

Expert Opinion

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Emerging GLP-1 receptor agonists

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Introduction: Recently, glucagon-like peptide-1 receptor (GLP-1R) agonists have become available for the treatment of type 2 diabetes. These agents exploit the physiological effects of GLP-1, which is able to address several of the pathophysiological features of type 2 diabetes. GLP-1R agonists presently available are administered once or twice daily, but several once-weekly GLP-1R agonists are in late clinical development.

Areas covered: The present review aims to give an overview of the clinical data on the currently available GLP-1R agonists used for treatment of type 2 diabetes, exenatide and liraglutide, as well as the emerging GLP-1R agonists including the long-acting compounds.

Expert opinion: An emerging therapeutic trend toward initial or early combination therapy with metformin- and incretin-based therapy is anticipated for patients with type 2 diabetes. GLP-1-based therapy has so far proven safe and tolerable. The determination of which incretin-based therapy to choose necessitates comparisons between the various GLP-1R agonists. The available GLP-1R agonists cause sustained weight loss and clinical relevant improvement of glycemic control. The long-acting GLP-1R agonists in late development may improve the effects of GLP-1 even further with optimized pharmacokinetic profiles resulting in fewer side effects. Meta-analyses have shown promising effects on cardiovascular disease and data from ongoing multicenter trials with cardiovascular endpoints are expected in 2015.

Keywords: albiglutide, CJC-1134-PC, dulaglutide, exenatide, exenatide once-weekly, glucagon-like peptide-1 receptor agonists, liraglutide, lixisenatide, semaglutide, type 2 diabetes

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1. Background

Oral glucose administration elicits a greater insulin response than intravenous (i.v.) glucose at identical plasma glucose profiles. This is called the incretin effect, and is conveyed by the two incretin hormones: glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [1]. GIP is a 42 amino acid peptide, synthesized and released from enteroendocrine K cells mainly located in the duodenum and upper jejunum [1]. GLP-1 is a 30 amino acid peptide, a product of proglucagon gene expression in the intestinal enteroendocrine L cells and is, like GIP, secreted after meal ingestion [1,2]. Together the insulintropic effect of GIP and GLP-1 accounts for up to 70% of the insulin secreted after a meal in healthy subjects, and, thus, plays a very important role in postprandial glucose homeostasis [1]. In patients with type 2 diabetes, the ability of exogenous GIP and GLP-1 to stimulate insulin secretion is severely diminished when compared with healthy subjects. However, the glucose-lowering effect of supraphysiological infusion of GLP-1 is preserved [3] while that of GIP is absent [4,5].

GLP-1 asserts its effects on the beta cells through binding to the GLP-1 receptor (GLP-1R), a cell surface receptor highly expressed on the cell membrane of pancreatic beta cells [2,6]. Receptor binding of GLP-1 results in stimulation of insulin secretion in a strict glucose-dependent manner [7,8]. GLP-1 also has potential effects on beta cell mass as pre-clinical studies have shown: stimulation of beta

cell proliferation [9,10], differentiation of new beta cells from progenitor cells [11] and by inhibition of beta cell apoptosis [12]. Furthermore, GLP-1 robustly inhibits glucagon secretion, and the combined effects on insulin and glucagon secretion results in inhibition of hepatic glucose production, which contributes significantly to the overall glucose-lowering effect of GLP-1 [13]. Additionally, GLP-1 decreases gastrointestinal motility [14] and promotes satiety [15], probably through activation of GLP-1Rs in the brain in combination with GLP-1-induced decrease in gastric emptying. Chronic administration of GLP-1 therefore leads to weight loss [16]. All of these effects are potentially beneficial in the treatment of patients with type 2 diabetes, and much attention have, therefore, been given to the development of pharmacological strategies based on the effects of GLP-1.

One of the major challenges in developing GLP-1-based therapy is that native GLP-1 is very rapidly degraded in the circulation by the enzyme dipeptidyl peptidase 4 (DPP-4), which cleaves off the two N-terminal amino acids and leaves the molecule inactive with regard to insulin secretion [17], resulting in a half-life of less than 2 min [18]. Because of the rapid elimination, native GLP-1 is unsuitable for clinical use. Two different strategies of circumventing this problem have been successful so far. One approach is to inhibit DPP-4, thereby enhancing the survival and therefore the effect of endogenously released GLP-1. The other strategy is to use GLP-1R agonists that are resistant to inactivation by DPP-4 and modified in a way that prolongs the effect of the hormone. In the following sections, the emerging GLP-1R agonists are reviewed.

2. Medical need

Type 2 diabetes is a progressive and multifactorial disease. There were an estimated 285 million adults with type 2 diabetes in 2010 worldwide, and, as the western lifestyle is making its entry into the developing countries, this number will continue to increase [19]. Projections for 2030 show that the prevalence of type 2 diabetes is likely to reach almost 450 million [20]. Type 2 diabetes leads to serious complications that broadly can be classified as microvascular (neuropathy, nephropathy and retinopathy) or macrovascular (atherosclerosis resulting in myocardial infarction and stroke). The ultimate goal of diabetes therapy is to prevent these complications in order to improve life expectancy and quality of life. The United Kingdom Prospective Diabetes Study (UKPDS) showed that improved glycemic control (HbA1c) resulted in less microvascular complications in patients with type 2 diabetes [21]. Furthermore, recent follow-up studies from the UKPDS have shown that tight glucose control in the early years of disease impacts dramatically on the development of complications related to the disease [22].

Despite recognition that type 2 diabetes is a huge public health concern, and major efforts to attract attention to the importance of tight glycemic control, data from World

Health Organization (WHO) show that the percentage of individuals reaching International Diabetes Federation (IDF) treatment goals is still very low [23]. Common barriers to patient adherence include concern about unwanted weight gain [24], fear of hypoglycemia and perceived inconvenience [25], and these may all indirectly undermine glycemic control if the prescribed therapy is not followed.

3. Existing treatment

International guidelines for the treatment of patients with type 2 diabetes have been suggested by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) [26]. Based on data from the UKPDS it is recommended that metformin should be started in all patients with newly diagnosed type 2 diabetes who do not have contraindications to metformin treatment (e.g., renal disease) [26-29]. However, often metformin is not enough to treat the patients with the target HbA1c levels below 7%. Therefore, the guidelines suggest additional treatment options on which agents to add to metformin treatment [29]. Classical therapeutic additives are: i) the insulin secretagogues sulfonylureas (SU), ii) the insulin-sensitizing thiazolidiones (TZD) and iii) exogenous insulin. However, all of these agents are associated with different adverse effects including risk of hypoglycemia (SU and insulin), weight gain (SU, insulin and TZD) and increased risk of bone fractures and even heart disease (TZD) [30]. Additionally, none of these medications are able to correct either the impairment or the progressive decline of beta cell function. Recently, the incretin-based therapies including GLP-1R agonists and DPP-4 inhibitors were introduced into clinical practice, and these agents are now widely used for the treatment of type 2 diabetes [31], with the GLP-1R agonists being part of the latest ADA/EASD treatment guidelines [26].

The development of the GLP-1R agonists is based on two different approaches. One strategy exploits the structure of native human GLP-1, modified in a way so that it is resistant to degradation by DPP-4, as the backbone for the compounds (Figure 1). The other approach uses a naturally occurring protein – exendin-4, originally isolated from the saliva of the lizard *Heloderma suspectum* – as the backbone of the compounds (Figure 1). Exendin-4 has a 53% sequence homology with human GLP-1 in its first 30 amino acids [32], and binds to and activates the GLP-1R with equal potency as native GLP-1. Two GLP-1R agonists have so far been approved for the treatment of type 2 diabetes: exenatide, based on exendin-4, for twice-daily subcutaneous (s.c.) injection and liraglutide, based on the structure of native GLP-1, for once-daily s.c. injection.

3.1 Exenatide

Exenatide (Byetta[®], Amylin Pharmaceuticals, Inc., San Diego, CA, US/Eli Lilly, Indianapolis, Indiana, US), the first GLP-1R agonist to reach the market, was approved by the US Food

GLP-1 receptor agonists for sc injection			
GLP-1-based		Exendin-4-based	
Daily	Weekly	Daily	Weekly
Liraglutide	Albiglutide	Exenatide	Exenatide-LAR
	Dulaglutide	Lixisenatide	CJC-1134-PC
	Semaglutide		

Figure 1. Overview of the existing and emerging GLP-1R agonists; two approaches based on human GLP-1 and exendin-4.

GLP-1R: Glucagon-like peptide-1 receptor.

and Drug Administration (FDA) in April 2005 and by European Medicines Agency (EMA) in 2007 (Table 1). Exenatide is a synthetic version of exendin-4, a 39 amino acid peptide (Table 2) [1,32], and is resistant to inactivation by DPP-4. Exenatide is primarily cleared in the kidneys by glomerular filtration [33], and the half-life after s.c. injection is approximately 2–3 h [34]. Exenatide, therefore, has to be administered twice daily to achieve 24-h pharmacological plasma concentrations. In the early clinical AC2993: Diabetes Management for Improving Glucose Outcome (AMIGO) trials, the effects of exenatide was investigated in a total of 1446 randomized patients [35–37]. Exenatide was given as add-on therapy to metformin, SU or both and these studies reported statistically significant improvement of glycemic control in the exenatide treatment groups (change of HbA1c of -1.0% (baseline of 8.2%) vs. an increase of approximately 0.2% in the placebo groups) and change in fasting plasma glucose (FPG) (-0.5 mM vs. an increase of nearly 1 mM in the placebo groups). On average, the weight loss in the three studies comparing exenatide with oral anti-diabetics amounted to 1.6 kg (baseline of 95 kg) in the exenatide-treated patients [38]. Additionally, significant reduction in systolic blood pressure compared with placebo (difference of 2.8 mmHg) or insulin (difference of 3.7 mmHg) have been reported after 6 months of treatment with exenatide [39]. In 2011, a large retrospective database analysis looking at the relative incidence of cardiovascular disease (CVD) events in patients with type 2 diabetes either treated with exenatide twice-daily (n = 39,275) or with other glucose-lowering agents (n = 381,218) was published [40]. The study reported that treatment with exenatide twice-daily was associated with a significantly lower risk of CVD events than treatment with other glucose-lowering agents.

3.2 Liraglutide

Liraglutide (Victoza[®], Novo Nordisk, Bagsværd, Copenhagen, Denmark) is an acylated analog of human GLP-1 (with 97% homology with native GLP-1), which was approved for

clinical use in Europe in 2009 and in the USA in 2010 (Table 1). In liraglutide, a C-16 acyl chain is linked to amino acid 20 via a γ -glutamic acid spacer and the lysine in position 28 of native GLP-1 is exchanged with arginine (Table 2) [41]. These changes results in a half-life in the range of approximately 11–15 h after s.c. administration [42], making it suitable for once-daily dosing [43]. The clinical effects of liraglutide treatment have been investigated in the Liraglutide Effect and Action in Diabetes (LEAD) series of Phase III studies. These trials lasting up to 52 weeks, showed that treatment with liraglutide both as monotherapy and in combination with metformin, SU or TZD plus metformin lowered HbA1c and body weight. Liraglutide-induced change in HbA1c varied from -0.8 to -1.5% (baseline HbA1c of 8.2–8.5%) [44–49], reductions that in most cases were similar or greater than compared with the oral comparator drug [42]. Overall, a reduction in body weight was seen in all trials in the range of 2–3 kg, much like other Phase III studies with liraglutide compared with placebo, and not different from exenatide. In the LEAD-6 study, liraglutide and exenatide were compared head-to-head [47]. A significantly greater reduction in HbA1c with liraglutide than with exenatide treatment was observed (1.1 vs. 0.8%), as well as greater reduction in FPG (1.6 vs. 0.6 mM). Greater reductions in triglycerides (0.4 vs. 0.2 mM) and free fatty acids (0.17 vs. 0.10 mM) in the liraglutide group were observed. Both liraglutide and exenatide caused significant decreases in blood pressure. Newly published data from a 14-week extension of the LEAD-6 Phase IIIb study, where subjects either continued with liraglutide or switched from exenatide to liraglutide, showed that switching from exenatide to liraglutide further and significantly reduced HbA1c (0.3%), FPG (0.9 mM), body weight (0.9 kg) and systolic blood pressure (3.8 mmHg) [50].

3.3 Side effects of exenatide and liraglutide

The side effects during treatment with exenatide and liraglutide are mild to moderate nausea and vomiting. These side effects are dose-dependent and often decline over time [51]. The incidence of treatment-associated hypoglycemia is reported to be low. In fact, occurrence of hypoglycemia during exenatide treatment combined with metformin is similar to when metformin is used as monotherapy [52]. However, combined with SU the risk of minor hypoglycemic episodes is reported to be in the range of 15–36% for exenatide [51] and 8–25% for liraglutide [53]. Approximately 50% of exenatide-treated patients in long-term, placebo-controlled studies developed low titres of anti-exenatide antibodies, and an additional 6% developed higher levels of antibodies, during the initial 30 weeks of treatment [51]. Among liraglutide-treated patients, 4–13% developed antibodies (low titres) [44–46,48,49]. The exact impact of autoantibodies on efficacy and safety in the longer term remains to be established, but patients with high titres seem to have an impaired effect on glycemic control [54]. After the approval of exenatide and liraglutide post-marketing reports of several incidents of

Table 1. Overview of the existing and emerging GLP-1R agonists, their state of development and ongoing trials.

Compound	Company	Formulation	Status of development	Ongoing trials
Exenatide	Eli Lilly/Amylin Pharmaceuticals, Inc.	Twice-daily	Launched	Combination with insulin/obesity + CVD
Liraglutide	Novo Nordisk	Once-daily	Launched	Combination with insulin/obesity + CVD
Exenatide once-weekly	Eli Lilly/Amylin Pharmaceutical, Inc./Alkermes, Inc.	Once-weekly	Expected 2011	Combination with insulin/obesity
Lixisenatide	Zealand Pharma A/S/Sanofi-Aventis	Once-daily	Expected 2011	Phase III, GetGoal
CJC-1134-PC	ConjuChem	Once-weekly	Phase I/II	Phase I/II
Albiglutide	GlaxoSmithKline	Once-weekly	Expected 2012	Phase III, Harmony
Dulaglutide (LY2189265)	Eli Lilly	Once-weekly	Expected 2013	Phase III, Award
Semaglutide (NN9535)	Novo Nordisk	Once-weekly	Phase II	On hold

CVD: Cardiovascular disease; GLP-1R: Glucagon-like peptide-1 receptor.

Table 2. Amino acid structures of GLP-1 and the GLP-1R agonists on the market or in late clinical development (published data).

Name	Structure
Native GLP-1	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg
Liraglutide	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly Glu-C16 fatty acid
Albiglutide	(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg) ₂ – linked to human albumin
Exenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser
Lixisenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys
CJC-1134-PC	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-C13H19O6N3 (linker molecule)

GLP-1: Glucagon-like peptide-1; GLP-1R: Glucagon-like peptide-1 receptor.

acute pancreatitis in patients treated with exenatide and liraglutide have been disclosed [55]. However, it is not evident that the incidence of acute pancreatitis is higher in those receiving exenatide or liraglutide than in the background diabetic population [56]. Still it is recommended that these GLP-1R agonists should not be used in subjects with a history of or increased risk of pancreatitis. Lately, the risk of pancreatic cancer has been discussed in patients treated with exenatide compared with other anti-diabetic medications [57,58]. However, the EMA recently concluded that a relationship between GLP-1R agonists and pancreatic malignancies could not yet be confirmed nor excluded [59]. In carcinogenicity studies with liraglutide, C cell tumors were observed in thyroid tissue of mice and rats [60]. However, recent data identify key differences between rodent models, non-human primates and humans with regard to this, and the long-term

consequences of sustained GLP-1R activation in the human thyroid require further investigation [61], but so far no changes in thyroid function have been reported in clinical trials with GLP-1R agonists. Furthermore, large studies are underway aiming to assess and confirm the cardiovascular safety of both exenatide and liraglutide.

4. Current research goals

The GLP-1R agonists have already proved to be a valuable asset to the treatment of patients with type 2 diabetes. However, despite the many beneficial effects of the GLP-1R agonists on weight loss and improved glycemic control, the gastrointestinal intolerance and daily s.c. administration may lead to discontinuation [62]. Currently, GLP-1R agonists with optimized pharmacokinetic profiles and a lower number

of adverse events are under development. Most of the emerging GLP-1R agonists are for once-weekly s.c. administration. The once-weekly regime is thought to improve compliance, and to offer an improved throughout-the-day glycemic control compared with the currently available GLP-1R agonists (exenatide and liraglutide).

5. Competitive environment

5.1 Exenatide once-weekly

Exenatide has been developed in a sustained-release formulation planned for once-weekly s.c. administration by Amylin Pharmaceuticals, Inc., Eli Lilly and Alkermes Inc. (Table 1). The exenatide molecules are encapsulated in injectable microspheres, which consist of a biodegradable medical polymer also used in other extended-release pharmaceuticals [63]. These microspheres allow gradual drug delivery at a controlled rate by diffusion and erosion of the microspheres. The drug is now in late clinical development, and the clinical effects of exenatide once-weekly have been examined in the 'Diabetes therapy Utilization: Researching changes in HbA1c weight and other factors Through Intervention with exenatide Once-weekly' (DURATION) 1 – 6 trials [64–69]. In DURATION-1, exenatide once-weekly was studied in a head-to-head comparison with exenatide twice-daily in 295 patients with type 2 diabetes (HbA1c $8.3 \pm 1\%$, weight 103 ± 20 kg, BMI 35 ± 5 kg/m², diabetes duration 7 ± 5 years) over 30 weeks [69]. Exenatide once-weekly was superior to exenatide twice-daily in terms of glycemic parameters (HbA1c change: -1.9 vs. -1.5% , proportion of patients reaching HbA1c of 7.0% or less: 77 vs. 61%; FPG: -2.3 vs. -1.4 mM). Interestingly, glucagon levels decreased significantly more with exenatide once-weekly vs. exenatide twice-daily, likely contributing to the improvement in FPG levels. Additionally, significantly greater reductions in total cholesterol and low-density lipoprotein cholesterol were observed with the once-weekly exenatide compared with the twice-daily exenatide. Equal significant improvements in fasting triglyceride and systolic and diastolic blood pressures were observed with both treatments. No difference in body weight reduction was observed (3.7 vs. 3.6 kg), and about 75% of the patients lose weight [69]. A 22-week *open-label* extension of the DURATION-1 study, where patients either continued with exenatide once-weekly or switched from exenatide once-daily to exenatide once-weekly, showed that the improved glycemic control and weight loss were sustained over the 52 weeks of therapy and patients who switched from exenatide twice-daily to once-weekly achieved a further reduction in HbA1c, ending up with the same improvements in glycemic control as the group treated with exenatide once-weekly for the entire 52 weeks [70].

In the DURATION-2 to 5 studies, exenatide once-weekly was compared against: a TZD, a DPP-4 inhibitor, insulin glargine, metformin and the commercial formulation of exenatide once-weekly was compared against exenatide

twice-daily [64–67]. In all studies, exenatide once-weekly lowered HbA1c and body weight significantly. The HbA1c reduction by exenatide once-weekly was up to 1.6%, and in most cases this reduction was greater or similar to that of the comparator. Overall, a reduction in body weight by exenatide once-weekly was seen in the range of 2.1 – 2.6 kg. Very recently, the preliminary results from the DURATION-6 study comparing exenatide once-weekly with liraglutide once-daily were reported in a press release [68]. This 26-week head-to-head, *open-label*, study enrolled approximately 900 patients with type 2 diabetes who were not achieving adequate HbA1c with diet and exercise in conjunction with metformin, SU, metformin plus a SU or metformin plus a TZD. The study revealed that patients receiving exenatide once-weekly experienced a reduction in HbA1c of 1.3% compared with 1.5% for liraglutide. Exenatide once-weekly did, therefore, not meet the pre-specified primary end point of non-inferiority to liraglutide with regard to HbA1c reduction since liraglutide was significantly more efficacious than exenatide once-weekly. However, exenatide once-weekly did appear to be slightly better tolerated than liraglutide with less gastrointestinal side effects (such as nausea and vomiting), although more patients experienced local site reactions with exenatide compared with liraglutide [68]. Data on changes in body weight have not yet been reported.

The most frequently reported adverse events among exenatide once-weekly-treated patients in the DURATION studies were nausea (predominately mild in intensity) (9 – 26%) and vomiting (4 – 11%) [64–70]. Other side effects included diarrhea (6 – 18%), and injection site adverse effects (pruritus, erythema, induration or pain) (10 – 18%) [64–70]. Pooled data of the safety and tolerability of exenatide once-weekly from 1095 patients (from the DURATION 1, 2 and 3 studies) showed that exenatide once-weekly were generally well tolerated, and that the overall incidence rates of adverse events, serious adverse events and discontinuations due to serious adverse events were similar for exenatide once-weekly versus the pooled comparators. No major episodes of hypoglycemia have been observed and the incidence of mild to moderate hypoglycemic events observed with exenatide once-weekly treatment was lower compared with the pooled comparator cohort (16 vs. 22%) [71].

Recently, a probable correlation between plasma exenatide concentrations and changes from baseline in the QT interval in healthy subjects was discussed [72]. Thus, the FDA recently requested a thorough QT interval study with exenatide levels higher than typical therapeutic levels of exenatide once-weekly [73]. Additionally, the FDA requested the results of the DURATION-5 study to evaluate the efficacy, safety and effectiveness, of the commercial formulation of exenatide once-weekly. Amylin Pharmaceuticals, Inc., Eli Lilly and Alkermes, Inc. are planning to submit their reply to the FDA by the end of 2011. In April 2011, the EMA has issued a positive opinion and exenatide once-weekly will reach the European market (tradename: Bydureon) by the end of 2011.

5.2 Lixisenatide

Lixisenatide is a GLP-1R agonist, in late clinical development by Sanofi-Aventis, Paris, France under license from Zealand Pharma A/S, Copenhagen, Denmark (Table 1). The peptide contains 44 amino acids and is based on the structure of exendin-4, with the deletion of a proline and an addition of six lysine residues at the C-terminus (Table 2) [74]. The affinity of lixisenatide to the GLP-1R have been shown to be approximately four times higher as compared with native GLP-1 [75], and half-life in plasma of lixisenatide is reported to be approximately 3 h [76,77]. Lixisenatide is probably administered as a s.c. injection once-daily. Data from a randomized controlled trial including 361, drug naïve, patients with type 2 diabetes, showed that 13 weeks of lixisenatide administration once-daily in monotherapy provided significant improvements in glycemic control (HbA1c reduction between 0.7 and 0.8%, mean FPG reduction between 0.7 and 0.9 mM) [78]. A body weight reduction of approximately 2 kg was observed. The efficacy of lixisenatide as add-on therapy to metformin was evaluated in a dose-finding study of 542 patients with type 2 diabetes [79]. In this 13-week trial, 12 separate arms were initiated: eight active treatment arms with escalating doses of s.c. lixisenatide (target dose 5, 10, 20 or 30 µg once-daily or twice-daily) and four placebo arms. The results showed that lixisenatide significantly and dose-dependently lowered mean HbA1c levels from baseline by -0.5 to -0.8% for once-daily dosing and -0.7 to -0.9% with twice-daily dosing (placebo -0.2%). The percentage of patients achieving HbA1c < 7.0% ranged from 47 to 77% with increasing doses of lixisenatide compared with 32% with placebo. Lixisenatide induced dose-dependent weight losses ranging from 2 to 3.9 kg; weight loss in the placebo group was 1.9 kg and, thus, only in the relatively high-dose lixisenatide groups (20 and 30 µg once-daily and 30 µg twice-daily) the weight loss was statistically significant. The conclusion of the study was that lixisenatide 20 µg administered once-daily demonstrated the best efficacy:tolerability ratio.

The most common adverse events to lixisenatide treatment were of gastrointestinal origin, much consistent with other GLP-1R agonists. With lixisenatide as monotherapy (20 µg once-daily), these were reported to be approximately 32 versus 14% in the placebo group with nausea being the most frequent [78]. In the 13-week dose-ranging study (5 – 60 µg) the gastrointestinal side effects occurred dose-dependently: nausea 7 – 35% (placebo 5%), vomiting 4 – 19% (placebo 1%) and diarrhea 6 – 26% (placebo 7%) [79]. No major hypoglycemic episodes and only few mild to moderate hypoglycemic episodes have been reported, with a similar frequency as during metformin treatment [80]. Antibody formation to lixisenatide was frequent in the only study reporting exact numbers; ranging from 43 (10 µg once-daily) to 71% (20 µg twice-daily) [79]. No cases of suspected pancreatitis or thyroid tumors have been reported during treatment with lixisenatide, but a few emergent adverse events have been reported. These include one hypersensitivity reaction and four possible allergic reactions [80].

The ongoing Phase III clinical trial program of lixisenatide is called GetGoal and was initiated in May 2008. The program has so far enrolled more than 4500 patients and will assess efficacy and safety of lixisenatide in patients with type 2 diabetes. The results from the first head-to-head study comparing lixisenatide with another GLP-1R agonist (GetGoal-X) were recently reported in a press release [81]. This randomized, *open-label* multicenter study with 639 patients with type 2 diabetes compared the effect of lixisenatide versus exenatide twice-daily as add-on therapy to metformin. The study did meet the pre-defined end point of non-inferiority in HbA1c reduction of lixisenatide compared with exenatide twice-daily, and significantly fewer episodes of hypoglycemia were reported with lixisenatide versus exenatide twice-daily [81]. The full study and additional results from the GetGoal program are expected in 2011. Furthermore, a large trial evaluating cardiovascular outcomes in high-risk patients (i.e., patients with a recent history of acute coronary syndrome) has been undertaken, estimated study completion date is late 2013. Randomized trials with direct comparisons with sitagliptin and liraglutide have been completed but no reports are available currently.

5.3 CJC-1134-PC

CJC-1134-PC, Montreal, Canada (ConjuChem) comprises a modified exendin-4 molecule and human recombinant albumin (Table 1). The exendin-4 derivative includes amino acids 1 – 39 of native exendin-4 and a lysine residue at position 40 (Table 2) [82]. Despite being a much larger molecule than exendin-4, pre-clinical data have shown that CJC-1134-PC retains the ability to bind to and activate the GLP-1R [82]. Preliminary results from clinical trials in patients with type 2 diabetes indicate that CJC-1134-PC has a half-life of approximately 8 days (like circulating albumin), making it suitable for once-weekly dosing [83]. At present, only very limited data on the clinical pharmacology of CJC-1134-PC are available, and results of Phase I and II studies have been published solely as abstracts [83,84]. A Phase I/II clinical dose-finding study (n = 58) with daily administration of s.c. CJC-1134-PC at doses between 310 and 5000 µg evaluated efficacy and safety in patients with type 2 diabetes [83]. Doses above 1250 µg produced reductions in mean daily and FPG levels, persisting for 1 – 3 weeks after a single s.c. dose. Body weight reduction of 2.5 kg (placebo: 1.2 kg) was observed at the 3000 µg dose after 3 weeks [83]. The efficacy on HbA1c of CJC-1134-PC compared with placebo was evaluated in a 3-month Phase II clinical trial comprising two individual studies with a total of 224 patients with type 2 diabetes inadequately controlled on metformin. CJC-1134-PC reduced HbA1c by 0.8% (1.5 – 2 mg once-weekly) and 1.4% (1.5 mg twice-weekly), compared with a 0.4% reduction with placebo. Body weight decreased during the 3-month treatment period with reductions of 1.2 kg (with 1.5 mg twice-weekly); however, this difference was not significantly different to the weight reductions seen with placebo (0.4 kg) [84]. At present, it is unclear why the CJC-1134-PC

compound seems to have little (or no) effect on body weight as compared with most other GLP-1R agonists. In the Phase II clinical trial, across all treatment arms, drug-related nausea (23%), vomiting (11%) and diarrhea (10%) were observed with corresponding values of 10, 6 and 8%, respectively, with placebo treatment [84]. The gastrointestinal side effects were reported to diminish over time [84].

5.4 Albiglutide

Albiglutide is a long-acting GLP-1R agonist developed by fusion of two GLP-1 analogs coupled to human albumin (Table 1) [85]. Albiglutide, previously named albugon, is under development by GlaxoSmithKline, London, UK. The resistance of cleavage by DPP-4 is obtained by an amino acid substitution (Ala to Gly) at the DPP-4 sensitive hydrolysis site (Table 2). Peak plasma levels of albiglutide are achieved 2 – 5 days after a single injection, and half-life is approximately 5 – 8 days, hence albiglutide is planned as a once-weekly s.c. injection dosing [62,86–88]. The efficacy of albiglutide was evaluated in a Phase II clinical trial [62] in which 356 patients with type 2 diabetes, treated with metformin or drug naïve, were randomized to receive 16 weeks of double-blinded s.c. treatment with placebo, exenatide (5 µg twice-daily for 4 weeks followed by 10 µg twice-daily), or albiglutide in three dosing schedules: weekly (4, 15 or 30 mg), biweekly (15, 30 or 50 mg) or monthly (50 or 100 mg). Albiglutide reduced HbA1c dose-dependently in each dosing schedule by 0.9% (30 mg once-weekly), 0.8% (50 mg biweekly) and 0.9% (100 mg monthly), whereas placebo and exenatide twice-daily reduced HbA1c by 0.2 and 0.5%, respectively. Reductions in FPG amounted to 1.4 mM (30 mg once-weekly), 1.2 mM (50 mg biweekly) and 1.2 mM (100 mg monthly) compared with placebo and exenatide twice-daily reductions of 0.1 and 0.8 mM, respectively. There was a trend toward decreased body weight with average weight losses between 1.1 and 1.7 kg with the highest albiglutide doses in each schedule, compared with reductions of 0.7 kg in the placebo and 2.4 kg in the exenatide twice-daily-treated group. No significant impact on lipid profiles was reported, but a trend toward blood pressure reduction seemed to be evident [62]. The most common adverse effects in this study were nausea and vomiting and occurred dose-dependently in 29% (30 mg once-weekly), 54% (50 mg biweekly) and 56% (100 mg monthly). Anti-albiglutide antibodies were found in 2.5% of subjects, but have so far not been associated with efficacy or any safety problems. A universal rash occurred in one patient and was considered a serious adverse event [62].

The Phase III clinical research program of albiglutide, called Harmony, will be investigating albiglutide as monotherapy, in combination with metformin, and as triple therapy with metformin and sitagliptin or metformin and glimepiride. Albiglutide will also be compared against a DPP-4 inhibitor, a TZD, a SU, insulin and liraglutide. The Phase III trials have an estimated completion date in late 2012.

5.5 Dulaglutide

Dulaglutide (LY2189265) is a GLP-1R agonist in preparation by Eli Lilly, Indianapolis, Indiana, US (Table 1). In this compound, a DPP-4 protected GLP-1 analog is fused to a modified IgG4 Fc fragment that acts as a large carrier for the GLP-1 molecule, hence slowing the *in vivo* clearance [89]. Half-life of dulaglutide has been reported to be approximately 4 days making it a candidate for once-weekly dosing [90,91]. A Phase Ib, double-blind, placebo-controlled, 5-week clinical trial assessed the effects of dulaglutide (0.05 – 8 mg once-weekly) in 43 patients with type 2 diabetes [90]. Significant reductions in HbA1c were observed at all dose levels (ranging from 0.7 to 1.3%), and fasting and postprandial glucose excursions were reduced with dulaglutide doses ≥ 1 mg, compared with placebo. Significant weight losses of 2.5 and 2.0 kg were observed in the treatment groups receiving dulaglutide doses of 5 and 8 mg, respectively. A Phase II, double-blinded, placebo-controlled clinical trial assessed the safety and efficacy of dulaglutide in 262 patients with uncontrolled type 2 diabetes (HbA1c: 8.2%) [92]. Patients were randomized into three treatment groups or a matched placebo group. The treatment in the dulaglutide groups were: 0.5 mg for 4 weeks titrated to 1.0 mg for 12 weeks, 1.0 mg for 16 weeks or 1.0 mg for 4 weeks titrated to 2.0 mg for 12 weeks. At 16 weeks, the mean reductions in HbA1c were 1.3, 1.3 and 1.5% in the 0.5/1.0, 1.0/1.0 and 1.0/2.0 mg dose groups, respectively, compared with a reduction of 0.3% in the placebo group. Reductions were also evident in FPG (2.1, 2.0 and 2.6 vs. 0.5 mM) and body mass (1.6, 1.4 and 2.5 vs. 0.1 kg). In the Phase Ib trial, dulaglutide was generally well tolerated. Nausea, vomiting and diarrhea were the most common adverse events. Antibodies against dulaglutide were not detected [90]. In the Phase II trial, the most common adverse events were nausea (13%) and diarrhea (9%). The frequency of hypoglycemic episodes did not differ among treatment groups [92]. Currently, a large (estimated 1566 patients with type 2 diabetes) Phase II/III, placebo-controlled, efficacy and safety study comparing dulaglutide with the DPP-4 inhibitor sitagliptin is ongoing. Furthermore, the Phase III clinical research program for dulaglutide called Award includes long-term studies assessing the efficacy and safety of dulaglutide compared with placebo, exenatide twice-daily, insulin glargine and metformin. The Phase III trials have an estimated completion date in 2012/2013.

5.6 Semaglutide

Semaglutide (NN9535) is a long-acting GLP-1R agonist planned for once-weekly s.c. injections, based on the GLP-1 backbone, in preparation by Novo Nordisk, Bagsværd, Copenhagen, Denmark (Table 1). Only limited data are currently available on semaglutide, and no papers or abstracts have been presented. So far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide

with placebo and liraglutide have been completed (NCT00696657). At the end of March 2011, a Phase I study looking at the influence of the pharmacokinetics of an oral contraceptive combination drug after administration of semaglutide was initiated (NCT01324505).

6. Conclusion

The GLP-1R agonists offer a new promising treatment modality in diabetes treatment, and several new GLP-1R agonists are in late clinical development. Whether based on exendin-4 or a modified GLP-1 analog, the GLP-1R agonists seem to utilize the beneficial pleiotropic effects of native GLP-1. Most of the novel GLP-1R agonists in development are characterized by extended half-lives entailing fewer injections (once-weekly). So far, only three head-to-head trials comparing a once-weekly GLP-1R agonist with daily GLP-1R agonists have been reported [62,68–69]. Two of these studies comparing exenatide once-weekly or albiglutide (once-weekly) with exenatide twice-daily demonstrated that the longer-acting agonists were superior with regard to glycemic control but inferior in terms of body weight reduction [62,69]. In a very recent press release, preliminary results from the first trial comparing a once-weekly compound (exenatide once-weekly) with liraglutide (once-daily) reported that the longer-acting agonist was inferior with regard to HbA1c reduction, but slightly better tolerated (data on body weight have not been published yet) [68].

From published data so far it seems that the longer-acting GLP-1R agonists have a more pronounced efficacy on glycemic control compared with the shorter-acting GLP-1R agonists, whereas the effect on body weight does not seem to differ significantly. Currently, additional clinical trials (including head-to-head trials) are underway for the emerging GLP-1R agonists. These trials will hopefully elucidate further information regarding differences on efficacy (e.g., on glycemic control, body weight, cardiovascular effects and beta cell protection), side effects and safety.

7. Expert opinion

Most of the currently available 'traditional' anti-diabetic agents only target one aspect of the pathophysiology of type 2 diabetes, and notably neither tackle the progressive deterioration in beta cell mass and function nor the hyperglucagonemia that accompanies the disease. By contrast, GLP-1R agonists are pleiotropic with positive effects on both alpha and beta cell dysfunction. In addition, severe limitations associated with existing therapies, including the risk of hypoglycemia (as observed with insulin and SUs), unsuitability for patients with renal impairment (metformin) or significant CVD (TZD), create opportunity for incretin-based therapies in an expanding diabetic drug market. Furthermore, there are several potential future indications for the GLP-1R agonists: i) treatment

of obesity, ii) treatment of patients with CVD (e.g., post-myocardial infarction), iii) adjunction to insulin therapy in patients with type 1 diabetes (exploiting the glucagon-suppressive effects of GLP-1) and iv) protective effect in pre-diabetes and eventually also in subjects after pancreatic islet transplantation where the GLP-1R agonists might have positive long-term effects.

The emerging GLP-1R agonists, to be introduced to the market in the next 1 – 5 years, seem to be well tolerated (with some clinical relevant differences in head-to-head trials, see section 5. Competitive environment). Nevertheless, the general, and probably limiting issues, with regard to the treatment of patients with type 2 diabetes are the gastrointestinal side effects (nausea and diarrhea). In spite of these side effects being mild to moderate, transient and probably less frequent with the once-weekly GLP-1R agonists compared with the GLP-1R agonists currently on the market (likely because of reduced peak concentrations with the once-weekly compounds), the use will still be limited in some patients. Second, the importance of antibody formation is not fully known. So far, the available data do not indicate that moderate antibody formation attenuates the clinical efficacy of the GLP-1R agonists. However, patients with high titres of antibodies seem to have less benefit of their GLP-1R agonist treatment with regard to glycemic control compared with patients who do not develop antibodies [54]. It seems that the compounds based on the exendin-4 backbone have a tendency to induce antibody formation at higher rates compared with the compounds build on the backbone of modified human GLP-1, plausible because of the closer resemblance to native GLP-1. So far, no safety problems have been reported with the formation of antibodies against the GLP-1R agonists.

Currently, the ADA/EASD treatment algorithm suggests lifestyle and metformin therapy as the initial treatment for type 2 diabetes [26]. As a second line-of-attack therapy, either SU or insulin is recommended as the well-validated Tier 1 approach and TZD or GLP-1R agonists as the less-validated, but acceptable, Tier 2 approach. This recommended treatment algorithm has recently raised a lot of debate [93], and especially the place of the GLP-1R agonists in this guideline is currently disputed. An emerging therapeutic trend toward initial or early combination therapy with metformin- and incretin-based therapy could probably gain acceptance in the short-term future because it represents a more exhaustive attempt to negate the multiple pathophysiological features of type 2 diabetes. We believe that the role of the emerging GLP-1R agonists will continue to evolve as we gain more information on the safety and efficacy of GLP-1R agonists, including the interesting studies to evaluate long-term cardiovascular outcomes.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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