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R&D INSIGHT REPORT

Dulaglutide: First Global Approval

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Abstract Dulaglutide (Trulicity™) is a long-acting, glucagon-like peptide-1 (GLP-1) receptor agonist that has been developed by Eli Lilly and Company for the treatment of type 2 diabetes mellitus. It consists of a dipeptidyl peptidase-IV-protected GLP-1 analogue covalently linked to a human IgG4-Fc heavy chain by a small peptide linker. The subcutaneous formulation is approved for use in type 2 diabetes in the US, has been recommended for approval in the EU in this indication, and is under regulatory review in other countries. This article summarizes the milestones in the development of subcutaneous dulaglutide leading to this first approval for type 2 diabetes.

1 Introduction

Type 2 diabetes mellitus is a progressive disease characterized by dysfunction of β cells, insulin resistance and hyperglucagonaemia, which all contribute to uncontrolled hyperglycaemia [1, 2]. Glucagon-like peptide-1 (GLP-1) is an incretin hormone that promotes glucose-dependent secretion of insulin from β cells and suppresses postprandial glucagon secretion from α cells, thereby supporting glucose homeostasis. Thus, GLP-1 has been recognized as a possible therapy for type 2 diabetes, although native GLP-1 has limited therapeutic potential, as it is rapidly inactivated by dipeptidyl peptidase-IV (DPP-IV) and then excreted (half-life 1–2 min). However, analogues of GLP-1 have been developed with longer-lasting effects and with proven efficacy in type 2 diabetes. Subcutaneous GLP-1 analogues that have reached the market include exenatide (twice-daily and once-weekly formulations), lixisenatide (administered once daily), liraglutide (once daily) and albiglutide (once-weekly). The longer acting GLP-1 analogues offer the promise of greater convenience to the patient [1, 2].

Dulaglutide (Trulicity™) is a once-weekly, GLP-1 receptor agonist, consisting of a DPP-IV-protected GLP-1 analogue covalently linked to a human IgG4-Fc heavy chain by a small peptide linker. In September 2014, the US FDA approved once-weekly subcutaneous dulaglutide, as an adjunct to diet and exercise, for the treatment of adult patients with type 2 diabetes mellitus [3]. Dulaglutide 0.75 mg and 1.5 mg single dose pens are expected to be available by the end of 2014 [4]. In the EU, the Committee for Medicinal Products for Human Use have recently recommended approval of subcutaneous dulaglutide in type 2 diabetes [5]. Phase III/IIIb development of dulaglutide is also in progress in other countries worldwide, and the drug is under regulatory review in other countries [4].

In the USA, dulaglutide can be used in combination with other regimens [3]. Dulaglutide was approved with a Risk Evaluation and Mitigation Strategy, and the label contains a boxed warning, based on a potential risk of thyroid tumours, which were observed in rodent studies after lifetime exposure to dulaglutide [3]. The FDA approval requires that the company conducts five additional post-marketing studies for dulaglutide [6]. These include: a paediatric study to evaluate the safety, efficacy and dosing of dulaglutide; a preclinical study in immature rats to

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Features and properties of dulaglutide

Alternative names	Trulicity™; LY 2189265; LY-2189265; LY2189265
Class	Recombinant-fusion-proteins
Mechanism of action	Glucagon-like peptide-1 receptor agonist
Route of administration	Subcutaneous injection
Pharmacodynamics	Activates human glucagon-like peptide-1 receptors, thus increasing intracellular cyclic AMP in beta cells, resulting in glucose-dependent insulin release. Dulaglutide also reduces glucagon secretion and slows gastric emptying
Pharmacokinetics	After subcutaneous administration, dulaglutide is slowly absorbed into the systemic circulation, reaching maximum plasma concentration at steady state in 24–72 h. At doses of 0.75 mg and 1.5 mg, the elimination half-life is ≈5 days
Adverse events	
Common	Nausea, diarrhoea, vomiting, abdominal pain, decreased appetite, dyspepsia and fatigue
Hypoglycaemia	Infrequent when administered with metformin or metformin plus pioglitazone; more frequent when administered with a sulfonylurea or insulin
ATC codes	
WHO ATC code	A10B-X (other oral blood glucose lowering drugs, excl. insulins)
EphMRA ATC code	A10S (GLP-1 agonist antidiabetics)
Chemical name	7-37-glucagon-like peptide I [8-glycine, 22-glutamic acid, 36-glycine] (synthetic human) fusion protein with peptide (synthetic 16-amino acid linker) fusion protein with immunoglobulin G4 (synthetic human Fc fragment), dimer

assess drug effects on sexual maturation, reproduction and CNS development; a case registry spanning at least 15 years to determine effects of the drug on incidence of medullary thyroid cancer; a comparative study with insulin glargine in patients with type 2 diabetes mellitus with moderate-to-severe renal impairment; and a study to assess the impact of the drug on cardiovascular risk in patients with high baseline risk of cardiovascular events [6]. The ongoing NCT01621178 and NCT01394952 studies have been designed to evaluate dulaglutide in patients with renal impairment and high baseline cardiovascular risk, respectively [7].

2 Scientific Summary

2.1 Pharmacodynamics

Dulaglutide is a fusion protein produced using mammalian cell culture and consisting of two identical disulphide-linked chains, each with a *N*-terminal GLP-1 analogue sequence that is covalently linked by a peptide linker to the Fc component of a modified human immunoglobulin G4 heavy chain (IgG4 Fc) [1, 3]. Fusion to this large carrier moiety slows its clearance from the body. The GLP-1 analogue component is 90 % homologous to endogenous human GLP-12 (7-37), but with structural modifications in the area of the molecule that interacts with DPP-IV. Additional modifications were made in areas of the GLP-1 molecule that have potential as epitopes for T cells, and in areas of the IgG4 Fc component that bind Fc receptors and contribute to half-antibody formation. These modifications are intended to reduce the immunogenicity of the protein [1, 3].

The dulaglutide mechanism of action involves activation of the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase in β cells [3]. Thus, it increases intracellular cyclic AMP in these cells, leading to a glucose-dependent release of insulin. Dulaglutide also reduces secretion of glucagon and slows gastric emptying [3].

In clinical studies in patients with type 2 diabetes, once-weekly subcutaneous dulaglutide 0.75 or 1.5 mg reduced both fasting and postprandial serum glucose concentrations and postprandial serum glucose incremental area under the concentration-time curve (AUC) and increased first-and second-phase insulin secretion more than placebo [3]. Compared with baseline, continued administration of dulaglutide increased fasting insulin and C-peptide concentrations and reduced fasting glucagon concentrations [3].

In a thorough QTc study, there was no evidence of QTc prolongation at dulaglutide doses of 4 and 7 mg [3].

2.2 Pharmacokinetics

Healthy adults and patients with type 2 diabetes have similar dulaglutide pharmacokinetics [3]. Dulaglutide is slowly but well absorbed into the systemic circulation, reaching maximum plasma concentrations (C_{max}) in 24–72 h (median 48 h) after a subcutaneous injection administered at steady state. With once-weekly injections, steady-state plasma concentrations were reached after

2–4 weeks. The site of the injection (abdomen, upper arm, thigh) had no statistically significant effect on dulaglutide systemic exposure. Following subcutaneous dulaglutide 0.75 and 1.5 mg, the mean absolute bioavailability values were 65 and 47 %, respectively; at corresponding doses, the mean volumes of distribution were 19.2 and 17.4 L [3].

It is assumed that dulaglutide is broken down into its component amino acids via pathways for general protein catabolism [3]. After administration of 0.75 or 1.5 mg doses, the elimination half-life for both doses was ≈5 days [3], which is consistent with once-weekly administration.

There were no clinically important effects of age, sex, race, ethnicity or bodyweight on the dulaglutide C_{max} or AUC; no dose adjustment is necessary based on these factors [3]. Similarly, there were no clinically important changes in the dulaglutide C_{max} and AUC values in patients with mild, moderate or severe renal impairment (small increases were observed) or in patients with mild, moderate or severe hepatic impairment (small decreases were observed) [3].

2.2.1 Drug Interactions

As dulaglutide slows gastric emptying, it could reduce the rate and extent of absorption of orally administered drugs, although in clinical pharmacological studies no clinically important effects on absorption of tested drugs was observed [3]. However, caution is recommended when coadministering dulaglutide with orally administered drugs, with adequate monitoring of those drugs that have a narrow therapeutic index [3].

In drug interaction studies with pharmacokinetic probes and drugs that might be coadministered with dulaglutide, there were no clinically important effects of dulaglutide on the C_{max} or AUC of the coadministered drugs [3].

In a study of dulaglutide coadministered with sitagliptin, there was no clinically relevant effect of sitagliptin on dulaglutide exposure [3].

2.3 Therapeutic Trials

The efficacy and tolerability of once-weekly subcutaneous dulaglutide 0.75 or 1.5 mg in patients with type 2 diabetes has been evaluated in the AWARD [Assessment of Weekly AdministRation of LY2189265 (dulaglutide)] programme of clinical studies conducted by Eli Lilly. This section summarizes the main findings from the AWARD-1, -2, -3, 4, -5 and -6 studies [8–13] (final results from the AWARD-7, -8 and -9 trials are not yet available).

The studies were all randomized trials versus active comparators in patients with type 2 diabetes who were treatment-naïve or had inadequate control with current diabetic regimens [8–13]. AWARD-1 and -5 included a placebo arm that received the same background therapy as the active comparators [9, 12]. Trials were open-label (AWARD-2, -4, -6) [10, 11, 13] or blinded (AWARD-1, -3, -5) [8, 9, 12]. Treatments included an active comparator arm and a dulaglutide 1.5 mg once-weekly arm (AWARD-6) [12] or dulaglutide 0.7 and 1.5 mg once-weekly arms (AWARD-1, -2, -3, -4 and -5) [8–11, 13]. Across trials, the primary endpoint was the change from baseline in the least squares mean (LSM) glycosylated haemoglobin level (HbA1c) at week 26 (AWARD-1, -3, -4, -6) or 52 (AWARD-2, -5). For the primary analyses, AWARD-1 tested superiority of dulaglutide to placebo [12], whereas the remaining trials first tested non-inferiority of dulaglutide once-weekly to the comparator, before assessing superiority to the comparator [8–11, 13].

Across trials, once-weekly dulaglutide 0.75 or 1.5 mg was efficacious in type 2 diabetes, based on changes from baseline in HbA1c. Dulaglutide was efficacious as monotherapy (vs. metformin) (Sect. 2.3.1) and in combination with metformin (vs. sitagliptin and vs. liraglutide) (Sect. 2.3.2), metformin plus glimepiride (vs. insulin glargine) (Sect. 2.3.3), metformin plus pioglitazone (vs. exenatide) (Sect 2.3.4) and insulin lispro ±metformin (vs. insulin glargine) (Sect 2.3.5).

2.3.1 Monotherapy

The AWARD-3 trial ($n = 807$) evaluated the efficacy of dulaglutide monotherapy versus metformin (dosages up to 2,000 mg/day, as tolerated) in patients with HbA1c of ≥6.5 and ≤9.5 % with diet and exercise with or without low-dose oral antihyperglycaemic medication (OAM) monotherapy (OAMs were discontinued at the start of the 2-week lead-in period of the trial) [8]. The LSM changes in HbA1c from baseline to week 26 were −0.71, −0.78 and −0.56 % in the dulaglutide 0.75, 1.5 mg and metformin groups, respectively (both dulaglutide groups $p < 0.025$ vs. metformin; noninferiority criterion met). In the dulaglutide 0.75, 1.5 mg and metformin groups, 63, 62 and 54 % of patients, respectively, met the HbA1c target of <7.0 % at week 26 (both dulaglutide groups $p < 0.05$ vs. metformin) [8].

2.3.2 In Combination with Metformin

The AWARD-5 trial ($n = 1,098$) evaluated the efficacy of dulaglutide versus sitagliptin 100 mg once daily or placebo in patients with HbA1c >8.0 and ≤9.5 % on diet and exercise alone or ≥7 and ≤9.5 % despite treatment with OAM monotherapy or combination therapy. During the

lead-in period of the trial, all patients were stabilized on metformin ≥1500 mg/day and other OAMs were discontinued [9]. The LSM changes in HbA1c from baseline to week 52 were −0.87, −1.10 and −0.39 % in the dulaglutide 0.75, 1.5 mg and sitagliptin groups, respectively (both dulaglutide groups $p < 0.001$ vs. sitagliptin; noninferiority criterion met). In the dulaglutide 0.75, 1.5 mg and sitagliptin groups, 49, 58 and 33 % of patients, respectively, met the HbA1c target of <7.0 % at 52 weeks (both dulaglutide groups $p < 0.001$ vs. sitagliptin). Compared with placebo, at week 26 dulaglutide groups had significantly ($p < 0.001$) greater LSM changes from baseline in HbA1c and greater proportions of patients met the HbA1c target of <7.0 % [9].

The AWARD-6 trial ($n = 599$) evaluated the efficacy of dulaglutide 1.5 mg once-weekly versus liraglutide 1.8 mg once-daily in patients with HbA1c ≥7.0 % and ≤10.0 % despite treatment with metformin [10]. The LSM changes in HbA1c from baseline to week 26 were −1.42 and −1.36 % in the dulaglutide and liraglutide groups (noninferiority criterion met). In both the dulaglutide and liraglutide groups, 68 % met the HbA1c target of <7.0 % at week 26 [10].

2.3.3 In Combination with Metformin Plus Glimepiride

The AWARD-2 trial ($n = 807$) evaluated the efficacy of dulaglutide versus once-daily insulin glargine (titrated to fasting glucose targets) in patients with type 2 diabetes inadequately controlled with metformin plus glimepiride (data are from an abstract) [11]. At week 52, the LSM changes from baseline in HbA1c were −0.76. −1.08 and −0.63 % in the dulaglutide 0.75, 1.5 mg and insulin glargine groups, respectively (noninferiority criterion met for both dosages; $p < 0.001$ vs. insulin glargine for the dulaglutide 1.5 mg once-weekly group). At Week 52, the HbA1c target of <7.0 % was met by 37, 53 and 31 % of patients in the dulaglutide 0.75, 1.5 mg and insulin glargine groups, respectively ($p < 0.05$ for dulaglutide 1.5 mg vs. insulin glargine) [11].

2.3.4 In Combination with Metformin Plus Pioglitazone

The AWARD-1 ($n = 976$) trial evaluated the efficacy of dulaglutide versus exenatide 10 μg twice-daily or placebo in patients with a baseline HbA1c between 7–11 % (on OAM monotherapy) or 7–10 % (on combination OAM therapy). During the lead-in period of the trial, all patients were stabilized on maximum tolerated dosages of metformin plus pioglitazone and other OAMs were discontinued. After treatment stabilization, patients with HbA1c >6.5 % were then randomized to dulaglutide or exenatide therapy [12]. The LSM changes in HbA1c from baseline to week 26 were −1.30, −1.51 and −0.99 % in the dulaglutide 0.75, 1.5 mg and exenatide groups, respectively, versus −0.46 % in the placebo group (both dulaglutide groups $p < 0.001$ vs. placebo and vs. exenatide; exenatide group $p < 0.001$ vs placebo). In the dulaglutide 0.75, 1.5 mg and exenatide groups, 66, 78 and 52 % of patients met the HbA1c target of <7.0 % at week 26 (vs. 43 % in the placebo group; $p < 0.001$ for both dulaglutide groups vs. placebo) [12].

2.3.5 In Combination with Insulin Lispro with or without Metformin

The AWARD-4 trial ($n = 884$) evaluated the efficacy of dulaglutide versus insulin glargine in patients whose type 2 diabetes was uncontrolled with conventional insulin therapy (HbA1c ≥7.0 and ≤11.0 %); all patients received insulin lispro three-times daily with or without metformin; insulin glargine and insulin lispro were titrated to achieve glycaemic targets (data are from an abstract) [13]. The LSM changes in HbA1c from baseline to week 26 were −1.59, −1.64 and −1.41 % in the dulaglutide 0.75, 1.5 mg and insulin glargine groups (both dulaglutide groups $p < 0.05$ vs. insulin glargine; noninferiority criterion met). At week 26, 69, 68 and 57 % of patients in the dulaglutide 0.75, 1.5 mg and insulin glargine groups met the HbA1c target of <7.0 % (both dulaglutide groups $p < 0.05$ vs. insulin glargine) [13].

Phase III studies of dulaglutide (Trulicity™) in patients with type 2 diabetes conducted by Eli Lilly

Comparators	Background treatment during trial	Status	Treatment at enrolment (comorbid condition)[a]	Location(s)	Identifier
Exenatide Placebo	Metformin/ pioglitazone	Completed	Metformin plus pioglitazone	Argentina, Mexico, Puerto Rico, South Korea, USA	NCT01064687 (AWARD-1)
Insulin glargine	Metformin/ glimepiride	Completed	Metformin plus glimepiride	Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Greece, Hungary, India, Italy, Mexico, Poland, Romania, Slovakia, South Korea, Spain, Sweden, Taiwan	NCT01075282 (AWARD-2)

continued

Comparators	Background treatment during trial	Status	Treatment at enrolment (comorbid condition)[a]	Location(s)	Identifier
Metformin	None	Completed	TN or low-dose OAM monotherapy	Argentina, Brazil, Canada, Czech Republic, England, Finland, France, Germany, India, Mexico, Poland, Puerto Rico, Romania, Slovakia, South Africa, South Korea, Spain, USA	NCT01126580 (AWARD-3)
Insulin glargine	Insulin lispro +/− metformin	Completed	Insulin regimen	Argentina, Australia, Belgium, Canada, Denmark, Greece, Hungary, Mexico, Poland, Puerto Rico, Russia, South Africa, Spain, Sweden, Taiwan, USA	NCT01191268 (AWARD-4)
Sitagliptin Placebo	Metformin	Completed	Metformin, metformin plus other OAM, or other OAM monotherapy	Brazil, France, Germany, Hungary, India, Mexico, Poland, Puerto Rico, Romania, Russia, South Korea, Spain, Taiwan, USA	NCT00734474 (AWARD-5)
Liraglutide	Metformin	Completed	Metformin	Czech Republic, Germany, Hungary, Mexico, Poland, Romania, Spain, Slovakia, USA	NCT01624259 (AWARD-6)
Insulin glargine	Insulin lispro	Recruiting	Insulin or insulin plus OAM (CKD)	Brazil, Hungary, Mexico, Poland, Romania, South Africa, Spain, Ukraine, USA	NCT01621178 (AWARD-7)
Placebo	Glimepiride	Recruitment complete	Sulfonylurea	Argentina, Austria, Croatia, Mexico, Romania, Slovenia, South Africa, USA	NCT01769378 (AWARD-8)
Placebo	Insulin glargine +/− metformin	Recruiting	Insulin glargine +/−metformin	Czech Republic, Hungary, Italy, Puerto Rico, Spain, UK, USA	NCT02152371 (AWARD-9)
Placebo	Current anti-diabetic regimen	Recruitment complete	TN or ≤2 OAM +/−GLP1 analogue or basal insulin, or basal insulin monotherapy (cardiovascular risk factors)	Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, Germany, Hungary, India, South Korea, Latvia, Lithuania, Mexico, New Zealand, Poland, Puerto Rico, Romania, Russia, South Africa, Spain, Sweden, Taiwan, UK, USA	NCT01394952 (REWIND)
Glimepiride Placebo	None	Recruitment complete	TN or OAM monotherapy	China, South Korea, Taiwan	NCT 01644500
Insulin glargine	Metformin and/or sulfonylurea	Recruitment complete	Metformin and/or sulfonylurea	China, Mexico, South Korea, Russia	NCT01648582
Insulin glargine	Sulfonylurea and/or biguanide	Completed	Sulfonylurea and/or biguanide	Japan	NCT01584232
Liraglutide Placebo	None	Completed	TN or OAM monotherapy except thiazolidinedione	Japan	NCT01558271
None	Sulfonylurea, biguanide, TZD, α-G1 or glinide	Completed	Sulfonylurea, biguanide, TZD, α-G1 or glinide	Japan	NCT01468181

α-GI α-glucosidase inhibitor, *CKD* chronic kidney disease, *OAM* oral antihyperglycaemic medication, *TN* antihyperglycaemic treatment-naive

[a] All treatment groups continued pre-recruitment diet and exercise programmes

2.4 Adverse Reactions

In pooled data from placebo-controlled trials, adverse reactions occurring in ≥5 % of dulaglutide 0.75 mg ($n = 836$) or 1.5 mg ($n = 834$) groups and at a higher rate than in placebo groups ($n = 568$) were nausea (12.4 and 21.1 vs. 5.3 % with placebo), diarrhoea (8.9 and 12.6 vs. 6.7 %), vomiting (6.0 and 12.7 vs. 2.3 %), abdominal pain

(6.5 and 9.4 vs. 4.9 %), decreased appetite (4.9 and 8.6 vs. 1.6 %), dyspepsia (4.1 and 5.8 vs. 2.3 %) and fatigue (4.2 and 5.6 vs. 2.6 %) [3]. Overall, gastrointestinal (GI) reactions occurred in 31.6, 41.0 and 21.3 % of dulaglutide 0.75, 1.5 mg and placebo recipients, respectively. In the corresponding groups, 1.3, 3.5 and 0.2 % of patients discontinued treatment because of GI adverse reactions. In the dulaglutide 0.75 and 1.5 mg groups, most GI adverse reactions were mild or moderate, with 7 and 11 % severe. A similar pattern of adverse reactions was seen in pooled analyses of placebo and active-comparator trials [3].

At week 26 in placebo-controlled trials in which dulaglutide was added to metformin or to metformin plus pioglitazone, symptomatic hypoglycaemia (serum glucose $\leq$70 mg/dL) occurred in $\leq$6 % of dulaglutide recipients and 1 % of placebo recipients (no cases of severe hypoglycaemia were observed). When administered with a sulfonylurea, $\approx$40 % of dulaglutide recipients had documented symptomatic hypoglycaemia (severe in $<$ 1 % of patients) and when administered with prandial insulin 80–85 % of dulaglutide recipients had documented symptomatic hypoglycaemia (severe in 2–3 %) [3].

A dose-duration-dependent increase in thyroid C-cell tumours has been observed in male and female rats following lifetime exposure.[3] The relevance of this finding to humans is unknown. One case of medullary thyroid carcinoma has been reported in a patient treated with dulaglutide whose calcitonin levels prior to treatment were 8-fold the upper limit of normal [3]. The US prescribing information contains a black box warning about a possible risk of thyroid C-cell tumours, noting that dulaglutide is contraindicated in patients with a personal or family history of these tumours and in patients with multiple endocrine neoplasia syndrome type 2 [3].

In clinical trials, dulaglutide was associated with small increases in mean heart rate (HR) (2–4 beats/min); long-term clinical effects of these increases in HR are unknown [3]. Sinus tachycardia, persistent sinus tachycardia, and episodic sinus tachycardia with an increase in HR of $\geq$15 beats/min occurred more often in dulaglutide than placebo recipients; for instance, sinus tachycardia occurred in 2.8, 5.6 and 3.0 % of dulaglutide 0.75, 1.5 mg and placebo recipients, respectively. Dulaglutide recipients had mean increase in the PR interval of 2–3 ms (vs. 0.9 ms with placebo) and AV block occurred in 1.7, 2.3 and 0.9 % of dulaglutide 0.75, 1.5 mg and placebo recipients, respectively. In the corresponding groups, 2.5, 3.2 and 0.7 % of patients had an increase in the PR interval to $\geq$220 ms [3].

In pooled data, 1.6 % of dulaglutide recipients developed anti-dulaglutide antibodies. In 64 patients with antibodies, 34 had neutralizing antibodies and 36 (0.9 % of the total population) had antibodies against native GLP-1 [3].

Injection site reactions occurred in 0.5 % of dulaglutide recipients and 0 % of placebo recipients [3]. In the four phase II and III studies, systemic hypersensitivity adverse reactions occurred in 0.5 % of dulaglutide recipients [3].

Other adverse reactions that may be of clinical relevance include increases in lipase and/or pancreatic lipase, acute pancreatitis, and acute renal failure or worsening of chronic renal failure [3]. The US prescribing information contains warnings related to these possible reactions and necessary monitoring precautions [3].

2.5 Ongoing Clinical Trials

The AWARD programme includes three further ongoing randomized, multinational trials. These are AWARD-7 (NCT01621178) comparing dulaglutide plus insulin lispro with insulin glargine plus insulin lispro in patients with type 2 diabetes and chronic kidney disease; AWARD 8 (NCT01769378) comparing dulaglutide plus glimepiride versus placebo plus glimepiride in patients receiving a sulfonylurea; and AWARD-9 (NCT02152371) comparing dulaglutide plus insulin versus placebo plus insulin in patients with poor glycaemic control despite insulin with or without metformin [7].

The REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) study (NCT01394952) is a randomized, placebo controlled trial of dulaglutide 1.5 mg once-weekly in patients with type 2 diabetes with HbA1c of $\leq$9.5% who are receiving stable therapy for diabetes and who are aged $\geq$50 years with established clinical vascular disease, aged $\geq$55 years with subclinical vascular disease, or aged $\geq$60 years with $\geq$2 cardiovascular risk factors [7]. The trial will evaluate the effect of weekly dulaglutide therapy for up to 8 years on cardiovascular endpoints, such as cardiovascular death, myocardial infarction, stroke, diabetic retinopathy and chronic renal replacement therapy.

Two further trials are being conducted in Japan: (1) comparing dulaglutide with insulin glargine (NCT01584232) and (2) comparing dulaglutide with liraglutide (NCT01558271) in patients with type 2 diabetes receiving OAMs [7].

3 Current Status

Dulaglutide received its first global approval on 18 September 2014 for use in adult patients with type 2 diabetes in the USA and on 25 September 2014 it received a positive opinion for use in adults with type 2 diabetes in the EU. Dulaglutide can be used as monotherapy or in combination with other regimens.

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