1. NAME OF THE MEDICINAL PRODUCT

Trulicity 0.75 mg solution for injection in pre-filled pen
Trulicity 1.5 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trulicity 0.75 mg solution for injection in pre-filled pen
Each pre-filled pen contains 0.75 mg of dulaglutide* in 0.5 ml solution.

Trulicity 1.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 1.5 mg of dulaglutide* in 0.5 ml solution.

*Produced in CHO cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 Diabetes Mellitus

Trulicity is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

Monotherapy
The recommended dose is 0.75 mg once weekly.

Add-on therapy
The recommended dose is 1.5 mg once weekly.

Combination therapy

When Trulicity is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When Trulicity is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued. When it is added to existing therapy of a sulphonylurea or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

The use of Trulicity does not require blood glucose self-monitoring. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Trulicity therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

Missed doses

If a dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days (72 hours) remain before the next scheduled dose, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Special population

Elderly
No dose adjustment is required based on age (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment (eGFR <90 to ≥15 mL/min/1.73m^2).

There is very limited experience in patients with end stage renal disease (<15 ml/min/1.73m^2), therefore Trulicity cannot be recommended in this population (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment.

Paediatric population
The safety and efficacy of dulaglutide in children aged less than 18 years have not yet been established. No data are available.

Method of administration

Trulicity is to be injected subcutaneously in the abdomen, thigh or upper arm. It should not be administered intravenously or intramuscularly.

The dose can be administered at any time of day, with or without meals.

The day of weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days (72 hours) before.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Type 1 diabetes mellitus or diabetic ketoacidosis

Dulaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Dulaglutide is not a substitute for insulin.

Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Severe gastrointestinal disease

Dulaglutide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients. Events related to impaired gastric emptying, including severe gastroparesis, have been reported. Monitor and consider dose modification or discontinuation in patients who develop severe gastrointestinal symptoms while on treatment.

Dehydration

Dehydration, sometimes leading to acute renal failure or worsening renal impairment, has been reported in patients treated with dulaglutide, especially at the initiation of treatment. Many of the reported adverse renal events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Patients treated with dulaglutide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Acute pancreatitis

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. In clinical trials, acute pancreatitis has been reported in association with dulaglutide (see section 4.8).

Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued. If pancreatitis is confirmed, dulaglutide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see section 4.8).

Hypoglycaemia

Patients receiving dulaglutide in combination with sulphonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea or insulin (see sections 4.2 and 4.8).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

Dulaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. In the clinical pharmacology studies described below, dulaglutide doses up to 1.5 mg did not affect the absorption of the orally administered medicinal products tested to any clinically relevant degree.

For patients receiving dulaglutide in combination with oral medicinal products with rapid gastrointestinal absorption or prolonged release, there is a potential for altered medicinal product exposure, particularly at the time of dulaglutide treatment initiation.

Sitagliptin

Sitagliptin exposure was unaffected when coadministered with a single 1.5 mg dose of dulaglutide. Following coadministration with 2 consecutive 1.5 mg doses of dulaglutide, sitagliptin $AUC_{(0-\tau)}$ and C_{max} decreased by approximately 7.4% and 23.1%, respectively. Sitagliptin t_{max} increased approximately 0.5 hours following coadministration with dulaglutide compared to sitagliptin alone.

Sitagliptin can produce up to 80% inhibition of DPP-4 over a 24-hour period. Dulaglutide (1.5 mg) coadministration with sitagliptin increased dulaglutide exposure and C_{max} by approximately 38% and 27%, respectively, and median t_{max} increased approximately 24 hours. Therefore, dulaglutide does have a high degree of protection against DPP-4 inactivation (see section 5.1, Mechanism of action). The increased exposure may enhance the effects of dulaglutide on blood glucose levels.

Paracetamol

Following a first dose of 1 and 3 mg dulaglutide, paracetamol C_{max} was reduced by 36% and 50%, respectively, and the median t_{max} occurred later (3 and 4 hours, respectively). After coadministration with up to 3 mg of dulaglutide at steady state, there were no statistically significant differences on $AUC_{(0-12)}$, C_{max} or t_{max} of paracetamol. No dose adjustment of paracetamol is necessary when administered with dulaglutide.

Atorvastatin

Coadministration of 1.5 mg of dulaglutide with atorvastatin decreased C_{max} and $AUC_{(0-\infty)}$ up to 70% and 21%, respectively, for atorvastatin and its major metabolite *o*-hydroxyatorvastatin. The mean $t_{1/2}$ of atorvastatin and *o*-hydroxyatorvastatin were increased by 17% and 41%, respectively, following dulaglutide administration. These observations are not clinically relevant. No dose adjustment of atorvastatin is necessary when administered with dulaglutide.

Digoxin

After coadministration of steady state digoxin with 2 consecutive 1.5 mg doses of dulaglutide, overall exposure (AUC_{τ}) and t_{max} of digoxin were unchanged; and C_{max} decreased by up to 22%. This change is not expected to have clinical consequences. No dose adjustment is required for digoxin when administered with dulaglutide.

Anti-hypertensives

Coadministration of multiple dulaglutide 1.5 mg doses with steady state lisinopril caused no clinically relevant changes in the AUC or C_{max} of lisinopril. Statistically significant delays in lisinopril t_{max} of approximately 1 hour were observed on Days 3 and 24 of the study. When a single 1.5 mg dose of dulaglutide and metoprolol were coadministered, the AUC and C_{max} of metoprolol increased by 19% and 32%, respectively. While metoprolol t_{max} was delayed by 1 hour, this change was not statistically significant. These changes were not clinically relevant; therefore, no dose adjustment of lisinopril or metoprolol is necessary when administered with dulaglutide.

Warfarin

Following dulaglutide (1.5 mg) coadministration, S- and R-warfarin exposure and R-warfarin C_{max} were unaffected, and S-warfarin C_{max} decreased by 22%. AUC_{INR} increased by 2%, which is unlikely to be clinically significant, and there was no effect on maximum international normalised ratio response (INR_{max}). The time of international normalised ratio response ($tINR_{max}$) was delayed by 6 hours, consistent with delays in t_{max} of approximately 4 and 6 hours for S- and R-warfarin, respectively. These changes are not clinically relevant. No dose adjustment for warfarin is necessary when given together with dulaglutide.

Oral contraceptives

Coadministration of dulaglutide (1.5 mg) with an oral contraceptive (norgestimate 0.18 mg/ethinyl estradiol 0.025 mg) did not affect the overall exposure to norelgestromin and ethinyl estradiol. Statistically significant reductions in C_{max} of 26% and 13% and delays in t_{max} of 2 and 0.30 hours were observed for norelgestromin and ethinyl estradiol, respectively. These observations are not clinically relevant. No dose adjustment for oral contraceptives is required when given together with dulaglutide.

Metformin

Following coadministration of multiple 1.5 mg doses of dulaglutide with steady state metformin (immediate release formula [IR]), metformin AUC_{τ} increased up to 15% and C_{max} decreased up to 12%, respectively, with no changes in t_{max}. These changes are consistent with the gastric emptying delay of dulaglutide and within the pharmacokinetic variability of metformin and thus are not clinically relevant. No dose adjustment for metformin IR is recommended when given with dulaglutide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of dulaglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Therefore, the use of dulaglutide is not recommended during pregnancy.

Breast-feeding

It is unknown whether dulaglutide is excreted in human milk. A risk to newborns/infants cannot be excluded. Dulaglutide should not be used during breast-feeding.

Fertility

The effect of dulaglutide on fertility in humans is unknown. In the rat, there was no direct effect on mating or fertility following treatment with dulaglutide (see section 5.3).

4.7 Effects on ability to drive and use machines

Trulicity has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

In the completed phase 2 and phase 3 studies to support the initial registration of dulaglutide 0.75 mg and 1.5 mg, 4,006 patients were exposed to dulaglutide alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions in clinical trials were gastrointestinal, including nausea, vomiting and diarrhoea. In general, these reactions were mild or moderate in severity and transient in nature. Results from the long-term cardiovascular outcome study with 4,949 patients randomised to dulaglutide and followed for a median of 5.4 years were consistent with these findings.

Tabulated list of adverse reactions

The following adverse reactions have been identified based on evaluation of the full duration of the phase 2 and phase 3 clinical studies, the long-term cardiovascular outcome study and post-marketing reports. The adverse reactions are listed in Table 1 as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000; very rare: < 1/10,000 and not known: cannot be estimated from available data). Within each incidence grouping, adverse reactions are presented in order of decreasing frequency. Frequencies for events have been calculated based on their incidence in the phase 2 and phase 3 registration studies.

Table 1: The frequency of adverse reactions of dulaglutide

System organ class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity	Anaphylactic reaction[#]	
Metabolism and nutrition disorders	Hypoglycaemia* (when used in combination with insulin, glimepiride, metformin[†] or metformin plus glimepiride)	Hypoglycaemia* (when used as monotherapy or in combination with metformin plus pioglitazone)	Dehydration		
Gastrointestinal disorders	Nausea, diarrhoea, vomiting[†], abdominal pain[†]	Decreased appetite, dyspepsia, constipation, flatulence,		Acute pancreatitis, delayed gastric emptying	Non-mechanical intestinal obstruction

		abdominal distention, gastroesophageal reflux disease, eructation			
Hepatobiliary disorders			Cholelithiasis, cholecystitis		
Skin and subcutaneous tissue disorders				Angioedema[#]	
General disorders and administration site conditions		Fatigue	Injection site reactions		
Investigations		Sinus tachycardia, first degree atrioventricular block (AVB)			

[#] From post-marketing reports.
***** Documented, symptomatic hypoglycaemia with blood glucose ≤ 3.9 mmol/L
† For dulaglutide 0.75 mg, adverse reaction met frequency for next lower incidence grouping.

Description of selected adverse reactions

Hypoglycaemia
When dulaglutide 0.75 mg and 1.5 mg were used as monotherapy or in combination with metformin alone or metformin and pioglitazone, the incidences of documented symptomatic hypoglycaemia were 5.9% to 10.9% and the rates were 0.14 to 0.62 events/patient/year, and no episodes of severe hypoglycaemia were reported.

The incidences of documented symptomatic hypoglycaemia when dulaglutide 0.75 mg and 1.5 mg, respectively, were used in combination with a sulphonylurea and metformin were 39.0% and 40.3% and the rates were 1.67 and 1.67 events/patient/year. The severe hypoglycaemia event incidences were 0% and 0.7%, and rates were 0.00 and 0.01 events/patient/year for each dose, respectively. The incidence of documented symptomatic hypoglycaemia when dulaglutide 1.5 mg was used with sulphonylurea alone was 11.3% and the rate was 0.90 events/patient/year, and there were no episodes of severe hypoglycaemia.

The incidence of documented symptomatic hypoglycaemia when dulaglutide 1.5 mg was used in combination with insulin glargine was 35.3% and the rate was 3.38 events/patient/year. The severe hypoglycaemia event incidence was 0.7% and the rate was 0.01 events/patient/year.

The incidences when dulaglutide 0.75 mg and 1.5 mg, respectively, were used in combination with prandial insulin were 85.3% and 80.0% and rates were 35.66 and 31.06 events/patient/year. The severe hypoglycaemia event incidences were 2.4% and 3.4%, and rates were 0.05 and 0.06 events/patient/year.

Gastrointestinal adverse reactions

Cumulative reporting of gastrointestinal events up to 104 weeks with dulaglutide 0.75 mg and 1.5 mg, respectively, included nausea (12.9% and 21.2%*)*, diarrhoea (10.7% and 13.7%) and vomiting (6.9% and 11.5%). These were typically mild or moderate in severity and were reported to peak during the first 2 weeks of treatment and rapidly declined over the next 4 weeks, after which the rate remained relatively constant.

In clinical pharmacology studies conducted in patients with type 2 diabetes mellitus up to 6 weeks, the majority of gastrointestinal events were reported during the first 2-3 days after the initial dose and declined with subsequent doses.

Acute pancreatitis
The incidence of acute pancreatitis in phase 2 and 3 registration studies was 0.07% for dulaglutide compared to 0.14% for placebo and 0.19% for comparators with or without additional background antidiabetic therapy. Acute pancreatitis and pancreatitis have also been reported in the post-marketing setting.

Pancreatic enzymes
Dulaglutide is associated with mean increases from baseline in pancreatic enzymes (lipase and/or pancreatic amylase) of 11% to 21% (see section 4.4). In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Heart rate increase
Small mean increases in heart rate of 2 to 4 beats per minute (bpm) and a 1.3% and 1.4% incidence of sinus tachycardia, with a concomitant increase from baseline ≥ 15 bpm, were observed with dulaglutide 0.75 mg and 1.5 mg, respectively.

First degree AV block/PR interval prolongation
Small mean increases from baseline in PR interval of 2 to 3 msec and a 1.5% and 2.4% incidence of first-degree AV block were observed with dulaglutide 0.75 mg and 1.5 mg, respectively.

Immunogenicity
In registration studies, treatment with dulaglutide was associated with a 1.6% incidence of treatment emergent dulaglutide anti-drug antibodies, indicating that the structural modifications in the GLP-1 and modified IgG4 parts of the dulaglutide molecule, together with high homology with native GLP-1 and native IgG4, minimise the risk of immune response against dulaglutide. Patients with dulaglutide anti-drug antibodies generally had low titres, and although the number of patients developing dulaglutide anti-drug antibodies was low, examination of the phase 3 data revealed no clear impact of dulaglutide anti-drug antibodies on changes in HbA1c. None of the patients with systemic hypersensitivity developed dulaglutide anti-drug antibodies.

Hypersensitivity
In the phase 2 and phase 3 registration studies, systemic hypersensitivity events (e.g., urticaria, edema) were reported in 0.5% of patients receiving dulaglutide. Cases of anaphylactic reaction have been rarely reported with marketed use of dulaglutide.

Injection site reactions
Injection site adverse events were reported in 1.9% of patients receiving dulaglutide. Potentially immune-mediated injection site adverse events (e.g., rash, erythema) were reported in 0.7% of patients and were usually mild.

Discontinuation due to an adverse event

In studies of 26 weeks duration, the incidence of discontinuation due to adverse events was 2.6% (0.75 mg) and 6.1% (1.5 mg) for dulaglutide versus 3.7% for placebo. Through the full study duration (up to 104 weeks), the incidence of discontinuation due to adverse events was 5.1% (0.75 mg) and 8.4% (1.5 mg) for dulaglutide. The most frequent adverse reactions leading to discontinuation for 0.75 mg and 1.5 mg dulaglutide, respectively, were nausea (1.0%, 1.9%), diarrhoea (0.5%, 0.6%), and vomiting (0.4%, 0.6%), and were generally reported within the first 4-6 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

Effects of overdose with dulaglutide in clinical studies have included gastrointestinal disorders and hypoglycaemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, ATC code: A10BJ05

Mechanism of action

Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist. The molecule consists of 2 identical disulfide-linked chains, each containing a modified human GLP-1 analogue sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small peptide linker. The GLP-1 analog portion of dulaglutide is approximately 90% homologous to native human GLP-1 (7-37). Native GLP-1 has a half-life of 1.5 - 2 minutes due to degradation by DPP-4 and renal clearance. In contrast to native GLP-1, dulaglutide is resistant to degradation by DPP-4, and has a large size that slows absorption and reduces renal clearance. These engineering features result in a soluble formulation and a prolonged half-life of 4.7 days, which makes it suitable for once-weekly subcutaneous administration. In addition, the dulaglutide molecule was engineered to prevent the Fcγ receptor-dependent immune response and to reduce its immunogenic potential.

Dulaglutide exhibits several antihyperglycaemic actions of GLP-1. In the presence of elevated glucose concentrations, dulaglutide increases intracellular cyclic AMP (cAMP) in pancreatic beta cells leading to insulin release. Dulaglutide suppresses glucagon secretion which is known to be inappropriately elevated in patients with type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. Dulaglutide also slows gastric emptying.

Pharmacodynamic effects

Dulaglutide improves glycaemic control through the sustained effects of lowering fasting, pre-meal and postprandial glucose concentrations in patients with type 2 diabetes starting after the first dulaglutide administration and is sustained throughout the once weekly dosing interval.

A pharmacodynamic study with dulaglutide demonstrated, in patients with type 2 diabetes, a restoration of first phase insulin secretion to a level that exceeded levels observed in healthy subjects on placebo, and improved second phase insulin secretion in response to an intravenous bolus of glucose. In the same study, a single 1.5 mg dose of dulaglutide appeared to increase maximal insulin secretion from the β-cells, and to enhance β-cell function in subjects with type 2 diabetes mellitus as compared with placebo.

Consistent with the pharmacokinetic profile, dulaglutide has a pharmacodynamic profile suitable for once weekly administration (see section 5.2).

Clinical efficacy and safety

Glycaemic control
The safety and efficacy of dulaglutide were evaluated in nine randomised, controlled, phase 3 trials involving 6,193 patients with type 2 diabetes. Of these, 1,206 were ≥ 65 years of which 119 were ≥ 75 years. These studies included 3,808 dulaglutide-treated patients, of whom 1,558 were treated with Trulicity 0.75 mg weekly and 2,250 were treated with Trulicity 1.5 mg weekly. In all studies, dulaglutide produced clinically significant improvements in glycaemic control as measured by glycosylated haemoglobin A1c (HbA1c).

Monotherapy
Dulaglutide was studied in a 52-week active controlled monotherapy study in comparison to metformin. Trulicity 1.5 mg and 0.75 mg were superior to metformin (1500-2000 mg/day) in the reduction in HbA1c and a significantly greater proportion of patients reached an HbA1c target of < 7.0% and ≤ 6.5% with Trulicity 1.5 mg and Trulicity 0.75 mg compared to metformin at 26 weeks.

Table 2. Results of a 52-week active controlled monotherapy study with two doses of dulaglutide in comparison to metformin

	Baseline HbA1c (%)	Mean change in HbA1c (%)	Patients at target HbA1c < 7.0% (%)[a]	Patients at target HbA1c ≤ 6.5% (%)[b]	Change in FBG (mmol/L)	Change in body weight (kg)
26 weeks						
Dulaglutide 1.5 mg once weekly (n=269)	7.63	-0.78††	61.5#	46.0##	-1.61	-2.29
Dulaglutide 0.75 mg once weekly (n=270)	7.58	-0.71††	62.6#	40.0#	-1.46	-1.36#
Metformin 1500-2000 mg/day (n=268)	7.60	-0.56	53.6	29.8	-1.34	-2.22
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 269)	7.63	-0.70††	60.0#	42.3##	-1.56#	-1.93
Dulaglutide 0.75 mg once weekly (n = 270)	7.58	-0.55†	53.2	34.7	-1.00	-1.09#
Metformin 1500-2000 mg/day (n = 268)	7.60	-0.51	48.3	28.3	-1.15	-2.20

† multiplicity adjusted 1-sided p-value < 0.025, for noninferiority; †† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to metformin, assessed for HbA1c only

# $p < 0.05$, ## $p < 0.001$ dulaglutide treatment group compared to metformin

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

FBG = fasting blood glucose; DCCT = Diabetes Control and Complications Trial; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine

The rate of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and 0.75 mg, and metformin were 0.62, 0.15, and 0.09 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed.

Combination therapy with metformin

The safety and efficacy of dulaglutide was investigated in a placebo and active controlled (sitagliptin 100 mg daily) study of 104 weeks duration, all in combination with metformin. Treatment with Trulicity 1.5 mg and 0.75 mg resulted in a superior reduction in HbA1c compared to sitagliptin at 52 weeks, accompanied by a significantly greater proportion of patients achieving HbA1c targets of < 7.0% and ≤ 6.5%. These effects were sustained to the end of the study (104 weeks).

Table 3. Results of a 104-week placebo and active controlled study with two doses of dulaglutide in comparison to sitagliptin

	Baseline HbA1c (%)	Mean change in HbA1c (%)	Patients at target HbA1c < 7.0% (%)[a]	Patients at target HbA1c ≤ 6.5% (%)[b]	Change in FBG (mmol/L)	Change in body weight (kg)
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 304)	8.12	-1.22‡‡,##	60.9**,##	46.7**,##	-2.38**,##	-3.18**,##
Dulaglutide 0.75 mg once weekly (n = 302)	8.19	-1.01‡‡,##	55.2**,##	31.0**,##	-1.97**,##	-2.63**,##
Placebo (n = 177)	8.10	0.03	21.0	12.5	-0.49	-1.47
Sitagliptin 100 mg once daily (n = 315)	8.09	-0.61	37.8	21.8	-0.97	-1.46
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 304)	8.12	-1.10††	57.6##	41.7##	-2.38##	-3.03##
Dulaglutide 0.75 mg once weekly (n = 302)	8.19	-0.87††	48.8##	29.0##	-1.63##	-2.60##
Sitagliptin 100 mg once daily (n = 315)	8.09	-0.39	33.0	19.2	-0.90	-1.53
104 weeks						
Dulaglutide 1.5 mg once weekly (n = 304)	8.12	-0.99††	54.3##	39.1##	-1.99##	-2.88##
Dulaglutide 0.75 mg once weekly (n = 302)	8.19	-0.71††	44.8##	24.2##	-1.39##	-2.39
Sitagliptin 100 mg once daily (n = 315)	8.09	-0.32	31.1	14.1	-0.47	-1.75

†† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide compared to sitagliptin, assessed only for HbA1c at 52 and 104 weeks

‡‡ multiplicity adjusted 1-sided p-value < 0.001 for superiority of dulaglutide compared to placebo, assessed for HbA1c only

** p < 0.001 dulaglutide treatment group compared to placebo

p < 0.001 dulaglutide treatment group compared to sitagliptin

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and 0.75 mg, and sitagliptin were 0.19, 0.18, and 0.17 episodes/patient/year, respectively. No cases of severe hypoglycaemia with dulaglutide were observed.

The safety and efficacy of dulaglutide was also investigated in an active controlled study (liraglutide 1.8 mg daily) of 26 weeks duration, both in combination with metformin. Treatment with Trulicity 1.5 mg resulted in similar lowering of HbA1c and patients achieving HbA1c targets of < 7.0% and ≤ 6.5% compared to liraglutide.

Table 4. Results of a 26-week active controlled study of one dose of dulaglutide in comparison to liraglutide

	Baseline HbA1c	**Mean change in HbA1c**	**Patients at target HbA1c**		**Change in FBG**	**Change in body weight**
	(%)	**(%)**	**< 7.0 % (%)[a]**	**≤ 6.5 % (%)[b]**	**(mmol/L)**	**(kg)**
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 299)	8.06	-1.42‡	68.3	54.6	-1.93	-2.90#
Liraglutide+ 1.8 mg daily (n = 300)	8.05	-1.36	67.9	50.9	-1.90	-3.61

‡ 1-sided p-value p < 0.001, for noninferiority of dulaglutide compared to liraglutide, assessed only for HbA1c.

# p < 0.05 dulaglutide treatment group compared to liraglutide.

+ Patients randomised to liraglutide were initiated at a dose of 0.6 mg/day. After Week 1, patients were up-titrated to 1.2 mg/day and then at Week 2 to 1.8 mg/day.

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rate of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg was 0.12 episodes/patient/year and with liraglutide was 0.29 episodes/patient/year. No cases of severe hypoglycaemia were observed.

Combination therapy with metformin and sulphonylurea
In an active controlled study of 78 weeks duration, dulaglutide was compared to insulin glargine, both on a background of metformin and a sulphonylurea. At 52 weeks, Trulicity 1.5 mg demonstrated superior lowering in HbA1c to insulin glargine which was maintained at 78 weeks; whereas lowering in HbA1c with Trulicity 0.75 mg was non-inferior to insulin glargine. With Trulicity 1.5 mg a significantly higher percentage of patients reached a target HbA1c of < 7.0% or ≤ 6.5% at 52 and 78 weeks compared to insulin glargine.

Table 5. Results of a 78-week active controlled study with two doses of dulaglutide in comparison to insulin glargine

	Baseline HbA1c (%)	**Mean change in HbA1c** (%)	**Patients at target HbA1c** **< 7.0% (%)[a]**	**≤ 6.5% (%)[b]**	**Change in FBG** (mmol/L)	**Change in body weight** (kg)
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 273)	8.18	-1.08††	53.2##	27.0##	-1.50	-1.87##
Dulaglutide 0.75 mg once weekly (n = 272)	8.13	-0.76†	37.1	22.5#	-0.87##	-1.33##
Insulin glargine+ once daily (n = 262)	8.10	-0.63	30.9	13.5	-1.76	1.44
78 weeks						
Dulaglutide 1.5 mg once weekly (n = 273)	8.18	-0.90††	49.0##	28.1##	-1.10#	-1.96##
Dulaglutide 0.75 mg once weekly (n = 272)	8.13	-0.62†	34.1	22.1	-0.58##	-1.54##
Insulin glargine+ once daily (n = 262)	8.10	-0.59	30.5	16.6	-1.58	1.28

† multiplicity adjusted 1-sided p-value < 0.025, for noninferiority; †† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to insulin glargine, assessed for HbA1c only

# $p < 0.05$, ## $p < 0.001$ dulaglutide treatment group compared to insulin glargine

+ Insulin glargine doses were adjusted utilising an algorithm with a fasting plasma glucose target of < 5.6 mmol/L

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and 0.75 mg, and insulin glargine were 1.67, 1.67, and 3.02 episodes/patient/year, respectively. Two cases of severe hypoglycaemia were observed with dulaglutide 1.5 mg and two cases of severe hypoglycaemia were observed with insulin glargine.

Combination therapy with sulphonylurea

The safety and efficacy of dulaglutide as add-on to a sulphonylurea was investigated in a placebo controlled study of 24 weeks duration. Treatment with Trulicity 1.5 mg in combination with glimepiride resulted in a statistically significant reduction in HbA1c compared to placebo with glimepiride at 24 weeks. With Trulicity 1.5 mg, a significantly higher percentage of patients reached a target HbA1c of < 7.0% and ≤ 6.5% at 24 weeks compared to placebo.

Table 6. Results of a 24-week placebo controlled study of dulaglutide as add-on to glimepiride

	Baseline HbA1c	**Mean change in HbA1c**	**Patients at target HbA1c**		**Change in FBG**	**Change in body weight**
	(%)	**(%)**	**< 7.0% (%)[a]**	**≤ 6.5% (%)[b]**	**(mmol/L)**	**(kg)**
24 weeks						
Dulaglutide 1.5 mg once weekly (n=239)	8.39	-1.38‡‡	55.3‡‡	40.0**	-1.70‡‡	-0.91
Placebo (n=60)	8.39	-0.11	18.9	9.4	0.16	-0.24

‡‡ $p < 0.001$ for superiority of dulaglutide compared to placebo, with overall type I error controlled

** $p < 0.001$ for dulaglutide treatment group compared to placebo

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and placebo were 0.90 and 0.04 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed for dulaglutide or placebo.

Combination therapy with SGLT2 inhibitor with or without metformin

The safety and efficacy of dulaglutide as add-on to sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy (96% with and 4% without metformin) were investigated in a placebo controlled study of 24 weeks duration. Treatment with Trulicity 0.75 mg or Trulicity 1.5 mg in combination with SGLT2i therapy resulted in a statistically significant reduction in HbA1c compared to placebo with SGLT2i therapy at 24 weeks. With both Trulicity 0.75 mg and 1.5 mg, a significantly higher percentage of patients reached a target HbA1c of < 7.0% and ≤ 6.5% at 24 weeks compared to placebo.

Table 7. Results of a 24-week placebo controlled study of dulaglutide as add-on to SGLT2i therapy

	Baseline HbA1c	**Mean change in HbA1c**	**Patients at target HbA1c**		**Change in FBG**	**Change in body weight**
	(%)	**(%)**	**< 7.0%^ (%)[a]**	**≤ 6.5% (%)[b]**	**(mmol/L)**	**(kg)**
24 weeks						
Dulaglutide 0.75 mg once weekly (n = 141)	8.05	-1.19‡‡	58.8‡‡	38.9**	-1.44	-2.6
Dulaglutide 1.5 mg once weekly (n = 142)	8.04	-1.33‡‡	67.4‡‡	50.8**	-1.77	-3.1
Placebo (n=140)	8.05	-0.51	31.2	14.6	-0.29	-2.3

‡‡ $p < 0.001$ for superiority of dulaglutide compared to placebo, with overall type I error controlled

** $p < 0.001$ for dulaglutide treatment group compared to placebo

^ Patients who withdrew from randomised treatment before 24 weeks were considered as not meeting the target

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 0.75 mg, dulaglutide 1.5 mg, and placebo were 0.15, 0.16 and 0.12 episodes/patient/year, respectively. One patient reported severe hypoglycaemia with dulaglutide 0.75 mg in combination with SGLT2i therapy and none with dulaglutide 1.5 mg or placebo.

Combination therapy with metformin and pioglitazone
In a placebo and active (exenatide twice daily) controlled study, both in combination with metformin and pioglitazone, Trulicity 1.5 mg and 0.75 mg demonstrated superiority for HbA1c reduction in comparison to placebo and exenatide, accompanied by a significantly a greater percentage of patients achieving HbA1c targets of < 7.0% or ≤ 6.5%

Table 8. Results of a 52-week active controlled study with two doses of dulaglutide in comparison to exenatide

	Baseline HbA1c	**Mean change in HbA1c**	**Patients at target HbA1c**		**Change in FBG**	**Change in body weight**
	(%)	**(%)**	**< 7.0% (%)[a]**	**≤ 6.5% (%)[b]**	**(mmol/L)**	**(kg)**
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 279)	8.10	-1.51‡‡,††	78.2**,##	62.7**,##	-2.36**,##	-1.30**
Dulaglutide 0.75 mg once weekly (n = 280)	8.05	-1.30‡‡/††	65.8**/##	53.2**/##	-1.90**/##	0.20 */##
Placebo (n = 141)	8.06	-0.46	42.9	24.4	-0.26	1.24
Exenatide[+] 10 mcg twice daily (n = 276)	8.07	-0.99	52.3	38.0	-1.35	-1.07
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 279)	8.10	-1.36††	70.8##	57.2##	-2.04##	-1.10
Dulaglutide 0.75 mg once weekly (n = 280)	8.05	-1.07††	59.1#	48.3##	-1.58#	0.44#
Exenatide[+] 10 mcg twice daily (n = 276)	8.07	-0.80	49.2	34.6	-1.03	-0.80

†† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to exenatide, assessed for HbA1c only
‡‡ multiplicity adjusted 1-sided p-value < 0.001 for superiority of dulaglutide compared to placebo, assessed for HbA1c only
* $p < 0.05$, **$p < 0.001$ dulaglutide treatment group compared to placebo
\# $p < 0.05$, ##$p < 0.001$ dulaglutide treatment group compared to exenatide
[+] Exenatide dose was 5 mcg twice daily for first 4 weeks and 10 mcg twice daily thereafter

[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and 0.75 mg, and exenatide twice daily were 0.19, 0.14, and 0.75 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed for dulaglutide and two cases of severe hypoglycaemia were observed with exenatide twice daily.

Combination therapy with titrated basal insulin, with or without metformin
In a 28-week placebo controlled study, Trulicity 1.5 mg was compared to placebo as add-on to titrated basal insulin glargine (88% with and 12% without metformin) to evaluate the effect on glycaemic control and safety. To optimise the insulin glargine dose, both groups were titrated to a target fasting serum glucose of < 5.6 mmol/L. The mean baseline dose of insulin glargine was 37 units/day for patients receiving placebo and 41 units/day for patients receiving Trulicity 1.5 mg. The initial insulin glargine doses in patients with HbA1c < 8.0% were reduced by 20%. At the end of the 28-week treatment period the dose was 65 units/day and 51 units/day, for patients receiving placebo and Trulicity 1.5 mg, respectively. At 28 weeks, treatment with once weekly Trulicity 1.5 mg resulted in a statistically significant reduction in HbA1c compared to placebo and a significantly greater percentage of patients achieving HbA1c targets of < 7.0% and ≤ 6.5% (Table 9).

Table 9. Results of a 28-week study of dulaglutide compared to placebo as add-on to titrated insulin glargine

	Baseline HbA1c	**Mean change in HbA1c**	**Patients at target HbA1c**		**Change in FBG**	**Change in body weight**
	(%)	**(%)**	**< 7.0% (%)[a]**	**≤ 6.5% (%)[b]**	**(mmol/L)**	**(kg)**
28 weeks						
Dulaglutide 1.5 mg once weekly and insulin glargine (n = 150)	8.41	-1.44‡‡	66.7‡‡	50.0**	-2.48‡‡	-1.91‡‡
Placebo once weekly and insulin glargine (n = 150)	8.32	-0.67	33.3	16.7	-1.55	0.50

‡‡ $p < 0.001$ for superiority of dulaglutide compared to placebo, overall type I error controlled
** $p < 0.001$ dulaglutide treatment group compared to placebo
[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and insulin glargine were 3.38 episodes/patient/year compared to placebo and insulin glargine 4.38 episodes/patient/year. One patient reported severe hypoglycaemia with dulaglutide 1.5 mg in combination with insulin glargine and none with placebo.

Combination therapy with prandial insulin with or without metformin
In this study, patients on 1 or 2 insulin injections per day prior to study entry, discontinued their prestudy insulin regimen and were randomised to dulaglutide once weekly or insulin glargine once daily, both in combination with prandial insulin lispro three times daily, with or without metformin. At 26 weeks, both Trulicity 1.5 mg and 0.75 mg were superior to insulin glargine in lowering of HbA1c and this effect was sustained at 52 weeks. A greater percentage of patients achieved HbA1c targets of < 7.0% or ≤ 6.5% at 26 weeks and < 7.0% at 52 weeks than with insulin glargine.

Table 10. Results of a 52-week active controlled study with two doses of dulaglutide in comparison to insulin glargine

	Baseline HbA1c	**Mean change in HbA1c**	**Patients at target HbA1c**		**Change in FBG**	**Change in body weight**
	(%)	**(%)**	**< 7.0% (%)[a]**	**≤ 6.5% (%)[b]**	**(mmol/L)**	**(kg)**
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 295)	8.46	-1.64††	67.6#	48.0#	-0.27##	-0.87##
Dulaglutide 0.75 mg once weekly (n = 293)	8.40	-1.59††	69.0#	43.0	0.22##	0.18##
Insulin glargine+ once daily (n = 296)	8.53	-1.41	56.8	37.5	-1.58	2.33
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 295)	8.46	-1.48††	58.5#	36.7	0.08##	-0.35##
Dulaglutide 0.75 mg once weekly (n = 293)	8.40	-1.42††	56.3	34.7	0.41##	0.86##
Insulin glargine+ once daily (n = 296)	8.53	-1.23	49.3	30.4	-1.01	2.89

†† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to insulin glargine, assessed for HbA1c only
# $p < 0.05$, ## $p < 0.001$ dulaglutide treatment group compared to insulin glargine
+ Insulin glargine doses were adjusted utilizing an algorithm with a fasting plasma glucose target of < 5.6 mmol/L
[a] HbA1c value of 7.0% (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5% (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and 0.75 mg, and insulin glargine were 31.06, 35.66, and 40.95 episodes/patient/year, respectively. Ten patients reported severe hypoglycaemia with dulaglutide 1.5 mg, seven with dulaglutide 0.75 mg, and fifteen with insulin glargine.

Fasting blood glucose
Treatment with dulaglutide resulted in significant reductions from baseline in fasting blood glucose. The majority of the effect on fasting blood glucose concentrations occurred by 2 weeks. The improvement in fasting glucose was sustained through the longest study duration of 104 weeks.

Postprandial glucose
Treatment with dulaglutide resulted in significant reductions in mean post prandial glucose from baseline (changes from baseline to primary time point -1.95 mmol/L to -4.23 mmol/L).

Beta-cell function
Clinical studies with dulaglutide have indicated enhanced beta-cell function as measured by homeostasis model assessment (HOMA2-%B). The durability of effect on beta-cell function was maintained through the longest study duration of 104 weeks.

Body weight
Trulicity 1.5 mg was associated with sustained weight reduction over the duration of studies (from baseline to final time point -0.35 kg to -2.90 kg). Changes in body weight with Trulicity 0.75 mg ranged from 0.86 kg to -2.63 kg. Reduction in body weight was observed in patients treated with dulaglutide irrespective of nausea, though the reduction was numerically larger in the group with nausea.

Patient reported outcomes
Dulaglutide significantly improved total treatment satisfaction compared to exenatide twice daily. In addition, there was significantly lower perceived frequency of hyperglycaemia and hypoglycaemia compared to exenatide twice daily.

Blood pressure
The effect of dulaglutide on blood pressure as assessed by Ambulatory Blood Pressure Monitoring was evaluated in a study of 755 patients with type 2 diabetes. Treatment with dulaglutide provided reductions in systolic blood pressure (SBP) (-2.8 mmHg difference compared to placebo) at 16 weeks. There was no difference in diastolic blood pressure (DBP). Similar results for SBP and DBP were demonstrated at the final 26 week time point of the study.

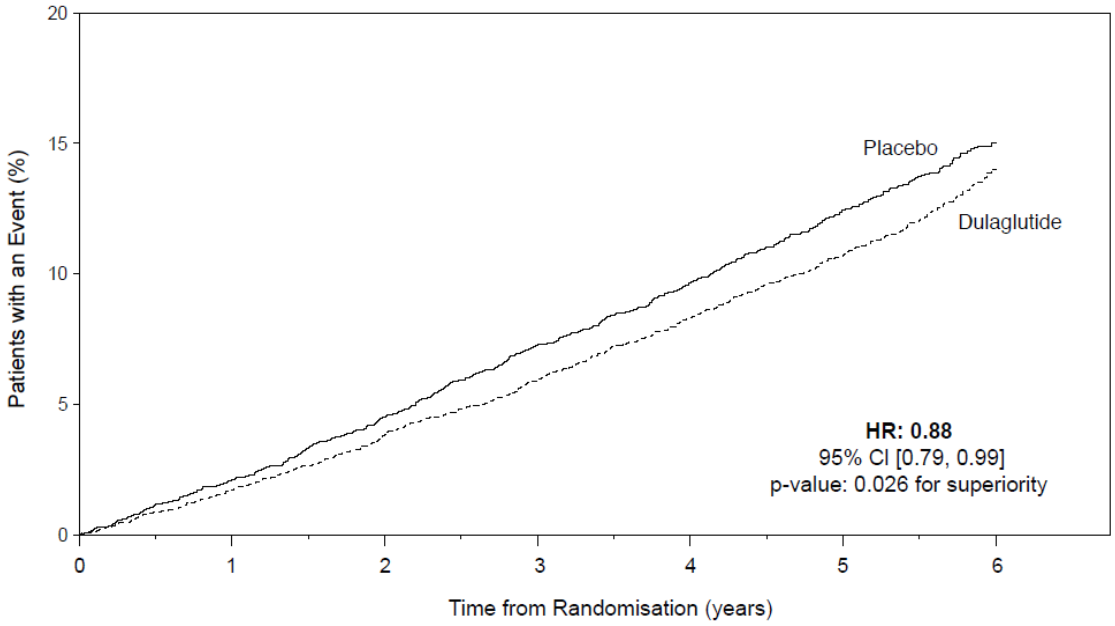
<u>Cardiovascular Evaluation</u>

Meta-analysis of phase 2 and 3 studies
In a meta-analysis of phase 2 and 3 registration studies, a total of 51 patients (dulaglutide: 26 [N = 3,885]; all comparators: 25 [N = 2,125]) experienced at least one cardiovascular (CV) event (death due to CV causes, nonfatal MI, nonfatal stroke, or hospitalisation for unstable angina). The results showed that there was no increase in CV risk with dulaglutide compared with control therapies (HR: 0.57; CI: [0.30, 1.10]).

Cardiovascular outcome study
The Trulicity long-term cardiovascular outcome study was a placebo-controlled, double-blind clinical trial. Type 2 diabetes patients were randomly allocated to either Trulicity 1.5 mg (4,949) or placebo (4,952) both in addition to standards of care for type 2 diabetes (the 0.75 mg dose was not administered in this study). The median study follow-up time was 5.4 years.

The mean age was 66.2 years, the mean BMI was 32.3 kg/m², and 46.3% of patients were female. There were 3,114 (31.5%) patients with established CV disease. The median baseline HbA1c was 7.2%. The Trulicity treatment arm included patients ≥ 65 years (n = 2,619) and ≥ 75 years (n = 484), and patients with mild (n = 2,435), moderate (n = 1,031) or severe (n = 50) renal impairment.

The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke. Trulicity was superior in preventing MACE compared to placebo (Figure 1). Each MACE component contributed to the reduction of MACE, as shown in Figure 2.



Number of patients at risk

Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

Figure 1. Kaplan-Meier plot of time to first occurrence of the composite outcome: CV death, non-fatal myocardial infarction or non-fatal stroke, in the dulaglutide long-term cardiovascular outcome study

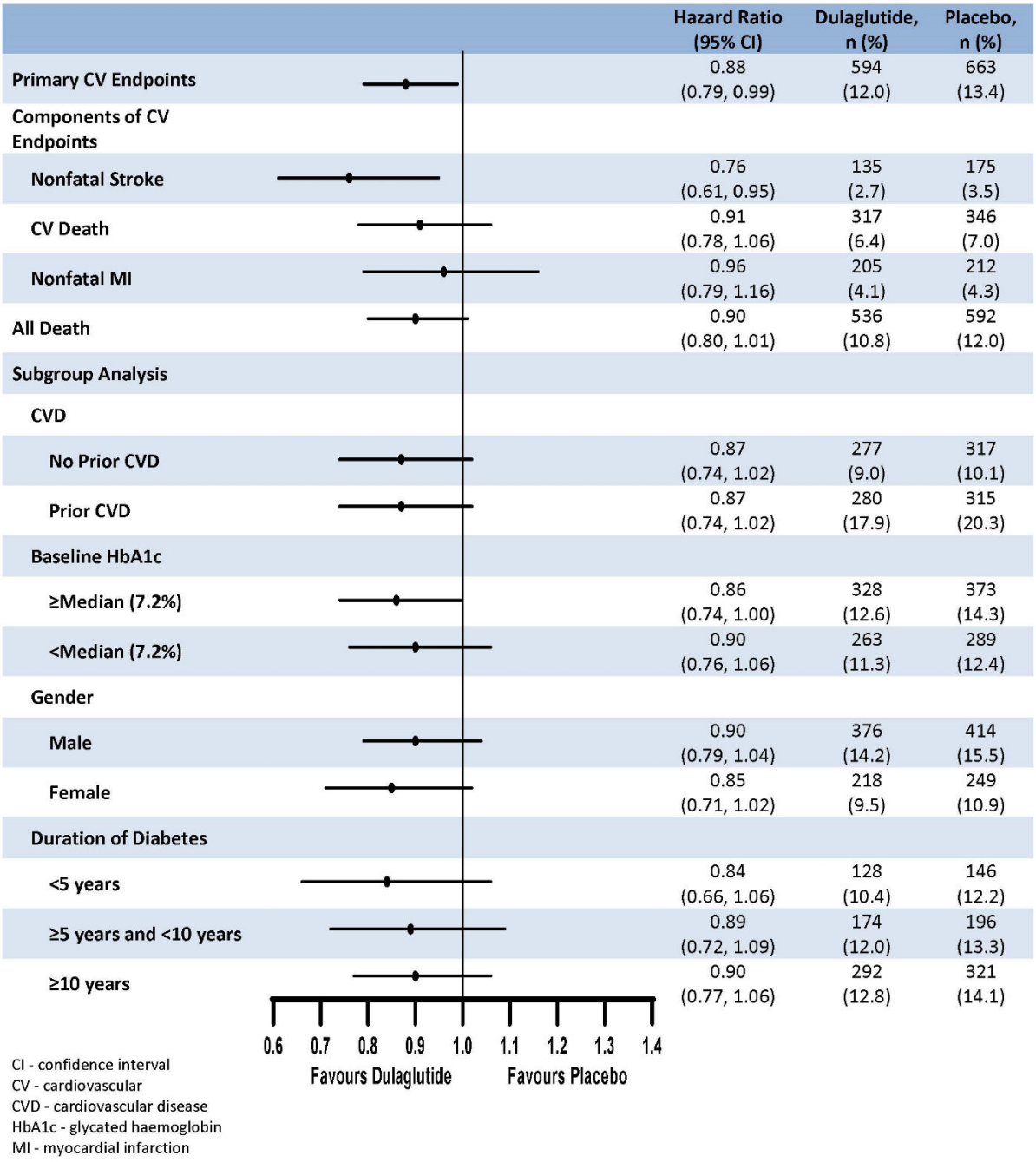


Figure 2. Forest plot of analyses of individual cardiovascular event types, all cause death, and consistency of effect across subgroups for the primary endpoint

A significant and sustained reduction in HbA1c levels from baseline to month 60 was observed with Trulicity vs placebo, in addition to standard of care (-0.29% vs 0.22%; estimated treatment difference -0.51% [-0.57; -0.45]; $p < 0.001$). There were significantly fewer patients in the Trulicity group who received an additional glycaemic intervention compared to placebo (Trulicity: 2,086 [42.2%]; placebo: 2,825 [57.0%]; $p < 0.001$).

Special populations

Use in patients with renal impairment
In a 52 week study, Trulicity 1.5 mg and 0.75 mg were compared to titrated insulin glargine as add-on to prandial insulin lispro to evaluate the effect on glycaemic control and safety of patients with moderate to severe chronic kidney disease (eGFR [by CKD-EPI] < 60 and ≥ 15 mL/min/1.73 m^2). Patients discontinued their pre-study insulin regimen at randomisation. At baseline, overall mean eGFR was 38 mL/min/1.73 m^2, 30% of patients had eGFR < 30 mL/min/1.73 m^2.

At 26 weeks, both Trulicity 1.5 mg and 0.75 mg were non-inferior to insulin glargine in lowering of HbA1c and this effect was sustained at 52 weeks. A similar percentage of patients achieved HbA1c targets of < 8.0% at 26 and 52 weeks with both dulaglutide doses as well as insulin glargine.

Table 11. Results of a 52-week active controlled study with two doses of dulaglutide in comparison to insulin glargine (in patients with moderate to severe chronic kidney disease)

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c < 8.0% (%)[a]**	**Change in FBG (mmol/L)**	**Change in body weight (kg)**
26 weeks					
Dulaglutide 1.5 mg once weekly (n = 192)	8.60	-1.19[†]	78.3	1.28[##]	-2.81[##]
Dulaglutide 0.75 mg once weekly (n = 190)	8.58	-1.12[†]	72.6	0.98[##]	-2.02[##]
Insulin glargine[+] once daily (n = 194)	8.56	-1.13	75.3	-1.06	1.11
52 weeks					
Dulaglutide 1.5 mg once weekly (n = 192)	8.60	-1.10[†]	69.1	1.57[##]	-2.66[##]
Dulaglutide 0.75 mg once weekly (n = 190)	8.58	-1.10[†]	69.5	1.15[##]	-1.71[##]
Insulin glargine[+] once daily (n = 194)	8.56	-1.00	70.3	-0.35	1.57

[†] 1-sided p-value < 0.025, for non-inferiority of dulaglutide to insulin glargine
[##] p < 0.001 dulaglutide treatment group compared to insulin glargine
[+] Insulin glargine doses were adjusted utilizing an algorithm with a fasting plasma glucose target of ≤ 8.3 mmol/L
[a] HbA1c value of 8.0% (DCCT) corresponds to 63.9 mmol/mol (IFCC) (average blood glucose: 10.1 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and dulaglutide 0.75 mg, and insulin glargine were 4.44, 4.34, and 9.62 episodes/patient/year, respectively. No patients reported cases of severe hypoglycaemia with dulaglutide 1.5 mg, six with dulaglutide 0.75 mg, and seventeen with insulin glargine. The safety profile of dulaglutide in patients with renal impairment was similar to that observed in other studies with dulaglutide.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration to patients with type 2 diabetes, dulaglutide reaches peak plasma concentrations in 48 hours. The mean peak (C_{max}) and total (AUC) exposures were approximately 114 ng/ml and 14,000 ngh/ml, respectively, after multiple subcutaneous 1.5 mg doses of dulaglutide in patients with type 2 diabetes. Steady-state plasma concentrations were achieved between 2 to 4 weeks of once-weekly administration of dulaglutide (1.5 mg). Exposures after subcutaneous administration of single dulaglutide (1.5 mg) doses in the abdomen, thigh, or upper arm were comparable. The mean absolute bioavailability of dulaglutide following single-dose subcutaneous administration of single 1.5 mg and 0.75 mg doses was 47% and 65%, respectively.

Distribution

The apparent population mean central volume of distribution was 3.09 L and the apparent population mean peripheral volume of distribution was 5.98 L.

Biotransformation

Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways.

Elimination

Apparent population mean clearance of dulaglutide was 0.142 L/h. and the elimination half-life was approximately 5 days.

Special populations

Elderly
Age had no clinically relevant effect on the pharmacokinetic and pharmacodynamic properties of dulaglutide.

Gender and race
Gender and race had no clinically meaningful effect on the pharmacokinetics of dulaglutide.

Body weight or body mass index
Pharmacokinetic analyses have demonstrated a statistically significant inverse relationship between body weight or body mass index (BMI) and dulaglutide exposure, although there was no clinically relevant impact of weight or BMI on glycaemic control.

Renal impairment
The pharmacokinetics of dulaglutide were evaluated in a clinical pharmacology study and were generally similar between healthy subjects and patients with mild to severe renal impairment (CrCl < 30 ml/min), including end stage renal disease (requiring dialysis). Additionally, in a 52-week clinical study in patients with type 2 diabetes and moderate to severe renal impairment (eGFR [by CKD-EPI] < 60 and ≥ 15 mL/min/1.73 m^2), the pharmacokinetic profile of Trulicity 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies. This clinical study did not include patients with end stage renal disease.

Hepatic impairment
The pharmacokinetics of dulaglutide were evaluated in a clinical pharmacology study, where subjects with hepatic impairment had statistically significant decreases in dulaglutide exposure of up to 30% to 33% for mean C_{max} and AUC, respectively, compared to healthy controls. There was a general increase in t_{max} of dulaglutide with increased hepatic impairment. However, no trend in dulaglutide exposure was observed relative to the degree of hepatic impairment. These effects were not considered to be clinically relevant.

Paediatric population
Studies characterising the pharmacokinetics of dulaglutide in paediatric patients have not been performed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeat-dose toxicity.

In a 6-month carcinogenicity study in transgenic mice, there was no tumorigenic response. In a 2-year carcinogenicity study in rats, at ≥ 7 times the human clinical exposure following 1.5 mg dulaglutide per week, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas combined). The clinical relevance of these findings is currently unknown.

During the fertility studies, a reduction in the number of corpora lutea and prolonged oestrous cycle were observed at dose levels that were associated with decreased food intake and body weight gain in maternal animals; however, no effects on indices of fertility and conception or embryonic development were observed. In reproductive toxicology studies, skeletal effects and a reduction in foetal growth were observed in the rat and rabbit at exposures of dulaglutide 5- to 18-fold higher than those proposed clinically, but no foetal malformations were observed. Treatment of rats throughout pregnancy and lactation produced memory deficits in female offspring at exposures that were 7-fold higher than those proposed clinically. Dulaglutide dosing of male and female juvenile rats did not produce memory deficits at 38-fold the highest human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Trisodium Citrate Dihydrate
Polysorbate 80
Citric acid, anhydrous
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2ºC – 8ºC).
Do not freeze.
Store in original package in order to protect from light.

In use

Trulicity may be stored unrefrigerated for up to 14 days at a temperature below 30ºC. If the pen has been left out of the refrigerator for more than 14 days, the pen must be discarded even if it has not reached the expiration date.

6.5 Nature and contents of container

Glass syringe (type I) encased in a disposable pen.
Each pre-filled pen contains 0.5 ml of solution.
Packs of 4 pre-filled pens.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use

The pre-filled pen is for single-use only.
The instructions for using the pen, included with the package leaflet, must be followed carefully.
Trulicity should not be used if particles appear or if the solution is cloudy and/or discoloured.
Trulicity that has been frozen must not be used.

7. LICENSE HOLDER

Eli Lilly Israel Ltd.,
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8. MANUFACTURER

Eli Lilly and Company
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9. LICENSE NUMBER

Trulicity 0.75 mg: 154-39-34356-00
Trulicity 1.5 mg: 154-40-34357-00

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