findings in glucose and lipid panels.
Lipid panel	Every 8–12 weeks	Oxandrolone suppresses HDL and raises LDL. Baseline lipids before starting and interval monitoring throughout. Ezetimibe available if LDL rises significantly.
Blood pressure	At each monitoring visit	Testosterone and Anavar elevate blood pressure through increases in red cell mass and aldosterone-independent mechanisms. Telmisartan or tadalafil adjustments if consistently hypertensive.

10.0 Costs and Sourcing

The three oral research compounds; infigratinib, TMP269, and KY19382, as well as vosoritide were sourced through an API supplier established with verified listings on a multitude of platforms. Contact was established directly. Certificates of analysis for all compounds include HPLC purity at or above 99 percent, HNMR structural confirmation, and LCMS molecular weight verification. I would be more than happy to do a group buy, but I'm not comfortable providing my source for these API powders. The HGH entry in the table has been left for individual sourcing, as pre-lyophilized kits are available from multiple suppliers at varying price points, and the individual should verify supplier quality independently. As an example, to provide a 2-year estimate, I will use my current sources and their corresponding prices as to doses relevant to my body weight (80kg).

Compound	Supplier	Unit Price	2-Year Qty	2-Year Cost
rHGH (Somatropin)	[redacted]	$200/500IU	21 Kits	**$4,200**
Infigratinib	[redacted]	$300 / g	10 g	**$3,000**
Vosoritide (BMN 111)	[redacted]	$3,500 / g	1g	**$3,500**
TMP269	[redacted]	$950 / g	10 g	**$9,500**
KY19382	[redacted]	$600 / g	10 g	**$6,000**
TOTAL — 2-YEAR SUPPLY (primary compounds only)	**$26,200**			