

CJC-1131 ConjuChem

Nick Giannoukakis

Address

University of Pittsburgh School of Medicine
Diabetes Institute
3460 Fifth Avenue
Pittsburgh
PA 15213
USA
Email: ngiann1@pitt.edu

Current Opinion in Investigational Drugs 2003 4(10):1245-1249
© Current Drugs ISSN 1472-4472

ConjuChem is developing CJC-1131, a drug affinity complex conjugate of glucagon-like peptide 1 for the potential treatment of type 2 diabetes. In August 2003, a phase I/II trial was completed and a phase II trial was expected to begin in October.

Introduction

The ever-increasing incidence of diabetes means that new therapies and approaches are needed to treat this disorder. Recent interest in bioactive peptides has spawned efforts culminating in the discovery of a class of proteins termed incretins [478031]. The production and release of these proteins, originally identified in the gut, is stimulated by insulin at physiological concentrations in the presence of elevated blood glucose concentrations. The prototype incretin of pharmaceutical interest is glucagon-like peptide (GLP)-1, produced from the endocrine L-cells of the gut in response to food intake [306812], [362275]. GLP-1 functions as an incretin hormone promoting insulin secretion, and its glucoregulation activity has led to its consideration as a potential therapeutic agent in the treatment of type 2 diabetes. A number of studies have confirmed its potential as a glucoregulator and as an appetite regulator [233337], [306810], [478018], [478025], [478028]. The short duration of action of GLP-1 *in vivo* (due primarily to NH₂-terminal cleavage and inactivation by dipeptidyl peptidase (DPP)-IV) [233314], [505939] has, however, precluded the maintenance of therapeutic levels by subcutaneous dosing, prompting the search for analogs with longer durations of action [439496], [478018], [478025], [478028].

Injectable GLP-1 analogs enhance glucose-dependent insulin synthesis and secretion in the pancreas, increase peripheral glucose utilization and decrease insulin resistance, lower postprandial glucose spikes by slowing down gastric emptying, decrease glucagon production and hepatic glucose genesis, and act as β -cell growth factors [478018], [478025], [478028]. GLP-1 analogs have demonstrated very good safety profiles with few side effects compared with currently prescribed antidiabetic agents. Insulin secretion is only stimulated in the presence of hyperglycemia; therefore, the drugs have the potential to induce normoglycemia effectively. GLP-1 analogs appear to have positive effects on type 2 diabetes-related hyperlipidemia and may promote moderate weight loss. As mentioned, the promise of GLP-1 analogs is counterbalanced by their limited serum half-life (approximately 5 min), which is due to the activity of peptidases [478018], [478025], [478028].

Originator ConjuChem Inc

Status Phase II Clinical

Indications Non-insulin dependent diabetes

Actions Glucagon-like peptide 1 agonist, Hypoglycemic agent, Insulin metabolism modulator

Synonyms DAC:GLP-1

CJC-1131 is a peptidase-resistant GLP-1 analog which selectively and covalently binds to serum albumin using drug affinity complex (DAC) technology developed by ConjuChem. This enables a long plasma elimination half-life of approximately 20 days. The DAC conjugates selectively with albumin, yet still retains full biological activity [374863]. CJC-1131 is thus expected to be as potent as the stabilized GLP-1 analog from which it was derived, and to retain the pharmacokinetic (PK) profile of the DAC conjugate [410194].

Synthesis and SAR

In order to circumvent the rapid cleavage of GLP-1 and thus prolong the *in vivo* half-life, amino acid substitutions can be made that reduce the affinity of GLP-1 for DPP-IV. In the case of this DAC-GLP-1 affinity complex, it was also important that CJC-1131 bound covalently to albumin. To achieve these effects, GLP-1 was subjected to a single amino acid substitution of L-Ala⁸ to D-Ala⁸ at position 2 and a Lys³⁷ addition to the C-terminus with selective attachment of a [2-[2-[2-maleimidopropionamido]ethoxy]ethoxy]acetamide to the ϵ amino group of Lys³⁷ to create CJC-1131 [498249].

CJC-1131 was produced using solid-phase peptide synthesis utilizing 9-fluorenylmethyloxycarbonyl chemistry. It binds selectively and irreversibly to Cys³⁴ of circulating serum albumin. Albumin is known to exhibit a longer half-life *in vivo* (approximately 19 days in humans [240408]), which is much longer than the half-life of short regulatory peptides, such as GLP-1. In rodents, CJC-1131 bound purified human serum albumin with an efficiency of approximately 98%. The CJC-1131-albumin complex bound to the human GLP-1 receptor with nanomolar affinity and stimulated cAMP production in human GLP-1 receptor-transfected CHO cells with near identical activity to native GLP-1 [454095].

Preclinical Development

In vitro the CJC-1131-albumin conjugate bound the GLP-1 receptor and activated cAMP formation in heterologous fibroblasts expressing the GLP-1 receptor. The conjugate had a similar potency to native GLP-1, with EC₅₀ values of 11 to 13 and 13 nM, respectively. The displacement of [¹²⁵I]GLP-1 by native GLP-1 and CJC-1131 was also similar over a range of CJC-1131 concentrations, with K_i values of 5.16 and 12 nM, respectively [498249].

Oral glucose tolerance testing in normal rodents demonstrated that the ability of CJC-1131 to reduce blood glucose to normal following a glucose challenge was nearly

identical to the parent GLP-1 peptide. In diabetic *db/db* mice, CJC-1131 normalized blood glucose for up to 24 h after an oral glucose load. Basal glucose levels were also stabilized at physiological levels for the same time period [410194]. Acute administration of CJC-1131 to normal Wistar rats or CD1 mice during intraperitoneal or oral glucose challenge increased circulating insulin and decreased glycemic excursion. Long-term administration of CJC-1131 to C57BL/6 mice lowered fasting and postprandial blood glucose over a 4-week period [454256]. CJC-1131 was inactive in GLP-1 receptor-deficient mice, yet significantly reduced glycemic excursion following oral glucose tolerance testing in *db/db* mice. Basal glucose and glycemic excursion remained reduced 12 h following CJC-1131 administration [454479].

The safety and efficacy of CJC-1131, native GLP-1, metaclopramide and CCK-8 were compared in a study of gastric emptying in rats. CJC-1131 and GLP-1 significantly inhibited gastric emptying, whereas metaclopramide increased gastric emptying in control experiments. Single and escalating CJC-1131 dose regimens (0.2 to 8.0 mg/kg) produced a decrease in food and water intake and a decrease in fecal output, particularly at the higher doses [454061].

The efficacy of CJC-1131 to treat severe experimental diabetes and insulin resistance was examined in 9-week-old *db/db* mice treated with CJC-1131 (25 µg) or saline twice daily for 4 weeks. Following oral and intraperitoneal glucose challenge, CJC-1131 significantly reduced glycemic excursion ($p < 0.01$ to 0.05); however, levels of glucose-stimulated insulin were comparable in control- and CJC-1131-treated groups. CJC-1131 significantly reduced food intake in short-term, 24-h feeding studies in non-diabetic wild-type and *db/db* mice; however, over the 4-week study period, body weight was not significantly lowered. Weekly glucose levels were significantly lower in CJC-1131-treated wild-type and *db/db* mice over the study period and remained significantly lower at 1 week, but not 2 weeks following discontinuation of CJC-1131 administration. The levels of pancreatic pro-insulin mRNA transcripts were markedly increased in *db/db* mice treated with CJC-1131 for 4 weeks, but returned to control levels 3 weeks after discontinuation of therapy [454479], [498249].

Metabolism and Pharmacokinetics

Human plasma stability experiments demonstrated that native GLP-1 is rapidly hydrolyzed to the inactive GLP-1(9-36) metabolite; in contrast, no metabolites were generated from CJC-1131. PK studies in rodents demonstrated that CJC-1131 binds selectively to rat albumin *in vivo*. GLP-1 radioimmunoassays indicated a terminal half-life of 15 to 20 h (consistent with that of the DAC conjugate), volume of distribution at steady state ($V_{d_{ss}}$) value of 150 ml/kg and systemic clearance rate of between 0.1 and 0.6 ml/min/kg, suggesting exclusion from the liver and kidney [410194], [454095].

A phase I study was conducted to determine the PK profile of CJC-1131 following administration of a single subcutaneous dose to healthy human volunteers. CJC-1131

(1.5 to 20.5 µg/kg) was administered to seven sequential cohorts of healthy male and female volunteers (five to six individuals per cohort) and revealed an average T_{max} ranging from 23 to 76 h; C_{max} and AUC_{∞} values suggested dose proportionality. CJC-1131 exhibited a multicompartmental PK profile and the elimination half-life was generally slow, with group averages ranging from 221 to 353 h [492844].

Toxicity

The toxicity of CJC-1131 was assessed using a range of drug doses considerably above the expected therapeutic dosing range for GLP-1 analogs *in vivo*. To assess the acute toxicity of CJC-1131, CD rats were administered single doses (0.75 to 6 mg/kg sc); the drug was generally well tolerated, with decreased fecal output and decreased food and water consumption at all doses. A sub-chronic study in which CJC-1131 (0.12 to 3 mg/kg sc) was administered to rats every other day for 14 days gave similar results of decreased fecal output, reduced food intake and reduced water consumption compared with control animals. At 3 mg/kg, there was also a dose-dependent decrease in body weight gain. There were no other effects noted and minimal depletion of vacuoles in the cytoplasm of treated rats was observed. CJC-1131 was generally well tolerated at up to 3 mg/kg [498254].

The acute toxicity of CJC-1131 was also examined in beagle dogs following single subcutaneous doses (2 to 8 mg/kg). Clinical signs included decreased fecal output at doses of ≥ 4 mg/kg and emesis at 8 mg/kg; however, there were no treatment-related effects on survival, physical examination, blood pressure, organ weights, clinical pathology or gross necropsy. Decreased food consumption in both sexes and decreased water consumption in male rats was attributed to the pharmacological action of GLP-1. A sub-chronic study of CJC-1131 (0.25 to 4 mg/kg), administered every other day for 14 days, produced a slight dose-dependent weight loss and transient decreases in food and water consumption compared with control animals. Mild reversible inflammation at the injection site in all dose groups was also observed. The authors concluded that CJC-1131 was generally well tolerated in beagle dogs up to 4 mg/kg every other day [454061], [498258].

A 7-day repeat dose administration study in rats demonstrated that CJC-1131 (2.4 mg/kg/day) was well tolerated, with decreases in food and water consumption and a 15 to 20% weight loss observed at the end of the study period. No abnormalities were detected in clinical pathology or biochemistry studies conducted during single- and multiple-dose regimens in either rats or dogs [454061].

Clinical Development

Phase I/II

Four phase I/II trials have been initiated, investigating single- and multidose subcutaneous administration, single-dose intravenous administration and re-challenge subcutaneous administration, to evaluate the immunogenicity risk of CJC-1131 [488830], [493231].

The multidose program was divided into two parts. In the first part, three cohorts consisting of both healthy volunteers and diabetic patients received 2, 4, 8 or 12 µg/kg/day of CJC-1131 for 14 days, and were then followed and assessed on safety, PK and preliminary efficacy parameters. The objective of the first part of the program was to build the plasma concentration of CJC-1131 to an efficacious level with minimal unwanted side effects. The second part of the study was aimed at determining the dosage required to maintain the efficacy with longer intervals between administrations [482594]. Patients (n = 9) received CJC-1131 at 2, then 4, then 8 µg/kg/day, each for 3 days, followed by 12 µg/kg/day for the next 11 days (ie, 20 days in total). Average mean daily glucose level and fasting glucose level were significantly reduced. Glucose normalization or near normalization was achieved in all patients in the cohort (both for the mean daily glucose level and the fasting glucose level); glucose excursions were also significantly reduced 7 days post-treatment. An average body-weight reduction of 3 kg occurred [502385].

In the immunogenicity trial in healthy volunteers (n = 12) and diabetic patients (n = 21), the former were previously exposed to CJC-1131 and received two re-challenge doses of 2 µg/kg 6 weeks apart. Patients received the drug subcutaneously every day for up to 20 days and were monitored for up to 70 days after receiving their last dose. There were no signs of clinical immunogenicity, specific IgG or IgE antibodies, lymphocyte activation, nor change in plasma concentration (no neutralizing antibodies) [502385].

The single-dose intravenous trial was designed to enroll type 2 diabetics (n = 30) in five cohorts of six patients each (five patients given CJC-1131 and one given placebo); each cohort was to receive an ascending dose (0.5, 1, 2, 4 or 8 µg/kg), and safety, tolerability, PKs and preliminary efficacy were assessed. If successful, ConjuChem plans to follow this trial with a multidose protocol [488830].

Side Effects and Contraindications

To date, the compound has been well tolerated in phase I/II trials. Side effects are consistent with other GLP-1 compounds and included mild nausea and vomiting. In the multidose studies, where only two cases of nausea were reported in the patient population, this symptom substantially decreased or was eliminated with repeat administration of CJC-1131. After 14 consecutive days of administration, there were no clinical or biological signs of immunogenicity or irritation at the injection site [493231], [502385].

Current Opinion

The use of insulinotropic drugs currently available for the treatment of diabetes, mainly sulfonylureas, is hampered by two major drawbacks, the risk of hypoglycemia and the loss of efficacy after several years of treatment. In conjunction with the inhibitory effects on gastric emptying and glucagon secretion, GLP-1 receptor stimulation appears to be a promising new treatment strategy for type 2 diabetes. The preclinical and clinical data on CJC-1131 demonstrate efficacy and safety; however, results of phase II trials will be pivotal in determining the ultimate outcome and utility of this agent. A number of other competing GLP-1 analogs are also currently in development and include the acylated albumin-bound GLP-1 analog liraglutide (Novo Nordisk A/S) and two exendin-4 derivatives (exenatide; Eli Lilly & Co/Amylin Pharmaceuticals Inc and ZP-10; Aventis SA). Exendin-4 is more potent at lowering glucose concentrations than human GLP-1 and has a longer half-life; clinical studies with exendin-4 derivatives have demonstrated their good activity and safety profile. Marketing will be a crucial determinant of commercial success of these agents, in addition to the ability to co-administer such agents with other glucoregulatory compounds.

Commercial Opinion

In September 2003, analysts at Dlouhy Merchant predicted the launch of CJC-1131 in 2008, with 2008 sales of US \$19.4 million [506488].

Development history

In July 2002, a phase I trial was initiated, with data expected by the end of 2002 [457323]. However, in October 2002, the company revealed that results would not be disclosed until the first half of 2003, as a result of the need to manufacture a reformulated clinical batch of the compound to complete the trial [466084]. In February 2003, ConjuChem resolved the formulation issues and resumed its single-dose phase I trial [479418]. In March 2003, ConjuChem initiated the multidose component of a phase I/II trial [482594], and in May 2003 began the final stages of the study [488830]. In August 2003, a phase I/II trial was completed and a phase II trial was expected to begin in October of the same year [502385].

Developer	Country	Status	Indication	Date	Reference
ConjuChem Inc	Canada	Phase II	Non-insulin dependent diabetes	19-MAR-03	482594
ConjuChem Inc	US	Phase II	Non-insulin dependent diabetes	27-MAY-03	488830

Literature classifications

Chemistry

Study Type	Result	Reference
Synthesis and SAR.	A single amino acid substitution of L-Ala ⁸ to D-Ala ⁸ at position 2 and a Lys ³⁷ addition to the C-terminus with selective attachment of a [2-[2-[2-maleimidopropionamido]ethoxy]ethoxy]acetamide to the ε amino group of Lys ³⁷ created CJC-1131.	498249

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Binding and activation of the GLP-1 receptor.	Heterologous fibroblasts transfected with GLP-1 receptor cDNA.	The CJC-1131 albumin conjugate bound the GLP-1 receptor and activated cAMP formation in heterologous fibroblasts expressing the GLP-1 receptor. Native GLP-1 exhibited an EC ₅₀ of 13 nM compared with 11 to 13 nM for CJC-1131.	498249
<i>In vitro</i>	Binding specificity of conjugate.	Radioligand competition assay.	The displacement of [¹²⁵ I]GLP-1 by native GLP-1 versus CJC-1131 was similar over a range of CJC-1131 concentrations (K _i = 5.16 nM for native GLP-1 versus 12 nM for CJC-1131).	498249
<i>In vivo</i>	Efficacy in reducing glucose levels.	Diabetic <i>db/db</i> mice.	CJC-1131 was effective for up to 24 h in normalizing blood glucose after an oral glucose load. Basal glucose levels were also stabilized at physiological levels over the same period.	410194
<i>In vivo</i>	Efficacy on gastric emptying and effect on food intake.	Single and escalating CJC-1131 dose regimens ranging from 0.2 to 8.0 mg/kg in normal rats.	CJC-1131 and GLP-1 significantly inhibited gastric emptying, decreased food and water intake, and decreased fecal output, particularly at the higher doses.	454061
<i>In vivo</i>	Safety and toxicity.	Normal rats and dogs administered CJC-1131.	No abnormalities were detected in clinical pathology or biochemistry studies conducted during single- and multiple-dosing regimens in either rats or dogs.	454061

Metabolism

Study Type	Effect Studied	Model Used	Result	Reference
<i>In vivo</i>	Pharmacokinetics.	Healthy human volunteers administered a single subcutaneous dose of CJC-1131 (1.5 to 20.5 mg/kg) in seven sequential cohorts (five to six individuals per cohort).	Average T _{max} ranged from 23 to 76 h. The elimination half-life was generally slow, with group averages ranging from 221 to 353 h. C _{max} and AUC _∞ values suggested dose-proportionality.	492844
<i>In vivo</i>	Pharmacokinetics.	Rats administered CJC-1131.	GLP-1 radioimmunoassays indicated a terminal half-life of 15 to 20 h, V _{dss} value of 50 ml/kg and systemic clearance rate of between 0.1 and 0.6 ml/min/kg.	454095

Clinical

Study Type	Model Used	Result	Reference
Safety and tolerability.	Phase I/II trial of single, increasing CJC-1131 doses to establish the minimal tolerated dose.	A single subcutaneous dose had an average half-life of 10 to 12 days and was well tolerated.	479418
Efficacy.	A multidose trial (n = 9) in which patients received escalating doses of CJC-1131 (2 to 12 µg/kg/day sc).	Average mean daily glucose levels and fasting glucose levels were significantly reduced. An average body weight reduction of 3 kg also occurred.	502385
Immunogenicity.	Phase I/II trial in type 2 diabetics and healthy volunteers (n = 33).	There were no signs of clinical immunogenicity, specific IgG or IgE antibodies, lymphocyte activation, nor change in plasma concentration of CJC-1131.	502385

Associated patent

Title Insulinotropic peptides with improved stability and longer duration of action and their value in the treatment of diabetes.

Assignee Conjuchem Inc/Benoit L'Archeveque

Publication WO-00069911 23-NOV-00

Priority US-00134406 17-MAY-99

Inventors Bridon DP, L' Archeveque B, Ezrin AM, Holmes DL, Leblanc A, St Pierre S.

Associated references

233314 **Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 *in vitro* and *in vivo* by dipeptidyl peptidase IV.** Kieffer TJ, McIntosh CH, Pederson RA *ENDOCRINOLOGY* 1995 **136** 8 3585-3596

233337 **Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man.** Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ *DIG DIS SCI* 1993 **38** 4 665-673

240408 **Serum albumin.** Peters T Jr *ADV PROTEIN CHEM* 1985 **37** 161-245

306810 **A role for glucagon-like peptide-1 in the central regulation of feeding.** Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP *et al NATURE* 1996 **379** 6560 69-72

306812 **Glucagon-like peptides.** Drucker DJ *DIABETES* 1998 **47** 2 159-169

362275 **Glucagon-like peptide 1 (GLP-1): An intestinal hormone, signalling nutritional abundance, with an unusual therapeutic potential.** Holst JJ *TRENDS ENDOCRINOL METAB* 1999 **10** 8 229-235

374863 **Product Pipeline.** ConjuChem Inc *COMPANY WORLD WIDE WEB SITE* 2000 July 18

410194 **ConjuChem Inc announces preclinical progression of its DAC:GLP-1 compound for type II diabetes.** ConjuChem Inc *PRESS RELEASE* 2001 May 23

439496 **Development of glucagon-like peptide-1-based pharmaceuticals as therapeutic agents for the treatment of diabetes.** Drucker DJ *CURR PHARM DESIGN* 2001 **7** 14 1399-1412

454061 **CJC-1131, the novel long acting GLP-1 analogue, delays gastric emptying and demonstrates safety and tolerability in preclinical testing.** Lawrence B, Wen SY, Jette L, Thibadeau K, Castaigne JP *DIABETES* 2002 **51** 2 A340-OR

454095 **The long-acting GLP-1 agonist CJC-1131 exhibits high potency and extended pharmacokinetics *in vivo*.** Bridon DP, Thibaudeau K, Archeveque BP, Pham H, Robitaille MF, Drucker DJ, Leger R, Castaigne JP *DIABETES* 2002 **51** 2 A378-P

454256 **Development and characterization of long-acting degradation resistant GLP-1-DAC compounds for the treatment of type 2 diabetes.** Thibaudeau K, Smith DC, Jette L, Castaigne JP, Bridon DP, Kim JG, Baggio LL, Drucker DJ *DIABETES* 2002 **51** 2 A471-P

454479 **The GLP-1-DAC analogue CJC-1131 upregulates insulin gene expression and exerts a memory effect on glycemic control in *db/db* mice.** Kim JG, Baggio LL, Drucker DJ *DIABETES* 2002 **51** 2 A1391-P

457323 **ConjuChem announces start of phase I trial for DAC:GLP-1, a type II diabetes drug candidate.** ConjuChem Inc *PRESS RELEASE* 2002 July 08

466084 **ConjuChem updates status of phase I trial for diabetes drug candidate.** ConjuChem Inc *PRESS RELEASE* 2002 October 07

478018 **Novel peptides under development for the treatment of type 1 and type 2 diabetes mellitus.** Baron AD, Kim D, Weyer C *CURR DRUG TARGETS IMMUNE ENDOCR METABOL DISORD* 2002 **2** 63-82

478025 **Insulinotropic actions of exendin-4 and glucagon-like peptide-1 *in vivo* and *in vitro*.** Parkes DG, Pittner R, Jodka C, Smith P, Young A *Metabolism* 2001 **50** 5 583-589

478028 **Glucagon-like peptide-1: A major regulator of pancreatic β -cell function.** Perfetti R, Merkel P *EUR J ENDOCRINOL* 2000 **143** 6 717-725

478031 **The entero-insular axis in type 2 diabetes - incretins as therapeutic agents.** Creutzfeldt W *EXP CLIN ENDOCRINOL DIABETES* 2001 **109** Suppl 2 S288-S303

479418 **ConjuChem resumes DAC:GLP-1 clinical program, provides updates.** ConjuChem Inc *PRESS RELEASE* 2003 February 20

482594 **ConjuChem's DAC:GLP-1 clinical program advances.** ConjuChem Inc *PRESS RELEASE* 2003 March 19

488830 **ConjuChem starts US trial for DAC(TM):GLP-1.** ConjuChem Inc *PRESS RELEASE* 2003 May 08

492844 **CJC-1131, a long acting GLP-1 derivative, exhibits an extended pharmacokinetic profile in healthy human volunteers.** Lawrence B, Dreyfus JF, Wen S, Guivarc'h PH, Drucker DJ, Castaigne J-P *DIABETES* 2003 **52** Suppl 6 Abs 534-P

493231 **ConjuChem reports positive preliminary DAC:GLP-1 results.** ConjuChem Inc *PRESS RELEASE* 2003 June 11

498249 **Development and characterization of a glucagon-like peptide 1-albumin conjugate: The ability to activate the glucagon-like peptide 1 receptor *in vivo*.** Jung-Guk K, Baggio LL, Bridon DP, Castaigne J-P, Robitaille MF, Jette L, Benquet C, Drucker DJ *DIABETES* 2003 **52** 3 751-759

498254 **CJC-1131, a long-acting GLP-1 analogue, is well tolerated in rats up to 14 days.** Lawrence B, Wen S, Dunn D, Iordanova V, Castaigne J *TOXICOL SCI* 2003 **72** S-1 49

498258 **CJC-1131, a long-acting GLP-1 analogue, exhibits safety and tolerability in dogs.** Wen S, Wilson S, Trebec D, Pham K, Castaigne J, Lawrence B *TOXICOL SCI* 2003 **72** S-1 48

502385 **ConjuChem's strong clinical results hit primary endpoints in type 2 diabetes trials.** ConjuChem Inc *PRESS RELEASE* 2003 August 21

502385 **ConjuChem's strong clinical results hit primary endpoints in type 2 diabetes trials.** ConjuChem Inc *PRESS RELEASE* 2003 August 21

505939 **Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum.** Mentlein R, Gallwitz B, Schmidt WE *EUR J BIOCHEM* 1993 **214** 3 829-835

506488 **Analyst evaluation of ConjuChem Inc.** Loe DW *DLOUHY MERCHANT GROUP* 2003 September 15 1-6