CLINICAL INVESTIGATION

Dulaglutide: a novel once-weekly glucagon-like peptide-1 receptor agonist

Dulaglutide is a novel continuous-acting glucagon-like peptide-1 (GLP-1) receptor agonist developed for the treatment of Type 2 diabetes. It consists of two modified 'GLP-1' moieties covalently linked to a human immunoglobulin (IgG) 4-FC heavy chain. The large size of the molecule prolongs plasma half-life and allows for once-weekly administration. Clinical Phase II and III trials show dose-dependent reductions of HbA1c up to 1.6%, reduction in fasting plasma glucose up to 2.7 mmol/l and weight reductions up to 3.2 kg. Presumably, a dose of 1.5 mg once weekly will be the intended dose for treatment. Safety data indicate a low incidence of hypoglycemia and the most frequently reported adverse events are gastrointestinal, primarily nausea, which seem to reduce over time.

Keywords: antidiabetic medication • dulaglutide • GLP-1 receptor agonist • incretin-based therapy • LY2189265 • Type 2 diabetes

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The increasing variety of pharmacological agents for the treatment of Type 2 diabetes has improved the possibility of tailoring individual treatment regimens, but at the same time it has complicated the management of patients with Type 2 diabetes and increased the demand of in-depth pharmacological knowledge among healthcare providers.

Type 2 diabetes is associated with increased morbidity and mortality and up to 80% of patients with Type 2 diabetes are overweight or obese. As little as 1-kg reduction in bodyweight has been shown to improve glycemic control and reduce morbidity and mortality [1]. The glucagon-like peptide-1 (GLP-1) receptor agonists constitute a group of antidiabetic medications, which in addition to glycemic control confer bodyweight reduction [2].

The mode of action of GLP-1 receptor agonist is based on the effects of the naturally occurring gut hormone, GLP-1. GLP-1 is secreted from enteroendocrine L cells lining the epithelium of the intestines into the blood stream in response to ingestion of food. The physiological effects of GLP-1 are mediated by a G protein-coupled receptor [3], which has been shown to be widely distributed across different tissues, including the brain, heart, stomach, pancreas, blood vessels, kidneys and fat cells [4–6]. In the pancreas, GLP-1 augments insulin release in the context of hyperglycemia and suppresses glucagon secretion, thereby limiting postprandial hyperglycemia [7]. In addition to its insulinotropic and glucagonostatic effects, GLP-1 exerts several effects of potential benefit for patients with Type 2 diabetes. These include improvement of β-cell function [8–10], improved left ventricular function and relaxing of conduit vessels/arteries [11,12], delayed gastric emptying, increased feeling of satiety and decreased energy intake [13]. In general, patients with Type 2 diabetes exhibit normal postprandial plasma responses of GLP-1 [14]; however, reduced postprandial GLP-1 levels have been reported by some studies [15–17]. It is noteworthy that the glucagonostatic effect of GLP-1 is preserved in Type 2 diabetes [18] and that robust insulin secretory responses can be attained after administration of GLP-1 resulting in supraphysiological plasma

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levels [19]. Therefore, it has been demonstrated that parenteral administration of native GLP-1 can increase the insulin response in patients with Type 2 diabetes and completely normalize their blood glucose levels [20–22]. However, the rapid breakdown of GLP-1 by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4) incurs the critical drawback (with respect to pharmacological utility) of a very short half-life of native GLP-1 (1–2 min) following intravenous administration [23]. To circumvent this physiological degradation stable, DPP-4-resistant GLP-1 receptor agonists with increased half-lives have been developed. The GLP-1 receptor agonists can be classified based on their pharmacokinetic profile and the resulting exposure pattern of the GLP-1 receptor. This can be as either short-acting or continuous-acting compounds, that is short acting with short-lasting bursts of pharmacological plasma levels associated with administration, and continuous acting with constant pharmacological plasma levels. Currently, two short-acting GLP-1 receptor agonists are approved for the treatment of Type 2 diabetes; exenatide twice-daily (a synthetic version of exendin-4, a hormone isolated from the saliva of the Gila monster lizard) with a half-life of 2.4 h, and lixisenatide (a 44-amino-acid peptide, consisting of exendin-4 modified C-terminally by deletion of a proline residue and addition of six C-terminal lysine residues) with a half-life of 3 h [24]. In addition, two continuous-acting GLP-1 receptor agonists are approved for the treatment of Type 2 diabetes; liraglutide (an acylated GLP-1 analog with 97% amino acid sequence homology to endogenous human GLP-1) with a half-life of 11–15 h administered once daily, and exenatide once weekly; a biodegradable microsphere comprising the exenatide molecule allows slow release. Three additional continuous-acting GLP-1 receptor agonists are in late-stage clinical development, albiglutide (GlaxoSmithKline, DE, USA), semaglutide (Novo Nordisk, Bagsvaerd, Denmark) and dulaglutide (Eli Lilly, IN, USA) [25–27]. The focus of this review is the novel, continuous-acting, once-weekly administered GLP-1 receptor agonist, dulaglutide, being developed for the treatment of Type 2 diabetes.

Structure of dulaglutide

The main feature that distinguishes dulaglutide from the other GLP-1 receptor agonists is the unique structure and the resulting pharmacokinetic profile [27]. Dulaglutide consists of two identical, but separate modified 'GLP-1' moieties, which are protected from DPP-4 cleavage by amino acid substitutions in order to prolong the insulinotropic activity of the molecules (Figure 1). The two modified 'GLP-1' molecules are covalently linked by small peptide-based linkers to a human immunoglobulin (IgG) 4-FC heavy chain, also modified to reduce immunogenicity and antibody functions and to increase stability [28]. The combination of dulaglutide's large size that limits renal clearance, and the amino acid substitutions that promote DPP-4 resistance substantially prolongs biological activity, which allows for once-weekly administration [29,30]. The clinical effects of dulaglutide have been investigated in four published, randomized, controlled Phase I and II trials [29–32] and in five long-term Phase III trials [33–37], referred to as the assessment of weekly administration of dulaglutide in diabetes (AWARD) trials. Data from the AWARD-1, -3 and -5 trials were presented at the 49th Annual Meeting of the European Association for the Study of Diabetes in Barcelona, September 2013 [33–37].

Pharmacokinetics of dulaglutide

Two studies have analyzed dulaglutide's pharmacokinetic profile in healthy subjects and patients with Type 2 diabetes, respectively [29,30]. The time to maximal plasma drug concentration (T_{max}) after single dose subcutaneous administration ranged from 12 to 72 h in patients with Type 2 diabetes, which illustrates a slow absorption rate. The resulting observed mean plasma half-life was 90 [30] and 95 h [29], respectively, in the two studies. Steady state was achieved after two weekly doses of dulaglutide. The mean apparent volume of distribution was 21.5 l in patients with Type 2 diabetes and 14 l in healthy volunteers. There are no publically available data on dulaglutide's metabolism or bioavailability. Dulaglutide has a clearance of 0.107 l/h for healthy subjects and 0.157 l/h for Type 2 diabetics [29,30].

Pharmacokinetic parameters have also been determined in animal models. After a single subcutaneous dose of 0.1 mg/kg dulaglutide, maximum concentration was 179 ng/ml for rats and 292.2 nm/ml for monkeys and T_{max} was reached after 24 h for rats and 17 h for monkeys. Area under the curve (AUC) was 10.5 µg/ml × h for rats and 15.2 µg/ml × h for monkeys [28].

Pharmacodynamics & efficacy of dulaglutide

Phase II studies

The efficacy and safety of dulaglutide in patients with Type 2 diabetes has been reported from two Phase II studies [31,32]. In a 12-week, double-blind, placebo-controlled, dose-response study, 167 patients with Type 2 diabetes were enrolled at 44 sites in seven countries [31]. Patients were antidiabetic medication-naive (19%) or had discontinued metformin monotherapy for 8 weeks before randomization (81%), and were randomized to four dose groups of once-weekly subcutaneous dulaglutide (0.1, 0.5, 1.0 or 1.5 mg) or placebo.

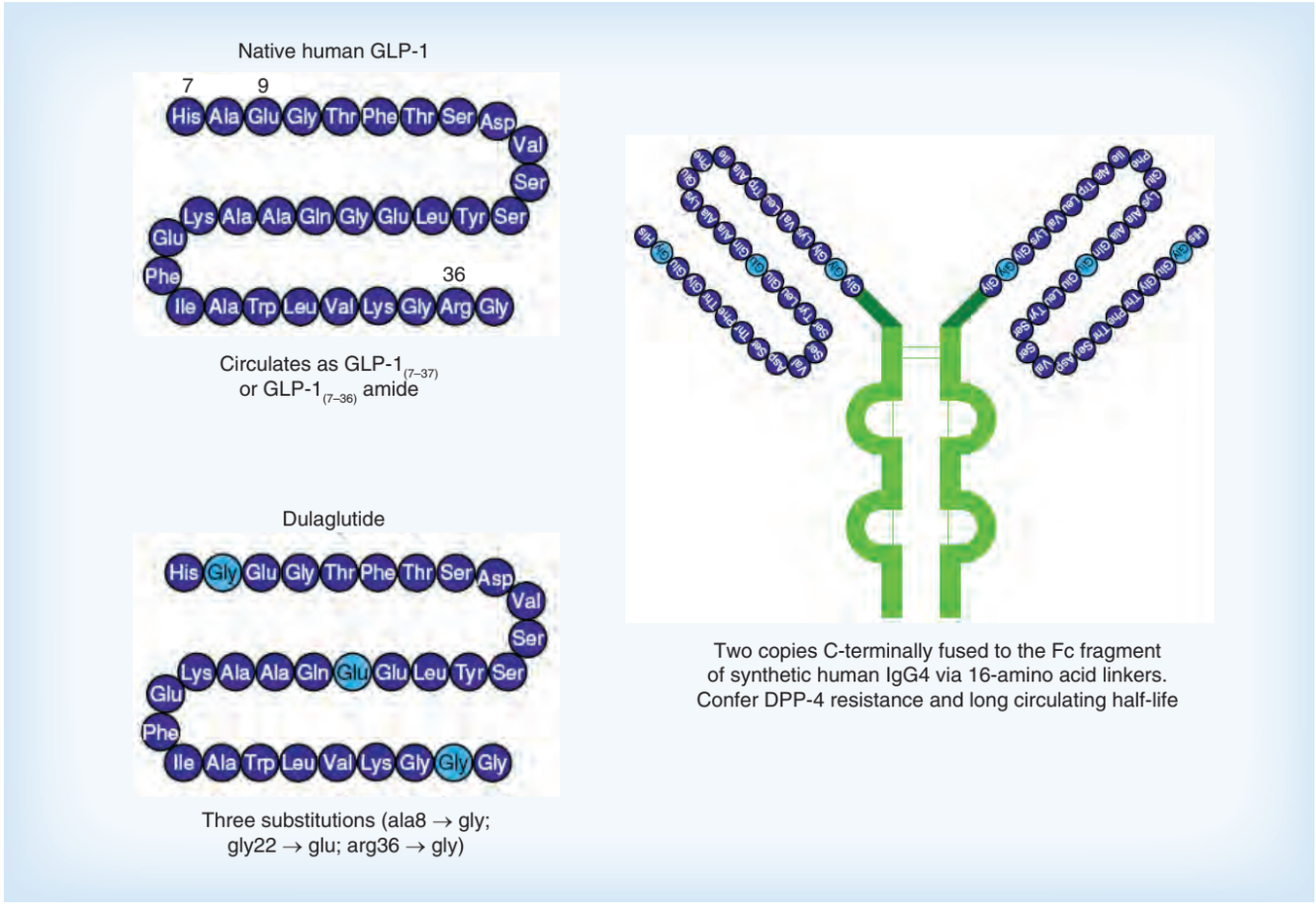

Figure 1. Strutcture of dulaglutide.
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On average, patients were well regulated (mean ± standard error of the mean [SEM] glycated hemoglobin [HbA1c]: 7.2 ± 0.6% [56 ± 6 mmol/mol]) and mildly obese (mean ± SEM BMI: 32.1±4.8 kg/m^2) with a mean ± SEM bodyweight of 88.2 ± 18.6 kg. The majority (93%) of patients completed the study and only 2.4% discontinued primarily owing to side effects. All dulaglutide doses, except dulaglutide 0.1 mg ($p = 0.069$), resulted in significant ($p < 0.05$) HbA1c reductions after 12 weeks compared with placebo (which did not change baseline HbA1c): -0.9% (0.5 mg), -1.0% (1.0 mg) and -1.0% (1.5 mg). Changes in fasting plasma glucose were -0.4 mmol/l (0.1 mg), -1.5 mmol/l (0.5 mg), -1.7 mmol/l (1.0 mg), -1.9 mmol/l (1.5 mg) and -0.2 mmol/l (placebo; $p < 0.001$ compared with placebo, except for the 0.1-mg dose group [$p = 0.456$]). In addition, a dose-dependent reduction in postprandial plasma glucose was reported; with a significantly greater decrease than that of placebo in the dulaglutide 0.5-, 1.0- and 1.5-mg groups (data not reported). β-cell function assessed by the homeostatic model assessment (HOMA2-%B) increased by 15.2% (0.1 mg, $p > 0.05$), 33.7% (0.5 mg), 41.1% (1.0 mg) and 31.4% (1.5 mg) in the dulaglutide groups, whereas a significant decrease (-2.1%; $p = 0.036$) was observed in the placebo-treated group. There was also a dose-dependent reduction in bodyweight across the dulaglutide groups ($p = 0.009$): -0.2 kg (0.1 mg), -0.3 kg (0.5 mg), -1.1 kg (1.0 mg) and -1.5 kg (1.5 mg), however, compared with placebo (-1.4 kg) this was not significant. The authors note that two of the patients in the placebo group experienced weight loss of 11.2 and 11.3 kg as a result of hemorrhagic pancreatitis and participation in a weight-loss program, respectively, and that the nonsignificant differences in bodyweight between active and placebo treated groups may partly be related to this [31].

In the other Phase II study, the EGO study [titration effect of dulaglutide (GLP-1 analog) in overweight/obese], a 16-week, double-blind, placebo-controlled, multiple-dose, parallel-group study, 262 patients with Type 2 diabetes and a BMI between 27 and 40 kg/m^2, with a mean age of 57 years, race: 58% white, bodyweight: 96.2 kg, BMI: 33.9 kg/m^2, duration of diabetes: 8.3 years and HbA1c of 8.24%

received two different oral antidiabetic medications of either metformin, sulfonylurea, thiazolidinedione or DPP-4 inhibitor (73% received metformin in combination with sulfonylurea) [32]. Patients were randomized to one of three dulaglutide groups or placebo. The three groups were dulaglutide 0.5 mg once weekly for 4 weeks, then dulaglutide 1.0 mg once weekly for 12 weeks (0.5/1.0 mg); dulaglutide 1.0 mg once weekly for 16 weeks (1.0/1.0 mg); or dulaglutide 1.0 mg once weekly for 4 weeks, then dulaglutide 2.0 mg once weekly for 12 weeks (1.0/2.0 mg). At 16 weeks HbA1c was reduced significantly in all groups: -1.4% (0.5/1.0 mg), -1.3% (1.0/1.0 mg), -1.6% (1.0/2.0 mg) and -0.2% (placebo) (all $p < 0.001$ vs placebo). The changes in HbA1c did not differ significantly between the three dulaglutide groups ($p > 0.05$). Fasting plasma glucose after 16 weeks was significantly reduced in all groups by 2.1 mmol/l (0.5/1.0 mg), 2.1 mmol/l (1.0/1.0 mg), 2.7 mmol/l (1.0/2.0 mg) and 0.5 mmol/l (placebo), respectively (all $p < 0.001$ vs placebo). Compared with baseline, mean changes in bodyweight after 16 weeks were -1.4 kg (0.5/1.0 mg), -1.3 kg (1.0/1.0 mg), -2.6 kg (1.0/2.0 mg), and -0.1 kg (placebo; all $p < 0.05$ vs placebo). β-cell function (assessed by HOMA2-%B) increased by 39.2% (0.5/1.0 mg), 44.3% (1.0/1.0 mg), 45.6% (1.0/2.0 mg) and 1.0% (placebo) (all $p < 0.01$ vs placebo) [32].

Phase III studies

In the AWARD-5, a Phase II/III, multicenter, randomized, double-blind, placebo-controlled, 24-month, parallel clinical trial, the initial phase of the study aimed to identify two safe and efficacious doses of dulaglutide [38]. A total of 230 patients with Type 2 diabetes taking metformin (≥1500 mg/day) as the only glucose-lowering medication were randomized to one of nine treatment arms: placebo, sitagliptin 100 mg once daily or one of seven different dulaglutide doses ranging from 0.25 to 3.0 mg once weekly. The optimal dose based on tolerability and efficacy was selected to be dulaglutide 1.5 mg once weekly, and dulaglutide 0.75 mg once weekly was selected as the lower dose [35]. After dose selection, AWARD-5 continued for a total of 104 weeks. Nonselected dulaglutide dose groups were discontinued and the study included additional patients and continued in four arms. Therefore, ultimately, a total population of 1098 patients (with a background concomitant therapy of metformin ≥1500 mg/day) was randomized to dulaglutide 0.75 mg (n = 302), dulaglutide 1.5 mg (n = 304), sitagliptin 100 mg (n = 315) and placebo (n = 177). After 26 weeks the patients in the placebo arm transitioned to the sitagliptin arm [34]. The mean baseline characteristics of the enrolled patients were as follows: age: 54 years, race: 52% white, bodyweight: 86.4 kg, BMI: 31.3 kg/m^2, duration of diabetes: 7.1 years, HbA1c: 8.1% (65 mmol/mol) and fasting plasma glucose: 9.7 mmol/l. The primary objective of the second phase of the study was to compare safety and efficacy of dulaglutide to sitagliptin. The mean HbA1c changes from baseline after 26/52/104 weeks amounted to -1.01/-0.87/-0.71% (0.75 mg), -1.22/-1.10/-0.99% (1.5 mg) and -0.61/-0.39/-0.32% (sitagliptin; all $p < 0.001$ vs sitagliptin). Mean changes in fasting plasma glucose after 52/104 weeks amounted to -1.6/-1.4 mmol/l (0.75 mg), -2.4/-2.0 mmol/l (1.5 mg) and -0.9/-0.5 mmol/l (sitagliptin; all $p < 0.001$ vs sitagliptin). Percentage of patients achieving HbA1c <7.0% (53 mmol/mol) after 26/52/104 weeks were 55/49/45% (0.75 mg), 61/58/54% (1.5 mg) and 38/33/31% (sitagliptin; all $p < 0.001$ vs sitagliptin). Weight changes from baseline after 52/104 weeks of treatment were -2.7/-2.4 kg (0.75 mg), -3.2/-2.9 kg (1.5 mg) and -1.6/-1.8 kg (sitagliptin; all $p < 0.05$ vs sitagliptin, except dulaglutide 0.75 at 104 weeks, p-value not shown) [33,34].

The AWARD-1, a 52-week, randomized, placebo-controlled study compared the effect of dulaglutide (0.75 mg and 1.5 mg once weekly) with exenatide twice daily (BID) and placebo [37]. A total of 978 patients with Type 2 diabetes treated with metformin (1500–3000 mg) and pioglitazone (30–45 mg) were randomized to nonblinded exenatide 10 µg BID (first 4 weeks 5 µg twice daily) or to 0.75 or 1.5 mg once weekly dulaglutide, or placebo. The mean baseline characteristics of patients were: age: 55.7 years, race: 74% white, bodyweight: 95.8 kg, BMI: 33.4 kg/m^2, duration of diabetes: 8.8 years and HbA1c: 8.1% (645 mmol/mol). After 26 weeks, patients receiving placebo were randomly assigned to 0.75 or 1.5 mg once-weekly dulaglutide for an additional 26 weeks. Changes in HbA1c from baseline after 26/52 weeks amounted to -1.3/-1.1% (0.75 mg), -1.5/-1.4% (1.5 mg) and -1.0/-0.8% (exenatide BID; all $p < 0.001$ vs exenatide BID). Significantly higher percentages of patients reached the HbA1c target of <7.0% (53 mmol/mol) in the dulaglutide arms after 26/52 weeks (66/59% [0.75 mg] and 78/71% [1.5 mg]) than in the exenatide arm (52/49%). After 52 weeks fasting serum glucose levels were significantly reduced in all three arms (-1.6 mmol/l [0.75 mg], -2.0 mmol/l [1.5 mg] and -1.0 mmol/l [exenatide], $p < 0.05$ vs exenatide BID). Weight change from baseline after 52 weeks amounted to +0.5 kg (0.75 mg), -1.1 kg (1.5 mg), and -0.8 kg (exenatide). There was no significant difference in weight between exenatide BID and dulaglutide 1.5 mg (p-value not shown), whereas exenatide BID showed significantly greater weight reduction than dulaglutide 0.75 mg ($p < 0.05$) [37].

The AWARD-3, a Phase III, randomized, double-blind, parallel-arm study compared the efficacy and safety of dulaglutide (0.75 and 1.5 mg) to metformin (2000 mg) in 807 patients with early Type 2 diabetes treated with diet or exercise alone or in combination with one oral antidiabetic medication. Patients were randomized to one of three treatment arms; dulaglutide 1.5 mg, dulaglutide 0.75 mg or metformin 1000 mg twice daily [36]. The mean characteristics of the enrolled patients were: age: 55.6 years, bodyweight: 92.3 kg, duration of diabetes of 2.6 years and HbA1c 7.6%. Both dulaglutide doses were superior to metformin after 26 weeks with regard to HbA1c change from baseline, but after 52 weeks only dulaglutide 1.5 mg was superior to metformin. The change in HbA1c after 26/52 weeks was: -0.7/-0.6% (0.75 mg), -0.8/-0.7% (1.5 mg) and -0.6/-0.5% (metformin) ($p < 0.025$ vs metformin). Change in bodyweight was greater in the metformin-treated group after 52 weeks than in both of the dulaglutide-treated groups and amounted to -1.4/-1.1 kg (0.75 mg), -2.3/-1.9 kg (1.5 mg) and -2.2/-2.2 kg (metformin) after 26/52 weeks. The proportion of patients with HbA1c <7% after 26/52 weeks was 63/53% (0.75 mg), 62/60% (1.5 mg) and 54/48% (metformin) (all $p < 0.05$ vs metformin, except dulaglutide 0.75 mg after 52 weeks) [36].

Table 1 provides an overview of the efficacy data of dulaglutide 1.5 mg (as this probably will be the recommended dose for treatment of Type 2 diabetes). In one study the 1.5-mg dose was not tested, and therefore data of dulaglutide 1.0 mg for 4 weeks and 2.0 mg for 12 weeks are displayed.

Safety of dulaglutide

Phase I & II studies

In a study of 20 healthy subjects adverse events with escalating doses of dulaglutide (0.1–12 mg) were mainly gastrointestinal and dose dependent [30]. The most common adverse events reported were dyspepsia (80%), nausea (60%), anorexia (55%), abdominal pain (45%), dizziness (40%) and vomiting (40%). A total of 30% experienced hypoglycemia (plasma glucose <3.9 mmol/l), the lowest glucose level measured was 2.9 mmol/l and none of the episodes was associated with symptoms. A dose-dependent increase in heart rate of 1 bpm (0.1 mg) to 15 bpm (12 mg) was observed. In addition, a significant increase in diastolic blood pressure of 4.2 mmHg in dulaglutide 12-mg-treated patients compared with placebo was observed, whereas no changes in systolic blood pressure were seen. Four serious adverse events occurred; all in one subject following administration of 12-mg dulaglutide: hematemesis, increased blood bilirubin, esophagitis and gastritis. No subjects developed antibodies to dulaglutide [30].

Table 1. Efficacy data on subcutaneous dulaglutide 1.5 once weekly.

Phase II and III studies of dulaglutide	Dulaglutide dose (mg)	Background therapy	Comparator	HbA1c change from baseline (%)		Change in fasting blood glucose from baseline (mmol/l)		Weight change from baseline (kg)		Ref.
				DG	Comp.	DG	Comp.	DG	Comp.	
EGO (n = 262)	1.0/2.0	Two oral antidiabetics	Placebo	-1.6*	-0.2	-2.7*	0.5	-2.6*	-0.1	[32]
Grunberger *et al.* (n = 167)	1.5	None or metformin	Placebo	-1.0*	0.0	-1.9*	-0.2	-1.5 (ns)	-1.4	[31]
AWARD 1 52 weeks (n = 978)	1.5	Metformin and pioglitazone	Exenatide BID 10 µg	-1.4*	-0.8	-2.0*	-1.0	-1.1 (ns)	-0.8	[37]
AWARD 3 52 weeks (n = 807)	1.5	None or one oral antidiabetic	Metformin 2000 mg	-0.7*	-0.5	-1.6	-1.3	-1.9 (ns)	-2.2	[36]
AWARD 5 52 weeks (n = 1098)	1.5	Metformin	Sitagliptin 100 mg	-1.1*	-0.4	-2.4*	-0.9	-3.2*	-1.6	[34]
AWARD 5 104 weeks (n = 1098)	1.5	Metformin	Sitagliptin 100 mg	-1.0*	-0.3	-2.0*	-0.5	-2.9*	-1.8	[33]

*Significant vs comparator.
Data from the EGO study [32] are of dulaglutide doses: 1.0 mg for 4 weeks and 2.0 mg for 12 weeks.
BID: Twice daily; Comp.: Comparator; DG: Dulaglutide; ns: Nonsignificant.

In a study including 43 patients with Type 2 diabetes treated with metformin (65%), thiazolidinediones (5%) or no antidiabetic medication (30%), patients received increasing doses of dulaglutide (0.05, 0.3, 1.0, 3.0, 5.0 and 8.0 mg) [29]. The most commonly reported adverse effects were nausea (37%), headache (23%), vomiting (19%) and diarrhea (14%). Three patients were withdrawn because of adverse events; two because of nausea and vomiting (1.0- and 8.0-mg doses) and one because of increased eosinophil count and creatinine levels (5-mg doses). One serious adverse event was reported during the study: a case of chest pain related to first dose of dulaglutide. This was determined to be of gastrointestinal etiology. Significant increases in supine pulse rate were observed at doses of 1 mg or greater; with the greatest change at 5-mg dose (10 bpm change from baseline after 5 weeks). There was no significant change in blood pressure in any of the dulaglutide groups. The study reported one case of hypoglycemia (plasma glucose of 3.78 mmol/l; 0.3 mg dulaglutide). No subjects developed antibodies to dulaglutide [29].

In a study with dulaglutide monotherapy for 12 weeks in patients with Type 2 diabetes (n = 167), there was no obvious dose dependency across the different groups (0.1, 0.5, 1.0 or 1.5 mg), but the most frequent treatment-emergent adverse events were gastrointestinal; nausea (8%), diarrhea (6%), constipation (5%), dyspepsia (4%) and vomiting (3%). 10.3% reported hypoglycemia in the 1.5-mg dulaglutide group, compared with 3.1% in the placebo group. There were no severe incidences of hypoglycemia. There were three serious adverse events of which two were considered possibly related to the drug: one abdominal pain/distension and one atrial flutter. One case of antidulaglutide antibody was reported [31].

In a study of obese/overweight patients with Type 2 diabetes (n = 262) with a background therapy of two oral antidiabetics (73% received metformin and sulfonylurea) patients were treated with dulaglutide in titrated or fixed doses (0.5/1.0 mg, 1.0/1.0 mg and 1.0/2.0 mg) for 16 weeks [32]. The most common adverse events were nausea (15%), diarrhea (9%), abdominal distension (9%) and constipation (8%), but only the incidence of constipation was statistically higher than in the placebo group ($p = 0.039$). Hypoglycemia was an uncommon event, but more frequent with dulaglutide than placebo through the initial 4 weeks of the study ($p < 0.05$). There were three serious adverse reactions possibly related to dulaglutide; two cases of pancreatitis, one hallucination and one cryptogenic organizing pneumonia. No differences in cardiovascular events or blood pressure were shown between treatments. No patients showed significant treatment-emergent immunogenicity [32].

Phase III studies

In the AWARD-1 study dulaglutide was given on top of metformin and pioglitazone and compared with exenatide twice daily. In the course of 1 year, nausea was reported as the most frequent adverse event and was dose related, and in the relevant dulaglutide 1.5-mg dose 29% of the patients experienced nausea. Compared with exenatide-treated patients, of whom 28% reported nausea after 1 year, there was no significant difference. The majority of gastrointestinal adverse reactions were seen within the first 6 weeks, and then decreased over time. Vomiting was initially experienced by 17% of patients in the 1.5-mg dulaglutide group and by 12% in the exenatide group, but this adverse event decreased over time. There was no significant difference in reports of diarrhea compared with exenatide, and injection site reactions were few and did not differ from placebo or exenatide-treated patients. The incidence of documented hypoglycemia (≤3.9 mmol/l) was lower for both dulaglutide doses than for exenatide; 0.4 events/patient/year (1.5 mg), 0.9 events/patient/year (0.75 mg) and 1.15 events/patient/year (exenatide). There were no reports of severe hypoglycemia. In the dulaglutide groups there was one case of pancreatitis and one case of pancreas cancer [37].

In the AWARD-5 trial where dulaglutide was given on top of metformin and compared with sitagliptin in the course of 2 years, the most frequent adverse event was nausea, which was experienced by 17% of patients in the 1.5-mg dulaglutide group. Nausea was dose dependent, decreased over time and the frequency was significantly higher among dulaglutide-treated patients than sitagliptin-treated patients (6.7%). Other gastrointestinal side effects such as vomiting, diarrhea and decreased appetite were also more frequent in the dulaglutide-treated groups than in the sitagliptin group. Of patients in the 1.5-mg dulaglutide group, 13% experienced hypoglycemia (≤3.9 mmol/l) compared with 9% in the sitagliptin group. No severe hypoglycemia was reported. Only 1% of patients experienced injection site-related adverse reactions. Both dulaglutide 1.5 mg and dulaglutide 0.75 mg increased heart rate compared with sitagliptin, beginning at 2 weeks and continuing throughout the duration of the trial (2 years). Least square mean treatment difference ranged from 1.5 to 3.5 bpm [33]. After 52 weeks there were three events of acute pancreatitis, all three were in the sitagliptin or placebo-treated groups [34]. In the AWARD-3 where dulaglutide was given as monotherapy or in combination with one other antidiabetic medication and compared with metformin, the incidence of serious adverse events was 5.2% for dulaglutide 1.5 mg, 7.4% for dulaglutide 0.75 mg and 6% for metformin. Documented symptomatic hypoglycemia (≤3.9 mmol/l) was 6.3%

for dulaglutide 1.5 mg, 5.9% for dulaglutide 0.75 mg and 4.9% for metformin. The rank order of incidence of gastrointestinal adverse events among groups was: dulaglutide 1.5 mg > metformin > dulaglutide 0.75 mg [36].

Table 2 summarizes the frequency of the most common adverse events of dulaglutide 1.5 mg matched with the comparing drug or placebo. In one study the dulaglutide dose of 1.0 mg for 4 weeks and subsequent 2.0 mg for 12 weeks are shown.

Ongoing & recently completed clinical trials

There are three additional AWARD trials that have been completed, but only a few results have been published. In AWARD-2, a randomized, open-label, 78-week comparison study of the effects of dulaglutide and insulin glargine in 807 patients treated with metformin and glimepiride. The dulaglutide 1.5-mg dose demonstrated statistically superior reduction in HbA1c from baseline compared with insulin glargine at 52 weeks [39]. In AWARD-4, a randomized, open-label, 52-week comparison of the effects of dulaglutide and insulin glargine both in combination with insulin lispro, in 884 patients with Type 2 diabetes, the dulaglutide 1.5-mg dose in combination with insulin lispro showed statistically superior reduction in HbA1c after 26 weeks compared with insulin glargine in combination with insulin lispro [39]. In AWARD-6, a randomized, open-label, 26 week, parallel arm study, comparing the effects of dulaglutide to once-daily liraglutide on 599 Type 2 diabetic patients on concomitant metformin. Dulaglutide 1.5 mg showed noninferiority to liraglutide 1.8 mg by HbA1c reduction after 26 weeks and adverse events were similar in both groups. Liraglutide-treated patients exhibited a 0.7 kg larger weight loss compared to dulaglutide-treated patients [40].

Tables 3 & 4 summarize the ongoing and recently completed clinical trials of dulaglutide: three of the trials are interaction studies with warfarin, digoxin and oral contraceptives, respectively. Two trials are studying the effects on patients with chronic kidney disease and varying degrees of hepatic impairment, and nine trials are investigating efficacy and safety compared with metformin, glimepiride, liraglutide, sitagliptin, insulin glargine and exenatide, respectively. Six trials are studies of dulaglutide in monotherapy, primarily looking at pharmacokinetic outcomes. The REWIND trial (researching cardiovascular events with a weekly incretin in diabetes) aims to assess the effect of 1.5-mg dulaglutide on cardiovascular outcomes when added to the existing antihyperglycemic regimen. The primary objective is to test whether dulaglutide can reduce the occurrence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke when added to glucose-lowering regimen of patients with Type 2 diabetes, compared with placebo. Several of the studies are reported to be completed, but the results have not yet been published [41].

Conclusion

After a long period with limited progress, the landscape of antidiabetic treatment options has vastly expanded within the last decade. A natural consequence of improved and diversified treatment options is that treatment guidelines now emphasize a tailored approach suited to the individual patient needs. Additionally, main focus points in antidiabetic treatment have shifted beyond glycemic control to encompass bodyweight control and risk of hypoglycemia as important factors to consider when choosing the optimal treatment for the individual patient [2].

Currently, clinical data with GLP-1 receptor agonists demonstrate sustainable reductions in glycemic indices (i.e., fasting plasma glucose and HbA1c) and bodyweight, while in comparison to 'classical' antidiabetic therapies exhibiting a very favorable safety profile; in particular with very little hypoglycemia combined with bodyweight loss. Nonetheless, the safety of incretin-based therapies in general (i.e., also DPP-4 inhibitors) has attracted massive attention owing to reports of a potential causal role in pancreatitis and pancreatic cancer [42–44]. With the large clinical evidence base and the extensive scrutiny it is reassuring that the regulatory authorities have reported that at present no consistent pancreatic safety issues exist with the incretin-based pharmacological agents [45], which the very few reports of pancreatitis and pancreas cancer in the dulaglutide trials also demonstrate.

Therefore, based on knowledge of efficacy and safety of incretin-based therapy in general and on recent clinical outcomes from dulaglutide Phase III studies in particular, how can dulaglutide be expected to be positioned among the other GLP-1 receptor agonists in the future? So far, the AWARD-1 study has shown superior effects of dulaglutide compared with exenatide twice-daily (Byetta, AstraZeneca, London, UK) in terms of glycemic control with similar frequencies of nausea and similar weight loss [37]. These findings are reassuring, but also expected when comparing a short-acting (Byetta) and continuous-acting GLP-1 receptor agonist [46]. The first sparse results of the AWARD-6 study showed noninferiority to liraglutide (Victoza, Novo Nordisk, Bagsvaerd, Denmark) in terms of HbA1c reduction [40], and such results of head-to-head trials are of obvious and major importance for the future fare and position of dulaglutide. Because dulaglutide is the newest GLP-1 receptor agonist with least safety data, healthcare providers and

Table 2. Safety data on subcutaneous dulaglutide 1.5 mg once weekly.

Phase II and III studies of dulaglutide	Dulaglutide dose (mg)	Background therapy	Comparator	Total adverse events (%)		Serious adverse events (%)		Nausea (%)		Vomiting (%)		Diarrhea (%)		Ref.
				DG	Comp.	DG	Comp.	DG	Comp.	DG	Comp.	DG	Comp.	
EGO (n = 262)	1.0/2.0	Two oral antidiabetics	Placebo	63.1	54.5	1.5	1.5	13.8	7.6	10.8	3.0	13.8	7.6	[32]
Grunberger *et al.* (n = 167)	1.5	None or metformin	Placebo	51.7	46.9	3.4	3.1	6.9	9.4	6.9	6.3	10.3	3.1	[31]
AWARD 1 (52 weeks; n = 978)	1.5	Metformin and pioglitazone	Exenatide BID 10 μg	81	80.1	–	–	29	27.9	16.8	12.0	12.9	7.6	[37]
AWARD 3 (52 weeks; n = 807)	1.5	None or one oral antidiabetic	Metformin 2000 mg	66.5	63.4	5.2	–	19.7	16.0	9.7	4.9	11.2	13.8	[36]
AWARD 5 52 weeks; n = 1098)	1.5	Metformin	Sitagliptin 100 mg	76.7	69.5	9	5	17.4	5.1	12.8	2.2	14.5	2.9	[34]
AWARD 5 104 weeks; n = 1098	1.5	Metformin	Sitagliptin 100 mg	85	77	12	10	17.4	6.7	13.5	3.5	16.1	5.7	[33]

Data from the EGO study [32] are of DG doses: 1.0 mg for 4 weeks and 2.0 mg for 12 weeks.
BID: Twice daily; Comp.: Comparator; DG: Dulaglutide.

Table 3. Clinical Phase I and II trials of dulaglutide.

Study	Phase	Study design	Outcome measurements	Number in study	NCT number	Start date	Status (expected end date)
Effect of LY2189265 on insulin secretion in response to intravenous glucose	Phase I	Crossover, double blind (subject, caregiver, investigator)	AUC and C_{max}	35	NCT01300260	February 2011	Completed
A study of the effect of LY2189265 on blood pressure and heart rate in Type 2 diabetes	Phase II	Parallel, double blind (subject, caregiver, investigator, outcomes assessor)	SBP, DBP, MAP, HbA1c, FBG, bodyweight and HR, rate of dulaglutide antidrug antibodies and hypoglycemic episodes	693	NCT01149421	June 2010	Completed
A single dose study of LY2189265 in subjects with varying degrees of hepatic (liver) impairment	Phase I	Single group, open label	C_{max}, T_{max}, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, $T_{½}$, CL/F, Vz/F	30	NCT01253304	November 2010	Completed
A study of the effect of dulaglutide on how body handles digoxin in healthy subjects	Phase I	Single group, open label	AUC, C_{max} and T_{max} for digoxin	24	NCT01436201	September 2011	Completed
A study of the effect of dulaglutide on the action of warfarin in healthy subjects	Phase I	Crossover, open label	Pharmacokinetics: AUC, AUC_{INR}, C_{max}, INR_{max} and T_{max} for warfarin	28	NCT01432938	September 2011	Completed
A study of LY2189265 and sitagliptin in patients with Type 2 diabetes	Phase I	Crossover, open label	AUC, C_{max} and T_{max} for sitagliptin	32	NCT01408888	August 2011	Completed
A study of the effect of dulaglutide on how the body handles oral contraceptive in healthy female subjects	Phase I	Single group, open label	Pharmacokinetics: C_{max}, T_{max} and AUC for ortho-cyclen	22	NCT01458210	October 2011	Completed
A study to compare the effect of giving dulaglutide using an auto-injector versus a manual syringe	Phase I	Crossover, open label	Pharmacokinetics: C_{max}, T_{max} and AUC	50	NCT01524770	March 2012	Completed
A study of dulaglutide in Chinese participants	Phase I	Parallel, double blind	Pharmacokinetics: C_{max}, T_{max}, AUC and $T_{½}$	68	NCT01667900	August 2012	Ongoing (August 2014)

Please see [41] for more details for each study.
AUC: Area under the concentration versus time curve; AUC_{INR}: Area under the international normalized ratio curve; CL/F: Apparent total plasma clearance; C_{max}: Maximum observed drug concentration; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HR: Heart rate; INR_{max}: Maximum observed international normalized ratio; MAP: Mean arterial pressure; SBP: Systolic blood pressure; T_{max}: Time of maximum observed drug concentration; Vz/F: Apparent volume of distribution.

Table 4. Clinical Phase III trials of dulaglutide.

Study	Phase	Study design	Outcome measurements	Number in study	NCT number	Start date	Status (expected end date)
A study in patients with Type 2 diabetes mellitus (AWARD-1)	Phase III	Parallel, double blind	HbA1c reduction at 26 weeks compared with exenatide	980	NCT01064687	February 2010	Completed
A study in patients with Type 2 diabetes mellitus (AWARD-3)	Phase III	Parallel, double blind	HbA1c reduction at 26 weeks compared with metformin	807	NCT01126580	May 2010	Completed
A study of LY2189265 compared to sitagliptin in patients With Type 2 diabetes mellitus on metformin (AWARD-5)	Phase II/ Phase III	Parallel, double blind	HbA1c, FBG, HOMA2-%S, bodyweight and waist circumferance. Rate of hypoglycemic episodes	1098	NCT00734474	August 2008	Completed
A study in patients with Type 2 diabetes mellitus (AWARD-4)	Phase III	Parallel, open label	HbA1c reduction at 26 weeks compared with insulin glargine	884	NCT01191268	November 2010	Completed
A study in patients with Type 2 diabetes mellitus (AWARD-2)	Phase III	Parallel, open label	HbA1c reduction at 26 weeks compared with glimepiride	807	NCT01075282	February 2010	Completed
A study of dulaglutide in Japanese participants with Type 2 diabetes mellitus	Phase III	Parallel, open label	Change in HbA1c, FBG, SMBG and bodyweight. Rate of hypoglycemic episodes	360	NCT01584232	April 2012	Completed
A study comparing the effect of dulaglutide with liraglutide in Type 2 diabetes (AWARD-6)	Phase III	Parallel, open label	Changes in HbA1c, BMI, FBG, SMBG, HOMA2-%B, ECG, HR, BP, calcitonin, lipase and amylase. Number of participants with acute pancreatitis, hypo- or hyper-glycemic events, allergic or hypersensitivity reactions, or antidrug antibodies	599	NCT01624259	June 2012	Completed
A study of LY2189265 in Japanese participants with Type 2 diabetes mellitus	Phase III	Single group, open label	HbA1c, FBG, SMBG, HOMA2-%S, HOMA2-%B and bodyweight. Rate of hypoglycemic episodes and treatment-emergent adverse events	365	NCT01468181	November 2011	Completed
A study of LY2189265 in Japanese participants with Type 2 diabetes mellitus	Phase III	Parallel, double blind	HbA1c, FBG, SMBG, HOMA2-%S, HOMA2-%B and bodyweight. Rate of hypoglycemic episodes	490	NCT01558271	March 2012	Ongoing (May 2014)

Please see [41] for more details for each study.
AUC: Area under the concentration versus time curve; AUC0-∞: AUC from time zero to infinity; AUC0-tlast: Area under the concentration versus time curve from time zero to the last quantifiable concentration; AUCINR: Area under the international normalized ratio curve; BP: Blood pressure; CL/F: Apparent total plasma clearance; C_{max}: Maximum observed drug concentration; DBP: Diastolic blood pressure; ECG: Electrocardiogram; eCrCl: Estimated creatinine clearance; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; HOMA2-%B: Homeostasis model assessment 2 steady-state β-cell function; HOMA2-%S: Homeostasis model assessment 2 insulin sensitivity cell function; HR: Heart rate; INR_{max}: Maximum observed international normalized ratio; MAP: Mean arterial pressure; SBP: Systolic blood pressure; SCr: Serum creatinine; SMBG: Self-monitored blood glucose; T_{max}: Time of maximum observed drug concentration; UACR: Urinary albumin to creatinine ratio; Vz/F: Apparent volume of distribution.

Table 4. Clinical Phase III trials of dulaglutide (cont.).

Study	Phase	Study design	Outcome measurements	Number in study	NCT number	Start date	Status (expected end date)
A study comparing the effects and safety of dulaglutide with glimepiride in Type 2 diabetes mellitus	Phase III	Parallel, double blind	Change in HbA1c, FBG, SMBG and HOMA2-%B	789	NCT01644500	July 2012	Ongoing (August 2014)
A study comparing the effects and safety of dulaglutide with insulin glargine in Type 2 diabetes mellitus	Phase III	Parallel, open label	Changes in HbA1c, FBG, SMBG, HOMA2-%B and HOMA2-%S. Rate of hypoglycemic episodes	789	NCT01648582	July 2012	Ongoing (November 2014)
Study of how dulaglutide compares to placebo in participants with Type 2 diabetes who are also on sulfonylurea therapy (AWARD-8)	Phase III	Parallel, double blind	Changes in HbA1c, BMI, FBG, SMBG, calcitonin, lipase, number of participants with acute pancreatitis, persistent hyperglycemia or cardiovascular events. Dulaglutide antidrug antibodies	285	NCT01769378	January 2013	Ongoing (December 2014)
A study comparing dulaglutide with insulin glargine on glycemic control in participants with Type 2 diabetes (T2D) and moderate or severe chronic kidney disease (CKD)	Phase III	Parallel, open label	Changes in HbA1c, FBG, SMBG, average glucose, Scr, eGFR, eCrCl, UACR and bodyweight. Rate of hypoglycemic episodes, allergic or hypersensitivity reactions	564	NCT01621178	July 2012	Ongoing (January 2016)
Researching cardiovascular events with a weekly incretin in diabetes (REWIND)	Phase III	Parallel, double blind	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, all-cause mortality and heart failure	9622	NCT01394952	July 2011	Ongoing (April 2019)

Please see [41] for more details for each study.
AUC: Area under the concentration versus time curve; AUC0-∞: AUC from time zero to infinity; AUC0-tlast: Area under the concentration versus time curve from time zero to the last quantifiable concentration; AUCINR: Area under the international normalized ratio curve; BP: Blood pressure; CL/F: Apparent total plasma clearance; C_{max}: Maximum observed drug concentration; DBP: Diastolic blood pressure; ECG: Electrocardiogram; eCrCl: Estimated creatinine clearance; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; HOMA2-%B: Homeostasis model assessment 2 steady-state β-cell function; HOMA2-%S: Homeostasis model assessment 2 insulin sensitivity cell function; HR: Heart rate; INR_{max}: Maximum observed international normalized ratio; MAP: Mean arterial pressure; SBP: Systolic blood pressure; SCr: Serum creatinine; SMBG: Self-monitored blood glucose; T_{max}: Time of maximum observed drug concentration; UACR: Urinary albumin to creatinine ratio; Vz/F: Apparent volume of distribution.

patients will demand data that confirm dulaglutide to have at least with comparable efficacy or show superiority compared with other continuous-acting GLP-1 receptor agonists, and liraglutide (Victoza) being the benchmark. In addition, as indicated from the 'competition' between the once-weekly administered form of exenatide (Bydureon, AstraZeneca, London, UK) and the once-daily liraglutide, the once-weekly dosing regimen will most probably not help dulaglutide to take market shares without showing similar or superior efficacy to liraglutide [47]. Similarly, head-to-head comparisons with other glucose-lowering drugs, especially with those that also possess low risk of hypoglycemia (DPP-4 inhibitors), and bodyweight-lowering capabilities (SGLT-2 inhibitors), will help to differentiate and position the individual antidiabetic treatment modalities.

A common strength of the GLP-1 receptor agonists is their robust effects on HbA1c when combined with basal insulin; without increasing risk of hypoglycemia and at the same time preventing insulin-induced weight gain. From a theoretical point of view, it may be an advantage to combine basal insulin (effective on fasting plasma glucose) with a short-acting GLP-1 receptor agonist (effective with regard to postprandial glucose excursions). However, new studies (combining the GLP-1 receptor agonist liraglutide and the new basal insulin, degludec) show good results in terms of Hba1c reduction in dysregulated patients with Type 2 diabetes [48]. Therefore, the few, but encouraging results from the AWARD-4 trial, where dulaglutide in combination with insulin lispro showed statistically significant reductions in HbA1c compared with insulin glargine in combination with insulin lispro [39], emphasize that dulaglutide-basal insulin regimens may also be worth pursuing.

Future perspective

The results of long-term cardiovascular safety outcomes with continuous-acting GLP 1 receptor agonists (demanded by the US FDA) will be of major importance for the future fare of this drug class. The severely heightened risk of cardiovascular disease such as myocardial infarction and stroke in patients with Type 2 diabetes is incompatible with anything else than neutral or positive cardiovascular effects of any glucose-lowering drugs. In addition, future long-term cardiovascular efficacy studies (designed to establish long-term beneficial cardiovascular effects) with hard end points will be of great interest for patients and healthcare providers. The purpose of the ongoing REWIND trial [41] is to assess whether dulaglutide can reduce major cardiovascular events in Type 2 diabetic patients with established clinical vascular disease, and trials that resemble this, looking at other long-term cardiovascular outcomes and investigating the safety of other GLP-1 receptor agonists will be of great interest.

Data on the elimination of dulaglutide and its safety and efficacy in patients with reduced renal function are awaited in order to evaluate its utility in this growing group of patients. If some of the abovementioned expectations are met, the potential for dulaglutide to be a success is apparent: approximately 36.7 mil-

Executive summary

Structure of dulaglutide

- Dulaglutide, a novel glucagon-like peptide-1 (GLP-1) receptor agonist, consists of two modified 'GLP-1' moieties covalently linked to a human immunoglobulin (IgG) 4-FC heavy chain, also modified to reduce immunogenicity and antibody functions, and to increase stability.

Pharmacokinetics of dulaglutide

- The mean plasma half-life is approximately 4 days, allowing once weekly dosing. The mechanism of elimination is unknown.

Pharmacodynamics & efficacy of dulaglutide

- In two Phase II studies dulaglutide showed reductions of HbA1c of up to 1.6%, fasting blood glucose of up to 2.6 mmol/l and bodyweight of up to 2.6 kg. β-cell function (assessed by HOMA2-%B) increased up to 45%.
- In three long-term Phase III studies (AWARD-1, -3, -5), the efficacy of dulaglutide was compared with sitagliptin, exenatide twice daily and metformin. It showed significant HbA1c reductions up to 1.4%, significant fasting blood glucose reductions up to 2.4 mmol/l and bodyweight reduction up to 3.2 kg.

Safety of dulaglutide

- Safety data from both Phase II and III trials are mainly gastrointestinal, nausea being the most frequent reported and decreasing over time. Few hypoglycemia incidences and minimal increase in heart rate was found (up to 3.5 bpm). Very few reports of pancreatitis and pancreas cancer occured.

Ongoing & recently completed clinical trials

- A large number of ongoing trials are looking at efficacy and safety compared with other antidiabetics, interaction studies with different medications, studies of dulaglutide in renal and hepatic impairment and dulaglutide and the effects of cardiovascular events.

lion people have diabetes in the USA, and more than 56.3 million in Europe alone [48], and the growing prevalence of diabetes worldwide poses a major public health challenge that requires new and effective treatment modalities.

The fare and future position of dulaglutide looks promising, but will depend further results from head-to-head comparisons with other glucose-lowering drugs in general and other continuous-acting GLP-1 receptor agonists in particular. In addition, safety and efficacy studies in subpopulations of Type 2 diabetic patients (e.g., patients with reduced renal function) and the ongoing large and long-term (>5 years) cardiovascular outcome trial REWIND together with post-trial pharmacovigilance will help to clarify, whether dulaglutide reduces mortality without significant safety issues.

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