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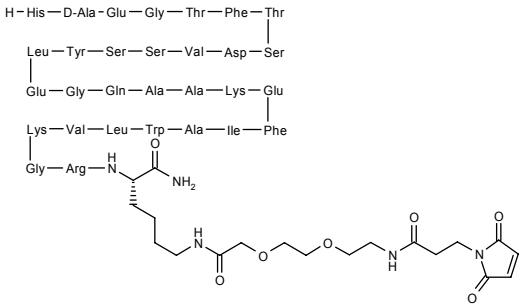
CJC-1131

Agent for Type 2 Diabetes
Glucagon-Like Peptide-1 (GLP-1) Analogue

DAC™:GLP-1

L-Histidyl-D-alanyl-L-α-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-α-glutamylglycyl-L-glutaminyl-L-alanyl-L-alanyl-L-lysyl-L-α-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-lysylglycyl-L-arginyl-N^6-[2-[2-[2-[3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propionamido]ethoxy]ethoxy]acetyl]-L-lysinamide



$C_{168}H_{254}N_{44}O_{52}$
Mol wt: 3722.0797
CAS: 532951-64-7
EN: 285272

Abstract

Glucagon-like peptide-1 (GLP-1) has significant effects on insulin secretion and glucose regulation and levels of this gastrointestinal hormone are reduced in type 2 diabetes. However, exogenous GLP-1 is rapidly degraded by enzymatic cleavage and GLP-1 analogues are currently under investigation as treatments for this metabolic disorder. CJC-1131 is covalently bound to serum albumin *in vivo* and is thereby protected from degradation. Preclinical studies have demonstrated that CJC-1131 displays a spectrum of activity similar to GLP-1, with long-term control of hyperglycemia and inhibition of gastric emptying in rats and dogs, and an extended albumin-adopted pharmacokinetic profile. Safety studies in humans, dogs and rats also demonstrated that this compound is not associated with immunogenic or toxic effects. Clinical investigations have indicated that CJC-1131 significantly reduces glycemia in type 2 diabetic patients and enhances the metformin-induced reduction in glycosylated hemoglobin. A novel diluent for CJC-1131 has resulted in improvement in the tolerability profile of the compound by reducing the incidence of nausea and vomiting.

Synthesis

CJC-1131 is synthesized by standard methods of solid-phase peptide chemistry. *N*-Fmoc-2-[2-(2-aminoethoxy)ethoxy]acetic acid is introduced into the sequence in the same manner as an amino acid, followed by maleinimidopropionic acid (1, 2).

Introduction

There are currently 4 different classifications of diabetes mellitus: type 1, type 2, gestational and maturity-onset diabetes of the young (MODY). Type 2 diabetes (previously known as non-insulin-dependent diabetes mellitus, or NIDDM), or adult-onset diabetes, accounts for over 90% of the diabetic population in the Western world. Risk factors for type 2 diabetes include age, obesity, physical inactivity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance and race/ethnicity (3). Type 2 diabetes arises when the body is unable to effectively use the insulin it produces, even though it produces the hormone in sufficient quantities (4). As a result, persistent hyperglycemia ensues, which can contribute to a variety of acute or chronic complications.

The World Health Organization (WHO) reports 177 million patients with diabetes worldwide and the incidence is increasing by 6% annually in the United States, and more so in developing countries (5). This disorder shows no signs of abating, as the WHO predicts that by the year 2025 the prevalence of this metabolic syndrome will be nearly 300 million. This increase is the direct result of an aging population, unhealthy diet, obesity and sedentary lifestyles (6).

Glucagon-like peptide-1 (GLP-1) has significant effects on insulin secretion and glucose regulation. This gastrointestinal hormone, along with glucose-dependent insulinotropic peptide (GIP, or gastric inhibitory peptide),

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constitutes the class of molecules referred to as the incretins. Incretins enhance insulin secretion in response to oral glucose (7). In addition to its glucose-dependent insulinotropic effect, GLP-1 also delays gastric emptying and suppresses glucagon secretion (7, 8). Studies have shown that the GLP-1 response is decreased in type 2 diabetes (9, 10) and that i.v. administration of exogenous GLP-1 to type 2 diabetic patients is associated with a normalization of blood glucose levels (11, 12). However, the glucose-lowering effect of GLP-1 is rapidly terminated as a consequence of enzymatic cleavage by dipeptidyl-peptidase IV (DPP IV) (13), making it an ineffective therapeutic. Thus, GLP-1 analogues that are resistant to DPP IV degradation are attractive candidates for the treatment of type 2 diabetes (14-16). Table I outlines GLP-1 analogues currently under development.

CJC-1131 (DAC™:GLP-1) is a stable synthetic GLP-1 analogue that is protected from degradation by DPP IV by substitution of D-Ala^8 in place of L-Ala^8 and by the addition of a reactive moiety to the *C*-terminus which results in its covalent binding to human serum albumin *in vivo*. The compound was developed using ConjuChem's DAC™ (Drug Affinity Complex) technology enabling conjugation of a drug to albumin and thereby extending the half-life of the drug to that of albumin (approximately 15 days). Preclinical and clinical investigations of CJC-1131 have demonstrated that it represents a promising therapeutic strategy for type 2 diabetes (2, 15, 16).

Pharmacological Actions

A series of initial *in vitro* studies investigated GLP-1R binding and bioactivity of several GLP-1(7-36) analogues. This study revealed that CJC-1131 demonstrated the best combination of receptor binding (IC_{50} = 108 nM) and bioactivity (increase in cAMP production in human GLP-1R-expressing CHO cells: EC_{50} = 15 nM, E_{max} = 94%) (2).

Other *in vitro* studies also demonstrated that CJC-1131 binds specifically to human serum albumin in a 1:1 ratio. Nonspecific binding to the extracellular matrix of subcutaneous proteins was not evident, with minimal binding to IgG and fibrinogen (17).

CJC-1131 lowered blood glucose levels in wild-type but not GLP-1R$^{-/-}$ mice. In diabetic *db/db* mice, CJC-1131 significantly lowered basal glucose and glycemic excursions following an oral glucose challenge for up to 12 h. Repeated administration twice daily for 4 weeks to *db/db* mice with severe diabetes and insulin resistance also significantly lowered glycemic excursions, fed glucose levels and food intake, increased pancreatic proinsulin mRNA and stimulated islet cell proliferation and growth. The effects on glucose levels and proinsulin mRNA persisted even after discontinuation of treatment (18, 19).

In vivo studies in rats revealed that CJC-1131, like GLP-1, significantly inhibited gastric emptying (20).

Pharmacokinetics and Metabolism

In human plasma stability experiments, the native GLP-1 sequence was rapidly hydrolyzed to the inactive GLP-1(9-36) metabolite, whereas no metabolites were generated from CJC-1131. *In vivo* studies have demonstrated that CJC-1131 selectively binds to albumin and exhibits an extended pharmacokinetic profile, with a terminal half-life of 15-20 h in rodents (21). *In vivo* whole-body imaging to assess the dynamics of CJC-1131 distribution in rats revealed that, within 48 h of s.c. administration, less than 3% remained at the injection site (17).

The pharmacokinetic profile of CJC-1131 was also examined in healthy volunteers administered single doses of 1.5-20.5 mg/kg s.c. Mean t_{max} ranged from 23 to 76 h, with a long elimination half-life (9.2-14.7 days). C_{max} and AUC appeared to be proportional to dose. The data suggest a possible multicompartmental pharmacokinetic profile and indicate that weekly administration of CJC-1131 may be sufficient to maintain sustained circulating levels of the agent (22).

Healthy subjects and patients with type 2 diabetes were administered single s.c. doses of CJC-1131 or placebo to evaluate the pharmacokinetics of CJC-1131. Peak plasma levels of 1.5-9.5 μg/kg were dose-proportional, with a half-life of 9.5-15.5 days in healthy subjects and of 5.4-17.7 days in patients (23).

Toxicity

The acute and subchronic toxicity of CJC-1131 was investigated in rats and dogs administered doses (0.2-8.0 mg/kg) exceeding the expected therapeutic range. CJC-1131 decreased food and water intake, fecal output and body weight gain, effects consistent with the known action of GLP-1, but no effects on survival and no CNS or cardiovascular toxicity or laboratory abnormalities were detected (20, 24-26).

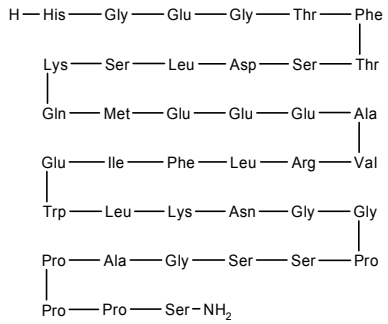
No immunogenicity was observed in a 3-month toxicity study in dogs and studies in healthy volunteers and diabetic patients confirmed the lack of immunogenicity of CJC-1131 (27).

Clinical Studies

In a randomized, double-blind, placebo-controlled study, 22 patients with type 2 diabetes were treated with CJC-1131 for 14 days as a daily injection of 2, 4 or 8 μg/kg, or for 20 days at a dose of 12 μg/kg. In general, the treatment was well tolerated and there were no signs of immunogenicity. Mild nausea and vomiting occurred in some cases, as expected with GLP-1 agents. The treatment reduced glycemia in a dose-dependent manner, with a significant mean 7-point glycemia decrease of up to 35% and a mean decrease in fasting plasma glycemia of up to 31% at the highest dose. At this dose, premeal and 2-h postmeal glycemia declined to below 7 and 11.1

Table I: GLP-1 analogues under active clinical development (from prous Science Integrity®).

Drug	Source	Phase
1. Exenatide (Byetta™)	Amylin/Lilly	L-2005
2. CJC-1131	ConjuChem	II
3. Liraglutide	Novo Nordisk	II
4. AVE-0010/ZP-10	Sanofi-Aventis/Zealand Pharma	II
5. BIM-51077/R-1583/ITM-077	Ipsen/Roche/Teijin	I/II



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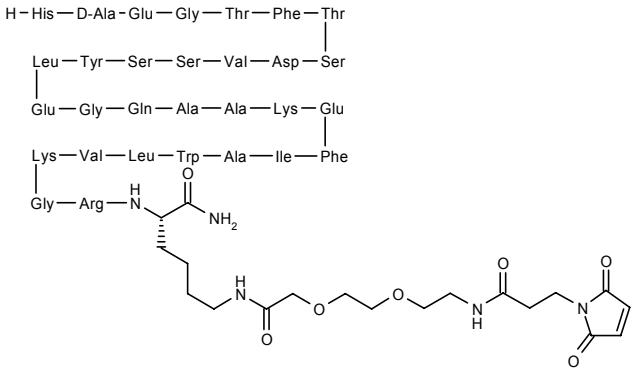

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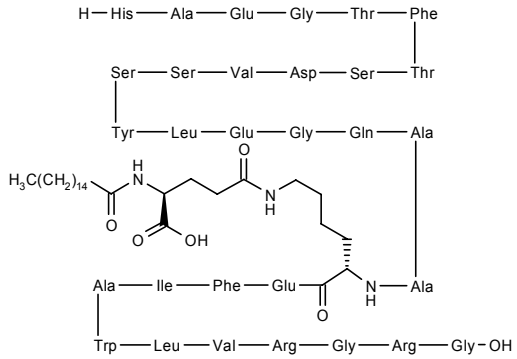

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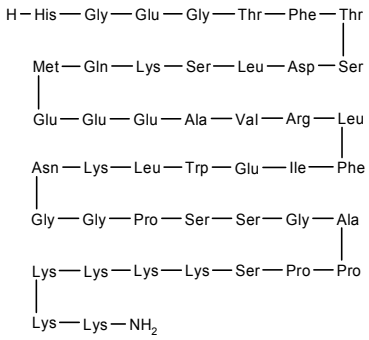

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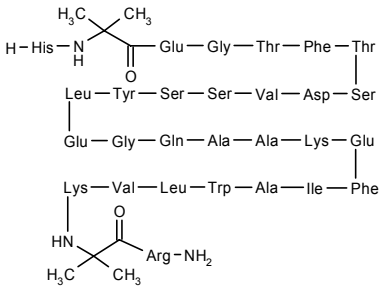

(5)

mmol/l in 62.5% and 50% of patients, respectively. No cases of hypoglycemia were observed and body weight was reduced dose-dependently by 1.7-3 kg (28).

An open-label clinical trial compared the efficacy and safety of different CJC-1131 regimens. Patients diagnosed with type 2 diabetes were given increasing doses of CJC-1131 once daily for 4 weeks and were subsequently randomized to receive CJC-1131 once daily, 2 or 3 times a week, or once weekly for 8 weeks. An interim analysis conducted on the first 48 patients to complete the 4-week dose-titration regimen revealed that CJC-1131 reduced glycosylated hemoglobin (HbA1c) levels by

an average of 0.6% and reduced body weight by ~2.3 kg. The most common adverse events were mild nausea and vomiting (29).

A multicenter, double-blind, placebo-controlled phase II trial determined the efficacy of a combination regimen of CJC-1131 plus metformin in the treatment of type 2 diabetes. Eighty-five patients with suboptimal glycemic control on metformin alone or metformin plus sulfonylurea were given metformin alone or supplemented with once-daily CJC-1131 (low dose: 1-4 μg/kg; high dose: 2-8 μg/kg) for 3 months. Compared to placebo, addition of high-dose CJC-1131 decreased plasma HbA1c levels by 0.85% and 1.30%, respectively, in patients who previously received metformin and metformin plus sulfonylurea treatments. Nausea and vomiting were the most common adverse events reported among the 54 patients included in the high-dose group, but 90% of the cases reported were mild (30, 31).

A number of diluents have also been screened clinically in an attempt to improve drug stability and decrease the incidence of adverse events. The incidence of nausea and vomiting was compared in healthy volunteers and type 2 diabetic patients following a single dose of CJC-1131 (150 μg) with the current (n=45) and a newly developed diluent (n=12). Nausea and vomiting occurred in 42.2% (n=19) and 0% of those subjects receiving CJC-1131 with the current and novel diluent, respectively. ConjuChem intends to conduct toxicology and dose-ranging studies with this new diluent, to be followed by a pivotal phase IIb trial with CJC-1131 plus metformin in diabetes (30, 31).

Source

ConjuChem, Inc. (CA).

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