An overview of once-weekly glucagon-like peptide-1 receptor agonists—available efficacy and safety data and perspectives for the future

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Incretin-based therapies, such as the injectable glucagon-like peptide-1 (GLP-1) receptor agonists and orally administered dipeptidyl peptidase-4 (DPP-4) inhibitors, have recently been introduced into clinical practice. At present, the GLP-1 receptor agonists need to be administered once or twice daily. Several once-weekly GLP-1 receptor agonists are in phase 3 development. This review examines the efficacy, safety and perspective for the future of the once-weekly GLP-1 receptor agonists: exenatide once weekly, taspogluttide, albiglutide, LY2189265 and CJC-1134-PC, and compared them to the currently available agonists, exenatide BID and liraglutide QD. A greater reduction in haemoglobin A1c (HbA1c) and fasting plasma glucose was found with the once-weekly GLP-1 receptor agonists compared with exenatide BID, while the effect on postprandial hyperglycaemia was modest with the once-weekly GLP-1 receptor agonist. The reduction in HbA1c was in most studies greater compared to oral antidiabetic drugs and insulin glargine. The reduction in weight did not differ between the short- and long-acting agonists. The gastrointestinal side effects were less with the once-weekly agonists compared with exenatide BID, except for taspogluttide. Antibodies seem to be more frequent with exenatide once weekly, while hypersensitivity has been described in few patients treated with taspogluttide. Injection site reactions differ among the long-acting GLP-1 receptor agonists and are observed more frequently than with exenatide BID and liraglutide. In humans, no signal has been found indicating an association between the once-weekly agonists and C-cell cancer. The cardiovascular safety, durability of glucose control and effect on weight will emerge from several ongoing major long-term trials. The once-weekly GLP-1 receptor analogues are promising candidates for the treatment of type 2 diabetes, although their efficacy may not be superior to once-daily analogue liraglutide.

Keywords: albiglutide, antidiabetic drug, CJC-1134-PC, exenatide once weekly, GLP-1 analogue, GLP-1 receptor agonists, incretin therapy, LY2189265, taspogluttide, type 2 diabetes mellitus

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Introduction

The incidence and prevalence of type 2 diabetes are rising steadily worldwide, primarily as a consequence of the increasing prevalence of obesity [1]. Type 2 diabetes mellitus is a complex disease that involves genetic susceptibility for abnormal β-cell function resulting in relative insulin deficiency and insulin resistance in liver, muscle and fat cells as well as excessive glucagon secretion [2]. The defective β-cell function also involves an impaired responsiveness to the two incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [2–4]. The increased morbidity and mortality in type 2 diabetes are both consequences of microvascular (renal disease, neuropathy, retinopathy) and macrovascular complications [5].

A variety of therapeutic options for the treatment of hyperglycaemia in people with type 2 diabetes are available. It is generally accepted that the initial therapy should consist of lifestyle changes plus metformin [6–9]. Some years after diagnosis most patients require combination therapy to achieve effective glycaemic control, but the lack of consensus regarding which agent to add to metformin has provoked debate among physicians [6–10]. Sulphonylurea (SU) and metformin represent together with insulin the ‘old agents’, while thiazolidinediones (TZD) have been used for the last decade. The incretin-based therapies, such as GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, were recently introduced into clinical practice [11–13]. In addition, all of the agents, used alone or in combination, are associated with different adverse events including hypoglycaemia (SU and insulin), weight gain (SU, insulin and TZD), gastrointestinal side effects (metformin and GLP-1 receptor agonist) and increased risk of fractures (TZD) [2,6–10,12]. The DPP-4 inhibitors are weight neutral [11,12,14,15].

The incretin-based therapies have been the focus of much attention during the last years because of their unique mechanisms of action [3,16–18]. The GLP-1 receptor agonists potentiate insulin secretion, inhibit glucagon release, delay gastric emptying and reduce appetite and thereby...
The present review provides an update on currently available clinical trials that have assessed the efficacy and safety of exenatide twice daily (BID) and liraglutide as well as the long-acting once-weekly GLP-1 receptor agonists: exenatide once weekly, taspoglutide and albiglutide (figure 1). The once-weekly GLP-1 receptor agonists illustrated with yellow are discussed in details in the present review.

Exenatide BID (Byetta) and Liraglutide (Victoza)

Currently, two GLP-1 receptor agonists with extended half-lives are available for the treatment of type 2 diabetes [13,25–29]. The first GLP-1 receptor agonist to reach the market (2005), exenatide (synthetic exendin-4; Byetta®, Amylin Pharmaceuticals, Inc., San Diego, CA; Eli Lilly Company, Indianapolis, IN, USA), shares 53% amino acid homology with human GLP-1 [26,28,29]. Liraglutide (Victoza®, Novo Nordisk, Bagsverd, Denmark) is 97% identical to the native hormone and has a fatty acid side chain promoting binding to human albumin after administration [25,27]. The half-life of exenatide after sc administration is about 2.4 h, and exenatide is therefore given twice daily, whereas the half-life of liraglutide is about 13 h and is administered as once-daily sc injection [13,25–29]. Exenatide is given in micrograms (mcg), starting with 5 mcg BID and 10 mcg BID after 4 weeks if tolerated [13,26]. Liraglutide treatment is initiated with 0.6 mg once daily, increasing to 1.2 mg after 1 week and in some patients up to 1.8 mg [13]. The concentration of liraglutide is much higher than that of exenatide, but the fraction of the hormones that is not bound to albumin is very low, so that the concentration of free hormone is probably similar to that of the peak concentration of exenatide [13,25,27]. Because of the large depot of bound liraglutide, its concentration varies little throughout the day (which also means that the timing of injection is uncritical), whereas the concentration of exenatide given twice daily (BID) varies from very low to therapeutic values [26,29]. The uptitration is employed to reduce gastrointestinal side effects [13,25–27,29]. As nausea probably occurs at high peak plasma concentrations of GLP-1 [30], the lower incidence of nausea with liraglutide compared with exenatide may be explained by its sustained release formulation and tachyphylaxis resulting from the sustained plasma level [25,27,31,32]. Exenatide BID is currently approved (2005) for use as an adjunct twice-daily (BID) formulation injected before breakfast and dinner [13,26,29]. Once-daily liraglutide was approved in 2009 in Europe and in 2010 in USA and Japan.

The reduction in haemoglobin A1c (HbA1c) with exenatide BID is about 0.5–1.0% in patients with a baseline HbA1c of 7.9–8.4%, whereas open-label comparator studies showed HbA1c reduction of 1.1–1.5% from baseline HbA1c values of 8.2–9.0% [13,26]. The reduction in HbA1c with liraglutide in clinical controlled trials of the LEAD (Liraglutide Effect and Action in Diabetes) programme was 0.8–1.5% in patients with an average baseline HbA1c of 8.2–8.5%. The reduction was in most cases greater or at least similar to oral comparator antidiabetic drugs [13]. In patients with a mean baseline HbA1c of about 8.5 and 9.8%, the reduction was 1.4 and 2.3%, respectively [13,33]. In a head-to-head comparison (LEAD 6), the reduction in HbA1c was 0.33% greater (−1.12 vs. −0.79%) with liraglutide compared with exenatide [31,32]. Also reduction in fasting plasma glucose was greater (−1.6 vs. −0.6 mmol/l), while weight loss did not differ significantly (−3.24 vs. −2.87 kg) [31,32]. In most phase 3 studies with exenatide and liraglutide, the weight loss was in the range of 2–3 kg after 26 weeks of treatment compared with placebo and greatest when added to metformin [13]. In LEAD 6 pancreatic β-cell function was improved, and triglycerides and free fatty acids were reduced to a greater extent with liraglutide than exenatide. However, the ability to reduce blood pressure (−2.5/1.1 vs. −2.0/1.9 mm Hg) was similar [31,32]. The gastrointestinal side effects were most pronounced with exenatide BID, 28% having nausea and 9.9% vomiting compared with 25.5 and 6.0%, respectively, during treatment with liraglutide [31,32]. After 8–10 weeks the percentage of patients reporting nausea with liraglutide was below 10%, while in the exenatide group the level remained at about 10% [31]. At week 26, only 2.5% of the liraglutide group
had nausea compared with 8.6% in the exenatide group [31]. Antibodies have been reported in approximately 50% during treatment with exenatide versus 4–13% in patients receiving liraglutide [13,34]. In most patients, the antibodies were of low titres and without apparent effect on efficacy [34,35]. In LEAD 6 liraglutide was less immunogenic than exenatide, and fewer than 10% of liraglutide-treated patients developed antibodies to liraglutide [34]. Overall, antiliraglutide antibodies were low, and did not impact the efficacy or safety of liraglutide treatment [34]. Overall, treatment satisfaction was rated slightly higher with liraglutide than exenatide BID [31,32].

Exenatide Once Weekly (Bydureon®)

An exenatide once-weekly (QW) formulation has been developed using biodegradable polymeric microspheres that entrap exenatide (Amylin Pharmaceutical, Ely Lilly and Alkermes Incorporated, Cambridge, MA, USA) [36,37]. Exenatide is incorporated into a matrix of poly(D,L-lactide-co-glycolide) (PLG), which previously has been used as a biomaterial in sutures and in extended release preparations that allow gradual drug delivery at controlled rates [38]. Once released, exenatide is eliminated via the kidneys. After sc injection of 2 mg of exenatide once weekly, a stable plasma exenatide level is obtained after 5–10 weeks, a level which is comparable to the peak concentrations observed with exenatide BID [36,37]. A plasma level of exenatide >50 pg/ml, which is known to reduce fasting plasma glucose concentration, is observed after about 2 weeks of treatment [36].

Clinical Controlled Studies With Exenatide Once Weekly

In a small clinical trial, patients with type 2 diabetes treated with diet and exercise or metformin monotherapy were randomized to placebo (n = 14), 0.8 mg exenatide once weekly (QW) (n = 16) or 2.0 mg exenatide QW (n = 15) [36]. The trial composed of 15 weeks of active treatment followed by a 12-week follow-up. Average baseline HbA1c was 8.5%, and the reduction in HbA1c was −1.4 and −1.7% in the 0.8 and 2 mg groups, compared with an increase of +0.4% in the placebo group. The final HbA1c was 7.2 and 6.6% for the 0.8 and 2.0 mg groups, respectively. More than 80% of patients treated with 2.0 mg reached HbA1c <7.0%. The study showed that the dose–response relationship for HbA1c reduction and weight control differs [36]. Thus, the 2.0 mg dose reduced weight significantly (−3.4 kg) compared with placebo treatment, while the 0.8 mg dose was without any effect on weight [36].

DURATION-1

In the DURATION-1 (Diabetes therapy Utilisation: Researching changes in HbA1c, weight and other factors Though Intervention with exenatide ONce weekly) trial, 10 mcg exenatide BID and 2 mg exenatide QW were compared in a 30-week trial including 295 type 2 patients [35]. Average baseline HbA1c was 8.2%, weight 102 kg, body mass index (BMI) 35 kg/m² and duration of diabetes 6–7 years. The reduction in HbA1c was greater in the exenatide QW group (−1.9%) compared with — 1.5% in the exenatide BID-treated patients (figure 2). Mean difference was 0.33% in HbA1c. Most of the patients reached HbA1c ≤7.0 (77% for QW vs. 61% for BID), and 49% in QW reached an HbA1c ≤6.5 and 25% reached HbA1c ≤6.0%. The reduction in fasting plasma glucose was −2.3 and −1.4 mmol/l in QW and BID groups, respectively. Also fasting plasma glucagon was reduced more with QW, while reduction in postprandial glucose excursions and slowing in gastric emptying were less pronounced in QW compared with BID. The weight loss did not differ between the two groups by 30 weeks (−3.7 kg for QW vs. −3.6 kg for BID), and about 75% of the patients lost weight (figure 3). Both treatments were associated with reduction in triglycerides and blood pressure [35].

After 30 weeks, patients treated with exenatide QW continued treatment, while patients who were treated with exenatide BID shifted to QW for 22 weeks [39]. Two hundred and twenty-eight of the initial 295 patients entered the open-label extension. Patients continuing exenatide QW maintained HbA1c improvement through 52 weeks (−2.0%). Patients switching from exenatide BID to QW achieved further improvements in HbA1c, and both groups displayed the same reduction and mean HbA1c (6.6%) at week 52, and 71 versus 54% achieved HbA1c ≤7.0 and ≤6.5%, respectively. In patients with a basal HbA1c >9.0%, the reduction in HbA1c was 2.6–2.8%. The mean reduction in weight was about −3.6 to −3.7 kg (figure 3) [39]. After 1 year about 78% achieved reduction in both HbA1c and weight. The reduction in fasting plasma glucose was −2.5 mmol/l, but during the shift at week 30 the BID patients experienced a transient increase in fasting plasma glucose for few weeks, which was followed by a further improvement the following weeks. After 52 weeks, the reductions in systolic and diastolic blood pressures were −6.2 and −2.8 mm Hg, respectively. Significant reductions in lipids, especially triglycerides, were shown [39].

Safety and Tolerability. In DURATION-1, the incidence of nausea (26 vs. 35%) and vomiting (11 vs. 19%) was lower in QW compared with BID [35]. Injection site pruritus, or erythema, or induration or pain was observed in 18% of exenatide QW [35]. Most patients developed antibodies to exenatide QW (110 of 148) compared with 71 of 147 patients in the BID group. Antibodies to exenatide peaked in week
The effect of exenatide once weekly compared with oral antidiabetic agents and insulin glargine on changes in weight (kg) from baseline. Baseline body mass index (BMI) in the individual studies is also given.

Most patients with type 2 diabetes often begin pharmacotherapy with metformin, but eventually need additional treatment. In DURATION-2, exenatide QW was compared with pioglitazone and sitagliptin to assess the potential differences between these antidiabetic drugs as add-on therapy to metformin [42]. The average baseline HbA1c was 8.5%, fasting plasma glucose 9.1 mmol/l and BMI 32 kg/m². Patients were randomly assigned to receive 2 mg exenatide QW (n = 170), 100 mg sitagliptin (n = 172) or 45 mg pioglitazone (n = 172) for 26 weeks. Treatment with exenatide QW reduced HbA1c (−1.5%) significantly more than sitagliptin (−0.9%) or pioglitazone (−1.2%) (figure 2). The final HbA1c levels were 7.2, 7.7 and 7.4%, respectively. Significantly more patients reached HbA1c <7.0% with exenatide compared with sitagliptin or pioglitazone. The reduction in fasting plasma glucose was significantly greater with exenatide (−1.8 mmol/l) than with sitagliptin (−0.9 mmol/l) but not with pioglitazone (−1.5 mmol/l). Weight loss with exenatide (−2.3 kg) was significantly greater than with sitagliptin (−1.5 kg) or pioglitazone (−2.8 kg) (figure 3). The reduction in systolic blood pressure was significantly greater with exenatide (−4 mm Hg) compared with sitagliptin, but not pioglitazone. Diastolic blood pressure did not differ between the groups. The improvement in high-density lipoprotein (HDL) and reduction in triglycerides were greatest with pioglitazone. As in other studies with GLP-1 receptor agonists, a reduction in B-type natriuretic peptide as well as microalbuminuria was observed in the exenatide-treated group [13]. No major hypoglycaemia occurred in any group. About 24 and 10% registered nausea with exenatide and sitagliptin, while diarrhoea was observed in 18 and 10%, respectively. Fewer patients withdrew from treatment with sitagliptin (13%) than with exenatide (21%) or pioglitazone (21%). The improvement in treatment satisfaction was greatest with exenatide QW. Thus, the addition of exenatide QW to metformin achieved better glycaemic control and weight loss than sitagliptin and pioglitazone (figures 2 and 3) [42].

It is relevant to compare these data with the results obtained during a 26-week head-to-head comparison between liraglutide and sitagliptin added to metformin in type 2 patients with a baseline HbA1c of 8.5%, fasting plasma glucose 10.0 mmol/l, BMI 33 kg/m² and mean duration of diabetes 6–7 years [43]. The lowering of HbA1c with liraglutide 1.2 and 1.8 mg was −1.24 and −1.50%, respectively, and −0.90% with sitagliptin 100 mg. Nausea was more common with liraglutide 1.2 mg (21%) and 1.8 mg (27%) than with sitagliptin (5%). These findings may suggest that the efficacies of exenatide QW and liraglutide 1.8 mg once daily are similar. Currently, a study comparing exenatide QW and liraglutide once daily is ongoing (further information about the design of the study can be obtained at NCT01029886).

DURATION-3

Both exenatide BID and liraglutide once daily have been compared with insulin glargine [13]. In the open-label DURATION-3 trial, once-weekly exenatide QW (2 mg) was compared with once-daily insulin glargine [44]. Seventy

Figure 3. The effect of exenatide once weekly compared with oral antidiabetic agents and insulin glargine on changes in weight (kg) from baseline. Baseline body mass index (BMI) in the individual studies is also given.
percent of the patients were treated with metformin and 30% metformin plus SU. Starting dose for insulin glargine increased from baseline 10 to 31 IU/day, targeting a fasting glucose range of 4.0–5.5 mmol/l following a prespecified titration algorithm. Average baseline HbA1c was 8.3%, fasting plasma glucose 9.8 mmol/l, BMI 32 kg/m² and duration of diabetes about 8.0 years. The reduction in HbA1c was greater in the exenatide group (−1.5%) than in those taken insulin glargine (−1.3%) (figure 2). Endpoint HbA1c was 6.8 versus 7.0%, and 60 versus 48% reached an HbA1c <7.0%. Mean weight changes were −2.6 kg in the exenatide group and +1.4 kg in the insulin glargine-treated patients (figure 3). Seventy-nine percent of the patients allocated to exenatide had both a reduction in HbA1c and weight, whereas 63% of the patients receiving insulin glargine had a reduction in HbA1c paired with a weight gain [44]. Fasting plasma glucose was reduced in both groups (exenatide −2.1 mmol/l, insulin glargine −2.8 mmol/l, p < 0.001). Mean heart rate at week 26 was raised compared with baseline in the exenatide but not in the insulin glargine group. No other cardiovascular risk factors including lipid concentrations differed between the groups. One hundred and twenty-seven of 233 patients assigned to exenatide developed antiexenatide antibodies, and a lower mean reduction in HbA1c was observed in the antibody-positive group compared with patients not developing antibodies (−1.3 vs. −1.6%) [44]. Minor hypoglycaemia was reported in 19 of 233 exenatide patients (46 events) compared with 58 of 233 insulin glargine patients (135 events), which was significantly different. One patient taking exenatide developed pancreatitis. Calcitonin concentrations were measured in few patients and were within normal limits in all patients. The number of patients, who discontinued treatment because of adverse effects, was 5 versus 1%, respectively. More patients discontinued exenatide QW than insulin glargine due to nausea and injection site reactions [44].

Thus, the exenatide once-weekly treatment resulted in greater HbA1c reduction after 26 weeks than insulin glargine. Insulin glargine produces greater reduction in fasting glucose than did exenatide, while significantly greater reductions in postprandial glucose excursions were obtained with exenatide. Risk of hypoglycaemia was reduced with exenatide, irrespective of background treatment. A notable strength of the study is that it included a standard next step (insulin treatment) in the treatment of patients not responding to two oral antidiabetic agents as an active comparator. An extension period planned for 2.5 years is in progress.

Exenatide BID has previously been compared with insulin glargine in a 6-month trial, where the reduction in HbA1c did not differ between the groups (i.e. reduction was 1.1% in both groups) [45]. Liraglutide has also been compared with insulin glargine in a 6-month study, with a difference in HbA1c treatment effect (0.2%) and body weight in favour of liraglutide (LEAD 5) [46].

**DURATION-4**

In the fourth of the series of DURATION studies (DURATION-4), exenatide once weekly is compared with sitagliptin 100 mg, pioglitazone 45 mg or metformin up to 2500 mg, all in monotherapy (the design of the study is given at NCT00876338). No data have been published.

**DURATION-5**

DURATION-5, like DURATION-1, compared exenatide QW and BID during a 26-week study in 252 type 2 patients with an average baseline HbA1c of 8.4%, fasting plasma glucose 9.1 mmol/l and weight 96 kg [47]. Patients were drug naïve (19%) or treated with one (47%) or a combination of (34%) oral antidiabetic drugs. After 26 weeks, the reduction in HbA1c was greater in QW (−1.6%) than in BID (−0.9%) (figure 2). Fifty-nine percent versus 30% reached the goal of <7.0%. Weight loss was −2.3 versus −1.4 kg after 24 weeks (p = NS) (figure 3). Nausea occurred less frequently with QW (14%) than with BID (35%), and was transient and mild or moderate in intensity in most patients. Injection site reactions were more common with QW. No change in mean calcitonin concentrations was observed, but one patient withdrew due to pancreatitis. Thus, also in DURATION-5 exenatide QW provides superior control compared to exenatide BID [47].

**DURATION-6**

Is a head-to-head comparison between exenatide QW and once-daily liraglutide 1.8 mg, including approximately 900 patients, estimated completion in 2011 (NCT01029886).

Figures 2 and 3 summarize the changes in HbA1c and weight in the DURATION-1, -2, -3 and -5 studies.

**Regulatory Affairs**

In a response letter in October 2010, US Food and Drug Administration (FDA) requested a thorough QT interval study with exposures of exenatide higher than typical therapeutic levels of exenatide QW. The background for the request could be that after a single dose of 10 mcg of exenatide in healthy subjects, a slight positive correlation between plasma exenatide concentrations and changes from baseline in QT interval has been observed [48]. Additionally, the FDA has requested the results of DURATION-5 study to evaluate the efficacy and the labelling of the safety and effectiveness of the commercial formulation of exenatide QW. The Amylin, Lilly and Alkermes’ goal is to submit their reply to the response letter by the end of 2011. Based on the requirements for additional data, the resubmission will likely require a 6-month review by FDA. The decision from the European Medical Agency (EMA) about exenatide QW can be expected in 2011.

**Taspoglutide**

The human GLP-1 receptor agonist taspoglutide (Roche, Basel, Switzerland; Ipsen, Paris, France) has 93% homology with the native hormone [49]. Taspoglutide contains two α-aminoisobutyric acid substitutions replacing Ala8 and Gly35 of hGLP-1(7-36)NH2 [49]. Taspoglutide is fully resistant to DPP-4 degradation [49]. The biological actions have been shown to be similar to those of native GLP-1, and after a single dose of 30 mg, a glucose-lowering effect was found for up to 2
weeks [49]. Taspoglutide has been shown to protect β cells by reducing apoptosis in Zucker diabetic fatty (ZDF) rats, a rodent model of type 2 diabetes [50]. In type 2 patients, taspoglutide restored both first- and second-phase insulin secretion [51]. Roche licensed the drug in 2006 from Ipsen SA.

At present, only two trials have been published as full articles [52,53]. In a phase 2 study, type 2 diabetic patients (n = 306, mean age 55 years, BMI 32.7 kg/m² and duration of disease 5 years) treated with metformin were randomized to 8-week treatment with placebo, taspoglutide, either 5, 10 or 20 mg once weekly or 10 or 20 mg once every second week [52]. Baseline HbA1c was 7.9%. The reduction in HbA1c was −1.0% (5 mg QW), −1.2% (10 mg QW), −1.2% (20 mg QW) and −0.9% (10 mg Q2W) and −1.0 (20 mg Q2W) versus −0.2% with placebo. The greatest reduction in fasting plasma glucose was observed with 10 and 20 mg QW (−2.5 mmol/l compared with −0.8 mmol/l with placebo). After 8 weeks, weight loss was greater in the 10 mg QW (−1.9 kg), 20 mg QW (−2.8 kg) and 20 mg Q2W (−1.9 kg) than in the placebo group (−0.8 kg) [52]. Taspoglutide has also been investigated in a smaller and shorter phase 2 studies [53,54].

During the 2010 meetings in the American Diabetes Association Meeting and the European Association for the Study of Diabetes, five phase 3 studies from the T-emerge (effect of human weekly GLP-1 for glycaemic control) programme were presented. All studies were of 24 weeks’ duration, but with an extension to 52 weeks. The results after 24 weeks were presented. About 6000 patients have been enrolled in the T-emerge programme.

**T-emerge 1**

The T-emerge 1 trial is a double-blinded placebo-controlled study in drug naïve patients [55]. Patients (mean age 55 years, BMI 32 kg/m², baseline HbA1c 7.6% and duration of diabetes about 3 years) were randomized to 10 mg taspoglutide QW (n = 112), 10 mg taspoglutide QW for 4 weeks titrated to 20 mg QW (n = 127) or placebo (n = 115) for 24 weeks. Reduction in HbA1c (−1.0, −1.2 vs. −0.1 %) (figure 4) and fasting plasma glucose (−1.6, −1.9 vs. −0.1 mmol/l) after 24 weeks was significantly greater in the taspoglutide groups compared with placebo, while weight reduction was significantly greater only in 20 mg taspoglutide QW compared with placebo (−1.5, −2.2 vs. −1.2 kg) (figure 5). An HbA1c target of ≤7.0 was reached by 76, 80 and 37%, respectively. Nausea was observed in 26, 31 and 4%, vomiting in 17, 18 versus 0% and diarrhoea in 14, 10 and 4% of the patients in the three groups, respectively. Withdrawal due to gastrointestinal side effects occurred in 5.2, 7.8 and 0.8% of the patients, respectively. Incidence of injection site nodules, or inductions, or pruritus was 4–12% in the taspoglutide groups versus about 1% in the placebo group. Incidence of hypoglycaemia did not differ between the groups [55].

**T-emerge 2**

In the T-emerge 2 trial, taspoglutide was compared with exenatide BID in type 2 patients inadequately controlled with metformin +/- TZD [56]. In this open-label trial, 1149 patients were randomized to 10 mg taspoglutide QW (n = 384), taspoglutide 10 mg for 4 weeks titrated to 20 mg QW (n = 392) or exenatide 5 mcg BID for 4 weeks titrated to 10 mcg BID (n = 373). Baseline characteristics were similar across the groups (age 56 years, duration 6.5 years, baseline HbA1c 8.1% and BMI 33 kg/m²). After 24 weeks, the reduction in HbA1c was significantly greater with both 10 mg taspoglutide QW (−1.2%) and 20 mg QW (−1.3%) compared with the −1.0% reduction with exenatide BID (figure 4). In patients with a baseline HbA1c of ≥8%, the reduction was −1.5, −1.7 and −1.3%, respectively. More patients treated with taspoglutide reached HbA1c ≤7.0% (62, 63 and 46%, respectively). The reduction in fasting plasma glucose was also greater in the taspoglutide groups (−2.1, −2.4, −1.8 mmol/l), whereas the weight reduction was significantly less with taspoglutide 10 mg QW (−1.6 kg) compared with both taspoglutide 20 mg QW (−2.3 kg) and exenatide (−2.3 kg) (figure 5).

A higher incidence of nausea (40, 47 vs. 30%) and vomiting (21, 24 vs. 11%) was observed in the patients treated with taspoglutide (10 and 20 mg) than exenatide BID, respectively. Vomiting occurred in 86 and 83% of the cases on the day of injection, primarily after the first injection with taspoglutide. The incidence of diarrhoea did not differ between the groups. Injection site nodules, or pruritus, or inductions, or erythema...
was observed in 4–10% of the patients given taspoglutide compared with 0.3–0.5% in the exenatide BID group. Incidence of hypoglycaemia did not differ between the groups and was about 8–10%. Total withdrawal was 16, 22 and 16% in the two taspoglutide groups and among the patients treated with exenatide, respectively. Thus, taspoglutide 20 mg QW showed a greater HbA1c reduction, the same weight reduction, but more pronounced gastrointestinal side effect, and more injection site reactions than exenatide BID [56].

After 26 weeks of treatment, during a meal test taspoglutide and exenatide BID reduced postprandial hyperglycaemia and glucagon to a similar extent [57].

T-emerge 3
This study compares taspoglutide 10 and 20 mg with placebo in patients inadequately controlled on metformin plus pioglitazone (more information can be obtained at NCT00744367). No data are available.

T-emerge 4
In the T-emerge 4 trial, taspoglutide was compared with sitagliptin and placebo for 24 weeks [58]. Six hundred and sixty-six type 2 patients treated with metformin in monotherapy were randomized to taspoglutide 10 mg QW, taspoglutide 10 mg QW for 4 weeks titrated to 20 mg QW, sitagliptin 100 mg QD or placebo. Average age was 55 years, HbA1c 8.0%, BMI 32 kg/m² and diabetes duration about 6 years. Reduction in HbA1c was −1.23, −1.30, −0.89 and −0.1%, respectively (figure 4). Fasting plasma glucose was reduced by −2.1, −2.2, −1.3 and 0.1 mmol/l, respectively. In patients with a basal HbA1c ≥ 8.0%, the reduction in HbA1c was −1.85, −1.71, −1.25 and −0.32%. HbA1c ≤ 7.0 was achieved by 64, 65, 50 and 14% of the patients. The weight was reduced with −1.8, −2.6, −0.9 and −0.5 kg in the four groups (figure 5). Nausea was registered in 44, 47, 10 and 9%, vomiting in 21, 28, 4 and 1%, diarrhea in 9, 7, 2 and 1%, and 12, 8, 0.5 and 0% of the patients withdrew because of nausea and vomiting in the taspoglutide 10 mg QW, 20 mg QW, sitagliptin- and placebo-treated groups, respectively. Eighty-four percent of all vomiting was observed on the day of injection of taspoglutide, indicating a burst of the concentration of the agonist shortly after injection. Hypoglycaemia was registered in 7, 5, 5 and 1%, respectively, of the patients. Lastly, injection site nodules, or pruritus or erythema was found in 4–16% of the patients treated with taspoglutide. Thus, taspoglutide provided superior glycaemic control and weight loss compared with sitagliptin and placebo, but at the cost of more gastrointestinal side effects [58].

T-emerge 5
Taspoglutide was compared with insulin glargine in the T-emerge 5 trial [59]. Type 2 patients inadequately controlled by metformin and SU were, after discontinuation of SU, randomized to 10 mg taspoglutide QW (n = 361), or 10 mg taspoglutide QW for 4 weeks and then 20 mg taspoglutide QW (n = 348), or insulin glargine at bedtime (n = 319). Insulin was titrated towards a fasting plasma glucose of 6.1 mmol/l. Mean age was 58 years, basal HbA1c 8.3%, BMI 32 kg/m² and duration of diabetes 9 years. The mean dose of insulin was 36 units after 24 weeks, where the reduction in HbA1c was −0.77, −0.98 and −0.84% in the 10 mg taspoglutide, 20 mg taspoglutide and insulin glargine groups, respectively (figure 4). The reduction in HbA1c did not differ significantly between the groups, but a greater proportion of the patients achieved HbA1c ≤ 7.0 with taspoglutide 10 mg and taspoglutide 20 mg compared with insulin glargine (34, 41 and 28%). Reduction in fasting plasma glucose was greater in the insulin glargine group (−4.0 mmol/l compared with −2.5 and −2.8 mmol/l in the taspoglutide groups). The weight loss was significantly greater in the 10 mg taspoglutide QW (−3.3 kg) and 20 mg taspoglutide QW (−4.1 kg) groups compared with insulin glargine (−0.4 kg) (figure 5). Incidence of hypoglycaemia was lower with taspoglutide (5, 6 vs. 17%), but withdrawal due to adverse events was higher in the taspoglutide groups (11, 17 and 2%, respectively). Total withdrawal was 21, 21 and 9% in the three groups. Nausea was registered in 39, 45 and 2%, vomiting in 20, 23 and 1% and diarrhoea in 13, 13 and 6% of the patients, respectively. Eighty-one percent and 84% of vomiting occurred on the day of injection of taspoglutide. Injection site nodules were observed in 11, 16 versus 0%, and injection site pruritus in 7.1, 4.8 versus 0.3% of the patients in the taspoglutide 10 mg, taspoglutide 20 mg and insulin glargine groups, respectively. Four patients treated with taspoglutide displayed hypersensitivity (see below). The results regarding glycaemic control and weight reduction seem to be quite similar to what have been observed with liraglutide and exenatide in comparison with insulin glargine [13,59].

T-emerge 6
Patients inadequately controlled with metformin and SU (n = 760) were randomized to treatment with taspoglutide 10 and 20 mg or pioglitazone as comparator (the design of the study can be found at NCT00909597). At present, no data are available.

T-emerge 7
In the T-emerge 7 trial, 20 mg taspoglutide QW (n = 149) or placebo (n = 143) was added to metformin in very obese inadequately controlled patients [60]. Baseline characteristics were age 54 years, BMI 37 kg/m² (22% had a BMI > 40 kg/m²), duration of diabetes 5.1 years and average baseline HbA1c was 7.6%. After 24 weeks, the reduction in HbA1c (−0.8 vs. −0.1%) (figure 4) and the reduction in fasting plasma glucose (−1.3 vs. 0.0 mmol/l) and weight (−3.2 vs. −1.9 kg) were significantly greater in the taspoglutide group (figure 5). In patients with a baseline HbA1c ≥ 8.0%, the reduction in HbA1c was −1.3 versus −0.3%. An HbA1c ≤ 7.0 was reached in 73 versus 36%, respectively. Gastrointestinal side effects lead to withdrawal in 3.9 versus 1.3% of the patients, and the incidence of gastrointestinal side effects was similar to that of the other T-emerge trials [60].
Hypersensitivity With Taspoglutide and Stop of Dosing of Taspoglutide in All Ongoing Studies. In a press release in June 2010 (http://www.roche.com/investors/ir_update/inv-update-2010-06-18b.htm), Roche announced that the incidence of hypersensitivity reactions, reported as related to taspoglutide, was higher than expected, although it remains uncommon (incidence <1%). The most frequently reported symptoms were skin reactions and gastrointestinal symptoms, while cardiovascular and respiratory symptoms were less frequent. Roche has identified a potential association between the reactions and antidrug antibodies, and a risk mitigation plan including routine measurements of drug antibodies has been implemented in the phase 3 programme. Nevertheless, September 2010, Roche decided to halt taspoglutide dosing in all on-going studies (http://www.bioportfolio.com...Roche-Stops-Dosing-Patients-In-Late-stage-Taspoglutide-Studies.html—USA).

Albiglutide (Syncria)
Albiglutide (GlaxoSmithKline, Brentford, London, UK) is a human GLP-1 receptor agonist consisting of two copies of a 30-amino acid sequence of a dipetidyl peptidase-4-resistant human GLP-1 (as a tandem repeat) coupled to serum human albumin [61]. Resistance to DPP-4 cleavage is obtained by a single substitution (ala to gly) at the cleavage site of the GLP-1 molecule [61,62]. Plasma half-life is about 5 days, enabling once-weekly dosing. The tandem structure of albiglutide was developed to increase the potency compared with only one GLP-1 molecule bound to albumin, thus the copy attached to albumin mainly functions as a linker. In vitro albiglutide has an IC50 of 0.606 versus 0.019 nM for native GLP-1 [63]. Resistance to DPP-4 cleavage has been observed up to 60 min after incubation with the enzyme [63]. In db/db mice albiglutide reduces blood glucose and delays gastric emptying, whereas in severe combined immunodeficiency (SCID) mice albiglutide exerts anorectic actions following both peripheral and intracerebroventricular administration [63].

In a dose–response study, time to maximum plasma concentration was 2–5 days after a single injection, and the mean half-life was in the range of 6–8 days [61,64]. Probably albiglutide will be developed for once-weekly dosing.

In a phase 2 study of 356 type 2 patients, drug naïve or treated with metformin, they were randomized to albiglutide dosing weekly, biweekly or monthly, or placebo or exenatide as comparator [65]. Albiglutide was given as 4, 15, 30 mg weekly; 15, 30 or 50 mg biweekly or 50 or 100 mg monthly [65]. Steady state for albiglutide was obtained after 4–5 weeks of treatment. A dose-dependent reduction in HbA1c was observed within all albiglutide schedules (baseline HbA1c: 8.0%). After 16 weeks, the HbA1c reduction was similar (−0.87%) for albiglutide 30 mg weekly, −0.79% for 50 mg biweekly and −0.97% for albiglutide 100 mg monthly, compared with −1.17% for placebo and −0.54% for the exenatide group. Similar proportion of the subjects achieved HbA1c <7.0% in 30 mg weekly (52%), 50 mg biweekly (53%) and 100 mg monthly (48%), compared with 20 and 35% in the placebo and exenatide groups, respectively [65].

The reductions in fasting blood glucose were also dose dependent and were corrected for placebo −1.4 mmol/l (30 mg weekly), −1.2 mmol/l (50 mg biweekly) and −1.2 mmol/l (100 mg monthly), respectively, and greater than with exenatide.

Weight loss did not differ significantly and was from −1.1 to −1.7 kg in the albiglutide groups compared with −0.7 kg in the placebo group and −2.4 kg in the exenatide group [65].

Similar to other GLP-1 receptor agonists, an improvement in β-cell function as evaluated by homeostasis model assessment-B (HOMA-B) and a reduction in systolic blood pressure were shown [65]. Lipid parameters were stable during the study.

Nausea was observed in 12% of placebo-treated patients against 40% in the exenatide group, and 14–54% in the patients receiving albiglutide, most frequent in the groups treated with the highest dose one monthly [65]. In the group receiving 30 mg weekly, the frequency of nausea/vomiting was 29% compared with 46% in the exenatide group [65]. For patients receiving the highest dose of albiglutide monthly, the occurrence of nausea followed each monthly administration. Antibodies to albiglutide were observed in only 5 out of 356 patients and were of low titres [65]. Skin reactions were observed in up to 28% of the patients. No systemic allergic reactions to albiglutide were recorded [65].

Thus, albiglutide shows significant reduction in HbA1c and fasting blood glucose and blood pressure. The adverse effects seem to be the well known of GLP-1, and were dose dependent.

Phase 3 Programme for Albiglutide
Albiglutide 30 mg weekly has been selected as the initial dose for the phase 3 programme, named HARMONY Clinical Research Program [65]. Albiglutide will be investigated in monotherapy, in combination with metformin and as a triple therapy in combination with metformin and glitazone and in combination with metformin and SU. Studies will also use active comparators as a DPP-4 inhibitor, a glitazone, a SU, liraglutide and insulin (http://www.clinical.trials.gov) [66]. The programme will investigate cardiovascular safety after FDA guidelines, and durability of treatment. The programme will include more than 4000 patients.

LY2189265 Once-weekly GLP-1 Receptor Agonist (Dulaglutide)
Fusion of GLP-1 to a larger ‘carrier’ moiety, hence slowing its in vivo clearance, is used in LY2189265 (Eli Lilly, Indianapolis, IN, USA), where a DPP-4-protected GLP-1 analogue is fused to a modified immunoglobulin G4 (IgG4) Fc fragment [67]. Thereby a flat profile with no burst effect allowing once-weekly dosing is obtained [67]. LY2189265 exhibits activity similar to native GLP-1, probably by allowing sufficient conformational freedom and distance from the carrier domain for receptor interaction. In animal studies, LY2189265 displayed significant attenuation of weight gain [67].

In a randomized placebo-controlled double-blinded study in obese type 2 patients treated with two oral antidiabetic
drugs, 262 patients with type 2 diabetes for about 8 years and a BMI of 34 kg/m² were randomized to once-weekly injections of either placebo for 16 weeks, or one of two titrated doses of LY2189265 (0.5 mg for 4 weeks followed by 1.0 mg for 12 weeks or 1.0 mg for 4 weeks followed by 2.0 mg for 12 weeks), or 1.0 mg for 16 weeks [68]. The reduction in HbA1c was −0.27, −1.28, −1.29 and 1.52%, and in fasting plasma glucose −0.49, −2.09, −2.04 and −2.64 mmol/l, respectively, for the placebo, LYS 2189265 (0.5/1.0 mg), LYS 2189265 (1.0/1.0) and the LYS 2189265 (1.0/2.0 mg) groups. Weight was reduced with −0.07, −1.58, −1.40 and −2.51 kg, respectively. Nausea (13%), diarrhoea (9%) and abdominal distension (8%) were the most frequently reported adverse events in the GLP-1 receptor agonist groups [68]. Nevertheless, more long-term studies are needed to evaluate the efficacy and safety of LY2189265.

**CJC-1134-PC**

Another GLP-1 receptor agonist in a phase 3 programme is CJC-1134-PC (ConjuChem, Montreal, Quebec, Canada), which consists of an exendin-4 molecule covalently linked to human recombinant albumin. Its half-life is similar to circulating albumin, approximately about 8 days [69]. In mice, Baggio and co-workers showed that the compound retains the ability to mimic the full spectrum of GLP-1 receptor-dependent actions [70]. At present, only abstracts have been published about its pharmacokinetics and about a single phase 1 and two phase 2 clinical studies [71,72] in two 12-week study including a total of 224 metformin-treated patients [72]. One hundred and forty-four patients were randomized to treatment with 1.5 mg weekly, 1.5 mg weekly titrated to 2.0 mg weekly after 1 month or placebo [72]. In the second trial, 80 patients were randomized to 1.5 mg twice weekly (3 mg weekly), 1.5 mg twice weekly titrated to 2.0 mg weekly after 1 month or placebo [72]. Both trials had the same entry criteria. The greatest reduction in hba1c was seen in the 3 mg group (1.5 mg twice weekly), in which patients achieve a decrease of −1.4%. HbA1c decreased in the 1.5, 2.0 mg and placebo groups by −0.8, −0.8 and 0.4%, respectively [72]. The reduction in weight in the CJC-1134-PC groups did not differ significantly from placebo treatment [72]. Nausea was observed in 23%, vomiting in 11% compared to 10 and 6%, respectively, in the placebo group [72]. At present, it is unclear whether the modest effect on body weight is explained by a reduced efficacy in engaging the central nervous system regions regulating appetite and body weight, because large proteins like albumin are not expected to cross the blood–brain barrier [73]. Alternatively, the compound can still regulate feeding and body weight via the vagus nerve [74,75].

**Discussion**

The limitations and side effects combined with the difficulties in achieving sustained glycaemic control with ‘older’ antidiabetic therapies for having intensified the quest for new medications [6–8,15]. This has turned focus towards the incretin-based therapies because of the pleiotropic effects of GLP-1 [3,16]. The GLP-1 receptor agonists have advantages by combining effective blood glucose control with weight loss, blood pressure reduction, improvements in some cardiovascular risk factors and β-cell function [13,14]. The long-acting GLP-1 receptor agonists are attractive for the treatment of people with type 2 diabetes, as the regulation of both insulin and glucagon is glucose dependent. Therefore, there is a reduced risk of hypoglycaemia [13,18,20,21,74]. Especially, when a GLP-1 analogue is combined with a metformin or a glitazone the risk of hypoglycaemia is minimal [13,18]. The GLP-1 receptor agonists have been investigated in monotherapy or as add-on therapy to other antidiabetic drugs [13].

**Is the Once-weekly GLP-1 Receptor Agonists an Important Advance for the Treatment of Type 2 Diabetes?**

Several once-weekly long-acting GLP-1 analogues are in phase 3 development programmes (figure 1). Head-to-head comparisons between exenatide BID versus exenatide QW, or taspoglutide or albiglutide, indicate greater HbA1c reduction with the once-weekly GLP-1 receptor agonists [35,39,56]. No direct head-to-head comparisons between the once-weekly GLP-1 receptor agonists to liraglutide have been published, but a direct comparison between liraglutide and exenatide QW has an estimated completion in 2011. Evaluated from the LEAD programme with liraglutide and the trials discussed earlier, the efficacy will probably not differ significantly between liraglutide and exenatide once weekly [13]. The long-acting GLP-1 receptor agonists as well as liraglutide have a more sustained effect on fasting plasma glucose, while the effect on postprandial hyperglycaemia is modest compared with the short-acting exenatide BID. With respect to weight control, no clinically significant differences seem to exist within the entire group of GLP-1 receptor agonists (figure 6), although it remains possible that the CJC-1134-PC is less effective [72,73].

The gastrointestinal side effects seem to be less with exenatide QW and albiglutide compared with exenatide BID, probably because of a reduced peak concentrations of exenatide QW and albiglutide [30,76]. The gastrointestinal side effects during a head-to-head comparison between liraglutide and...
exenatide BID were also in favour of liraglutide [31,32]. On the other hand, taspoglutide seems to display more side effects than the other long-acting analogues and even higher than registered with exenatide BID [56]. This phenomenon is probably explained by a burst of taspoglutide released from the injected depot. This is underscored by the observation that the most pronounced gastrointestinal side effects are observed on the day of administration, indicating that a small fraction of the injected compound is absorbed very rapidly, thereby producing the side effects.

Antibodies seem to be most frequent and with highest titres during treatment with exenatide QW (>50% of the patients) compared with taspoglutide and albiglutide, but overall the titre of antibodies was not predictive of individual HbA1c change or adverse events [31,32,34,35]. A drawback of the once-weekly agonists may be that it will take about 4–5 weeks before a steady-state situation in relation to blood glucose control is reached, and in relation to incidences of pancreatitis, it will take weeks before the agonist is cleared from the patients. With liraglutide a steady state is obtained within 3–5 days. Furthermore, problems associated with larger injected volume and injection site reactions are likely to be more frequent with the once-weekly GLP-1 receptor agonists.

Potential Risk of GLP-1 Receptor Agonists

Studies in rodents have suggested that liraglutide induces thyroid C-cell focal hyperplasia and C-cell tumours in a dose-related manner, which may lead to medullary thyroid cancer [77,78]. In contrast, once-daily administration of exenatide in rats was associated with a high incidence of C-cell lesions in female rats, but no carcinoma was observed [77,78]. In vitro studies in rodent C cells have shown that native GLP-1, liraglutide, exenatide, taspoglutide and lixisenatide all potently activate the GLP-1 receptor with the same maximal activity, while the GLP-1 receptor signal in a human C-cell line was very low [77]. The GLP-1 receptor expression is species dependent and the C cell in rats expresses a large number of GLP-1 receptors, while the expression of the GLP-1 receptor is very sparse in human C cell [77]. Accordingly, the C-cell stimulatory effect in rodents was more pronounced with continuous exposure to GLP-1 receptor agonists, which may have relevance for interpretation of experiments using short- versus long-acting agonists [77]. In parallel with this observation, exenatide and liraglutide administered continuously to mice elicited the same frequency of C-cell hyperplasia and calcitonin response [77]. Rats develop spontaneous C-cell lesions at a high frequency, while C-cell neoplasia is extremely rare in humans [79].

In humans, calcitonin, secreted by the C cells, can be used as a biomarker for the detection of medullary thyroid cancer [78]. In the LEAD programme and the phase 3 trial of the once-weekly GLP-1 receptor agonists, calcitonin levels stayed within the normal range, and did not differ between the groups treated with GLP-1 receptor agonists and control groups [77,78]. In relation to the FDA approval of liraglutide, a cancer registry to monitor the annual incidence of medullary cancer during the next 15 years was required [78]. At present, there is no signal in humans indicating an association between treatment with GLP-1 receptor agonists and C-cell cancer [77,78].

The notion of an increased risk of pancreatitis during GLP-1 receptor agonist treatment arose from postmarketing reports submitted to FDA associated with the use of exenatide [78]. It has been impossible to determine whether these sporadic reports support that the use of exenatide induces an increased risk. In the initial publication of 30 cases, more than 90% of the patients displayed other factors predisposing to pancreatitis. In a recent register study, the incidences of pancreatitis were 0.13% for exenatide and 0.12% for sitagliptin, respectively, which did not differ from that of the background type 2 diabetes population [80–82]. Accordingly, the risk of pancreatitis did not differ between exenatide compared with other antidiabetic agents [81,83]. At present, mechanistic studies are undertaken to elucidate whether an association between the GLP-1 receptor agonist treatment and pancreatitis may be real. Nevertheless, persistent abdominal pains or vomiting warrants discontinuation of treatment with a GLP-1 receptor agonist. Strict monitoring of pancreas function (amylase, lipase) in the ongoing long-term cardiovascular outcome trials of both GLP-1 analogues and DPP-4 inhibitors could produce decisive evidence of pancreatitis risk associated with incretin-based therapies. The hypersensitivity reactions observed with taspoglutide have not been a problem with the other GLP-1 receptor agonists.

The observation that GLP-1 analogues improve myocardial function in humans after myocardial infarction, improve endothelial function and reduce blood pressure raises hope for the outcomes of studies with cardiovascular endpoints such as mortality and cardiovascular events [84]. In December 2008, FDA published guidelines for assessing cardiovascular risk conferred by new antidiabetic drugs [78]. In relation to liraglutide, FDA required a postapproval study of cardiovascular safety. Of interest, data from post hoc analyses suggest that exenatide and liraglutide have not been associated with cardiovascular risks [13,85]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study will test the safety of liraglutide; it is already initiated and will include about 9000 patients. In relation to exenatide QW, the EXCEL (Exenatide Study of Cardiovascular Event Lowering) will include about 9500 patients; it started June 2010. The T-eme-rge 8 study has included about 2000 patients, but dosing was stopped in September 2010 because of gastrointestinal side effects and hypersensitivity reactions.

The Place of the Long-acting GLP-1 Receptor Agonists in the Treatment Algorithm

Most diabetologists agree that initial therapy in type 2 diabetic patients should comprise lifestyle changes plus metformin [6–9], but which antidiabetic agents to use when metformin fails or to use in patients intolerant for metformin has provoked debate among physicians. The different guidelines take different views on the place of the GLP-1 receptor agonists in the treatment algorithm [6–9]. The American Diabetes Association (ADA) and European Association for the Study of
Diabetes (EASD) consensus published in 2009 suggested SU and insulin as a second-line therapy in tier 1 approach, while the GLP-1 receptor agonists are allocated to tier 2 approach and only recommended for selected clinical settings when weight loss and risk of hypoglycaemia are a concern and HbA1c is lower than 8.0% [6]. The ADA/EASD consensus has raised a lot of debate regarding the optimal treatment of type 2 diabetes [10]. The UK National Institute for Health and Clinical Excellence (NICE) guidelines suggest a GLP-1 receptor agonist as an alternative to insulin, and where obesity is a specific problem (BMI > 35 kg/m²) [7]. NICE suggested that the GLP-1 receptor agonist treatment should be stopped if the HbA1c and weight responses are less than 1 and 3%, respectively [7]. The Canadian Diabetes Association and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) suggested GLP-1 receptor agonists as second-line agents after metformin on the background of their greater effectiveness on glucose control and the weight loss [8,9]. Probably, many physicians in the daily clinical practice will consider a long-acting GLP-1 receptor agonist as an alternative to insulin treatment in patients with treatment failure to oral agents. Compared with insulin, a GLP-1 receptor agonist may be preferable, as fewer injections are needed with less risk of hypoglycaemia, and there is weight loss as opposed to weight gain. Lastly, but not less importantly, the GLP-1 receptor agonists do not require titration of the dose on the basis of glucose self-monitoring. Therefore, the need of self-monitoring of glucose is much less with the GLP-1 receptor agonists, and on the whole GLP-1 receptor agonist treatment is much simpler than insulin treatment. Nevertheless, because of the complementary effects of metformin and a GLP-1 receptor agonist on weight and the low risk of hypoglycaemia with this combination, the most optimal approach for GLP-1 receptor agonist treatment may be in combination with metformin as an agent number 2 in the treatment algorithm [13]. This combination should be used early when the β-cell function may be more prone to benefit by a GLP-1 receptor agonist [86].

The new antidiabetic agents, the sodium-glucose transporter-2 (SGLT-2) inhibitors, block glucose reabsorption and, therefore, promote glycosuria and lower serum glucose in hyperglycaemic states without risk of hypoglycaemia [72,87,88]. In addition, the glycosuria equates to loss of calories and these agents cause similar weight loss as the GLP-1 agonists, but with less reduction in HbA1c [87,88]. The SGLT-2 inhibitors, which are administered in tablet form, might affect the future positioning of the GLP-1 receptor agonists.

A definitive answer regarding the positioning of the long-acting GLP-1 receptor agonists will emerge from ongoing long-term trials investigating the durability of glucose control, weight reduction, cardiovascular endpoint and safety. Clearly more information as to whether or not the GLP-1 receptor agonists can protect the β-cell function and thereby minimize the progression of the disease would be a key point in the positioning. Considering the various modes of actions of the different glucose-lowering agents, more studies comparing the efficacy and safety of the GLP-1 receptor agonists with other antidiabetic agents, including insulin in different combinations, will provide clinically relevant information about the appropriate place of the GLP-1 receptor agonists in clinical practice. The studies should include GLP-1 receptor agonists as first-line therapy.

Conflict of Interest

The idea and the preparation of the first draft were originated by the first author (S. M.) after the ADA meeting this year, inspired by the T-emerge presentations and the presentations on exenatide QW. Furthermore, when the review was written, many people believed that exenatide once weekly would be launched in USA and Europe in 2010/2011. The co-authors have all participated in the final revision of the paper. No commercial interests have, at any time, been involved, in any way (including funding), with the preparation of the review.

S. M. has served as a consultant or adviser to Novartis Pharmaceuticals, Novo Nordisk, Merck, Sharp and Dome, Phizer A/S, Abbott Laboratories, Sanofi-Aventis, Astra-Zeneca, Johnson & Johnson, Rosche, Mankind and Astra-Zeneca, and is a recipient of a research grant from Novo Nordisk. He has been a speaker for Novo Nordisk, Merck, Sharp and Dome, Astra-Zeneca, Johnson & Johnson, Abbott Laboratories, Phizer A/S, Rosche, Sering-Plaug, Sanofi-Aventis and Novartis Pharmaceuticals.

C. F. D. has received consultancy/lecture fees from companies with an interest in developing and marketing incretin-based therapies for the treatment of type 2 diabetes (Astra-Zeneca/BMS, Lilly, Merck, Novartis, Novo Nordisk, Servier). Her spouse is employed by Merck and hold stock options in Merck and Novo Nordisk.

J. J. H. has received lecture and/or consultancy fees from GlaxoSmithKline, Merck & Co., Novartis, Novo Nordisk and Roche. U. K., M. A. and S. S. T. have no declaration of interests.

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