

Incretin-based therapies for type 2 diabetes mellitus

Julie A. Lovshin and Daniel J. Drucker

Abstract | Incretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus. These agents regulate glucose metabolism through multiple mechanisms, their use is associated with low rates of hypoglycemia, and they either do not affect body weight (dipeptidyl peptidase 4 inhibitors), or promote weight loss (glucagon-like peptide-1 receptor agonists). The success of exenatide and sitagliptin, the first therapies in their respective drug classes to be based on incretins, has fostered the development of multiple new agents that are currently in late stages of clinical development or awaiting approval. This Review highlights our current understanding of the mechanisms of action of incretin-based drugs, with an emphasis on the emerging clinical profile of new agents.

Lovshin, J. A. & Drucker, D. J. *Nat. Rev. Endocrinol.* 5, 262–269 (2009); doi:10.1038/nrendo.2009.48

Introduction

The observation that the incretin hormone glucagon-like peptide 1 (GLP-1) stimulates insulin release in response to an enteric glucose load in humans¹ was followed by major advances in our understanding of how GLP-1 regulates glucose metabolism.^{2,3} In addition, GLP-1—unlike the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP)—retains its glucose-regulatory actions in patients with diabetes mellitus. These findings led to the discovery and generation of structurally distinct GLP-1 receptor (GLP-1R) agonists, which mimic the actions of GLP-1 *in vivo* in humans.^{2–4} Furthermore, characterization of the essential role of dipeptidyl peptidase 4 (DPP-4) in the inactivation of bioactive GLP-1 and GIP^{5,6} promoted the development of orally available DPP-4 inhibitors, administration of which stabilizes both incretin hormones at physiologically active levels. Herein, we review the data from clinical trials that have assessed GLP-1R agonists and DPP-4 inhibitors (Table 1) and highlight emerging incretin-based therapies that are in the late stages of clinical testing.

Incretin action and incretin mimetics

Biologically active GLP-1_{7–36} amide is derived from proglucagon through post-translational processing. Proglucagon is generated throughout the small and large intestines in specialized intestinal L-cells, the majority of

which are located in the distal part of the small intestine and in the colon. GLP-1 is secreted at low basal rates in the fasting state, and its secretion is increased following nutrient ingestion. GLP-1 exerts its actions through binding to GLP-1R, a heptahelical transmembrane surface receptor that is expressed on pancreatic β cells. GLP-1R signaling increases the β cells' sensitivity to glucose, directly protects rodent and human pancreatic β cells from apoptotic cell death, and triggers proliferative pathways that lead to expansion of the β -cell mass in animal experiments. GLP-1 also suppresses glucagon secretion from pancreatic α cells, which reduces hepatic glucose production and delays transit of nutrients from the stomach to the duodenum via inhibition of gastric emptying.⁷

Additional, extrapancreatic functions of GLP-1 include its actions on the hypothalamus to promote satiety, which results in body weight loss during chronic GLP-1 administration. Although GIP also exerts potent incretin-like effects on β cells in healthy individuals, the actions of GIP are impaired in patients with diabetes mellitus, which limits the possibilities of its clinical use.⁸ Moreover, sustained GIP administration promotes expansion of the adipocyte mass and insulin resistance in diabetic rodents, whereas the effect of GIP on human adipocyte biology is uncertain. New evidence suggests that the insulinotropic actions of GIP may be partially restored in patients with diabetes mellitus in whom hyperglycemia has been corrected as a result of insulin administration.⁹ Hence, the therapeutic role, if any, of GIP in the treatment of patients with diabetes mellitus requires further clarification.

Continuous, subcutaneous administration of native GLP-1 to patients with type 2 diabetes mellitus (T2DM) lowers fasting and postprandial levels of glucose and HbA_{1c} effectively, and also results in weight loss.¹⁰

Department of Medicine, Samuel Lunenfeld Research Institute, Mt Sinai Hospital, University of Toronto, Toronto, Canada (JA Lovshin, DJ Drucker).

Correspondence: DJ Drucker, Mt Sinai Hospital, Samuel Lunenfeld Research Institute, 60 Murray Street, Mail Box 39, Toronto, ON M5T 3L9, Canada. d.drucker@utoronto.ca

Competing interests

D. J. Drucker has declared associations with the following companies: Amylin Pharmaceuticals, Arena Pharmaceuticals, Arisaph Pharmaceuticals, Conjuchem, Eli Lilly, Emisphere Technologies, GlaxoSmithKline, Glenmark Pharmaceuticals, Hoffman LaRoche, Isis Pharmaceuticals, Mannkind, Merck Research Laboratories, Metabolex, Novartis Pharmaceuticals, Novo Nordisk, Phenomix, Takeda and Transition Pharmaceuticals. See the article online for full details of the relationships.

J. A. Lovshin declared no competing interests.

However, the expense and inconvenience of continuous GLP-1 delivery, together with the rapid enzymatic inactivation of native GLP-1 peptide (the plasma half-life of native GLP-1 is shorter than 2 min *in vivo*) necessitated the development of alternative therapeutic approaches. Two different drug classes have emerged, both of which potentiate the actions of incretin hormones: peptide-based, degradation-resistant GLP-1R agonists, which have to be administered by subcutaneous injection; and orally administered DPP-4 inhibitors, which suppress the enzymatic inactivation of GLP-1 and GIP.⁴ Although both forms of incretin-based therapy exert their glucose-regulatory effects largely through potentiation of the actions of GLP-1, several key features distinguish the mechanisms of action of these agents. Whereas both therapies act on pancreatic islets to stimulate insulin secretion and inhibit glucagon secretion, GLP-1R agonists also inhibit gastric emptying and promote satiety, which leads to weight loss, as shown in clinical studies (Figure 1). By contrast, DPP-4 inhibitors also stabilize the level of bioactive GIP, which raises the possibility that these agents lower glucose levels in part through GIP-mediated stimulation of insulin secretion (Figure 2).⁹ Following the successful clinical introduction of the first GLP-1R agonist (exenatide) and the first DPP-4 inhibitor (sitagliptin), multiple DPP-4 inhibitors and GLP-1R agonists have reached the final stages of clinical development. In this Review, we discuss each class separately, with an emphasis on emerging new therapeutic agents.

GLP-1R agonists

Exenatide

The first GLP-1R agonist to be approved for human clinical use was exenatide, a synthetic form of the naturally occurring *Heloderma suspectum* peptide exendin 4. This peptide exhibits about 50% amino acid identity with human GLP-1 and is a potent agonist of human GLP-1R. As exendin 4 contains a glycine residue at position 2, it is resistant to degradation by DPP-4 and thus has an increased circulating half-life *in vivo*. Three pivotal, phase III clinical trials, each of 30 weeks duration, examined the efficacy of twice-daily injections of 5 µg or 10 µg exenatide in individuals who had T2DM that was inadequately controlled with a sulfonylurea and/or metformin.^{11–13} Substantial changes were demonstrated in HbA_{1c} levels (an increase of 0.86% with exenatide plus a sulfonylurea; decreases of 0.78% with exenatide plus metformin and of 0.8% with exenatide plus a sulfonylurea and metformin), in association with modest reductions in body weight from baseline values (of 1.6 kg, 2.8 kg and 1.6 kg, respectively) after 30 weeks of therapy with 10 µg exenatide twice daily. Exenatide lowered both fasting and postprandial glucose concentrations, and was generally well tolerated; mild nausea and vomiting were the most common adverse effects. Nausea tended to dissipate over time in the majority of treated individuals. Consistent with the glucose-dependent mechanisms of GLP-1 action, exenatide therapy in the absence of

Key points

- Incretins exert antidiabetic actions in a glucose-dependent manner
- Glucagon-like peptide 1 receptor (GLP-1R) agonists, but not dipeptidyl peptidase-4 (DPP-4) inhibitors, inhibit gastric emptying and might cause weight loss
- DPP-4 inhibitors can be administered orally and are well tolerated
- GLP-1R agonists must be administered by subcutaneous injection and commonly cause nausea

Table 1 | Incretin-based therapies

Agent	Dose	Status
GLP-1R agonists (subcutaneous injection)		
Exenatide	5–10 µg twice daily	A
Liraglutide	1.2–1.8 mg once daily	F
AVA0010	5–30 µg once or twice daily	I
Exenatide QW	2 mg once weekly	I
Taspoglutide	20–30 mg once weekly	I
Albiglutide	30–50 mg once weekly	I
CJC-1134-PC	1.5–3 mg once or twice weekly	I
NN9535	0.1–1.6 mg once weekly	I
LY2189265	0.25–3 mg once weekly	I
LY2428757	0.5–17.6 mg once weekly	I
DPP-4 inhibitors (oral)		
Sitagliptin	25–100 mg once daily	A
Vildagliptin	50 mg twice daily	A
Alogliptin	12.5–25 mg once daily	F
Saxagliptin	5–10 mg once daily	F
Linagliptin	2.5–5 mg once daily	I
Dutogliptin	200–400 mg once daily	I

Abbreviations: QW, once weekly; A, approved; F, filed for regulatory approval; I, being investigated.

concomitant sulfonylurea use was not associated with any notable frequency of reports of hypoglycemia.

The results of these trials led to the approval of exenatide by the FDA in April 2005 and by the European Medicines Agency in November 2006 as adjunctive treatment in combination with metformin, sulfonylurea, or both, in patients with T2DM. A subsequent study examined the efficacy of exenatide therapy in combination with thiazolidinediones (pioglitazone and rosiglitazone). About 71% of the participants completed the 16-week study, and those who were treated with exenatide achieved substantial reductions from baseline values in fasting blood glucose (about 1.69 mmol/l), HbA_{1c} levels (0.98%) and weight loss (1.5 kg).¹⁴ On the basis of these results, exenatide was approved for use in combination with a thiazolidinedione, with or without metformin.

The efficacy of exenatide has been assessed in head-to-head comparison trials with insulin glargine in combination with metformin or a sulfonylurea. In an open-label study, similar improvements in blood glucose

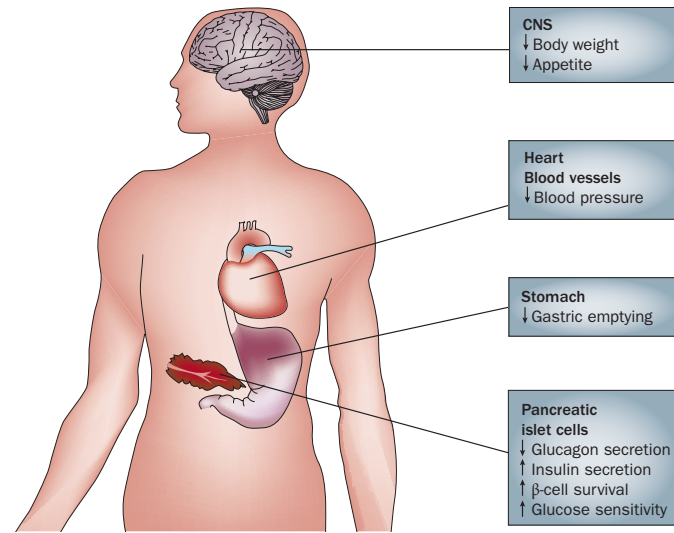


Figure 1 | GLP-1 receptor agonists exert diverse actions on distinct target tissues, which lead to reduction of blood glucose level and body weight in humans. Abbreviations: CNS, central nervous system; GLP-1, glucagon-like peptide 1.

control (reductions of 1.1% in HbA_{1c} after 26 weeks of therapy) were achieved in the two treatment groups. In contrast with insulin therapy, which generally led patients to gain weight, exenatide treatment resulted in weight loss (+1.8 kg versus -2.3 kg, respectively). Rates of hypoglycemia were comparable in the two groups, but the incidence of gastrointestinal malaise and drop-out rates were higher with exenatide therapy.¹⁵ Qualitatively similar results were obtained in a 52-week, open-label study: in patients who were already receiving metformin and a sulfonylurea, treatment with twice-daily, biphasic insulin aspart was markedly better tolerated than twice-daily exenatide.¹⁶ The insulin-treated patients had less nausea and a lower drop-out rate. However, only exenatide-treated patients lost weight (which led to an approximate 5.4 kg difference between the groups).¹⁶ Taken together, these studies suggest that exenatide represents a reasonable alternative to the initiation of insulin therapy in patients whose diabetic symptoms are suboptimally controlled with oral hypoglycemic agents, particularly for those who are concerned about their potential weight gain.

In a relatively small study, 69 patients with inadequate glycemic control were randomly assigned either exenatide ($n = 36$) or insulin glargine ($n = 33$) for 1 year. Both therapies produced similar improvements in glycemic control (0.7–0.8% reduction in HbA_{1c}). Although arginine-stimulated and glucose-stimulated insulin secretion improved to a greater extent in exenatide-treated patients than in insulin-treated patients, repeat analyses that were carried out 4 weeks after discontinuation of either exenatide or insulin revealed no significant, sustained differences in multiple parameters of β-cell

function.¹⁷ Thus, the available data do not yet support the hypothesis that therapy with GLP-1R agonists produces durable improvements in β-cell function.

Liraglutide

The success of exenatide has accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration. Liraglutide (Novo Nordisk, Bagsvaerd, Denmark) is a modified form of human GLP-1 (hGLP-1₇₋₃₇) that contains a Ser34Arg amino-acid substitution and has a C16 palmitoyl fatty-acid side-chain at Lys26. These modifications facilitate binding of liraglutide to serum albumin, self-oligomerization, and resistance to DPP-4-mediated inactivation, which result in a prolonged half-life of this molecule *in vivo*. Plasma levels of liraglutide remain stable for up to 13 h after a single subcutaneous injection. Dose-ranging, phase II studies demonstrated that liraglutide mimics all of the expected actions of GLP-1 in humans: its administration results in 24 h glucose control, low rates of hypoglycemia, and weight loss in most individuals. Nausea and diarrhea are the most commonly reported adverse events.¹⁸

Once-daily administration of low doses of liraglutide (0.1–0.9 mg daily) in a cohort of Japanese patients with T2DM was well tolerated and reduced HbA_{1c} levels, by up to 1.85%, without major episodes of hypoglycemia; no change in body weight was observed after 14 weeks of therapy.¹⁹ Several phase III clinical trials have investigated the efficacy of liraglutide (either as monotherapy or in combination with other drugs) versus that of other oral hypoglycemic agents, exenatide, or insulin. The results of these clinical trials suggest that liraglutide was at least as efficacious in lowering HbA_{1c} as comparator treatments and was usually associated with weight loss of several kilograms. Additive therapy with liraglutide (1.2 mg or 1.8 mg) given to patients whose diabetic symptoms were inadequately controlled with metformin and rosiglitazone resulted in a mean HbA_{1c} reduction of 1.5%, from a baseline value of 8.6%, in association with weight loss of about 2 kg and a reduction in systolic blood pressure.²⁰ Nausea, vomiting and diarrhea were the most common adverse events and the principal reasons for withdrawal from the study in liraglutide-treated patients.

A 52-week study compared glimepiride monotherapy with liraglutide monotherapy (1.2 mg or 1.8 mg daily) in patients with T2DM. Liraglutide was more effective than glimepiride for reducing HbA_{1c} level (by 0.84% and 1.14% versus 0.5%, respectively). Moreover, patients treated with liraglutide lost weight and exhibited a reduction in blood pressure, whereas those treated with glimepiride gained weight.²¹ The efficacy of liraglutide versus rosiglitazone therapy has also been assessed in patients who failed to achieve optimal glycemic control on glimepiride. Liraglutide, at doses of 1.2 or 1.8 mg daily, was more effective than rosiglitazone in producing additional reductions in fasting plasma glucose and HbA_{1c} levels over 26 weeks. Moreover, patients who received

liraglutide did not gain weight, in contrast to those in the rosiglitazone group, in whom an average weight gain of 2.1 kg was reported.²²

The efficacy of additive glimepiride 4 mg once daily was compared with that of a range of liraglutide doses, 0.6–1.8 mg daily, for 26 weeks in patients whose diabetic symptoms were not adequately controlled with metformin therapy.²³ Liraglutide was as effective as glimepiride in reducing HbA_{1c} levels (mean reductions of approximately 1%). Fewer episodes of minor hypoglycemia, a slight reduction (2–3 mmHg) in blood pressure, an increase in heart rate and more nausea were seen in liraglutide-treated patients compared with glimepiride-treated patients. Notably, body weight decreased in liraglutide-treated individuals but increased in those treated with glimepiride, whereas control of postprandial glycaemic excursions and reductions in the proinsulin:insulin ratio were similar in the two groups.²³

Similarly, liraglutide produced a greater reduction in HbA_{1c} level and body weight than insulin glargine on a background therapy of metformin and glimepiride. Glycaemic targets (HbA_{1c} ≤6.5% and <7%) were achieved by more patients in the liraglutide group (37.1% and 53.1%, respectively) than in the insulin glargine group (23.6% and 45.8%, respectively).²⁴ Moreover, patients treated with liraglutide had a reduction in waist circumference and lost about 1.8 kg in weight, whereas insulin glargine treatment was associated with weight gain of 1.6 kg. Liraglutide therapy improved the proinsulin:C-peptide ratio and reduced systolic blood pressure; however, some patients in the liraglutide group experienced episodes of major hypoglycemia (*n* = 5), whereas no such episodes occurred in the insulin glargine group.²⁴

Of particular interest, liraglutide 1.8 mg daily caused a greater reduction in fasting glucose and HbA_{1c} levels than exenatide 10 µg twice daily (1.1% versus 0.8%, respectively) over 30 weeks in an open-label study, whereas reductions in body weight and blood pressure were similar in the two groups.²⁵ The incidence of minor hypoglycemia was lower among liraglutide-treated patients than in those treated with exenatide. Patients who were treated with exenatide for 30 weeks and switched to liraglutide for the next 14 weeks exhibited a further reduction of about 0.3% in their HbA_{1c} level. A New Drug Application was filed for liraglutide in the US in May 2008. Liraglutide is also being investigated for the treatment of obesity in nondiabetic individuals at doses of up to 3 mg daily.

Modified forms of exenatide

AVE0010 (Sanofi-Aventis, Paris, France) is a modified exendin 4 molecule with additional lysine residues at the carboxy terminal. A phase IIb, dose-ranging study of AVE0010 was carried out in 542 patients who had T2DM that was inadequately controlled with metformin alone.²⁶ Patients were treated for 13 weeks with escalating doses of AVE0010 (5 µg, 10 µg, 20 µg, or 30 µg) once or twice daily, or placebo. Reductions were observed in

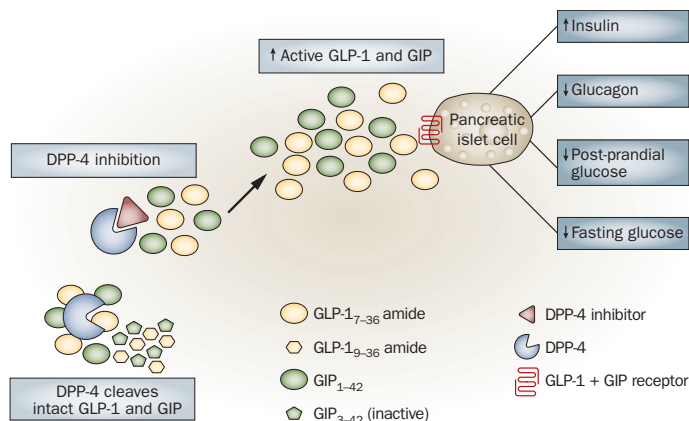


Figure 2 | Mechanism of action of DPP-4 inhibitors. These agents prevent the enzymatic inactivation of GLP-1 and GIP. The binding of active GLP-1 and GIP to incretin receptors of the pancreatic β cell potentiates insulin secretion and inhibits glucagon secretion. Abbreviations: DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.

HbA_{1c} levels from baseline with once daily (0.28–0.57%) and twice daily (0.47–0.69%) AVE0010, associated with decrements in body weight. AVE0010 is now being studied in phase III clinical trials.

A long-acting, once-weekly formulation of exenatide was evaluated at two doses, 0.8 mg and 2 mg, in patients with diabetes mellitus who were treated with diet and exercise and/or metformin for 15 weeks. Both cohorts exhibited marked reductions in their HbA_{1c} level (of 1.4% and 1.7% from baseline, respectively), however, only those treated with 2 mg exenatide lost weight.²⁷ Subsequently, a clinical trial compared the efficacy of 10 µg exenatide twice daily with that of 2 mg exenatide once weekly in 300 patients who were either not treated with oral hypoglycaemic agents or who were receiving one or two oral hypoglycaemic agents for 30 weeks.²⁷ Remarkable reductions were seen in HbA_{1c} level in both groups, with more substantial reductions in HbA_{1c} observed with once-weekly exenatide than with twice-daily exenatide (1.9% versus 1.5%, respectively). More patients treated with once-weekly exenatide achieved target levels of HbA_{1c} <7% than those who received twice-daily exenatide (77% versus 61%, respectively). Reductions in body weight were similar in both treatment groups (3.6–3.9 kg). Once-weekly exenatide was associated with a greater reduction in plasma glucagon levels and fasting plasma glucose levels than was twice-daily exenatide (decreases of 2.3 mmol/l versus 1.4 mmol/l, respectively), however, twice-daily exenatide was a more potent suppressor of postprandial glycaemic excursions. Nausea and vomiting were the most commonly reported adverse effects with both formulations, and were less frequently reported with once-weekly exenatide than with twice-daily exenatide. By contrast, injection-site reactions and antiexenatide antibodies were more common in individuals treated with once-weekly exenatide, and the subset of participants in

this group with the highest antibody titers exhibited a modest reduction in efficacy.²⁸

Albiglutide

Albiglutide (GlaxoSmithKline, Brentford, London, UK) is a long-acting, recombinant GLP-1R agonist, which consists of two tandem-linked copies of a modified human GLP-1 sequence within the large human serum albumin molecule; this structure enables sustained action and once-weekly administration. Despite the relatively large size of albiglutide, preclinical studies in rodents demonstrate that it activates the GLP-1R and reproduces a broad spectrum of GLP-1 actions, including inhibition of gastric emptying and perception of satiety following acute administration.²⁹ Moreover, chronic albiglutide administration prevents weight gain in mice fed a high-fat diet.³⁰ Analysis of the pharmacokinetic properties of albiglutide was carried out in patients with T2DM who received a range of albiglutide doses from 9–64 mg. Albiglutide reduced both fasting and postprandial glucose levels, and had a circulating half-life of 6–7 days.³¹ This agent entered phase III clinical studies in the first quarter of 2009.

Taspoglutide

Taspoglutide (Roche, Basel, Switzerland; Ipsen, Paris, France) is a GLP-1-based molecule that contains aminoisobutyric acid substitutions at positions 8 and 35, which confer resistance to degradation by DPP-4. A zinc-based formulation of taspoglutide is suitable for once-weekly administration. Pharmacokinetic and pharmacodynamic studies in 48 individuals who had T2DM that was suboptimally controlled with metformin demonstrated that plasma levels of taspoglutide were sustained for 14 days and were associated with reductions in the 24 h blood-glucose area under the curve, and with progressive weight loss of 0.9 kg, compared to placebo. A randomized, placebo-controlled, phase II clinical trial has investigated the efficacy and safety of either weekly or biweekly taspoglutide administration in 306 patients who had T2DM that was inadequately treated with metformin.³² Both taspoglutide regimens reduced HbA_{1c} levels after 8 weeks of therapy: 79% of those who received 10 mg taspoglutide per week and 81% of those who received 20 mg per week achieved HbA_{1c} levels <7%, and dose-dependent reductions were observed in body weight in both groups. Taspoglutide therapy was associated with transient nausea and vomiting, and some patients developed anti-peptide antibodies. A second phase II study examined taspoglutide dosing regimens in 133 metformin-treated patients who were randomly allocated placebo or 20 mg taspoglutide once weekly for 4 weeks, followed by a second 4-week treatment period with 20 mg, 30 mg or 40 mg once weekly. All patients experienced improvements in glucose control, with nausea as the most commonly reported adverse event.³³ Withdrawal from the study was more common in patients who received the two highest doses of taspoglutide. This drug is currently being evaluated in phase III clinical studies.

Other long-acting GLP-1R agonists

Additional long-acting GLP-1R agonists in clinical trials include CJC1134 (ConjuChem, Montreal, Canada), a protein that contains an exendin 4 peptide moiety covalently linked to human serum albumin through a chemical linkage, which proved to exert a broad range of GLP-1-receptor-dependent glucose-regulatory actions in preclinical studies.³⁴ Similarly, multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I–II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1), but few data are available on the structure or efficacy of these molecules.

Adverse effects of GLP-1R agonists

Nausea and vomiting are the principal adverse events that are observed following GLP-1R agonist administration; their incidence seems to be related to both the absolute maximal drug concentration and the time taken to reach this concentration. Although nausea and vomiting are usually mild, transient, and diminish over time in most individuals, some patients will not be able to tolerate or continue GLP-1-based therapy owing to persistent gastrointestinal discomfort.

Structurally distinct GLP-1R agonists, such as exenatide, are associated with induction of antiexenatide antibodies; up to 50% of patients who are treated with exenatide twice daily develop such antibodies, and a slightly greater proportion of patients develop them following treatment with once-weekly exenatide.²⁸ Although the presence of antiexenatide antibodies does not seem to be a major determinant of therapeutic effectiveness for the majority of patients who receive twice-daily treatment, a small subset of individuals who have high titers of antibodies (>1:625) may experience diminished therapeutic efficacy. Similarly, in comparison with patients without high titers of antiexenatide antibodies, patients with high antibody titers who were treated with once-weekly exenatide had a relatively small, but still highly remarkable (1.4%) reduction in HbA_{1c} after 30 weeks of therapy.²⁸ Much less information is available about antibody titers and their relationship to therapeutic outcomes following therapy with liraglutide or other emerging GLP-1R agonists.

Pancreatitis has been reported in patients who were treated with exenatide in postmarketing surveillance³⁵ and in several participants of the liraglutide clinical trial program.²¹ As pancreatitis can be associated with substantial morbidity and death, considerable apprehension has developed in relation to the potential relationship between therapy with a GLP-1R agonist and the new onset of or potential exacerbation of pancreatitis. Few clinical epidemiological data are available that allow ascertainment of an accurate incidence of pancreatitis among those with diabetes mellitus who are treated with exenatide as compared with those who receive other antidiabetic therapies. Similarly, although exendin 4 and GLP-1 have been shown to potentiate amylase release from pancreatic fragments in preclinical studies,³⁶ no evidence from animal experiments has suggested that

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.