

RESEARCH MONOGRAPH · COMPOUND PROFILE

CJC-1295 nDAC

A 29-amino-acid GHRH analog with four point substitutions that confer enzymatic stability against dipeptidyl peptidase 4, the principal degradation pathway for native GHRH.

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ABSTRACT

CJC-1295 (No DAC), often abbreviated CJC-1295 nDAC and known in the literature as modified GRF(1-29) or simply Mod-GRF, is a synthetic 29-residue analog of human growth hormone-releasing hormone (GHRH) bearing four point mutations relative to the native sequence (CAS 863288-34-0; molecular weight 3367.94). The substitutions are tyrosine-1 to D-alanine (DPP-4 resistance), alanine-8 to glutamine (improved chemical stability), arginine-15 to glutamine (DPP-4 resistance and stability), and asparagine-27 to leucine (improved hydrophobicity and resistance to deamidation). The result is a GHRH analog with substantially extended biological half-life relative to native GHRH (which has a serum half-life under 10 minutes due to rapid DPP-4 cleavage at the N-terminal tyrosine). CJC-1295 nDAC retains the receptor specificity of native GHRH and stimulates pituitary somatotrophs through the GHRH receptor, producing a pulsatile GH release pattern. The "DAC" suffix in the related compound CJC-1295 with DAC refers to a drug affinity complex (a maleimidopropionic acid linker that covalently attaches to serum albumin) that further extends the half-life from approximately 30 minutes to multiple days; the No DAC version omits the linker and the prolonged albumin binding. The two compounds have different pharmacokinetic profiles and different appropriate use cases. CJC-1295 nDAC was originally developed at ConjuChem, Inc., as the parent platform for the DAC-modified version that progressed to Phase 2 trials. The compound is not approved by any regulatory authority for human or veterinary use.

Compound identification

Nomenclature and synonyms

The compound is referred to in the literature as CJC-1295 (No DAC), CJC-1295 nDAC, modified GRF(1-29), Mod-GRF, or simply tetrasubstituted GRF(1-29). The CAS number is 863288-34-0. The "CJC-1295" designation derives from the original ConjuChem development code; the company filed Phase 2 trials in the late 2000s with the DAC-modified version and disclosed both forms in the patent literature.

A persistent point of confusion in the research-grade market is the distinction between CJC-1295 No DAC and CJC-1295 with DAC. The two compounds share the identical 29-residue tetrasubstituted GRF sequence, but the DAC version carries a maleimidopropionic acid moiety covalently attached at the C-terminal lysine that binds serum albumin, extending the plasma half-life from approximately 30 minutes (No DAC) to multiple days (with DAC). The biological consequences are markedly different: the No DAC version produces pulsatile GH release; the DAC version produces sustained elevation of basal GH and IGF-1. Investigators should confirm which form has been supplied; mass spectrometry distinguishes the two readily (the DAC form has an additional ~280 Da from the maleimidopropionic linker before albumin conjugation).

Structural chemistry

The full sequence of CJC-1295 nDAC is Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH₂. Compared to native GHRH(1-29) (which begins Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser...), the four substitutions are at positions 2 (Ala to D-Ala), 8 (Asn to Gln), 15 (Gly to Gln in some numbering schemes), and 27 (Asn to Leu). The N-terminal D-alanine is the most important of the substitutions; it eliminates the DPP-4 cleavage site at the Tyr₁-Ala₂ bond, which is the primary degradation pathway for native GHRH and is responsible for the under-10-minute serum half-life of the native peptide.

The molecular weight is 3367.94 g/mol; the C-terminus is amidated, increasing lipophilicity and metabolic stability. The peptide is approximately 29 residues, near the upper bound of routine SPPS without segment condensation.

Physicochemical properties

CJC-1295 nDAC is supplied as a white lyophilized powder. The lot of record (Kodiac biolabs lot 20251211) conforms to this description. Solubility in water and bacteriostatic water is high; concentrations up to 5 mg/mL are routinely prepared without precipitation. The peptide is also soluble in 0.9 percent saline, PBS, and standard biological buffers. Solubility in pure DMSO is poor.

The peptide is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months under standard light protection. Reconstituted solutions in bacteriostatic water are stable for at least 30 days at 2 to 8 degrees Celsius. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in the ConjuChem GRF program

CJC-1295 emerged from a program at ConjuChem, Inc., to develop long-acting GHRH analogs with predictable pharmacokinetics suitable for once-daily or less-frequent dosing. The company's drug affinity complex (DAC) platform attached a maleimidopropionic acid moiety to the C-terminal lysine, which then formed a covalent bond with cysteine-34 of serum albumin upon administration. The resulting albumin-bound conjugate has a half-life on the order of several days, dictated by albumin's natural half-life rather than peptide clearance.

The four point substitutions at positions 2, 8, 15, and 27 were optimized in parallel with the DAC chemistry to address chemical stability and DPP-4 resistance. The "No DAC" version was disclosed alongside the "with DAC" version in the patent literature and represents the tetrasubstituted GHRH(1-29) sequence without the albumin-binding extension.

Clinical translation

CJC-1295 with DAC was advanced through Phase 1 and Phase 2 trials by ConjuChem in the mid-2000s for adult GH deficiency, lipodystrophy, and HIV-associated wasting. Sustained elevations of GH and IGF-1 were demonstrated; tolerability was generally good. Development was subsequently discontinued for commercial reasons, although the compound retains research interest and has appeared in research-grade vendor literature continuously since 2010.

CJC-1295 No DAC has not been advanced through formal clinical trials. The pharmacokinetic and pharmacological case for the No DAC form is the pulsatile GH release pattern that more closely mimics endogenous physiology, in contrast to the sustained elevation produced by the DAC form. Research-grade investigators have generally favored the No DAC form for stack work with Ipamorelin or other GHS compounds, where pulsatile rather than sustained stimulation is the goal.

Mechanism of action

GHRH receptor agonism

The principal mechanism is agonism of the growth hormone-releasing hormone receptor (GHRHR), a Gs-coupled GPCR expressed at high density on anterior pituitary somatotrophs. Receptor activation triggers cyclic AMP elevation, protein kinase A activation, and a sequence of transcriptional and post-translational events that culminate in exocytosis of stored growth hormone. The receptor selectivity is high; CJC-1295 nDAC does not engage GHS-R1a (the ghrelin receptor, the target of Ipamorelin and GHRP-2), GLP-1R, GIPR, or other related GPCRs at pharmacologically relevant concentrations.

The four substitutions in CJC-1295 nDAC are designed to preserve receptor specificity while improving metabolic stability. The N-terminal D-alanine substitution at position 2 is the only one with a substantial effect on serum half-life; the other three substitutions are stability optimizations rather than pharmacokinetic improvements. The biological half-life of CJC-1295 nDAC at the GHRH receptor is approximately 30 to 60 minutes, considerably longer than native GHRH (under 10 minutes) but substantially shorter than the DAC form (several days).

Synergy with GHSs

Co-administration of CJC-1295 nDAC with a GHS-R1a agonist (Ipamorelin, GHRP-2, MK-0677) produces a GH pulse substantially larger than either compound alone, on the order of 2 to 3 times the additive expectation. The synergy reflects the convergence of two distinct pituitary signaling pathways (Gs/cAMP for GHRHR, Gq/IP3 for GHS-R1a) and the additive effect of stimulating both pathways simultaneously. This synergy is the rationale for the most-cited research-grade GHS stack: CJC-1295 nDAC paired with Ipamorelin.

IGF-1 axis effects

Repeated GH pulsing over a multi-day timeframe drives systemic increases in insulin-like growth factor 1 (IGF-1) production from the liver. The IGF-1 increase produced by CJC-1295 nDAC alone is modest (5 to 20 percent increase over baseline at standard research-grade doses) and is substantially augmented in stack with a GHS-R1a agonist. Sustained IGF-1 elevation is characteristic of the DAC form rather than the No DAC form; the pulsatile dosing of CJC-1295 nDAC produces transient IGF-1 elevation that returns to baseline between pulses.

Limits of the mechanistic model

The pharmacological mechanism is well characterized at the receptor and signaling level. The downstream physiological effects are well documented for short-term GH and IGF-1 release. The longer-term consequences of repeated pulsatile GHRHR stimulation are less well characterized than for the DAC form (which has a Phase 2 clinical record). Investigators should treat the published research-grade dose ranges and stack ratios as approximate guidance rather than validated dosing.

Pharmacokinetics

Routes of administration

Subcutaneous and intramuscular administration are the standard parenteral routes. Both produce predictable absorption with peak plasma concentrations within 30 to 60 minutes. Oral bioavailability is poor due to peptidase degradation. Intravenous administration produces the most rapid pharmacological effect but does not extend the duration of GH release. The peptide does not benefit from sustained-release formulation in the No DAC form; the pulsatile profile is the point.

Plasma half-life

The plasma half-life of CJC-1295 nDAC is approximately 30 minutes following parenteral administration, considerably longer than native GHRH (under 10 minutes). The terminal elimination phase reflects peptidase clearance from circulation. The duration of the GH pulse triggered by a single dose is approximately 2 hours.

Metabolism and excretion

CJC-1295 nDAC is hydrolyzed by serum and tissue peptidases. The N-terminal D-alanine substitution eliminates DPP-4 cleavage at the Tyr1-Ala2 bond, which is the dominant degradation pathway for native GHRH. Other peptidase cleavage sites remain operational, including endopeptidase cleavage in the central region. Major metabolites are biologically inactive. Renal excretion of intact peptide and shorter fragments is the primary clearance route.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 1 to 100 micrograms per kilogram subcutaneously, with the bulk of pharmacology studies clustering around 5 to 20 micrograms per kilogram per dose. Allometric scaling to human equivalent doses places the equivalent human exposure in the range of 0.7 to 14 micrograms per kilogram per dose, or approximately 50 to 1000 micrograms per dose for a 70 kg subject. The dose range commonly cited in research-grade vendor literature (100 micrograms per research subject, two to three times daily, in stack with 100 micrograms Ipamorelin) is at the upper end of the allometric range and is established by the GHS-R1a synergy rather than by CJC-1295 nDAC monotherapy efficacy.

Pulsatile dosing (one to three pulses spaced through the day) is preferred. Sustained CJC-1295 nDAC administration in continuous infusion produces partial GHRHR desensitization and reduces the GH pulse amplitude over 48 to 72 hours. The pulsatile profile mimics endogenous GHRH physiology and avoids tachyphylaxis. Investigators should treat the published research-grade dose ranges as approximate guidance.

Sourcing and quality verification

Synthesis route

CJC-1295 nDAC is produced by solid-phase peptide synthesis using Fmoc chemistry. The 29-residue length is at the upper bound of routine SPPS and the synthesis is technically demanding. The principal challenges are coupling efficiency in the central segment, which contains a stretch of similar hydrophobic residues (Leu-Leu-Gln-Asp-Ile-Leu) that are prone to chain aggregation on the resin during synthesis, and stereochemical preservation of the D-alanine at position 2.

The lot of record (Kodiak biolabs lot 20251211) was synthesized by the supplier of record and shipped in lyophilized acetate salt form. The vendor analytical report records 99.8 percent purity by HPLC (vendor COA value) with a supplementary HPLC report at 99.51 percent.

Common adulterants and impurities

The research-grade CJC-1295 nDAC supply chain has documented patterns of sub-standard product. Reported issues include:

1. Substitution of the No DAC form with the DAC form, or vice versa, without disclosure. The two compounds have different molecular weights (3367.94 for No DAC; approximately 3650 Da for DAC before albumin conjugation) and different biological profiles. Mass spectrometry distinguishes them readily.
2. Substitution of native GHRH(1-29) for the tetrasubstituted analog, producing a peptide with markedly shorter half-life and susceptibility to DPP-4 cleavage. Mass spectrometry distinguishes the two (the native sequence is approximately 70 daltons lighter due to the four substitutions).
3. Deletion sequences from incomplete coupling in the central hydrophobic segment. These shorter peptides are inactive and inflate apparent purity if they co-elute with the parent peak.
4. Epimerization at the D-alanine position during prolonged synthesis, producing a peptide of correct mass but with restored DPP-4 susceptibility. Chiral HPLC is required to detect this.

5. Excess acetate or trifluoroacetate counterions inflating apparent mass by 5 to 12 percent.
6. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC and mass spectrometry on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm and 280 nm, is the standard purity assay. Identity confirmation by LC-MS yields a series of multiply charged ions; the $[M+3H]^{3+}$ peak at approximately 1124 m/z is convenient. The acceptance criteria are: total purity above 98.0 percent at both wavelengths, identity confirmation within 0.5 ppm of theoretical mass, and absence of major impurity peaks above 0.5 percent of the parent peak.

Reconstitution and handling

Solvent system

CJC-1295 nDAC dissolves readily in water, bacteriostatic water, and 0.9 percent saline. The standard reconstitution protocol uses bacteriostatic water (0.9 percent benzyl alcohol preservative) for any solution intended to be stored beyond a single use. For acute in vitro experiments where preservative is undesired, sterile water for injection or PBS works. DMSO is not the appropriate vehicle.

Reconstitution protocol

Add the calculated volume of solvent slowly along the side wall of the vial. A 5 mg vial reconstituted in 2 mL produces a 2.5 mg/mL solution; in 1 mL produces a 5 mg/mL solution suitable for low-volume subcutaneous injection. Allow the vial to rest at room temperature for 60 to 90 seconds, then gently swirl until the powder fully dissolves. The peptide is highly soluble; full dissolution is typically complete within 90 seconds.

Storage stability

Lyophilized CJC-1295 nDAC in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted solutions: stable at 2 to 8 degrees Celsius for at least 30 days. Aliquot working solutions to avoid freeze-thaw cycles. Reconstituted solutions should not be stored at room temperature beyond 24 hours.

Stack interaction considerations

The most-cited research-grade GHS stack is CJC-1295 nDAC paired with Ipamorelin, typically 100 micrograms each pulsed together two to three times daily. The mechanistic basis is the synergy between GHRHR (Gs/cAMP) and GHS-R1a (Gq/IP3) signaling pathways, which produces a GH pulse 2 to 3 times the additive expectation. The pulsatile profile of both peptides combines well; sustained dosing of either compound erodes the synergy through receptor desensitization.

Combination with the DAC form of CJC-1295 in the same dosing regimen is generally not recommended because the two forms produce qualitatively different physiology (pulsatile vs. sustained). Co-administration of both forms at therapeutic doses produces a hybrid profile that is rarely the experimental goal.

Combination with Tesamorelin (a tesamorelin GHRH analog approved for HIV-associated lipodystrophy) is not commonly cited; the two compounds occupy similar receptor space and do not synergize the way GHRH analogs synergize with GHS-R1a agonists.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. CJC-1295 nDAC has no documented receptor-level interactions with conventional small-molecule pharmacotherapy.

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