

Ipamorelin

Selective GHSR1a agonism and GH secretion

Author

Valentine Wibowo, Clinical Researcher

Medical review

dr. I Wayan Cahyadi Surya Distira Putra, MPH

Updated

23 August 2026 · Evidence cutoff 23 Aug 2026

ABSTRACT

A short-lived pentapeptide activates GHSR1a and produces a temporally resolved GH pulse in humans.

This monograph evaluates ipamorelin as an independent pentapeptide agonist of the growth-hormone secretagogue receptor. It excludes CJC-1295 combinations and does not transfer data from ghrelin, other GHRPs or oral ghrelin agonists.

This monograph begins with the molecule and follows the causal chain through biochemistry, cellular mechanism, exposure and integrated physiology. Population studies enter only at the terminal stress-test: useful for the proposition actually tested, incapable of defining the molecule or replacing the causal model.

ESTABLISHED	UNRESOLVED
• Defined pentapeptide • GHSR1a target • Human IV PK and GH response	• Other-route pharmacokinetics • Outcome-specific efficacy • Longitudinal GH/IGF-1 consequences

EVIDENCE HIERARCHY

Mechanistic evidence is not a lower-grade substitute for population medicine. Physical constraints, biochemical measurements, historical and non-English records, exposure studies and clinical outcomes answer different questions. Controlled clinical trials test the complete implemented proposition; they cannot manufacture a missing identity, mechanism or exposure bridge.

I	Molecular identity and chemistry
II	Biochemistry and target architecture
III	Cells and ex-vivo tissues
IV	Animal and in-vivo pharmacology
V	Integrated physiology and translation
VI	Human PK and observational signal
VII	Controlled clinical trials

CONTENTS

- 01 Action ledger
- 02 Methods and coverage
- 03 Evidence atlas
- 04 Molecular dossier: the entity before the outcome

- 05 Historical and international corpus
- 06 1998-1999: Early receptor-selective secretagogue programme
- 07 2014-2016: A gastrointestinal proposition was directly stress-tested
- 08 Mechanistic calculus — MEASURED: Short plasma residence, earlier endocrine peak
- 09 Mechanistic calculus — CONSTRAINED: Route transformation requires new PK
- 10 Mechanistic calculus — MEASURED: Target engagement survived a negative outcome
- 11 Causal architecture: GHSR1a is not only a GH switch
- 12 Causal architecture: Pulse timing matters
- 13 Causal architecture: Selectivity narrows mechanism, not outcome
- 14 Causal architecture: The negative trial localises the failure
- 15 Molecular identity and entity resolution
- 16 Biochemical mechanism and target architecture
- 17 In-vivo pharmacology and exposure
- 18 Integrated physiology and individual terrain
- 19 Terminal human stress-test
- 20 Counterevidence and causal boundaries
- 21 Scientific conclusion
- 22 Molecular target and endocrine signal
- 23 Human pharmacokinetics and pharmacodynamics
- 24 Gastrointestinal mechanism
- 25 Controlled human counterevidence
- 26 Translation beyond the studied indication
- 27 Falsification map
- 28 Research agenda
- 29 Cited primary evidence corpus

ACTION LEDGER

Describe the action before judging its value.

Benefit is a downstream clinical judgement. The scientific object is the action itself: what moves, under which exposure, in which biological state, and where the inference stops.

01 Attributed biochemical action	A short-lived pentapeptide activates GHSR1a and produces a temporally resolved GH pulse in humans.
02 Exposure and reachability	In healthy male volunteers receiving intravenous infusions, pharmacokinetics were dose proportional, terminal half-life was approximately two hours, and GH release peaked at about 0.67 hours. These data belong to the intravenous protocol studied.
03 Physiological direction is contextual	Ipamorelin sits inside the ghrelin-growth-hormone network, where nutritional state, sleep, glucose regulation, pituitary reserve and feedback through IGF-1 modify the response. A transient GH pulse is a proximal physiological event. Whether it improves motility, recovery or composition depends on the downstream system and cannot be inferred from peak amplitude alone.
04 Individual adjudication boundary	Whether repeated route-specific pulses create a favourable tissue outcome without maladaptive GH/IGF-1 or glucose effects. Receptor selectivity or an acute GH pulse cannot establish sleep, recovery, body-composition or healthy-ageing benefit.

METHODS AND COVERAGE

A reproducible boundary, not an implied exhaustive review.

This curated mechanistic monograph uses primary indexed records and reference-chaining. It does not claim systematic-review completeness. Absence of a retrieved result is not evidence that an effect is absent.

SEARCH SURFACE	PubMed/MEDLINE primary records, Russian-language indexed abstracts, and reference-chaining for entity-defining, historical and translational studies. Language, geography, regulatory status and journal fashion are not evidence grades.
QUERY FRAME	ipamorelin · GHSR1a · ghrelin receptor · growth hormone secretagogue · pharmacokinetics · postoperative ileus
EVIDENCE CUTOFF	23 August 2026
ENTITY EXCLUSION	Ipamorelin evidence cannot be transferred from ghrelin, other GHRPs, oral ghrelin agonists or CJC combinations. Route and pulse kinetics are part of identity-in-use.
TRACEABILITY	10 extended claim units plus 2 historical records and 3 mechanistic-calculus records; 4 cited records in the complete corpus.
INTERPRETIVE RULE	Identity → physical constraint → measured reaction or binding → reachable exposure → system response → outcome. Statistical significance does not manufacture mechanism; mechanistic plausibility does not manufacture a patient outcome.

EVIDENCE ATLAS

Every claim keeps its experimental address.

10 claim units are mapped to evidentiary layer, experimental frame and source records. The layer describes the question answered; it is not a popularity score.

LAYER	EXPERIMENTAL FRAME	FINDING AND BOUNDARY	SOURCES
II/VMechanism and physiological translation	Molecular target and endocrine signal · claim 1	Ipamorelin is a defined pentapeptide that activates GHSR1a, the ghrelin receptor. Receptor activation can stimulate pituitary GH release and can also engage gastrointestinal motility pathways. These are related receptor effects but not interchangeable clinical indications.	[1][2][4]
VIHuman exposure or signal	Molecular target and endocrine signal · claim 2	Selectivity relative to earlier GH secretagogues was established in comparative experimental systems and is a pharmacological property, not a guarantee of a clean clinical phenotype. Endocrine response still depends on dose, route, baseline pituitary reserve, feedback through IGF-1, food state and repeated exposure.	[1][4]
VIHuman exposure or signal	Human pharmacokinetics and pharmacodynamics · claim 1	In healthy male volunteers receiving intravenous infusion, exposure was dose proportional and terminal half-life was approximately two hours. GH release peaked at roughly 0.67 hours. These observations define an intravenous experiment; they do not automatically describe subcutaneous exposure or repeated bedtime administration.	[1]
VIHuman exposure or signal	Human pharmacokinetics and pharmacodynamics · claim 2	A short plasma half-life can still produce a biological effect that outlasts measurable parent peptide, but duration must be demonstrated rather than assumed. GH pulse, downstream IGF-1 and patient outcome occupy different time scales and require separate measurement.	[1]
VIHuman exposure or signal	Gastrointestinal mechanism · claim 1	In a rodent postoperative-ileus model, ipamorelin accelerated gastric emptying and reversed impaired contractile responses through a ghrelin-receptor-mediated pathway involving cholinergic excitatory neurons. This provides a coherent mechanism for the indication subsequently tested in humans.	[3]

LAYER	EXPERIMENTAL FRAME	FINDING AND BOUNDARY	SOURCES
VI Human exposure or signal	Gastrointestinal mechanism · claim 2	The preclinical result is valuable because it connects receptor, tissue physiology and an outcome. It also demonstrates the limit of mechanistic prediction: a plausible and experimentally supported promotility pathway did not guarantee success of the human primary endpoint.	[2][3]
VII Controlled human proposition	Controlled human counterevidence · claim 1	The multicentre phase 2 postoperative-ileus trial randomised 117 bowel-resection patients to intravenous ipamorelin or placebo. Time to the primary composite endpoint was 25.3 hours with ipamorelin and 32.6 hours with placebo, but the difference was not statistically significant (p=0.15).	[2]
VII Controlled human proposition	Controlled human counterevidence · claim 2	This negative trial does not invalidate GHSR1a binding, GH release or promotility activity in animals. It constrains the claim that the studied intravenous regimen produces a reliable postoperative clinical benefit. Mechanism and clinical validation answer different questions and can legitimately diverge.	[1][2][3]
VI Human exposure or signal	Translation beyond the studied indication · claim 1	Claims concerning sleep, recovery, body composition or healthy ageing are not established by the ileus programme or by an acute GH pulse. Those propositions require their own route-specific pharmacokinetics, functional outcomes and longitudinal metabolic assessment.	[1][2]
IV Integrated in-vivo model	Translation beyond the studied indication · claim 2	Repeated stimulation of the GH/IGF-1 axis raises monitoring questions around glucose regulation, oedema, paraesthesia and proliferative context. These are mechanistically foreseeable domains, while their magnitude under a particular regimen remains an empirical question.	[1]

SECTION 01

Molecular dossier: the entity before the outcome

ENTITY — Defined pentapeptide; independent of all GHRH analogues

BIOCHEMICAL CLASS — Ghrelin-receptor secretagogue

PRIMARY SYSTEM — GHSR1a → pituitary GH and gastrointestinal neural signalling

IDENTITY BOUNDARY — Ipamorelin evidence cannot be transferred from ghrelin, other GHRPs, oral ghrelin agonists or CJC combinations. Route and pulse kinetics are part of identity-in-use.

SECTION 02

Historical and international corpus

Ipamorelin emerged in the late 1990s from the growth-hormone-secretagogue programme. It is not historically ancient, but its human PK and acute endocrine pharmacology are directly measured.

Selectivity and GH release are better established than subcutaneous repeated-use exposure or durable clinical benefit.

SECTION 03

1998-1999: Early receptor-selective secretagogue programme

Comparative pharmacology and first human PK established a selective GH-secretagogue identity and an acute response. These early records remain scientifically relevant because they define the molecule rather than merely reporting later outcomes.[1][4]

SECTION 04

2014-2016: A gastrointestinal proposition was directly stress-tested

The ileus programme translated pro-motility reasoning into a controlled endpoint. Its neutral primary result narrows that clinical proposition without deleting receptor engagement or acute GH pharmacology.[2][3]

SECTION 05

Mechanistic calculus — MEASURED: Short plasma residence, earlier endocrine peak

In the intravenous human experiment, terminal half-life was about two hours and GH peaked at roughly 0.67 hours. Parent-peptide exposure and downstream hormone response therefore require separate time functions.[1]

SECTION 06

Mechanistic calculus — CONSTRAINED: Route transformation requires new PK

An intravenous infusion defines complete vascular input. It cannot be transformed into subcutaneous bioavailability or a bedtime exposure curve without absorption and repeated-dose measurements.[1]

SECTION 07

Mechanistic calculus — MEASURED: Target engagement survived a negative outcome

The controlled ileus endpoint was not significantly improved under the studied regimen. This is a clean example of valid pharmacology failing to guarantee a chosen clinical result.[2]

SECTION 08

Causal architecture: GHSR1a is not only a GH switch

The ghrelin receptor links pituitary secretion, autonomic and gastrointestinal physiology. A single target can therefore generate endocrine and motility effects whose relevance depends on route, dose and tissue exposure.[1][2]

SECTION 09

Causal architecture: Pulse timing matters

Human IV work places peak GH response well before terminal peptide elimination is complete. Parent-peptide concentration, GH pulse and downstream IGF-1 occupy different time scales; they must be measured separately rather than collapsed into one effect.[1]

SECTION 10

Causal architecture: Selectivity narrows mechanism, not outcome

Relative selectivity over earlier secretagogues can reduce some off-target endocrine signalling, but it does not guarantee clinical cleanliness. Baseline pituitary reserve, food state, repeated exposure and feedback remain capable of changing the response.[1]

SECTION 11

Causal architecture: The negative trial localises the failure

A coherent promotility mechanism and animal physiology did not translate into a statistically resolved postoperative primary endpoint. That result constrains the studied clinical proposition while leaving receptor engagement and acute GH pharmacology intact.[2][3]

SECTION 12

Molecular identity and entity resolution

Ipamorelin is a defined pentapeptide growth-hormone secretagogue. Its molecular identity and evidence are independent of every other GH-axis peptide.

SECTION 13

Biochemical mechanism and target architecture

Ipamorelin activates the ghrelin receptor GHSR1a and produces growth-hormone release. Receptor selectivity defines mechanism but does not guarantee a meaningful clinical outcome.

SECTION 14

In-vivo pharmacology and exposure

In healthy male volunteers receiving intravenous infusions, pharmacokinetics were dose proportional, terminal half-life was approximately two hours, and GH release peaked at about 0.67 hours. These data belong to the intravenous protocol studied.

SECTION 15

Integrated physiology and individual terrain

Ipamorelin sits inside the ghrelin-growth-hormone network, where nutritional state, sleep, glucose regulation, pituitary reserve and feedback through IGF-1 modify the response. A transient GH pulse is a proximal physiological event. Whether it improves motility, recovery or composition depends on the downstream system and cannot be inferred from peak amplitude alone.

SECTION 16

Terminal human stress-test

A phase 2 postoperative-ileus trial enrolled 117 patients. The primary endpoint was 25.3 hours with ipamorelin versus 32.6 hours with placebo and was not statistically significant ($p=0.15$).

SECTION 17

Counterevidence and causal boundaries

The negative controlled trial is direct evidence that verified receptor pharmacology does not guarantee clinical translation for a chosen indication. It constrains that claim without negating GHSR1a engagement.

SECTION 18

Scientific conclusion

Ipamorelin has defined identity, human PK and human target engagement, alongside a clinically important negative trial. Any new proposition must specify route, phenotype and outcome rather than inherit a generic GH narrative.

SECTION 19

Molecular target and endocrine signal

Ipamorelin is a defined pentapeptide that activates GHSR1a, the ghrelin receptor. Receptor activation can stimulate pituitary GH release and can also engage gastrointestinal motility pathways. These are related receptor effects but not interchangeable clinical indications.[1][2][4]

Selectivity relative to earlier GH secretagogues was established in comparative experimental systems and is a pharmacological property, not a guarantee of a clean clinical phenotype. Endocrine response still depends on dose, route, baseline pituitary reserve, feedback through IGF-1, food state and repeated exposure.[1][4]

SECTION 20

Human pharmacokinetics and pharmacodynamics

In healthy male volunteers receiving intravenous infusion, exposure was dose proportional and terminal half-life was approximately two hours. GH release peaked at roughly 0.67 hours. These observations define an intravenous experiment; they do not automatically describe subcutaneous exposure or repeated bedtime administration.[1]

A short plasma half-life can still produce a biological effect that outlasts measurable parent peptide, but duration must be demonstrated rather than assumed. GH pulse, downstream IGF-1 and patient outcome occupy different time scales and require separate measurement.[1]

SECTION 21

Gastrointestinal mechanism

In a rodent postoperative-ileus model, ipamorelin accelerated gastric emptying and reversed impaired contractile responses through a ghrelin-receptor-mediated pathway involving cholinergic excitatory neurons. This provides a coherent mechanism for the indication subsequently tested in humans.[3]

The preclinical result is valuable because it connects receptor, tissue physiology and an outcome. It also demonstrates the limit of mechanistic prediction: a plausible and experimentally supported promotility pathway did not guarantee success of the human primary endpoint.[2][3]

SECTION 22

Controlled human counterevidence

The multicentre phase 2 postoperative-ileus trial randomised 117 bowel-resection patients to intravenous ipamorelin or placebo. Time to the primary composite endpoint was 25.3 hours with ipamorelin and 32.6 hours with placebo, but the difference was not statistically significant ($p=0.15$).[2]

This negative trial does not invalidate GHSR1a binding, GH release or promotility activity in animals. It constrains the claim that the studied intravenous regimen produces a reliable postoperative clinical benefit. Mechanism and clinical validation answer different questions and can legitimately diverge.[1][2][3]

SECTION 23

Translation beyond the studied indication

Claims concerning sleep, recovery, body composition or healthy ageing are not established by the ileus programme or by an acute GH pulse. Those propositions require their own route-specific pharmacokinetics, functional outcomes and longitudinal metabolic assessment.[1][2]

Repeated stimulation of the GH/IGF-1 axis raises monitoring questions around glucose regulation, oedema, paraesthesia and proliferative context. These are mechanistically foreseeable domains, while their magnitude under a particular regimen remains an empirical question.[1]

SECTION 24

Falsification map

Absent GH movement after verified exposure would challenge target engagement.

Repeated pulses without outcome improvement would refute GH-response-as-clinical-response reasoning.

The controlled ileus result already falsifies a reliable benefit claim for the studied regimen and endpoint.

RESEARCH AGENDA

What would materially change the conclusion?

01 Subcutaneous and intranasal route-specific PK

02 Repeated-dose GH and IGF-1 dynamics

03 Controlled recovery and body-composition outcomes

04 Glucose and sleep-related effects

05 Predictors of response despite the negative ileus trial

CITED PRIMARY EVIDENCE CORPUS

4 source records

This corpus documents the claims made in this monograph; it is not presented as an exhaustive systematic-review search.

Gobburu et al. Pharm Res. 1999;16:1412-1416. · PMID 10496658

Beck et al. Int J Colorectal Dis. 2014;29:1527-1534. · PMID 25331030

Venkova et al. Ipamorelin accelerates gastric emptying in a rodent model of postoperative ileus. Exp Biol Med. 2016. · PMID 27186127

Raun et al. Eur J Endocrinol. 1998;139:552-561. · PMID 9849822

AUTHORSHIP AND ACCOUNTABILITY

Valentine Wibowo performed the conceptualisation, evidence synthesis, scientific interpretation and drafting. dr. I Wayan Cahyadi Surya Distira Putra, MPH completed medical review and approved the publication. Internal medical review is not represented as independent journal peer review.

No new patient data or human research were undertaken. The author and reviewer declare no personal financial competing interests. Clinic Terrain and Klinik Pratama Cepat Sehat provide clinical services; that institutional relationship is disclosed.