CLINICAL LEARNING GUIDE

GHRP-2

Pralmorelin | Growth Hormone-Releasing Peptide-2

Mechanisms, Evidence, and Clinical Applications

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For educational and research purposes only. Not medical advice. GHRP-2 is not FDA-approved in the US (approved in Japan as a diagnostic agent). All US clinical use is off-label and investigational. Consult qualified healthcare providers.

SECTION 1 · PROFILE OF THE PEPTIDE

Overview

GHRP-2 (Growth Hormone-Releasing Peptide-2, also known as pralmorelin or KP-102) is a synthetic hexapeptide growth hormone secretagogue. It belongs to the GHRP family, all of which act on the same target — the growth hormone secretagogue receptor 1a (GHS-R1a), the ghrelin receptor. Among the traditional GHRPs, GHRP-2 is the most potent for stimulating growth hormone (GH) release, producing a GH response that exceeds that of the body's own growth hormone-releasing hormone (GHRH).

Its defining clinical behavior is that it stimulates pulsatile GH secretion — the physiologic, episodic pattern of GH release the body naturally produces (typically three to six pulses per day, depending on genetics), with the largest pulse at night. This is fundamentally different from exogenous recombinant GH, which produces a continuous, non-physiologic level. GHRP-2 raises IGF-1 transiently through the liver, and, most importantly, it attenuates somatostatin — the inhibitory hormone that normally brakes GH release. It also carries GH-independent properties: anti-inflammatory and cytoprotective effects through binding the CD36 scavenger receptor.

Peptide Profile

Property	Detail
Generic Name	GHRP-2 (pralmorelin); also KP-102 / KP-102D
Classification	Synthetic hexapeptide (6 amino acids) GH secretagogue; ghrelin-receptor agonist
Sequence	D-Ala-D-βNal-Ala-Trp-D-Phe-Lys-NH_2
Generation	Second-generation GHRP
Primary Target	GHS-R1a (ghrelin receptor); also binds CD36 scavenger receptor
Route of Administration	Subcutaneous injection (clinical); IV (diagnostic); intranasal (pediatric research)
Half-Life	~20–30 minutes
GH Peak	~15–30 minutes post-administration (up to ~60 min)

Property	Detail
FDA Status	NOT FDA-approved. Approved in Japan (2004) as a diagnostic agent for GH deficiency (KP-102D / pralmorelin)
Anti-Doping	WADA-prohibited at all times — Class S2 (Peptide Hormones, Growth Factors)

Where GHRP-2 Sits Among the GH Secretagogues

The GH secretagogues fall into two mechanistic families that work on two different receptors. The GHRH analogs (sermorelin, Mod GRF 1-29, CJC-1295, tesamorelin) act on the GHRH receptor. The GHRPs — GHRP-6, GHRP-2, ipamorelin, and hexarelin — act on the ghrelin receptor (GHS-R1a). GHRP-6 was the first generation and most closely mimics ghrelin; GHRP-2 followed as a more potent second-generation agent; ipamorelin is the cleaner third-generation standard. Because the GHRPs and GHRH analogs act through separate receptors on the same somatotroph cell, they are mechanistically synergistic when combined.

> ⚠ **GHRP-2 is not FDA-approved in the US and is WADA-prohibited at all times. Approved in Japan only as a diagnostic agent. All US clinical use is off-label and investigational, and competitive (drug-tested) athletes must avoid it entirely.**

SECTION 2 · MODES OF ACTION AND MECHANISMS

GHRP-2 works through several converging mechanisms. At the receptor level it acts at two sites and removes an inhibitory brake; intracellularly it drives both GH release and GH production; and beyond the GH axis it has its own cytoprotective signaling. The defining concept is that it amplifies the body's own physiologic, pulsatile GH — it does not replace GH from the outside.

Receptor Mechanism: Dual-Site Action Plus Somatostatin Attenuation

GHRP-2 binds GHS-R1a, a G-protein-coupled receptor located in both the hypothalamus and the anterior pituitary, and it acts at three levels at once:

- **Direct pituitary stimulation:** on the pituitary, where it directly stimulates the somatotroph cells to release GH;
- **Hypothalamic GHRH release:** on the hypothalamus, where it promotes the release of the body's own GHRH, which in turn drives GH production in the pituitary — so GHRP-2 both releases GH and helps build more of it;
- **Somatostatin attenuation:** by reducing somatostatin tone and down-regulating somatostatin receptor expression, lifting the inhibitory brake on GH release and amplifying the pulse. GHRP-2 is more resistant to somatostatin's opposing effect than GHRH is.

A clinically important point: somatostatin's inhibitory tone increases with age and with disease, which is part of why GH declines over time — and GHRP-2 directly counteracts that brake. Also, an intact GHRH receptor is not an absolute requirement for GHRP-2 to work, because it has its own separate receptor (GHS-R1a).

Intracellular Signaling

Once GHRP-2 activates GHS-R1a, several intracellular pathways carry out both the immediate release and the longer-term production of GH:

Pathway	Role
PLC → IP3/DAG → Ca^{2+} influx	Calcium entry through voltage-dependent channels drives GH vesicle exocytosis (release)
cAMP / PKA	GH gene transcription
Protein Kinase C (PKC)	Additive GH release
CREB activation	Up-regulates GH synthesis (building the GH supply)

Beyond GH: CD36 Binding and Cytoprotection

All GHRPs also bind the CD36 scavenger receptor, independently of GHS-R1a. For GHRP-2 this effect is mild-to-moderate (GHRP-6 and hexarelin have stronger CD36 activity), but it is real and entirely GH-independent. Through CD36, GHRP-2 activates the PI3K/AKT pro-survival pathway, which:

- reduces cellular apoptosis (notably in cardiac and neuronal tissue);
- reduces reactive oxygen species (ROS) spillover and enhances antioxidant defenses;
- lowers inflammatory cytokines (for example, a 66% reduction in IFN-γ in mice) and suppresses vascular superoxide production (in ApoE-deficient mice).

These are pleiotropic effects — a single peptide influencing many pathways that converge on the same goal the lecture emphasizes throughout: improving cell efficiency, cell flexibility, and the cell's ability to respond. The cytoprotective effects are largely demonstrated in preclinical (animal/in vitro) work and are separate from GHRP-2's downstream GH effects.

> **Key mechanistic point: GHRP-2 amplifies the body's own pulsatile GH on two fronts (releasing GH and building GH production) while removing the somatostatin brake — and it adds GH-independent, CD36-mediated cytoprotection on top. It augments physiology rather than overriding it.**

SECTION 3 · POINTS OF CLINICAL RELEVANCE

1. **It produces the strongest GH pulse in its class.** GHRP-2 is the most potent of the traditional GHRPs for GH release.

In healthy young adults, 1 mcg/kg IV produced a GH response greater than GHRH itself, with a further increase at 2 mcg/kg. The strength of this single-pulse release is why GHRP-2 is often used once daily at night — one well-timed injection captures the largest physiologic GH pulse.

2. **Efficacy is preserved with age.** It works just as well in older patients — age is not a limiting factor.

GH responses in the elderly were similar to those in young adults. The aging anterior pituitary retains its full machinery to release GH when properly stimulated; the problem of age-related decline is largely about reduced signaling and increased somatostatin tone, both of which GHRP-2 addresses.

3. **Direct pituitary action is proven.** It acts directly on the pituitary, confirmed in GHRH-receptor mutation patients.

In GH-deficient patients with a GHRH-receptor mutation, GHRP-2 still produced a 4.5-fold GH increase over baseline (controls showed a 79-fold increase). The fact that it works even when the GHRH receptor is non-functional confirms it acts through its own receptor on the pituitary.

4. **It stimulates ACTH/cortisol alongside GH.** It has a useful diagnostic role — and a revealing effect on the cortisol axis.

In Japan the GHRP-2 test diagnoses GH deficiency (GH peak cutoff 15.0 mcg/L). Notably, it also triggers a mild ACTH release, producing a small simultaneous cortisol rise — useful for detecting secondary adrenal insufficiency. Dr. Seeds adds a practical, not-yet-validated observation: he views GHRP-2 as a potential modulator of cortisol (helpful in patients with flattened cortisol curves), distinct from the much stronger ACTH/cortisol effect of GHRP-6.

5. **Orexigenic (appetite-increasing) effect.** It modestly stimulates appetite — useful in catabolic states.

As a ghrelin mimetic, GHRP-2 increased food intake in healthy men (about 36% over placebo) without changing macronutrient preference, and obese subjects retained this response. The effect is moderate — less than GHRP-6, more than ipamorelin (which is essentially neutral). This gives GHRP-2 a potential role in cachexia and anorexia, including cancer-related cachexia, where the literature has not shown increased cancer progression. Dr. Seeds notes appetite gains in practice may also reflect improved gut motility, gut-barrier integrity, and nutrient absorption.

6. **Desensitization is the key practical concern.** Response attenuates with repeated dosing — receptor desensitization is the central management issue.

With 100 mcg SC daily, peak GH fell from 83 mcg/L on day 1 to about 51 mcg/L by day 5 (still meaningful), then tends to level off; IGF-1 did not rise over five days. Higher doses cause more desensitization. This is why dosing discipline and cycling matter, and Dr. Seeds's strong recommendation is to hold the dose at 100 mcg rather than chase higher numbers.

7. **Understand the glucose/insulin interaction.** The transient glucose rise is an expected, benign effect — not a warning sign.

Like all GH secretagogues, GHRP-2 transiently antagonizes insulin and increases fat oxidation (beta-oxidation). This can cause a small, temporary rise in glucose — partly because increased fat-burning reduces GLUT4-mediated glucose uptake in muscle (sparing glucose for the brain) and the liver adds modest gluconeogenesis. Dr. Seeds frames this as a normal, transient effect of a system being pushed toward greater mitochondrial efficiency over months — not a reason for alarm — but diabetic patients must have glucose controlled first (often with a GLP-1 agent) before starting.

SECTION 4 · GENERAL DOSING INSTRUCTIONS AND DELIVERY OPTIONS

> **GHRP-2 is not FDA-approved; US use is off-label/investigational. The protocols below derive from clinical research and Dr. Seeds's practice frameworks. The subcutaneous route is the practical standard.**

Research / Clinical Dosing by Route

Route	Dose	Frequency	Context
IV bolus	1–2 mcg/kg	Single dose	Diagnostic / acute study
SC injection	100–300 mcg	Once daily	Therapeutic research
Intranasal	100–400 mcg	2–3× daily	Pediatric GHD trials (higher/more frequent dosing needed)

Route	Dose	Frequency	Context
SC (pediatric)	0.3–3.0 mcg/kg	Once daily	GHD children, growth

Dr. Seeds notes oral dosing is not viable (degraded in the gut, requiring impractically large, costly doses), and intranasal dosing in adults is generally avoided because enzymes degrade it quickly and much higher, repeated doses are needed. Subcutaneous is the route of choice.

Suggested Titration Framework (Research-Derived)

Phase	Dose / Timing	Notes
Weeks 1–2 (Initiation)	100 mcg SC once daily, evening	Assess tolerance; evening dosing aligns with the nocturnal GH pulse (deep sleep, glymphatic drainage)
Weeks 3–4 (Escalation)	Hold at 100 mcg; up to 150 mcg if needed	Lecturer prefers staying at 100 mcg to avoid desensitization; monitor GH/IGF-1, side effects, fasting glucose
Weeks 5–16 (Maintenance)	100 mcg (research protocols cite up to 200–300 mcg)	Some attenuation expected; consider 8–12 week cycles. Lecturer advises against the higher single doses

Dr. Seeds's Dosing Philosophy: Hold the Dose, Use Frequency Instead

The recurring theme is that desensitization is driven by dose magnitude, not just frequency — so a single 200–300 mcg dose can desensitize the receptor more than several smaller ones. The recommendation is to stay at 100 mcg per injection. Because that dose preserves receptor sensitivity, it can safely be given more than once daily when a stronger physiologic effect is the goal:

- Once daily (evening) is the standard — capturing the largest nocturnal GH pulse;
- Twice daily (fasted morning + evening) for a stronger response;
- Three times daily (adding a post-exercise dose) for the most physiologic, training-oriented response — 100 mcg each time.

Critically, allow at least a 3-hour window between doses: the GH response curve needs roughly three hours to recover before another pulse can be stimulated effectively. Dosing inside that window wastes the dose.

Cycling, Combinations, Administration

- Cycling: roughly 3 months on, then 4–6 weeks off, then restart if the response was good. Dr. Seeds repeatedly calls cycling "an art" — individualized and guided by clinical notes, not a fixed formula.
- Synergy with GHRH analogs: pairing GHRP-2 with a GHRH analog (Mod GRF 1-29, CJC-1295, or tesamorelin) is synergistic — the GHRP raises pulse amplitude and the GHRH raises pulse frequency, for greater total daily GH. (Note: GnRH/TRH peptides desensitize their receptors and have no place in continued clinical use.)
- Reconstitution & storage: reconstitute with bacteriostatic water; refrigerate at 2–8°C; use within ~28 days; protect from light.

- Injection technique: SC into abdomen, thigh, or arm with a 29–31 gauge insulin syringe at 45–90°; do not aspirate. Dr. Seeds prefers the thigh/hip over the abdomen, which has denser small-vessel vascularization and tends to produce more flushing or redness.
- Timing & food: take in a fasted state — about 30 minutes before eating after the dose, and roughly 1.5–2 hours after the last meal. Carbohydrate and fat blunt the GH release; pure protein does not. Bedtime and first-thing-in-the-morning are naturally fasted windows. Keep the timing consistent.

SECTION 5 · EVIDENCE PROFILE

GH Stimulation — Human Data

Setting	Key Finding
Healthy young adults (IV)	1 mcg/kg produced GH response greater than GHRH ($p<0.05$); 2 mcg/kg gave a further increase
Elderly	GH response similar to young adults — efficacy preserved with age
Healthy men (SC)	100 mcg produced a strong day-1 peak GH of 83 ± 31 mcg/L
GHD with GHRH-R mutation	4.5-fold GH increase vs baseline ($p=0.002$); controls 79-fold — confirms direct pituitary action
Diagnostic (Japan)	GHD cutoff 15.0 mcg/L; simultaneous ACTH/cortisol release useful for HPA-axis evaluation

Appetite, Attenuation, and Bone

- Food intake (healthy men): GHRP-2 infusion increased energy intake by ~35.9% over placebo ($p=0.005$), a ghrelin-mimetic effect; obese subjects remained responsive.
- Response attenuation (100 mcg SC × 5 days): peak GH 83 → 59 → 51 mcg/L (days 1, 3, 5; $p<0.01$); IGF-1 did not increase over the five days; osteocalcin rose from 3.2 to 4.2 mcg/L ($p<0.01$), a favorable bone marker.

Anti-Inflammatory & Cytoprotective — Preclinical

- Reduced arthritic inflammation, paw edema, and prevented body-weight loss in arthritic rats.
- Suppressed IFN-γ and pro-inflammatory cytokines; decreased aortic superoxide production in ApoE-deficient mice.
- Activated PI3K/AKT pro-survival signaling, reduced ROS, and enhanced antioxidant defenses in vitro.

Note: the anti-inflammatory and cytoprotective evidence is essentially all preclinical (animal/in vitro). Human RCTs validating these effects are lacking.

Comparative Analysis: The GHRP Family

Parameter	GHRP-2	GHRP-6	Ipamorelin
GH potency	Highest	High	Moderate
Receptor selectivity	Moderate	Low	Highest

Parameter	GHRP-2	GHRP-6	Ipamorelin
Appetite stimulation	Moderate	Strong	Minimal
Cortisol effect	Mild	Significant	Minimal
Prolactin effect	Mild	Significant	Minimal
Half-life	~20–30 min	~20–30 min	~2 hours
Generation	2nd	1st	3rd

Ipamorelin is the cleaner third-generation standard — modest GH effect with the least desensitization and the best selectivity. GHRP-2's advantage is raw potency: the strongest GH pulse of the group, which suits once-daily nighttime dosing.

Critical Evidence Gaps

- No large-scale Phase III RCTs for therapeutic indications.
- Long-term human safety data beyond ~6 months is sparse.
- Optimal cycling protocols are not established.
- Cytoprotective effects are not yet validated in human trials.
- Head-to-head comparisons with newer secretagogues, and Phase II combination trials with GHRH analogs, are still needed.

SECTION 6 · CLINICAL CONSIDERATIONS

Contraindications

- Active malignancy — avoid GH stimulation.
- Uncontrolled diabetes mellitus — stabilize metabolism first (GLP-1 agents are the preferred bridge) before introducing a secretagogue.
- Active pituitary tumors.
- Pregnancy and lactation.
- Known hypersensitivity to GHRP-2.
- WADA-tested athletes — prohibited at all times.

Adverse Effect Profile

Effect	Severity	Notes
Increased appetite	Mild	Ghrelin-mimetic effect; common
Cortisol elevation	Mild–Moderate	Via ACTH; similar to CRH response; less than GHRP-6
Prolactin elevation	Mild	Less than the TRH effect; common
Flushing / warmth	Mild	Transient, occasional; more likely with inadvertent IV/vascular injection
Glucose elevation	Monitor	Transient; screen diabetics (see Section 3)

Effect	Severity	Notes
Fluid retention / edema	Mild	Occasional; may present as nighttime wrist pain / carpal tunnel
Injection-site reaction	Mild	Redness, irritation

A practical tip from the lecture: if a patient on a GHRH + GHRP combination develops nighttime wrist pain, suspect fluid-retention-related carpal tunnel — remove one agent, then reintroduce, to identify the cause. Long-term human safety data is limited; monitor glucose, cortisol, and prolactin.

Drug Interactions & Cautions

- Glucocorticoids may blunt the downstream GH response (though CD36-mediated effects persist).
- Somatostatin analogs (octreotide) directly oppose GHRP-2 — avoid concurrent use.
- Concurrent exogenous GH risks supraphysiologic IGF-1.
- Insulin sensitivity may be transiently reduced (see glucose discussion in Section 3).
- Thyroid status, estrogen status, adiposity, and aging all influence the GH response — increased adiposity and aging modestly reduce peak GH. Dr. Seeds tends to address metabolism first and thyroid later.

Patient Selection

Favorable candidates: adults with confirmed or suspected GH deficiency; post-surgical or post-radiation pituitary insufficiency; age-related GH decline (somatopause); catabolic states/sarcopenia; recovery from injury or surgery; and cachexia syndromes (investigational).

Pre-treatment workup: confirm GHD with standard stimulation testing; baseline IGF-1, GH, cortisol, prolactin; fasting glucose and HbA1c; body composition (Dr. Seeds favors inexpensive, repeatable InBody testing each quarter to track lean mass and visceral fat); and documented informed consent for off-label use.

Monitoring Framework

Timepoint	Assessment
Baseline	IGF-1, GH, cortisol, prolactin, fasting glucose, HbA1c; body composition; hepatic and cardiovascular screening
Week 4	Repeat IGF-1 and fasting glucose; symptom assessment
Week 8	Full panel repeat; body composition
Week 12–16	Evaluate continuation vs cycling off (4–6 week break); body composition (InBody)
As indicated	Prolactin if hyperprolactinemia symptoms; morning cortisol if fatigue/HPA concerns

A note on IGF-1: Dr. Seeds cautions against over-weighting a single IGF-1 value — it is a momentary, physiologic reading that varies with timing of the injection, the test, exercise, and the day's activity. Follow the trend and the clinical picture, not one number.

SECTION 7 · A FINAL NOTE

GHRP-2 is the most potent of the traditional growth hormone-releasing peptides — a second-generation hexapeptide that produces a stronger GH pulse than the body's own GHRH, works equally well in older patients, and acts directly on the pituitary through its own ghrelin receptor while simultaneously lifting the somatostatin brake. Its single, powerful pulse makes once-daily nighttime dosing a clean and effective strategy, capturing the deep-sleep GH surge that supports recovery and glymphatic drainage.

Its value extends past GH. Through CD36 it adds GH-independent, PI3K/AKT-mediated cytoprotection and anti-inflammatory and antioxidant effects, and its moderate orexigenic action gives it a real role in cachexia and the appetite loss of aging — though these benefits rest largely on preclinical evidence and need human validation.

The honest framing is twofold. First, the central clinical skill is dose discipline: GHRP-2 desensitizes its receptor with higher doses, so Dr. Seeds's consistent advice is to hold the dose at 100 mcg and use frequency (with a 3-hour recovery window between doses) and cycling — "an art" guided by careful clinical notes — rather than chasing higher numbers. Second, the transient glucose rise and mild cortisol and prolactin effects are expected, manageable consequences of pushing the system toward greater cellular efficiency over months, not red flags — provided metabolism (and uncontrolled diabetes in particular) is addressed first, often with a GLP-1 agent.

For the practitioner, GHRP-2 is best understood as a potent, physiologic GH amplifier — most powerful when paired synergistically with a GHRH analog, most safely used at a disciplined 100 mcg dose, and most informative when tracked over time with body composition and a full metabolic panel. It is approved for diagnosis in Japan, well characterized at research doses, and investigational and off-label everywhere else — a peptide with strong mechanism and a real signal that still awaits the large, long-term human trials the field needs.

> **Bottom line: GHRP-2 (pralmorelin) is the most potent traditional GHRP — a dual-action ghrelin-receptor agonist that amplifies physiologic, pulsatile GH while removing the somatostatin brake, with added CD36-mediated cytoprotection and a moderate appetite effect. Most rationally dosed at 100 mcg SC, once daily at night (or up to 3× daily with a 3-hour window), cycled, and synergistic with GHRH analogs. Watch for receptor desensitization, transient glucose elevation, and mild cortisol/prolactin effects. Approved for diagnosis in Japan; WADA-prohibited; investigational/off-label in the US.**

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