EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/585102/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trulicity

International non-proprietary name: dulaglutide

Procedure No. EMEA/H/C/002825/II/0040

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 5 April 2019 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the new indication for Trulicity; "*to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke), in adults with type 2 diabetes mellitus who have multiple cardiovascular risk factors without established cardiovascular disease, and in adults with type 2 diabetes mellitus with established cardiovascular disease.*"
The data supporting this new indication is derived from Study GBDJ (Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)); a single pivotal Phase 3 long-term cardiovascular outcomes study, which assessed the efficacy and safety of treatment with once-weekly injection of dulaglutide 1.5 mg when added to glucose-lowering regimen of patients with type 2 diabetes (T2D), compared to the addition of a once weekly placebo injection. This study is a post-authorisation measure (PAM) (MEA 004) included in the dulaglutide RMP.
As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are proposed to be updated and the Package Leaflet is proposed to be updated accordingly.
In addition, the MAH is taking the opportunity to update the wording of the existing indication in section 4.1 of the SmPC and to implement a minor change in section 5.1 of the SmPC, in the glycaemic control summary subsection, based on the results from the dulaglutide study as add-on to sodium-glucose co-transporter 2 inhibitor therapy which was assessed as part of II/25.
An updated RMP version 3.1 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0227/2016 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0227/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	5 April 2019
Start of procedure	27 April 2019
CHMP Rapporteur Assessment Report	19 June 2019
PRAC Rapporteur Assessment Report	27 June 2019
PRAC members comments	4 July 2019
Updated PRAC Rapporteur Assessment Report	7 July 2019
PRAC Outcome	11 July 2019
CHMP members comments	18 July 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 July 2019
Request for supplementary information (RSI)	25 July 2019
PRAC Rapporteur Assessment Report	27 August 2019
PRAC members comments	28 August 2019
Updated PRAC Rapporteur Assessment Report	29 August 2019
CHMP Rapporteur Assessment Report	26 August 2019
PRAC Outcome	5 September 2019
CHMP members comments	9 September 2019
Updated CHMP Rapporteur Assessment Report	12 September 2019
Opinion	19 September 2019

2. Scientific discussion

2.1. Introduction

Dulaglutide (Trulicity) is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist with 90% amino acid sequence homology to endogenous human GLP-1 that exhibits GLP-1-mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss.

As of 31 December 2018, dulaglutide 0.75 mg or 1.5 mg is approved in 74 countries for once-weekly subcutaneous administration as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). The pharmacological class is incretin mimetic.

This application concerns Study H9X-MC-GBDJ, also known as REWIND (Researching cardiovascular Events with a Weekly INcretin in Diabetes), a Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group trial that was conducted to assess the superiority of dulaglutide 1.5 mg s.c. once weekly compared with placebo on the incidence of major adverse cardiovascular (CV) events (MACE; death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) when added to the existing antihyperglycemic regimen in patients with T2D.

The Applicant proposes that the results of the cardiovascular outcome trial (REWIND) can be used to support the following new therapeutic indication:

"Trulicity is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)

· in adults with type 2 diabetes mellitus who have multiple cardiovascular risk factors without established cardiovascular disease

· in adults with type 2 diabetes mellitus with established cardiovascular disease (see section 5.1)."

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Dulaglutide is a biological consisting of a peptide fused to an antibody fragment by a linker. All components consist of natural proteinogenic amino acids. It is assumed that the protein or peptide part will not be excreted in unchanged form and will not reach the environment. An environmental risk assessment is therefore not required.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, dulaglutide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The cardiovascular outcome study (Study H9X-MC-GBDJ/ REWIND) was performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The assessment of Study GBDJ (REWIND) did not reveal concerns regarding GCP non-compliance.

Primary Objective	Study Design	Study Drug	Intended Patient Population	Follow-up Time (median)	Treatment Duration (median)
Demonstrate that once-weekly injection of 1.5-mg dulaglutide reduces the occurrence of the composite primary endpoint of death from CV causes, nonfatal MI, or nonfatal stroke when added to glucose-lowering regimen of patients with T2D, compared to the addition of a once-weekly placebo injection.	Phase 3, multicenter, international, double-blind, placebo-controlled, parallel-group, randomized study	Dula: 1.5 mg once-weekly SC injection Placebo: once-weekly SC injection	Patients ≥ 50 years of age with T2D (HbA1c ≤ 9.5%) and had either prior CV disease, documented subclinical CV disease, or multiple CV risk characteristics	Dula 1.5 mg: 65.0 months Placebo: 65.1 months	Dula 1.5 mg: 61.9 months Placebo: 61.9 months

Abbreviations: CV = cardiovascular; Dula = dulaglutide; HbA1c = glycated hemoglobin; MI = myocardial infarction; SC = subcutaneous; T2D = type 2 diabetes.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: **R**esearching Cardiovascular **E**vents with a **W**eekly **IN**cretin in **D**iabetes (REWIND/ Study H9X-MC-GBDJ).

Methods

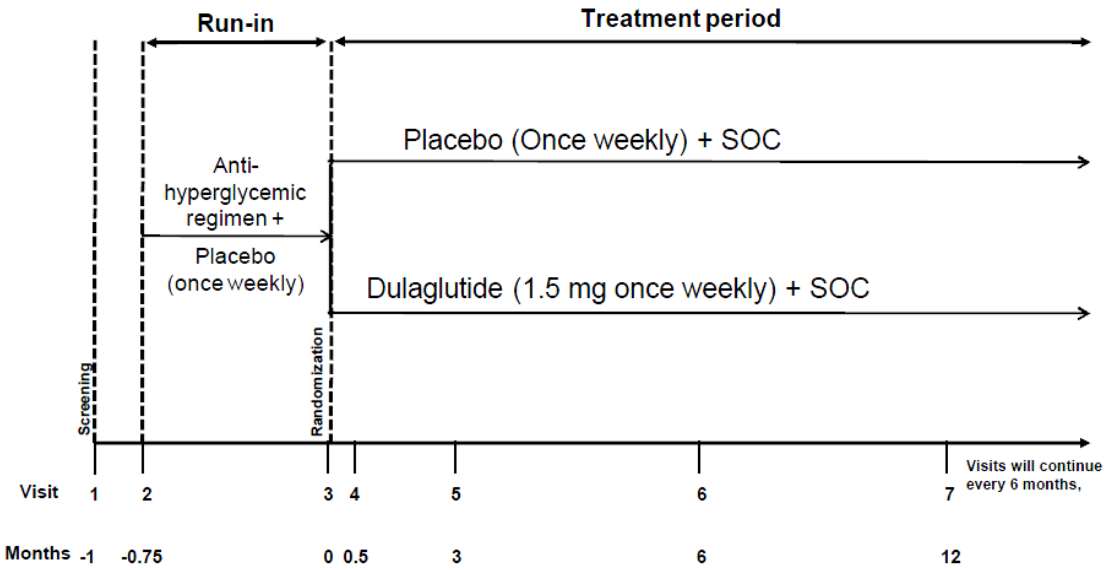
Objectives

The primary objective was to test the hypothesis that once weekly s.c. injection of dulaglutide 1.5 mg reduces the occurrence of the composite primary endpoint of death from cardiovascular (CV) causes, nonfatal myocardial infarction (MI), or nonfatal stroke when added to the glucose-lowering regimen of patients with type 2 diabetes (T2D), compared to the addition of a once-weekly placebo injection.

Study Design

Study H9X-MC-GBDJ (REWIND) was a Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study that assessed the effect of dulaglutide 1.5 mg s.c. once weekly compared to placebo on major adverse CV events in patients with T2D when added to their existing antihyperglycemic regimen. All eligible patients participated in a 3-week, single-blind, placebo run-in period. Patients who were adherent to study drug (placebo) during the run-in period were randomized in a 1:1 ratio to either dulaglutide 1.5 mg or placebo, injected subcutaneously once weekly. After randomization, patients were followed up for CV outcomes and other measures at 2 weeks, 3 months, 6 months, and then followed up at approximately 6-month intervals. Patients were to be followed-up until approximately 1200 patients experienced a Clinical Endpoint Committee (CEC)-adjudicated 3-component MACE. The median follow-up time of this study was 5.4 years.

Study Design (H9X-MC-GBDJ/ REWIND)



Abbreviation: SOC = standard of care.

Study Drug, Dose, and Mode of Administration

Dulaglutide, 1.5 mg dose, administered subcutaneously once weekly.

Comparator, Dose, and Mode of Administration

Placebo, administered subcutaneously once weekly.

Number of Patients

- Planned to be randomized: 9600
- Randomized: 4949 dulaglutide, 4952 placebo
- Treated (at least 1 dose): 4943 dulaglutide, 4949 placebo
- Completed (includes patients for whom vital status was ascertained during the study close-out period or had a 3-component MACE): 4932 dulaglutide, 4935 placebo
- Endpoint completers (had a 3-component MACE or died during the study or a final visit during close-out period): 4817 dulaglutide, 4793 placebo

Diagnosis and Criteria for Inclusion

- Men or women with previously diagnosed or newly diagnosed T2D
- HbA1c value of ≤9.5% (≤81 mmol/mol) at screening and body mass index (BMI) ≥23 kg/m2
- Were taking:
  - no glucose-lowering drugs;

  - 1 or 2 classes of oral glucose-lowering drugs, with or without GLP-1 RA, with or without basal insulin daily; patients taking a DPP-IV inhibitor or a GLP-1 RA must have been willing to stop the DPP-IV inhibitor or the GLP-1 RA after eligibility was confirmed; OR
  - basal insulin daily defined as 1 to 2 injections per day.
- No change in the number or class of glucose-lowering drugs, no change in excess of doubling or halving the dose of these drugs, and, if on insulin, no change in the dose of insulin in excess of 20% of the average daily dose, for at least 3 months before screening.
- If age ≥50 years and established clinical vascular disease defined as 1 or more of the following:
  - a history of MI
  - a history of ischemic stroke
  - a history of coronary, carotid, or peripheral artery revascularization. If prior CABG, the CABG should have been performed >2 years prior to randomization. If prior carotid or peripheral artery revascularization, the revascularization should have been performed >2 months prior to randomization.
  - hospitalization for unstable angina with ECG changes (new or worsening ST- or Twave changes), myocardial ischemia on imaging, or need for percutaneous coronary intervention (PCI);

  OR
- If age ≥55 years and subclinical vascular disease defined as 1 or more of the following:
  - a history of myocardial ischemia by a stress test or with cardiac imaging, with or without history of exertional angina
  - >50% vascular stenosis with imaging of the coronary, carotid, or lower extremity arteries, with or without claudication history
  - ankle-brachial index <0.9
  - 2 consecutive values or a documented history of persistent eGFR <60 mL/minute/1.73m2
  - a history of hypertension with documented LV hypertrophy on an ECG or echocardiogram
  - documented history of persistent microalbuminuria or macroalbuminuria, or 2 consecutive urine samples demonstrating microalbuminuria or macroalbuminuria;

  OR
- If age ≥60 years and at least 2 or more of the following risk factors for CV outcomes:
  - current tobacco use (any form of tobacco)
  - used at least 1 approved lipid-modifying therapy to treat hypercholesterolemia or a documented untreated low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L (130 mg/dL) within the past 6 months
  - documented treated or untreated high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months
  - used at least 1 BP medication to treat hypertension or untreated SBP ≥140 mm Hg or diastolic blood pressure (DBP) ≥95 mmHg
  - measured waist-to-hip ratio >1.0 for men and >0.8 for women

Primary efficacy measure

The primary efficacy measure was the time to first occurrence of the 3-component MACE.

Secondary efficacy measures

Time to the first occurrence of:

- the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy, or anti-VEGF therapy; and development of clinical proteinuria, a 30% decline in eGFR, or need for chronic renal replacement therapy
- hospitalization for unstable angina
- each component of the composite primary endpoint

- all-cause mortality
- heart failure requiring hospitalization or an urgent HF visit

Prespecified safety measures
- acute pancreatitis
- serious GI events
- any cancer (excluding basal or squamous cell skin cancer) and specific categories of
  -pancreatic cancer
  -medullary thyroid carcinoma (MTC) and C-cell hyperplasia
  -thyroid carcinomas
- severe hypoglycemia
- immune-mediated reactions including serious allergic and hypersensitivity reactions
- serious hepatic events
- clinically significant supraventricular arrhythmias and CV conduction disorders
- serious renal events
- discontinuation of study drug for any reason
- development of cholelithiasis

Other measures included vital signs (blood pressure [systolic and diastolic] and heart rate) and anthropometric measurements (weight, height, and waist/hip circumference), laboratory analytes, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), discontinuations due to adverse events (AEs), and safety evaluation of adjudication results of all deaths.

Statistical methods

The analysis methods were defined in the study SAP, which was finalized prior to the interim analysis.

Primary efficacy and safety analyses were conducted on the ITT population. This population included all randomized patients within the treatment group to which they were assigned, regardless of whether or not they took study drug or the correct study drug.
Analyses were also conducted using the Per-Protocol (PP) population.

The primary analyses of the primary endpoints and key secondary endpoints were based on adjudicated events that occurred after randomization. The primary analysis model was a Cox proportional hazards regression model for the time to the first occurrence of a 3-component MACE, with treatment as a fixed effect. Analyses were performed for the composite endpoint as well as for each of the components. The hazard ratio (dulaglutide/placebo) and the associated 95% CI (adjusted for interim analysis) were derived based on the Cox model. The between-treatment comparisons were based on the p-value from the Cox model. Kaplan-Meier (KM) estimates of the survival curve for each treatment were generated. Patients who completed the study but did not experience an outcome were censored on the last day of their follow-up. Patients who discontinued from the study were censored on their discontinuation dates or their last contact dates, whichever was later. Patients who died during the study were censored as of the date of death for all time-to-event analyses where death is not an outcome of interest. Patients who prematurely discontinued their assigned treatment were followed up until the end of the study.

Unless otherwise noted, all tests of treatment effects were conducted at a 2-sided alpha level of 0.05, and CIs were calculated at a 2-sided 95% confidence level.
An O'Brien-Fleming alpha spending function was used to control the Type I error across the interim and final analyses for the testing of the primary endpoint. The interim analysis for efficacy was performed when 756 patients had at least 1 event of the 3-component MACE, using an α =0.009. The interim analysis was performed by an independent statistical analysis center supporting the IDMC. The IDMC recommendation was to continue the study without alteration. The full alpha for the final analysis (adjusted for the interim analysis) with 1257 patients with 3-component MACE events was α =0.0467.

A graphical approach for multiple comparisons (Bretz et al. 2009, 2011) was used to strongly control the overall Type I error (2-sided alpha of 0.05) for testing the null hypothesis of no-treatment effect with respect to the secondary endpoints.

For adjudicated outcomes, the incidence rate per 100 person-years of follow-up was calculated for each treatment group. The numerator was the number of patients with the event, and the denominator was the event-specific total person-years of follow-up, divided by 100. Total person-years of follow-up was the sum, over patients, of the time on study until the first outcome (first event time or censoring time). The absolute risk difference (ARD) was then calculated by subtracting the incidence in the dulaglutide group from that in the placebo group.

For continuous measures, mixed-effects model repeated measures (MMRM) were used to analyze changes from baseline with the treatment as a fixed effect and the baseline value as the covariate. The MMRM model also included visit and the treatment-by-visit interaction as fixed effects and the patient as a random effect.

As sensitivity analysis, the primary endpoint and individual components were analysed based on a model stratified by site, an on-treatment analysis was performed, silent MI events were excluded, an analysis considering non-CV death as a competing risk factor was performed, an analysis adjusted for relevant baseline characteristics was conducted, an analysis stratified by baseline concomitant medications was performed, and a PP analysis.

Subgroup analyses were performed for the pre-specified subgroup variables gender, age, duration of diabetes, BMI, baseline HbA1c, region, and prior CV event.

Results

Recruitment

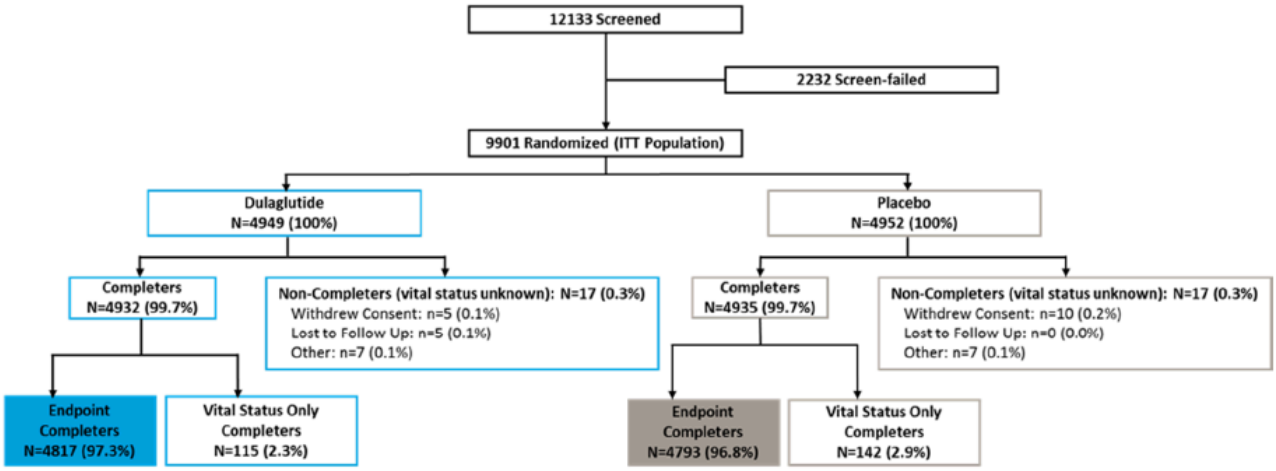
Study H9X-MC-GBDJ (REWIND) was conducted at 371 study centers in 24 countries. The first patient was enrolled on 22 July 2011 and the last patient completed the last visit on 21 August 2018.

Study population

The study population included patients with a mean HbA1c of 7.3% ± 1.1 at baseline. The population ranged from newly diagnosed patients to patients with a maximum diabetes duration of 55.5 years (the mean duration of diabetes was 10.5 years).
The majority (62.8%) of patients enrolled in Study H9X-MC-GBDJ (REWIND) did not have clinically manifest cardiovascular disease but did have multiple cardiovascular risk factors, while 31.5% of patients did have prior cardiovascular disease. For 5.7% of patients, baseline information regarding prior cardiovascular disease was missing or unknown.

Patient Disposition and Sample size

A sample size of approximately 9600 patients was required to show superiority of dulaglutide over placebo (with 90% power). A total of 9901 patients were randomized to either dulaglutide or placebo. A total of 9867 (99.7%) patients were study completers (endpoint completers or vital status only completers). A total of 9610 (97.1%) patients were endpoint completers (experienced a primary MACE endpoint, died of non-CV causes, or completed study) and 257 patients were vital status only completers. A total of 1257 patients experienced at least 1 adjudicated primary 3-component MACE events (dulaglutide; n=594, placebo; n=663).



Duration of Follow-up

The median follow-up time of Study H9X-MC-GBDJ (REWIND) was 5.4 years.

Adherence to the Study Treatment

The majority of patients in Study H9X-MC-GBDJ (REWIND) were adherent to study drug (dulaglutide, 89.3%; placebo, 91.3%).

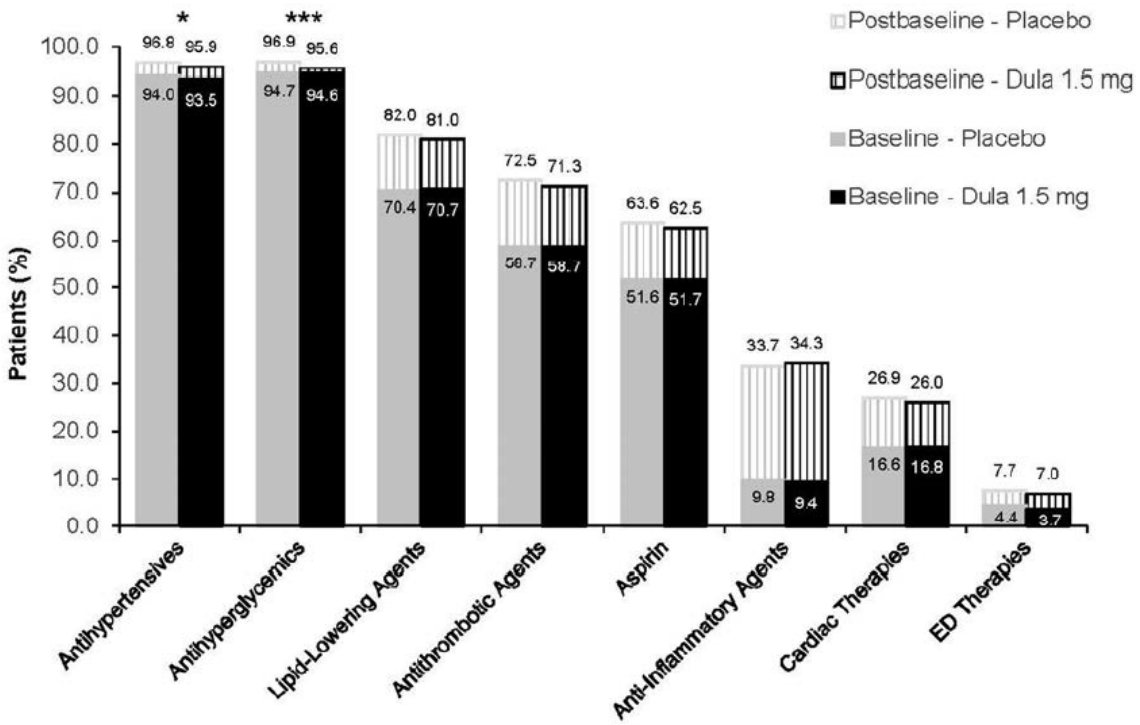
Demographics and Baseline CV Risk Characteristics

Demographic characteristics and relevant baseline CV risk characteristics were comparable and well balanced between the 2 treatment groups.

Use of Concomitant Medication

The use of concomitant medication is shown in the Figure below. The majority of patients were taking:

- Antihypertensives (dulaglutide: 93.5%; placebo: 94.0%)
- Antihyperglycemics (dulaglutide: 94.6%; placebo: 94.7%), and
- Lipid-lowering agents (dulaglutide: 70.7%; placebo: 70.4%)
- Antithrombotic Agents (dulaglutide: 58.7%; placebo: 58.7%)
- Aspirin (dulaglutide: 51.7%; placebo: 51.6%)



Patients on antihyperglycemic agents were primarily taking medications from either 1 (37.6%) or 2 (46.6%) classes; very few patients were taking 3 or more antihyperglycemic medication classes at baseline (10.5%), which did not differ between the 2 treatment groups. A high proportion of patients were taking metformin (81.2%) and sulfonylureas (46%) at baseline and a small proportion of patients were taking insulins (23.9%), which is consistent with the low mean HbA1c levels of the patients at baseline. Baseline use of dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose transporter-2 (SGLT-2) inhibitors, and thiazolidinediones was limited. The proportions of patients taking ACE inhibitors/ angiotensin receptor blockers, statins, aspirin, and beta-blockers at baseline were 81.5%, 66.1%, 51.7%, and 45.6%, respectively.

Efficacy results

Primary endpoint

During the REWIND study (median follow-up time 5.4 years), a total of 1257 patients with T2D had at least one primary 3-component MACE (death from CV causes, nonfatal MI, or nonfatal stroke): 12.0% (594/4949) of patients on dulaglutide vs. 13.4% (663/4952) of patients on placebo.

Once-weekly dulaglutide was superior to placebo for reducing the occurrence of the composite endpoint of 3-component MACE (death from CV causes, nonfatal MI, or nonfatal stroke) when added to the standard-of-care treatment of adult patients with T2D at risk for CV events (hazard ratio [95.33% confidence interval (CI), after adjustment for the interim analysis]): 0.88 [0.79, 0.99], p=0.026).

Analysis of the Primary 3-component MACE – ITT Population

	Dulaglutide[b] N=4949	Placebo[b] N=4952	Hazard Ratio (95% CI)[c]
3-component MACE (composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke)[a]	594 (12.0%)	663 (13.4%)	p=0.026 0.88 (0.79, 0.99)
Death from CV causes	317 (6.4%)	346 (7.0%)	0.91 (0.78, 1.06)
Nonfatal myocardial infarction	205 (4.1%)	212 (4.3%)	0.96 (0.79, 1.16)
Nonfatal stroke	135 (2.7%)	175 (3.5%)	0.76 (0.61, 0.95)

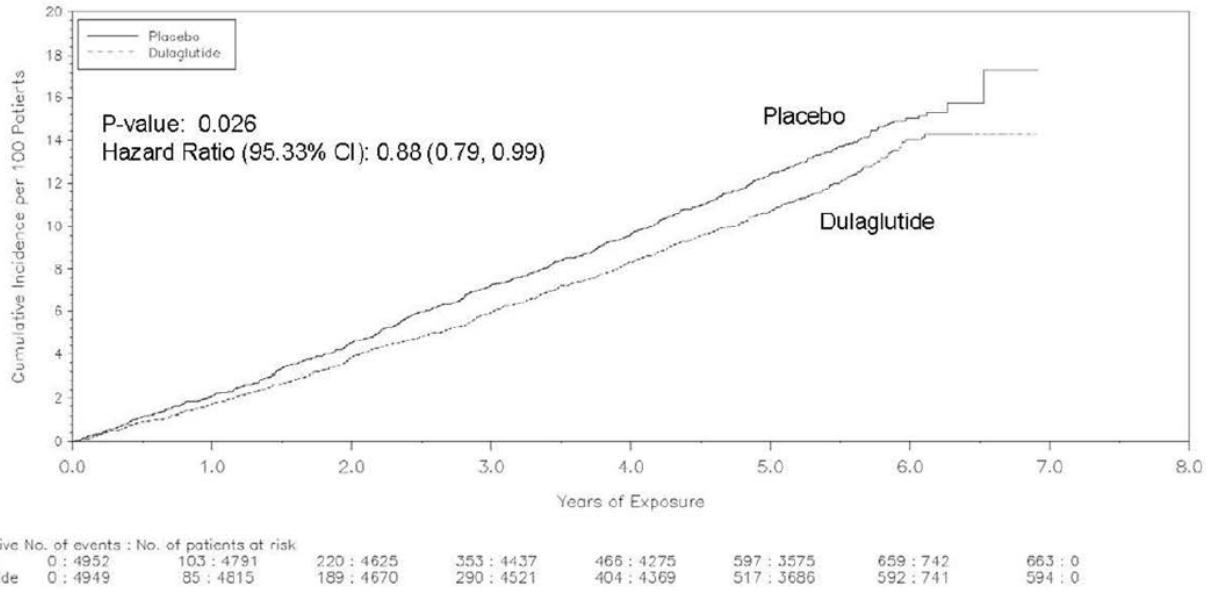
Abbreviations: 3-component MACE = a composite endpoint comprised of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke; CI = confidence interval; CV = cardiovascular; ITT = intent to treat; MACE = major adverse cardiovascular event.

a Cox-proportional hazards regression model with treatment as a factor, superiority achieved if p-value is smaller than the significance level of 0.0467.

b Number and percentage of patients.

c Adjusted confidence interval for composite primary endpoint 95.33%.

Kaplan-Meier Curve: Time to first CV primary endpoint event, ITT population.

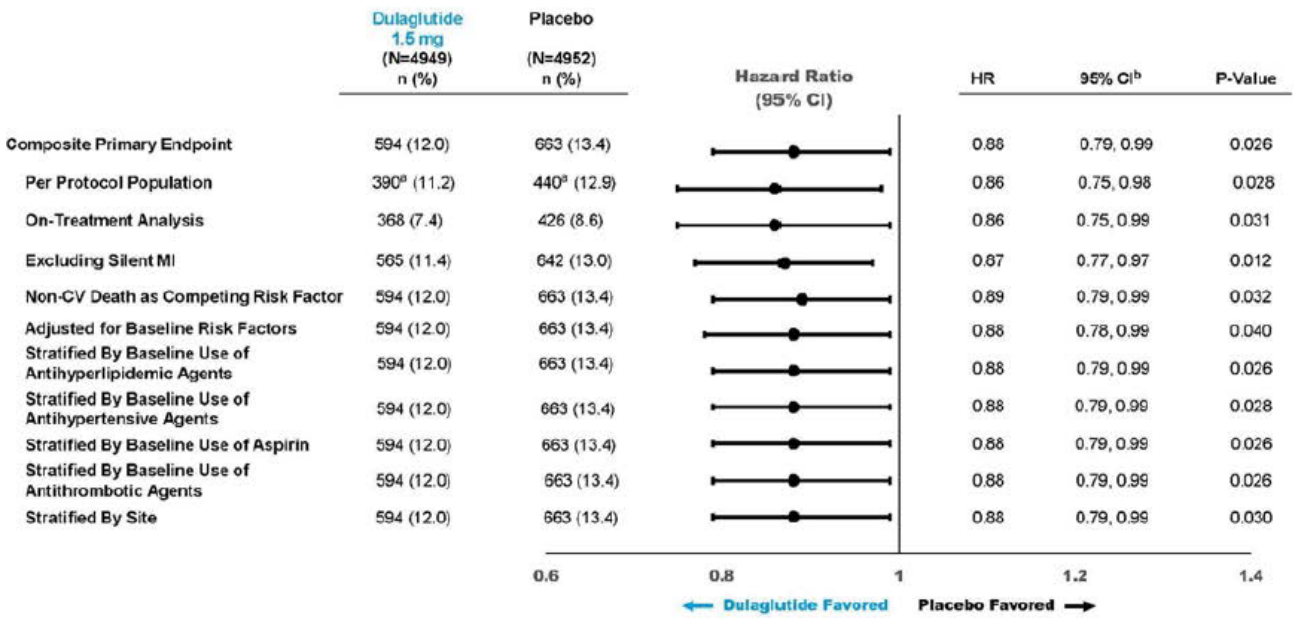


Cumulative No. of events : No. of patients at risk

Placebo	0 : 4952	103 : 4791	220 : 4625	353 : 4437	466 : 4275	597 : 3575	659 : 742	663 : 0
Dulaglutide	0 : 4949	85 : 4815	189 : 4670	290 : 4521	404 : 4369	517 : 3686	592 : 741	594 : 0

Sensitivity Analyses for the Composite Primary Endpoint

Sensitivity analyses were performed to assess the impact of several key variables on the composite primary endpoint.



Abbreviations:

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; n=number of patients in the specified category; N=number of patients in the treatment group.

[a] For the Per Protocol population analysis: dulaglutide, N = 3476; placebo, N=3416.

[b] The CI for the primary objective is an adjusted 95.33% CI, and the CI for all other endpoints is a nominal 95% CI.

Secondary and Additional Efficacy Endpoints, ITT Population

Objectives	Placebo (N=4952) n (%)	Dulaglutide (N=4949) n (%)	Hazard Ratio (95% CI)	p-Value	2-sided Significance Level[a]	Results of Significance Test (S/NS)
Type 1 Error Controlled Key Secondary Endpoints						
Death from CV causes	346 (7.0)	317 (6.4)	0.91 (0.78, 1.06)	0.211	0.0327	NS
Nonfatal MI	212 (4.3)	205 (4.1)	0.96 (0.79, 1.16)	0.652	0.0070	NS
Nonfatal stroke	175 (3.5)	135 (2.7)	0.76 (0.61, 0.95)	0.017	0.0070	NS
All-cause mortality	592 (12.0)	536 (10.8)	0.90 (0.80, 1.01)	0.067	N/A	Not tested
Composite microvascular endpoint	1241 (25.1)	1099 (22.2)	0.86 (0.79, 0.93)	< 0.001	N/A	Not tested
Composite nephropathy endpoint	1200 (24.2)	1042 (21.1)	0.84 (0.77, 0.91)	< 0.001	N/A	Not tested
Composite endpoint of diabetic retinopathy requiring treatment	76 (1.5)	95 (1.9)	1.24 (0.92, 1.68)	0.156	N/A	Not tested
Hospitalization for heart failure or UHFV	226 (4.6)	213 (4.3)	0.93 (0.77, 1.12)	0.456	N/A	Not tested
Hospitalization for unstable angina	77 (1.6)	88 (1.8)	1.14 (0.84, 1.54)	0.413	N/A	Not tested
Additional and Exploratory CV Endpoints Measures						
4-component MACE	720 (14.5)	666 (13.5)	0.91 (0.82, 1.01)	0.088	N/A	N/A
Composite revascularization endpoint	387 (7.8)	365 (7.4)	0.94 (0.81, 1.08)	0.370	N/A	N/A
All MI endpoints (fatal and nonfatal)	231 (4.7)	223 (4.5)	0.96 (0.79, 1.15)	0.625	N/A	N/A
All stroke endpoints (fatal and nonfatal)	205 (4.1)	158 (3.2)	0.76 (0.62, 0.94)	0.010	N/A	N/A
CV multiple events – 3-component MACE: First to Second	107 (2.2)	92 (1.9)	1.01 (0.76, 1.33)	0.948	N/A	N/A
Second to Third or higher order	21 (0.4)	18 (0.4)	0.94 (0.50, 1.77)	0.836	N/A	N/A

Abbreviations: CI = confidence interval; CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction; n = number of patients with adjudicated event; N = total number of patients in each treatment group; N/A = not applicable; NS = not significant; S = significant; UHFV = urgent heart failure visit.

Cox proportional hazards regression model for the time to the first occurrence of the event of interest with treatment as a fixed effect for all objective except CV multiple events.

[a] Significance was achieved if the p-value was less than the corresponding 2-sided significance level.

Other endpoints

HbA1c - Change from Baseline to Month 3 and Month 60

	Placebo (n=4937)	Dulaglutide (n=4939)	Treatment Comparison[a]
Baseline mean %, (SD)	7.35 (1.05)	7.34 (1.06)	
Month 3/Visit 5			
LS mean change from baseline (SE)	n=4772	n=4741	p<0.001
	0.08 (0.01)	-0.74 (0.01)	-0.82 (-0.86, -0.79)
Month 60/Visit 15			
LS mean change from baseline (SE)	n=3735	n=3877	p<0.001
	0.22 (0.02)	-0.29 (0.02)	-0.51 (-0.57, -0.45)

Abbreviations: CI = confidence interval; LS mean = least square mean; n = number of patients with non-missing baseline and non-missing data for specified postbaseline measure in specified treatment arm; SD = standard deviation; SE = standard error.

[a] P-value, LS mean difference (95% CI).

Body Weight - Change from Baseline to Month 12 and Month 60

	Placebo (N=4952)	Dulaglutide (N=4949)	Treatment Comparison[a]
Baseline mean kg, (SD)	n=4952	n=4948	-
	88.86 (18.64)	88.48 (18.38)	
Month 12/Visit 7			
LS mean change from baseline (SE)	n=4577	n=4619	p < 0.001
	-0.81 (0.08)	-2.56 (0.08)	-1.75 (-1.98, -1.53)
Month 60/Visit 15			
LS mean change from baseline (SE)	n=3754	n=3888	p < 0.001
	-2.16 (0.09)	-3.47 (0.09)	-1.31 (-1.56, -1.07)

Abbreviations: CI = confidence interval; LS = least square; SD = standard deviation; SE = standard error.

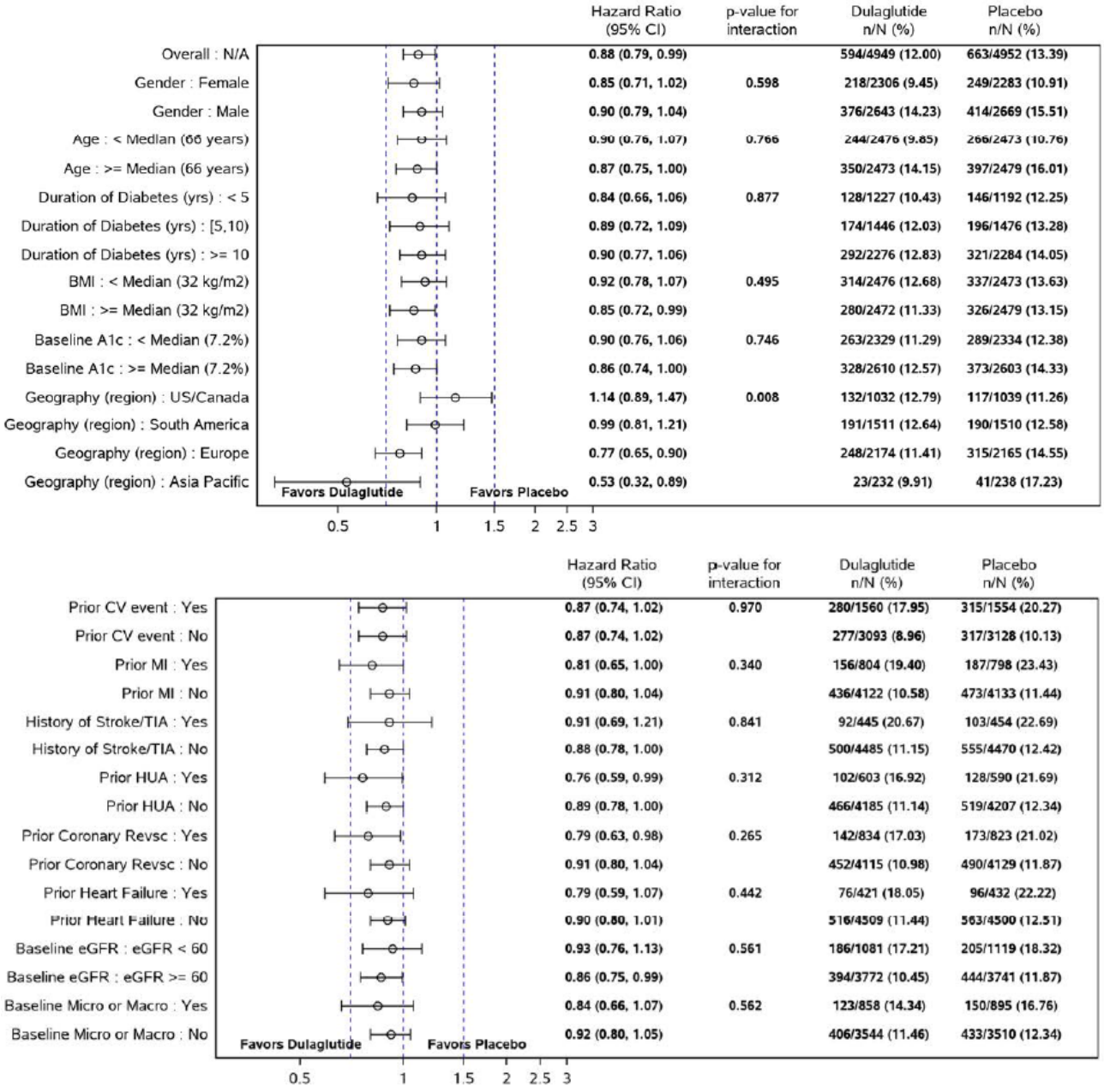
[a] p-value, LS mean difference (95% CI).

Blood Pressure and Heart Rate - Change from Baseline to Month 60

	Placebo (N=4952)	Dulaglutide (N=4949)	Treatment Comparison[a]
Systolic BP (mm Hg)			
Baseline mean (SD)	137.25 (16.97)	137.07 (16.64)	
LSM change from baseline at Month 60 (±SE)	-0.97 ± 0.23	-2.05 ± 0.23	p<0.001 -1.08 (-1.72, -0.44)[c]
Diastolic BP (mm Hg)			
Baseline mean (SD)	78.52 (9.87)	78.36 (9.79)	
LSM change from baseline at Month 60 (±SE)	-2.45 ± 0.14	-2.19 ± 0.14	p=0.180 0.26 (-0.12, 0.64)[c]
Heart Rate (beats/min)			
Baseline mean (SD)	71.55 (11.01)	71.40 (10.72)	
LSM change from baseline at Month 60 (±SE)	0.49 ± 0.15	1.87 ± 0.15	p<0.001 1.37 (0.96, 1.78)[c]

Ancillary analyses

Subgroup analyses for the primary endpoint, ITT population



Abbreviations:

A1c=glycated hemoglobin; BMI=body mass index; CI=confident interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HUA=hospitalization for unstable angina; ITT=intent-to-treat; Macro=macroalbuminuria; MI=myocardial infarction; Micro=microalbuminuria; n=number of patients in the specified category; N=number of patients randomized to the treatment group; Revsc=revascularization; TIA=transient ischemic attack; US=United States; yrs=years.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on the recently completed study REWIND. The REWIND study was an adequately designed multicenter, double-blind cardiovascular outcome trial (CVOT) with the 3-component MACE as primary composite efficacy endpoint (and components of the composite primary endpoint as key secondary endpoints). Other endpoints investigated (all-cause mortality, hospitalisation for heart failure or for unstable angina, HbA1c, body weight, blood pressure) are likewise considered relevant.
The study was conducted in 9901 adult T2DM patients (randomized in 1:1 ratio to dulaglutide 1.5 mg s.c. once weekly or placebo). The inclusion and exclusion criteria identified patients at different degrees of risk for CV events including patients with age ⩾50 years and established clinical vascular disease, ⩾55 years and subclinical vascular disease, or age ⩾60 years and at least 2 risk factors for CVD. Patients with previous or newly diagnosed T2D were eligible to enroll in the study, and patients were required to have HbA1c ⩽9.5% (no lower limit) at baseline.

Adherence to study treatment was high (approximately 90%) and almost all randomized patients completed the study (99.7% had vital status ascertained, and 97.1% had complete assessment of the primary endpoint status). This supports the reliability of the data.
As in other GLP-1 RA CVOTs, intensification of the concomitant treatment regimens was allowed for the management of glycemic control or other CV risk factors as required.

Sensitivity and subgroup analyses were performed to assess the impact of several key variables on the composite primary MACE endpoint. The statistical methodology is considered generally acceptable.

Efficacy data and additional analyses

There were no relevant imbalances between treatment groups with regard to demographic and baseline characteristics.

Mean HbA1c was 7.3% (± 1.1) at baseline. The majority of patients did not have prior CVD (62.8%), while 31.5% of patients had evidence of prior CVD at baseline and for 5.7% of patients it was unknown, whether they had prior CVD or not. Other cardiovascular outcome studies investigated a population at higher risk for cardiovascular events; however, definitions for cardiovascular disease differed between studies.
A minority of patients had evidence of renal dysfunction at baseline (22.2% of patients had eGFR<60 mL/min/1.73 m2), 27.9% had microalbuminuria, and 8.4% had macroalbuminuria.
The median follow-up time of this study was 5.4 years, which is longer than the follow-up period in other cardiovascular outcome studies (e. g. 3.8 years in LEADER, 2.1 in SUSTAIN-6).
Patients on antihyperglycemic agents were primarily taking medications from either 1 (37.6%) or 2 (46.6%) classes; very few patients were taking 3 or more antihyperglycemic medication classes at baseline (10.5%), which did not differ between the 2 treatment groups. A high proportion of patients in Study GBDJ were taking metformin (81.2%) and sulfonylureas (46%) at baseline and a small proportion of patients were taking insulins (23.9%), which is consistent with the low mean HbA1c levels of the patients at baseline. Baseline use of dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose transporter-2 (SGLT-2) inhibitors, and thiazolidinediones was limited.

Post-baseline, fewer patients in the dulaglutide treatment group reported use of antihypertensive and antihyperglycemic medications compared to placebo; no other notable differences between treatment groups were observed for other medication categories.

The primary analysis assessed the reduction of the incidence of 3-component MACE with dulaglutide compared to placebo. Superiority was confirmed for dulaglutide compared to placebo, and the hazard ratio for the 3-component MACE (death from CV causes, nonfatal MI, or nonfatal stroke) was significantly lower for patients in the dulaglutide group compared to the placebo group (hazard ratio [95.33% CI]) (0.88 [0.79, 0.99]); p=0.026.

Over multiple sensitivity and subgroup analyses, there was consistency of effect on the primary 3-component MACE endpoint across clinically relevant factors, including age, baseline HbA1c, duration of diabetes, and renal function. Of note, the effect of dulaglutide treatment was consistent, favoring dulaglutide, in the subpopulations of patients with or without a prior CV event.

The results of important secondary endpoints showed results consistent with the finding on the primary endpoint and showed a greater contribution of non-fatal stroke to the significant result of the primary analysis compared to cardiovascular death and non-fatal MI, where effects were rather modest: the incidence rate per 100 person-years of CV death was 1.22 patients with events for dulaglutide compared to 1.34 patients with events for placebo (HR 0.91); the incidence rate per 100 person-years of all-cause mortality was 2.06 patients with events for dulaglutide compared to 2.29 patients with events for placebo (HR 0.90); the incidence rate per 100 person-years of MI (nonfatal) was 0.80 patients with events for dulaglutide and 0.84 patients with events for placebo (HR 0.96); the incidence rate per 100 person-years of stroke (nonfatal) was 0.52 patients with events for dulaglutide compared to 0.69 patients.

As regards hospitalization for heart failure and hospitalisation for unstable angina results between dulaglutide and placebo can be regarded comparable (despite the fact, that there were slightly more events for HUA in the dulaglutide arm as compared to placebo, a finding that is not further pursued).

The dulaglutide group had a 16% lower hazard for the composite nephropathy endpoint (≥30% eGFR decline, renal replacement therapy, or macroalbuminuria) compared to the placebo group.

All of the 3 nephropathy components contributed to this effect with hazard ratios <1, but the primary contributing component was the development of macroalbuminuria with a 21% lower risk for the dulaglutide group. The effect of dulaglutide on reducing the onset of macroalbuminuria is also consistent with effects observed in previous dulaglutide studies (Tuttle et al. 2017, 2018) and other GLP-1 RAs (Marso et al. 2016; Mann et al. 2017).

Mean HbA1c at baseline was similar between the treatment groups (dulaglutide 7.34%; placebo 7.35%). Post-baseline, HbA1c was significantly reduced in the dulaglutide-treated patients, but significantly increased in placebo-treated patients at all time points assessed. Over the duration of the study, the HbA1c differences between the dulaglutide and placebo treatment groups became smaller. The effect on HbA1c at month 60 can be regarded as modest, which might be explained by the intended low baseline HbA1c (7.3%), the comparably long observational period and less use of concomitant antihyperglycemic drugs as compared to placebo.

Results on body weight, blood pressure and heart rate were consistent with previous dulaglutide studies that were designed to assess the efficacy and safety of dulaglutide for glycemic control, and the results are consistent with the descriptions in current labelling for the effects of dulaglutide on blood pressure and heart rate (Trulicity SmPC 2019): patients were moderately obese at study entry (mean baseline BMI, 32.3 kg/m2), with a mean weight of approximately 88.7 kg. During the study, weight was significantly reduced for patients of both treatment groups at all timepoints assessed. The LS mean change from baseline to Month 60 (± SE) was -3.47 kg ± 0.09 for dulaglutide (p<0.001) and -2.16 kg ± 0.09 for placebo (p<0.001). Mean baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were similar between the treatment groups. Post-baseline, significant decreases between baseline and month 60 were observed in both treatment groups for SBP (LS mean

change from baseline [± SE]: dulaglutide, -2.05 mmHg ± 0.23; placebo, -0.97 mmHg ± 0.23) and DBP (dulaglutide, -2.19 mmHg ± 0.14; placebo, -2.45 mmHg ± 0.14). Increases in heart rate between baseline and Month 60 were significant in both treatment groups (LS mean change from baseline [± SE]: dulaglutide, 1.87 beats/min ± 0.15; placebo, 0.49 beats/min ± 0.15); the increase in HR was significantly larger in the dulaglutide group compared to the placebo group.

2.4.3. Conclusions on the clinical efficacy

Study H9X-MC-GBDJ (REWIND) was a well-designed and well-conducted study in patients with a wide range of T2D disease severity and good glycemic control (mean HbA1c of 7.3% at baseline in both treatment groups), of whom a majority (62.8%) did not have established CVD at study initiation. Superiority of dulaglutide to placebo in reduction of the 3-component MACE endpoint compared to placebo was demonstrated. Results of secondary endpoints and in subgroups were consistent with the outcome of the primary analysis, further corroborating its validity.

Based on these results, the MAH proposed an extension of indication to include a new indication for dulaglutide (Trulicity) within section 4.1 of SmPC: *"to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke), in adults with type 2 diabetes mellitus who have multiple cardiovascular risk factors without established cardiovascular disease, and in adults with type 2 diabetes mellitus with established cardiovascular disease."*

Albeit, as compared to previous cardiovascular outcome studies, baseline HbA1c was somewhat lower in REWIND and the number of patients without prior cardiovascular disease (primary prevention population) was higher, all patients included had T2DM. Thus, there is complete overlap between the already labelled indication and the indication envisaged with regard to the target population.

Therefore, CHMP considered it not justified to include a separate reference in section 4.1 of the SmPC as applied by the MAH, as this population is already covered by the approved therapeutic indication. However the CHMP acknowledges the benefit in terms of cardiovascular outcome demonstrated in the REWIND and is therefore of the view that the current wording of the indication which only makes reference to the treatment goal "improvement of glycaemic control" does not fully reflect the demonstrated effects with dulaglutide. The wording "treatment of T2DM" was therefore considered more relevant in section 4.1 of the SmPC, as it encompasses both glycaemic control and results on clinical outcomes such as cardiovascular complications, and a cross-reference to section 5.1 of the SmPC where the study results of the REWIND are reflected.

2.5. Clinical safety

Introduction

The safety and tolerability of dulaglutide were investigated and documented in the original marketing authorisation application of dulaglutide for treatment of type 2 diabetes mellitus (T2DM).
With this submission, information on the safety and tolerability of dulaglutide from the cardiovascular outcome trial (CVOT) – Study H9X-MC-GBDJ (REWIND) is provided.
Study H9X-MC-GBDJ (REWIND) was the largest and longest clinical study to date within the dulaglutide clinical development program, contributing a total of 4949 dulaglutide and 4952 placebo-treated patients with T2D to the safety database. The median duration of follow-up (extent of the safety reporting period) for each treatment group was 5.4 years, translating to an overall 51,830.1 person-years of safety follow-up time.
The MAH has not pooled safety data from Study H9X-MC-GBDJ (REWIND) with data from the completed glucose-lowering studies of the dulaglutide clinical development program due to differences in

the study designs, study populations, and study measures. Safety data from Study H9X-MC-GBDJ (REWIND) are discussed below, and conclusions are discussed within the context of existing data from the original dulaglutide T2DM clinical program.

Methods

Overview of Study H9X-MC-GBDJ (REWIND)

Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Follow-up Time (median)
To test the hypothesis that dulaglutide reduces the occurrence of the composite primary endpoint of death from CV causes, nonfatal MI, or nonfatal stroke (3-component MACE) compared to placebo when both are added to the glucose-lowering regimen of patients with T2D	Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, event-driven, parallel-arm study	Dulaglutide: 1.5 mg (SC injection) once-weekly (prefilled syringe) Placebo: SC injection once-weekly (prefilled syringe)	ITT/randomized=9901 Dula 1.5 mg=4949 Placebo=4952	Adults with T2D (HbA1c ≤9.5%), with either CV risk factors or established CVD During the study, management of glycemic control, blood pressure, and lipids was expected to follow country-specific guidelines. However, use of other GLP-1 RAs or pramlintide was not allowed	The median follow-up duration was 5.4 years. A total of 1257 adjudicated primary endpoint events occurred

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; Dula = dulaglutide; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; ITT = intent-to-treat (all randomized patients); MACE = major adverse cardiovascular event; MI = myocardial infarction; SC = subcutaneous; T2D = type 2 diabetes.

Safety measures collected

Study H9X-MC-GBDJ (REWIND) included evaluations of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and deaths, and examination of several pre-specified adverse events of special interest (AESI): serious gastrointestinal (GI) events; acute pancreatitis; any cancer and in particular pancreatic cancer, medullary thyroid cancer (MTC), thyroid C-cell hyperplasia, and thyroid carcinomas; severe hypoglycemia; immune-mediated reactions and serious allergic hypersensitivity reactions; serious hepatic events; clinically significant supraventricular arrhythmias and CV conduction disorders; serious renal events; and discontinuation of study drug for any reason.

Patient exposure

A total of 9901 patients (dulaglutide: 4949; placebo: 4952) were randomized and included in the ITT population.

The median follow-up time in the study, defined as the time from randomization to the final visit regardless of study drug use, was 65.1 months for dulaglutide and 65.0 months for placebo. The percentage of patients with follow-up time in study of 60 months or greater was similar between both groups (dulaglutide: 78.6%; placebo: 77.0%).

The median treatment duration of study drug, defined as the time period over which the patient received study drug (irrespective of temporary study drug discontinuations), was 61.9 months for both treatment groups. The majority of patients were treated for 60 months or greater and the percentage was similar between both treatment groups (dulaglutide: 60.4%; placebo: 58.6%).

Total follow-up time in the study was 26 029.81 person-years in the dulaglutide group and 25 800.27 person-years in the placebo group. Total treatment duration was 21,940.27 person-years in the dulaglutide group and 21,973.76 person-years in the placebo group.
No significant differences were observed between the treatment groups in follow-up time in study or treatment duration.

Adverse events

Primary, secondary, and additional CV efficacy endpoint events (e.g., death from CV causes, nonfatal MI, nonfatal stroke, all-cause mortality, hospitalization for heart failure or an urgent heart failure visit, hospitalization for unstable angina, and revascularizations) were not required to be reported as AEs or SAEs unless the investigator deemed the event as related to study drug, drug delivery system, or study procedure. All of these efficacy endpoints were adjudicated and are discussed in the efficacy section of this report.

Treatment-Emergent Adverse Events

A total of 92.0% (n=9110) of patients experienced at least 1 Treatment-Emergent Adverse Event (TEAE) during the REWIND study. The high incidence of TEAEs was expected in this long-term cardiovascular outcome trial (median follow-up of 5.4 years) and given the age of the population enrolled (mean age 66.2 $\pm$ 6.5 years). The events were balanced across the two treatment groups (dulaglutide: 4575 [92.4%]; placebo: 4535 [91.6%]).

When evaluating overall TEAEs by SOC, higher proportions of patients treated with dulaglutide, compared to placebo, experienced TEAEs in the following system organ classes (SOCs):

- GI disorders: This result was primarily driven by higher incidence of nausea, diarrhea, constipation, and vomiting. Dulaglutide is known to cause GI events, especially within the first several weeks of administration, so higher incidences of nausea, diarrhea, constipation, and vomiting TEAEs in the dulaglutide patients were anticipated. These events were reported at a similar frequency as in the original application and are captured as adverse reactions in the Trulicity labels (Trulicity SmPC 2019).
- Metabolism and nutrition disorders: This result was driven by higher incidence of decreased appetite (dulaglutide: 6.6%; placebo: 2.1%) and dehydration (dulaglutide: 1.3%; placebo: 0.8%), both of which are reflected in current labelling (Trulicity SmPC 2019).

The TEAE profile of dulaglutide in the REWIND study was consistent with prior dulaglutide studies and the established safety profile of dulaglutide. No new adverse drug reactions were discovered.

Treatment-Emergent Adverse Events (TEAEs) with ⩾1% Incidence, ITT Population

Preferred Term	Treatment Group		P-Value
	Placebo (N=4952) n (%)	Dulaglutide (N=4949) n (%)	
Patients with ≥1 TEAE	4535 (91.6)	4575 (92.4)	0.113
Higher in Dulaglutide-Treated Patients Compared to Placebo			
Nausea	271 (5.5)	737 (14.9)	<0.001
Diarrhea	442 (8.9)	671 (13.6)	<0.001
Constipation	213 (4.3)	364 (7.4)	<0.001
Vomiting	159 (3.2)	330 (6.7)	<0.001
Decreased Appetite	105 (2.1)	326 (6.6)	<0.001
Dyspepsia	148 (3.0)	292 (5.9)	<0.001
Gastroenteritis	131 (2.7)	191 (3.9)	<0.001
Fatigue	143 (2.9)	179 (3.6)	0.041
Gastroesophageal Reflux Disease	126 (2.5)	166 (3.4)	0.017
Abdominal Upper Pain	107 (2.2)	157 (3.2)	0.002
Abdominal Distention	71 (1.4)	122 (2.5)	<0.001
Asthenia	85 (1.7)	121 (2.4)	0.011
Eructation	10 (0.2)	104 (2.1)	<0.001
Weight Decreased	53 (1.1)	100 (2.0)	<0.001
Flatulence	50 (1.0)	85 (1.7)	0.002
Carpal Tunnel Syndrome	47 (1.0)	76 (1.5)	0.008
Dehydration	39 (0.8)	64 (1.3)	0.013
Abdominal Discomfort	23 (0.5)	63 (1.3)	<0.001
Lower in Dulaglutide-Treated Patients Compared to Placebo			
Hypertension	455 (9.2)	363 (7.3)	<0.001
Hyperglycemia	372 (7.5)	199 (4.0)	<0.001
Edema Peripheral	243 (4.9)	187 (3.8)	0.006
Cardiac Failure	177 (3.6)	122 (2.5)	0.001
Glycosylated Hemoglobin Increased	151 (3.1)	96 (1.9)	<0.001
Basal Cell Carcinoma	90 (1.8)	51 (1.0)	<0.001

Abbreviations: ITT = intent-to-treat; n = number of patients in the specified group; N = number of patients in the analysis population; TEAE = treatment-emergent adverse event.

Source: GBDJ Clinical Study Report Table GBDJ.14.60.

Serious Adverse Events and Deaths

A total of 4053 patients (40.9%) experienced at least 1 SAE (dulaglutide: 1997 [40.4%]; placebo: 2056 [41.5%]). No treatment differences were observed in the overall proportion of patients who experienced at least 1 SAE.

The proportion of deaths was similar between the two treatment groups. However, fewer deaths with CV causes occurred with patients treated with dulaglutide compared to placebo; deaths adjudicated as having CV causes in Study H9X-MC-GBDJ (REWIND) are discussed in the efficacy section of this report.

No treatment-related differences were observed in the numbers of patients with causes of death adjudicated as non-CV (dulaglutide: 219 [4.4%]; placebo: 246 [5.0%]) or for which a cause could not be determined (dulaglutide: 59 [1.2%]; placebo: 66 [1.3%]).

Deaths, Serious Adverse Events and Discontinuation from Study Drug, ITT Population

Parameter	Placebo (N=4952) n (%)	Dulaglutide 1.5 mg (N=4949) n (%)	Total (N=9901) n (%)	p-Value
Deaths[a]	592 (12.0)	536 (10.8)	1128 (11.4)	0.078
SAEs	2056 (41.5)	1997 (40.4)	4053 (40.9)	0.238
Permanent Discontinuation from Study Drug due to TEAE	298 (6.0)	434 (8.8)	732 (7.4)	<0.001
Permanent Discontinuation from Study Drug due to AE[b]	310 (6.3)	451 (9.1)	761 (7.7)	<0.001
Temporary Discontinuation of Study Drug due to AE	257 (5.2)	389 (7.9)	646 (6.5)	<0.001
TEAEs	4535 (91.6)	4575 (92.4)	9110 (92.0)	0.113

Abbreviations: AE = adverse event; ITT = intent-to-treat; n = number of patients in the specified category; N = number of patients in the treatment group; SAEs = serious adverse events; TEAE = treatment-emergent adverse events.

a Includes 663 deaths adjudicated with CV causes (dulaglutide, 317 [6.4%]; placebo, 346 [7.0%]), which are discussed in Efficacy Section 2.5.4.2.

b Includes AEs that occurred before randomization.

Serious Adverse Events by System Organ Class

Patients most frequently reported SAEs in the SOCs of cardiac disorders (dulaglutide: 566 [11.4%]; placebo: 587 [11.9%]); infections and infestations (dulaglutide: 489 [9.9%]; placebo: 516 [10.4%]); neoplasms benign, malignant and unspecified (including cysts and polyps) (dulaglutide: 334 [6.8%]; placebo: 338 [6.8%]); and injury, poisoning and procedural complications (dulaglutide: 264 [5.3%]; placebo: 261 [5.3%]).

With the exception of the endocrine disorders SOC, no significant differences between the treatment groups were observed in any other SOC, including cardiac disorders, eye disorders, and hepatobiliary disorders. Although only a few patients in both treatment groups reported SAEs in the endocrine disorders SOC, the number of patients with SAEs in the dulaglutide group was significantly higher (p=0.042). However, there were no significant differences in any of the PTs under the endocrine disorders SOC.

Serious Adverse Events by System Organ Class, ITT Population

System Organ Class	Placebo (N=4952) n (%)	Dulaglutide (N=4949) n (%)
Cardiac disorders	587 (11.9)	566 (11.4)
Infections and infestations	516 (10.4)	489 (9.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	338 (6.8)	334 (6.8)
Injury, poisoning and procedural complications	261 (5.3)	264 (5.3)
Gastrointestinal disorders	239 (4.8)	244 (4.9)
Musculoskeletal and connective tissue disorders	239 (4.8)	260 (5.3)
Nervous system disorders	251 (5.1)	222 (4.5)
Renal and urinary disorders	183 (3.7)	159 (3.2)
Metabolism and nutrition disorders	201 (4.1)	173 (3.5)
Respiratory, thoracic and mediastinal disorders	180 (3.6)	152 (3.1)
Vascular disorders	174 (3.5)	159 (3.2)
Hepatobiliary disorders	111 (2.2)	119 (2.4)
General disorders and administration site conditions	108 (2.2)	90 (1.8)
Blood and lymphatic system disorders	50 (1.0)	61 (1.2)
Reproductive system and breast disorders	41 (0.8)	59 (1.2)
Eye disorders	54 (1.1)	39 (0.8)
Skin and subcutaneous tissue disorders	49 (1.0)	32 (0.7)
Psychiatric disorders	45 (0.9)	36 (0.7)
Endocrine disorders	14 (0.3)	27 (0.6)[a]
Investigations	25 (0.5)	18 (0.4)
Ear and labyrinth disorders	17 (0.3)	12 (0.2)
Congenital, familial and genetic disorders	7 (0.1)	12 (0.2)
Product issues	10 (0.2)	5 (0.1)
Immune system disorders	6 (0.1)	2 (0.0)
Social circumstances	1 (0.0)	1 (0.0)

Abbreviations: ITT = intent-to-treat; N = total number of randomized patients in each treatment group; n = number of patients with the adverse event in each treatment group.

[a] P=0.042.

Serious Adverse Events by Preferred Term

A summary of SAEs occurring with at least 1% incidence by Preferred Term (PT) in descending order is provided in the Table below.

The most frequent SAEs overall were osteoarthritis, pneumonia and fall (with no significant differences between treatment groups and consistent with the elderly population enrolled in the REWIND study). Significantly smaller proportions of patients in the dulaglutide group experienced SAEs of cardiac failure and hyperglycemia ($p<0.05$), whereas significantly higher proportions of patients in the dulaglutide group experienced SAEs of atrial fibrillation (dulaglutide: 93 [1.9%]; placebo: 63 [1.3%]; $p=0.015$). There were 328 patients (6.6%) in the dulaglutide group and 308 patients (6.2%) in the placebo group who reported pre-existing atrial fibrillation at baseline. There were no significant differences between the treatment groups for the overall TEAEs of atrial fibrillation (dulaglutide: 259 [5.2%]; placebo: 233 [4.7%]). Additional analyses conducted for SAEs of supraventricular arrhythmias and CV conduction disorders (summarized by PT based on the selected standardized MedDRA queries [SMQs] search criteria) did not show significant differences between the treatment groups.

Serious Adverse Events Occurring with ⩾1% Incidence, ITT Population

Preferred Term[a]	Placebo (N=4952) n (%)	Dulaglutide (N=4949) n (%)	p-Value[b]
Osteoarthritis	110 (2.2)	137 (2.8)	
Pneumonia	151 (3.1)	135 (2.7)	
Fall	124 (2.5)	110 (2.2)	
Atrial fibrillation	63 (1.3)	93 (1.9)	0.015
Cardiac failure	105 (2.1)	78 (1.6)	0.044
Urinary tract infection	61 (1.2)	64 (1.3)	
Hypoglycemia	72 (1.5)	63 (1.3)	
Acute kidney injury	67 (1.4)	61 (1.2)	
Coronary artery disease	59 (1.2)	58 (1.2)	
Angina pectoris	61 (1.2)	56 (1.1)	
Hyperglycemia	67 (1.4)	46 (0.9)	0.047
Angina unstable	56 (1.1)	44 (0.9)	
Cholelithiasis	51 (1.0)	44 (0.9)	
Acute myocardial infarction	53 (1.1)	39 (0.8)	

Abbreviations: ITT = intent-to-treat; N = total number of randomized patients in each treatment group; n = number of patients with the AE in each treatment group.

[a] Patients may be counted in more than 1 category.

[b] Frequencies are analyzed using Pearson Chi-Square test if the expected counts were ≥5 in at least 80% of the cells otherwise the Fisher's Exact test was performed. P-values are presented if p <0.05 for a preferred term.

Adverse Events of Special Interest (AESIs)

This section reports the results for Adverse Events of Special Interest (AESIs) prespecified as secondary safety measures and adjudicated, where appropriate by the Clinical Endpoint Committee (CEC), or as reported by the investigator, or both.

The following safety measures were prespecified as AESI in the REWIND study:

- Adjudicated Events confirmed by Clinical Endpoint Committee (CEC)
  - Acute pancreatitis
  - Thyroid Neoplasms
- Events Prospectively Collected on Specific eCRF
  - Severe hypoglycemia
  - Allergic and hypersensitivity reactions
- Events Reported as SAEs (investigator reported)
  - Immune-Mediated Reactions (based on anaphylactic reactions, angioedema, hypersensitivity, and severe cutaneous adverse reactions SMQs narrow terms.
  - SAEs of Supraventricular Arrhythmias or CV Conduction Disorders
  - Serious GI events
  - Serious hepatic events
  - Serious renal events
- Events Reported as AEs (investigator reported)
  - Benign and Malignant Neoplasms, excluding basal or squamous cell skin cancer
  - Any Cancer (malignant neoplasms, excluding basal or squamous cell skin cancer)
  - Pancreatic Cancer
- Discontinuations
  - Permanent discontinuation from study drug for any reason. Assessment of these AESIs

confirms the conclusions drawn from the original submission.

Adverse Events of Special Interest (AESI)

	Placebo (N=4952) n (%)	Dulaglutide (N=4949) n (%)
Adjudicated Events[a]		
Acute Pancreatitis	13 (0.3)	23 (0.5)
Thyroid Neoplasms	2 (0.0)	10 (0.2)
Papillary Thyroid Cancer	1 (0.0)	6 (0.1)
Carcinoma in-situ (microcarcinoma)	1 (0.0)	3 (0.1)
C-Cell Hyperplasia	0 (0.0)	1 (0.0)
Medullary Thyroid Cancer (MTC)	0 (0.0)	0 (0.0)
Events Prospectively Collected on Specific eCRF		
Severe Hypoglycemia	74 (1.5)	64 (1.3)
Allergic and Hypersensitivity Reactions	12 (0.2)	39 (0.8)
Rash	4 (0.1)	9 (0.2)
Urticaria	4 (0.1)	4 (0.1)
Angioedema	1 (0.0)	0 (0.0)
Other[b]	6 (0.1)	27 (0.5)
Events Reported as SAEs (investigator reported)		
Immune-Mediated Reactions (including serious allergic and hypersensitivity reactions)[c]	20 (0.4)	8 (0.2)
SAEs of Supraventricular Arrhythmias or CV Conduction Disorders[d]	192 (3.9)	217 (4.4)
Serious GI Events[e]	117 (2.4)	120 (2.4)
Serious Hepatic Events[f]	40 (0.8)	25 (0.5)
Serious Renal Events[g]	93 (1.9)	84 (1.7)
Events Reported as AEs (investigator reported)		
Benign and Malignant Neoplasms, excluding basal or squamous cell skin cancer	521 (10.5)	540 (10.9)
Any Cancer (malignant neoplasms, excluding basal or squamous cell skin cancer)	360 (7.3)	377 (7.6)
Pancreatic Cancer	11 (0.2)	16 (0.3)
Discontinuations		
Permanent Discontinuation from Study Drug for Any Reason[h]	1697 (34.3)	1621 (32.8)

Abbreviations: AE=adverse event; CV=cardiovascular; eCRF=electronic case report form; GI=gastrointestinal; n=number of patients in the specified category; N=number of patients in the analysis population; SAEs=serious adverse events; SMQ=standardized MedDRA queries.

[a] Clinical Endpoint Committee (CEC) confirmed.

[b] Additional descriptions provided by investigators for allergic and hypersensitivity reactions that were reported under "other" types show that many of these were related to GI events (19/27 patients in the dulaglutide group and 2/6 patients in the placebo group).

[c] based on anaphylactic reactions, angioedema, hypersensitivity, and severe cutaneous adverse reactions SMQs narrow terms.

[d] based on the arrhythmia-related investigations signs and symptoms SMQ (broad and narrow terms), supraventricular tachyarrhythmia SMQ (broad and narrow terms), tachyarrhythmia nonspecific terms SMQ (narrow terms), ventricular tachyarrhythmia SMQ (narrow terms), conduction defects SMQ (narrow terms), and cardiac conduction disorders high-levels terms (all PTs).

[e] based on the PT appendicitis, PT appendicitis perforated, gastrointestinal obstruction SMQ, gallstone-related disorders SMQ, gallbladder related disorders SMQ (broad and narrow terms).

[f] based on the hepatic SMQs (broad and narrow terms) search criteria.

[g] based on the acute renal failure SMQ (broad and narrow terms).

[h] includes death.

Acute Pancreatitis Events

Pancreatitis AEs have been reported with GLP-1 RAs; therefore, the risk of acute pancreatitis is included as a warning in the current labeling (Trulicity SmPC 2019; Trulicity USPI 2018).

Following adjudication, a total of 41 events in 37 patients were confirmed as pancreatitis. Of these, 1 patient in the dulaglutide group had 1 event adjudicated as chronic pancreatitis and 36 patients had acute pancreatitis (dulaglutide: 26 events in 23 patients [0.5%]; placebo: 14 events in 13 patients [0.3%]). The majority of acute pancreatitis cases were mild (dulaglutide: 21; placebo: 14). The numerical imbalance of acute pancreatitis was mainly driven by events of acute pancreatitis adjudicated based on symptoms and elevated pancreatic enzymes (dulaglutide: 15 events in 14 patients; placebo: 8 events in 8 patients); these effects (GI symptoms and elevations in pancreatic enzymes) are known to occur with GLP-1 RAs. The numbers of acute pancreatitis events adjudicated based on the presence of all 3 criteria (symptoms, elevated enzymes, and imaging) were similar between treatment groups (dulaglutide: 5 events in 5 patients; placebo: 4 events in 3 patients).

Five of the dulaglutide-treated patients experienced acute pancreatitis events at least 4.5 months after study drug discontinuation (2 based on symptoms and elevated enzymes, 2 based on symptoms and imaging, and 1 based on all 3 criteria); therefore, these events were not likely related to dulaglutide. Overall, pancreatitis events reported in Study GBDJ are consistent with the known safety profile of dulaglutide and do not alter the conclusions drawn in the original marketing application or presented in current labeling (Trulicity SmPC 2019; Trulicity USPI 2018).

Thyroid Neoplasms

Thyroid C-cell tumours in rodents are considered a class effect of GLP-1 RAs, but the relevance in human subjects has not been established (Trulicity SmPC 2019).

In Study GBDJ (REWIND), a total of 12 patients were adjudicated with thyroid neoplasms (dulaglutide: 10 patients; placebo: 2 patients), which included:

- C-cell hyperplasia (dulaglutide: 1 patient),
- Carcinoma in-situ (microcarcinoma; dulaglutide: 3 patients; placebo: 1 patient), and
- Papillary thyroid cancer (dulaglutide: 6 patients; placebo: 1 patient).

The results of Study GBDJ do not support a causal relationship between GLP-1 RA treatment and the development of thyroid C-cell tumors. No thyroid events were adjudicated as medullary thyroid cancer. The data also do not support a causal relationship between dulaglutide and papillary thyroid carcinoma. Of the 6 dulaglutide-treated patients with adjudicated papillary thyroid cancer, 4 patients had medical histories that included hypothyroidism, goiter, thyroid nodules, and papillary thyroid carcinoma. One patient in the dulaglutide treatment group had adjudicated papillary thyroid cancer reported 40.3 months after permanently discontinuing from study drug. Two patients had adjudicated papillary thyroid cancer within 1 year of starting dulaglutide, suggesting the pathology was pre-existing.

Increased calcitonin is a well-accepted measure of C-cell proliferation, particularly in medullary thyroid cancer, and was monitored at screening and then annually. Overall, serum calcitonin levels were not different between the treatment groups from baseline to last measurement, for treatment-emergent abnormal calcitonin values, or the proportion of patients with calcitonin values $\geqslant$20 ng/L.

Severe Hypoglycemia

Current labelling includes a warning indicating that hypoglycemia may occur when dulaglutide is used with insulin or an insulin secretagogue such as a sulfonylurea and that the dose of the concomitant medication may need to be lowered following the addition of dulaglutide (Trulicity SmPC 2019).

In Study GBDJ, severe hypoglycemia events were prospectively collected on a specific electronic case report form (eCRF). Severe hypoglycemia was defined as an event with clinical symptoms consistent with hypoglycemia requiring the assistance of another person (that is, the patient could not treat himself or

herself) to actively administer carbohydrates, glucagon, or other resuscitative measures and one of the following:
a) the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or parenteral glucagon administration; or
b) the event was associated with a fingerstick or laboratory plasma glucose level ⩽54 mg/dL (⩽3 mmol/L).
The overall incidence of severe hypoglycemia was small and no meaningful differences between the treatment groups were observed. The incidence rate (events/patient/year) was 0.0031 for dulaglutide and 0.0034 for placebo. The results of Study GBDJ show that there were no clinically meaningful study drug treatment-related differences in the incidence rates over time.

Serious Allergic and Hypersensitivity Reactions
Although uncommon, serious hypersensitivity reactions have occurred with dulaglutide as well as other GLP-1 RAs, as reported in the Trulicity labels (Trulicity SmPC 2019), and prescribers are directed to permanently discontinue use of dulaglutide in the event that one occurs. In Study GBDJ, the incidence of allergic and hypersensitivity reactions prospectively collected on the specific eCRFs was higher in the dulaglutide group compared with placebo. This difference is mainly due to the higher number of GI events that were reported under "other" as allergic and hypersensitivity reactions for the dulaglutide group. The incidence of the investigator-reported SAEs of immune-mediated reactions including serious allergic and hypersensitivity reactions (anaphylactic reaction, angioedema, hypersensitivity, and severe cutaneous adverse reactions standardized MedDRA queries [SMQs], narrow terms) was lower in the dulaglutide group compared with placebo.

SAEs of Supraventricular Arrhythmias and CV Conduction Disorders
The SAEs of supraventricular arrhythmias and CV conduction disorders were analyzed based on selected SMQ search criteria. Overall, the number of patients with at least 1 SAE reflective of clinically significant supraventricular arrhythmias and CV conduction disorders was similar between the 2 treatment groups, and reflective of the population in Study GBDJ with a range of CV risk factors.
Atrial fibrillation SAEs were reported by a statistically significantly higher proportion of patients in the dulaglutide group compared to the placebo group (dulaglutide: 93 [1.9%]; placebo: 63 [1.3%]; p=0.015). The proportions of patients who reported pre-existing atrial fibrillation at baseline were numerically higher for dulaglutide (328 patients [6.6%]) compared with placebo (308 patients [6.2%]). There were no significant differences between treatment groups for the overall TEAEs of atrial fibrillation (dulaglutide: 259 [5.2%]; placebo: 233 [4.7%]). In addition, qualitative assessment of ECGs did not show a difference in supraventricular arrhythmia. No other differences were observed between the treatment groups in the incidence of SAEs reflective of clinically significant supraventricular arrhythmias and CV conduction disorders.
Considering Study GBDJ enrolled a population with higher CV risks than previous dulaglutide studies, the overall profile with regards to clinically significant supraventricular arrhythmias and CV conduction disorders is consistent with the known safety profile of dulaglutide and did not raise any new safety concerns in this regard.

Serious GI Events
The following selected PTs and SMQs related to serious GI AEs were of particular interest: PT appendicitis, PT appendicitis perforated, GI obstruction SMQ, gallstone related disorders SMQ, and gallbladder-related disorders SMQ (broad and narrow terms). The incidence of serious GI AEs was similar in both treatment groups. The serious GI event data reported in Study GBDJ do not alter the conclusions drawn in the original marketing application.

Serious Hepatic Events

The following SMQs related to serious hepatic AEs were of particular interest: drug-related hepatic disorders, liver-related investigations, signs and symptoms SMQ, cholestasis and jaundice of hepatic origin SMQ, liver-related coagulation and bleeding disturbances SMQ, drug-related hepatic disorders (severe events only) SMQ, hepatic failure, fibrosis, cirrhosis and other liver damage SMQ, hepatitis, and noninfections SMQ (broad/narrow terms). The incidence of serious hepatic AEs was comparable in both treatment groups. There were no significant differences between the treatment groups in incidence of serious hepatic events for any PT. The serious hepatic event data reported in Study GBDJ do not alter the conclusions drawn in the original marketing application.

Serious Renal Events

SAEs of potential cases of acute renal failure were identified using the Acute Renal Failure SMQ (broad and narrow terms). No significant differences between treatment groups were observed in incidence of serious renal AEs potentially related to acute renal failure or in the progression to end-stage renal disease (defined as requirement for renal replacement therapy, or eGFR <15 mL/min/1.73m2) (dulaglutide: 110 [2.2%]; placebo: 126 [2.5%]). In general, these renal events occurred in numerically fewer patients in the dulaglutide group compared with the placebo group. These results are consistent with the original marketing application and also with the subsequent dulaglutide clinical trial conducted in patients with chronic kidney disease Stages 3 and 4, and consistent with the microvascular endpoint.

Serum creatinine, eGFR, and urine albumin to creatinine ratio (UACR) were used to evaluate kidney function in Study GBDJ. Significant increases were seen in serum creatinine and significant decreases were seen in eGFR over time in both treatment groups. However, these changes were not considered clinically meaningful and were within the expected range for this T2D population; no overall clinically meaningful differences were observed between the treatment groups. Significant increases in UACR were observed in the placebo group and the UACR changes in the dulaglutide group were significantly smaller than the placebo group for all postrandomization time points. The proportions of patients with UACR values shifting to microalbuminuria and macroalbuminuria were smaller in the dulaglutide group compared with placebo (microalbuminuria: 40.8% for dulaglutide, 44.3% for placebo; macroalbuminuria: 14.6% for dulaglutide, 18.2% for placebo).

Cancer

In Study GBDJ, the incidence of any neoplasm was summarized from malignant and nonmalignant neoplasms terms by high-level term, neoplasm type, and PT based on neoplasms SOC search criteria. The overall incidences of any neoplasm (excluding basal or squamous cell skin cancer) or any cancer (excluding basal or squamous cell skin cancer) were not different between the treatment groups. No differences between the treatment groups were observed in the incidence of pancreatic cancer.

Statistically significant differences were observed for 4 cancer categories. The numbers of events and differences between groups were small:

- the incidences were lower in patients receiving dulaglutide compared with placebo for:
    - basal or squamous and melanoma skin cancer (dulaglutide: 84 [1.7%]; placebo: 125 [2.5%]; p=0.004), and
    - liver cancer (dulaglutide: 7 [0.1%]; placebo: 17 [0.3%]; p=0.041).
- the incidences were higher in patients receiving dulaglutide compared with placebo for:
    - bone marrow cancer (dulaglutide: 26 [0.5%]; placebo: 11 [0.2%]; p=0.013), and
    - blood cancer (dulaglutide: 25 [0.5%]; placebo: 8 [0.2%]; p=0.003).

Ninteen patients had an event that was counted in both the blood cancer and bone marrow cancer types (dulaglutide: 14 patients; placebo: 5 patients); this was because some of the same PTs

were included under both cancer types.
There were no predominately reported terms, and none of the terms showed significant differences between the treatment groups. These observations could not be explained based on plausible biological mechanisms. The closest link between administration of a given treatment to the development of blood or bone marrow cancers is with deoxyribonucleic acid (DNA)-damaging chemotherapeutic agents for myeloid cancers (Bhatia 2013) or immunosuppressive agents in the context of lymphoid cancers (NCI 2015). Dulaglutide, as a large biotherapeutic molecule would not be expected to interact directly with DNA (ICH 2011). Additionally, no evidence of leukemogenic potential was observed in nonclinical carcinogenicity studies with dulaglutide. Since marketing authorization was first granted (September 2014), no related
signals have been observed in routine pharmacovigilance activities.

Permanent Discontinuation of Study Drug for Any Reason
A total of 2730 patients (27.6%) permanently discontinued study drug prematurely with no overall significant difference between treatment groups. An additional 588 patients (5.9%) discontinued study drug due to death. Most reasons for permanent discontinuation of study drug did not differ between the 2 treatment groups. However, fewer patients treated with dulaglutide discontinued from study drug due to "subject decision" compared with patients treated with placebo. More patients treated with dulaglutide discontinued from study drug due to AE than patients treated with placebo (dulaglutide: 451 [9.1%]; placebo: 310 [6.3%]). This treatment-related difference in permanent discontinuations of study drug occurred early in treatment and was primarily driven by a higher incidence of GI AEs.

Other Safety Results of Interest

Cholelithiasis
Development of cholelithiasis was defined as any new diagnosis of cholelithiasis after randomization, as evidenced on an imaging examination. Events of cholelithiasis reported during the study were prospectively collected on a specific eCRF. A total of 256 patients reported cholelithiasis in Study GBDJ (dulaglutide: 137 [3.2%]; placebo: 119 [2.8%]). The exposure-adjusted incidence rates (patients with events per 100 person-years) were 0.62 for dulaglutide and 0.56 for placebo. The results from Study GBDJ support the results from the original marketing application showing that patients treated with dulaglutide are not at an increased risk for cholelithiasis compared with patients treated with placebo.

Overdose
There were no significant differences between the treatment groups in the SAEs or TEAEs of overdose reported during the study (Summary of Clinical Safety, Section 2.7.4.2.1.6.3). A total of 20 patients had confirmed AE of dulaglutide overdose. Two were reported as serious ("other reason" or "medically significant"). The patients were not hospitalized for overdose, and the AEs or symptoms associated with the overdose events were nausea, fatigue, or loss of appetite. Both patients fully recovered from the overdose event.

Diabetic Retinopathy
Diabetic retinopathy requiring treatment with laser therapy, vitrectomy, or anti-VEGF therapy was a component of the composite microvascular efficacy endpoint. These events were reported by investigators but were not adjudicated. The hazard rate of the composite endpoint of diabetic retinopathy requiring treatment as well as the individual components (diabetic retinopathy requiring either laser therapy, vitrectomy, or anti-VEGF) was not significantly different between the 2 treatment groups (hazard ratio [95%CI]: 1.24 [0.92, 1.68], p=0.156), but numerically more events occurred in the dulaglutide group (dulaglutide: 95 [1.9%] and placebo: 76 [1.5%]). Importantly, the composite endpoint

of diabetic retinopathy requiring treatment was limited to procedural endpoints and does not reflect objective assessment of changes in retinal pathology by sequential fundal examinations. Compared to the overall ITT population, patients who experienced the composite endpoint of diabetic retinopathy requiring treatment had longer duration of diabetes and slightly higher baseline HbA1c.
Regardless of the treatment group, the incidence of the endpoint of diabetic retinopathy requiring treatment was notably higher in patients with baseline diabetic retinopathy.
At baseline, for the overall ITT population, the number of patients reporting diabetic retinopathy was numerically larger in the dulaglutide group compared with the placebo group (dulaglutide: 576 [11.6%] versus placebo: 545 [11.0%]). The numerically larger number of patients who experienced the composite endpoint of diabetic retinopathy requiring treatment in the dulaglutide group is likely due to the numerically larger numbers of patients with baseline diabetic retinopathy in the dulaglutide group. This is further supported by the lack of differences in diabetic retinopathy TEAEs between the treatment groups (dulaglutide: 126 [2.6%]; placebo: 122 [2.5%]).

Vital Signs and Electrocardiograms

Current labeling includes increased heart rate and sinus tachycardia as adverse reactions associated with dulaglutide treatment (Trulicity SmPC 2019; Trulicity USPI 2018). In Study GBDJ, at Month 60, SBP was significantly decreased, although the change was small (-1.08 mmHg, dulaglutide vs. placebo), and heart rate was significantly increased in dulaglutide-treated patients compared with the placebo group. Again, the difference was small (1.37 bpm). The decrease in DBP was very small (0.26 mmHg) and not significantly different between treatment groups. The increases in heart rate with dulaglutide treatment were not associated with increased reporting of tachyarrhythmia AEs, as reported for the original submission. Dulaglutide treatment was not associated with increased reporting of other arrhythmias assessed by qualitative ECGs, either in terms of changes from baseline or in the incidence of qualitative rhythm or conduction results.

Clinical Laboratory Evaluations

Clinical laboratory measurements for the analysis of safety included calcitonin, serum creatinine, UACR, and fasting lipids (total cholesterol, HDL-C, LDL-C, ratio of total cholesterol to HDL-C, and triglycerides). Key results from clinical laboratory measures are presented below. All laboratory measures were analyzed by a local laboratory with the exception of calcitonin, which was analyzed by a central laboratory.

Calcitonin

- No significant treatment differences were observed in mean serum calcitonin changes from baseline to last measurement, treatment-emergent abnormal calcitonin values, or the proportion of patients with elevated calcitonin values $\geqslant$20 ng/L (dulaglutide: 74 [1.6%]; placebo: 72 [1.5%]).

Lipids

- Larger decreases in total cholesterol, non-HDL-C, LDL-C, total cholesterol/HDL-C ratio, and triglycerides were observed in the dulaglutide group compared to the placebo group. However, these changes were small and of limited clinical relevance.

Serum Creatinine, eGFR, and UACR

Serum creatinine, eGFR, and UACR were used to evaluate kidney function in Study GBDJ (REWIND).

- Significant increases were seen in serum creatinine and significant decreases were seen in eGFR over time in both treatment groups. However, these changes were within the expected range for this older T2D population and no overall clinically meaningful differences were observed between the treatment groups.

Safety in Special Populations

Given that data available in the original dulaglutide submission was limited for patients >65 years of age and 22.2% of the GBDJ study population had eGFR <60 mL/min/1.73 m2, the safety profile of dulaglutide was reviewed based on TEAEs and SAEs for placebo and dulaglutide for age subgroups (<65 years or ⩾ 65 years of age; <75 years or ⩾75 years) and subgroups for baseline eGFR (<60 mL/min/1.73 m2 or ⩾ 60 mL/min/1.73 m2). Across the relevant subgroups of age and kidney function, the safety profile of dulaglutide was consistent; no clinically meaningful differences between the subgroups were observed for any TEAE or SAE.

Post marketing experience

The first marketing approval for dulaglutide occurred on 18 September 2014 when the US FDA approved dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with T2D.
Post-marketing data is continuously monitored through routine pharmacovigilance activities by a cross-functional team. Based on evaluation of the postmarketing data, the previously established favourable benefit-risk balance for dulaglutide in the treatment of adult patients with T2D is confirmed. At this time, no additional pharmacovigilance or other risk minimization activities beyond those previously specified are proposed.

2.5.1. Discussion on clinical safety

The data from Study GBDJ (REWIND) contributes a median follow-up of 5.4 years, which translates to 51,830.1 person-years of follow-up safety data, to the dulaglutide clinical development program, providing a robust safety data set. The length of the study contrasts with the duration of the Phase 2 and Phase 3 studies included in the original marketing application (studies of up to 2 years of exposure). Study GBDJ (REWIND) provides safety data from 4949 dulaglutide-treated and 4952 placebo-treated patients with T2D who, compared to patients of the initial dulaglutide studies, were approximately 10 years older (with 53.1% aged ≥65 years, and 9.7% aged ≥75 years), with more diabetes complications (22.2% with renal impairment as measured by baseline eGFR <60 mL/min/1.73m2, compared with 7.1% in the original application), and more CV risk factors. The safety profile from Study GBDJ (REWIND) reinforces the safety profile as described in the label for dulaglutide, and no new safety signals were identified.

Overall, the safety profile for patients treated with dulaglutide in Study GBDJ (REWIND) was consistent with the safety profile reflected in current labelling, as established by the clinical trials for the original and subsequent marketing applications for dulaglutide, and postmarketing data. There were no relevant differences between dulaglutide and placebo in the overall number of patients reporting SAEs or TEAEs. Consistent with the GLP-1 RA class, GI events were the most common AEs in patients treated with dulaglutide. The proportions of patients who discontinued treatment for any reason were similar between dulaglutide and placebo; however, the proportion of patients who permanently discontinued study treatment prematurely due to AEs was larger in the dulaglutide group (dulaglutide, 9.1% vs. placebo, 6.3%). This difference appeared to occur early and was primarily driven by a higher incidence of GI AEs. The overall incidence of severe hypoglycemia was small, and no meaningful differences between the treatment groups were observed. Small differences in the incidence rates over time were likely related to adjustments in other antihyperglycemic concomitant medications during this double-blinded study.

Adverse events of special interest that were adjudicated included pancreatitis and thyroid neoplasms, including medullary thyroid carcinoma and C-cell hyperplasia.

The number of patients with adjudicated acute pancreatitis events was higher in the dulaglutide group compared with placebo. This numerical imbalance was mainly driven by a higher number of events in the dulaglutide group adjudicated based on symptoms and elevated pancreatic enzymes, which are expected

to occur with GLP-1 RAs. In addition, the majority of the adjudicated acute pancreatitis events were mild, and in the dulaglutide treatment group approximately 22% of the events occurred at least 4.5 months after dulaglutide discontinuation. The numbers of acute pancreatitis events adjudicated based on the presence of all 3 criteria of symptoms, elevated enzymes, and imaging were very small in both treatment groups so that firm conclusions cannot be draw. Anyway, it is reassuring in respect to safety that the absolute number of pancreatitis events confirmed by imaging was small, even in the dulaglutide group.

No thyroid events were adjudicated as medullary thyroid carcinoma, 1 event was adjudicated as C-cell hyperplasia in the dulaglutide group, and calcitonin levels were not different between the treatment groups. Papillary thyroid cancer accounted for the majority of thyroid neoplasms, and were primarily observed in patients with medical history of related thyroid events. It is assumed that C-cell hyperplasia or neoplasia is a rodent-specific effect, the mechanism of which is understood. Therefore, the single case observed with C-cell hyperplasia in the REWIND study can be considered a chance finding.
No differences between the treatment groups were observed in the incidence of pancreatic cancer, serious GI AEs, serious renal events, serious hepatic AEs, or serious supraventricular arrhythmias or CV conduction disorders. Overall, the incidence of allergic and hypersensitivity reactions were similar and consistent with the previously observed safety profile for dulaglutide. No significant differences between treatment groups were observed in incidence of serious renal AEs potentially related to acute renal failure or in the progression to end-stage renal disease. In general, these renal events occurred in numerically fewer patients in the dulaglutide group compared to the placebo group.

While the composite endpoint of diabetic retinopathy requiring treatment with laser therapy, vitrectomy, or anti-VEGF therapy was not significantly different between dulaglutide and placebo groups, a numerically larger number of events occurred in the dulaglutide group. The number of patients reporting diabetic retinopathy at baseline was also slightly larger in the dulaglutide group compared to the placebo group, and interventions for treatment of diabetic retinopathy during the study was primarily observed in patients with pre-existing diabetic retinopathy. However, it is questionable whether this small baseline imbalance can explain the numerically markedly higher imbalance between dulaglutide and plc in patients needing intervention for retinopathy. On the other hand, since the difference was not statistically significant, no firm conclusions can be drawn. Investigator-reported AEs under the eye disorder SOC in general or selected PTs for retinopathy AEs were not significantly different between dulaglutide and placebo. These results are consistent with data from a large clinical practice cohort study in 77,115 patients (Douros et al. 2018) and an FDA AE reporting system analysis (Wang et al. 2019), both showing that use of GLP-1 RAs was not associated with increased risk of diabetic retinopathy overall. On the other hand, increase of diabetic retinopathy was observed in a recent CV outcome trial with another GLP1-RA, semaglutide. Further data are needed to decide whether GLP1-RAs could adversely affect the course of diabetic retinopathy. To date, no further actions appear warranted.

Evaluation of adverse events suggested that dulaglutide could be associated with an increased risk for atrial fibrillation. There is no obvious underlying mechanism so that a chance finding cannot be excluded. The efficacy evaluation of the REWIND study has shown that the net effect of dulaglutide on CV endpoints is positive so that an increase in atrial fibrillation – if true – obviously does not outweigh other (beneficial) CV effects of dulagutide.

In addition to comprehensive assessment of safety data, the MAH used standard operating procedures, including specific hierarchical statistical analyses in conjunction with medical review and judgement to identify adverse reactions informing the label. No new adverse reactions were identified and no changes have been proposed for adverse reactions in current labeling. Overall, the incidences of adverse reactions were similar in dulaglutide-treated patients in Study GBDJ compared to the cohort from the original marketing application. The study included a significant number of patients in elderly subpopulations (⩾ 65 years, ⩾75 years) and patients with renal impairment (<60 mL/min/1.73 m2). The consistency of the

safety profile of these subpopulations with the known safety profile of dulaglutide support the proposed changes to the product information.

2.5.2. Conclusions on clinical safety

The safety results of Study H9X-MC-GBDJ (REWIND) including 9901 patients with a median follow-up of 5.4 years reinforce the existing safety profile for dulaglutide. No new safety signals were identified, and no changes to the adverse reactions in the current product information are proposed.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.4 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.4 with the following content:

Safety concerns

Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	• Acute pancreatitis • Gastrointestinal events • Hypersensitivity, including anaphylactic reaction
Important Potential Risks	• Thyroid C-cell tumours • Pancreatic malignancy • Medication errors (more than 1 injection per week)
Missing Information	• Use in pregnant and/or breastfeeding women • Use in patients with congestive heart failure

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation None				
Category 2—Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances None				
Category 3—Required additional pharmacovigilance activities				
Medullary Thyroid Carcinoma (MTC) Surveillance Study (H9X-MC-B001) Ongoing	To determine the annual incidence of MTC in the US and to identify any possible increase related to the introduction of long-acting GLP-1 RAs, including dulaglutide, into the US market.	Potential risk of medullary thyroid carcinoma	Protocol Submission:	Provided in Annex 3 of this RMP
			Final Report: Estimated submission of study report	31/03/2032
Utilisation of Dulaglutide in European Countries (H9X-MC-B010)	To provide information on the use of dulaglutide after approval in the EU. It will address overall utilisation in real-world conditions as well as off-label use and use in subpopulations of patients identified as missing information.	• Diagnosed with severe renal failure • Patients with congestive heart failure • Patients with hepatic disease • Patients with severe GI disease • Use in children and adolescents aged <18 years • Use in the elderly • Use in pregnant and/or breastfeeding women • Medication errors	Protocol Submission:	Provided in Annex 3 of this RMP
			Final Report: Estimated submission of study report	31/12/2019

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3—Required additional pharmacovigilance activities				
Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009)	To monitor the occurrences of events of interest and ensure that the profile and rate remain consistent with what has been seen in clinical trials.	• Acute pancreatitis • Hypersensitivity • Pancreatic and thyroid cancers • CV events, including heart rate (tachycardia) and conduction abnormalities (atrioventricular block) • GI effects/gastric stenosis • Medication errors The above outcomes will also be described in the dulaglutide subpopulations identified as missing information.	Protocol Submission:	Provided in Annex 3 of this RMP
			Final Report: Estimated submission of study report	31/03/2020
Dulaglutide Retrospective Study (H9X-MC-B013)	To estimate the incidence rates of events of interest among T2DM patients treated with dulaglutide compared to other GLP-1 RAs.	• Pancreatitis • Pancreatic and thyroid cancers	Protocol Outline Submission:	Submitted: 28/06/2019
			Final Report: Estimated submission of study report	To be determined based on reimbursement status and use of dulaglutide in EU and proposed after Utilisation of Dulaglutide in European Countries sample size is 75% complete.

Abbreviations: CV = cardiovascular; EU = European Union; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; RA = receptor agonist; RMP = risk management plan; T2DM = type 2 diabetes mellitus; US = United States.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern Important Identified Risk	Risk Minimisation Measures	Pharmacovigilance Activities
Acute pancreatitis	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for pancreatitis Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU: A retrospective database prescription-event monitoring study using existing databases and registries in Europe. • H9X-MC-B013: Dulaglutide Retrospective Study: This study will estimate the incidence rates of events of interest among T2DM patients treated with dulaglutide compared to other GLP-1 RAs. It will address the safety concerns of pancreatitis and pancreatic and thyroid cancers.
Gastrointestinal events	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for gastrointestinal events Additional pharmacovigilance activities: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009): Described above. This study will address the safety concern of GI effects/gastric stenosis.
Hypersensitivity, including anaphylactic reaction	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up forms for allergy and anaphylaxis and similar events Additional pharmacovigilance activities: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009): Described above.

Safety Concern Important Potential Risk	Risk Minimisation Measures	Pharmacovigilance Activities
Thyroid C-cell tumours	Routine risk minimisation measures: SmPC Section 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up forms for hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, and cancer/neoplasm Additional pharmacovigilance activities: • H9X-MC-B001: Medullary Thyroid Carcinoma (MTC) Surveillance Study: This active surveillance programme aims to determine the annual incidence of MTC in the US and to identify any possible increase related to the introduction of long-acting GLP-1 RAs, including dulaglutide, into the US market. • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU: Described above. • H9X-MC-B013: Dulaglutide Retrospective Study: Described above.
Pancreatic malignancy	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for cancer/neoplasm Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU: Described above. • H9X-MC-B013: Dulaglutide Retrospective Study: Described above.

Medication errors (more than 1 injection per week)	Routine risk minimisation measures: • SmPC Section 4.2 • PL Section 3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for medication error Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU: Described above. • H9X-MC-B010: Utilisation of Dulaglutide in European Countries. This study will provide information on the overall utilisation of dulaglutide in real-world conditions as well as off-label use and use in subpopulations of patients identified as missing information.

Safety Concern Missing Information	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in pregnant and/or breastfeeding women	Routine risk minimisation measures: SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for breastfeeding • AE follow-up form for pregnancy data collection – paternal • AE follow-up form for pregnancy data collection – maternal Additional pharmacovigilance activities: Analyses of ongoing, planned studies including: • H9X-MC-B010: Utilisation of Dulaglutide in European Countries: Described above. • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU: Described above.

Use in patients with congestive heart failure	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for congestive heart failure Additional pharmacovigilance activities: Analyses of ongoing, planned studies including: • H9X-MC-B010: Utilisation of Dulaglutide in European Countries: Described above. • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU: Described above.

Abbreviations: AE = adverse event; EU = European Union; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; PL = package leaflet; RA = receptor agonist; SmPC = summary of product characteristics; T2DM = type 2 diabetes mellitus; US = United States.

2.7. Update of the Product information

As a consequence of this application, section 4.1 of the SmPC has been modified and sections 4.2, 4.4, 4.5, 4.8 and 5.1 have all been updated based on the data obtained with the Study H9X-MC-GBDJ (REWIND). The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to implement editorial changes and to align the annexes with the latest QRD template.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The estimated prevalence of CV disease in patients with T2DM ranges from 14.8% to 40.5% depending on age and region. CV disease is the most common cause of death in patients with T2DM, with at least 50% of T2DM patients globally dying from CV disease.

Trulicity (Dulaglutide) is **currently licensed for the indication:**

Trulicity is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on therapy

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for data with respect to different combinations).

With this application the MAH proposes to add the following **new therapeutic indication:**

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 (see section 5.1).

Trulicity is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)

· in adults with type 2 diabetes mellitus who have multiple cardiovascular risk factors without established cardiovascular disease

· in adults with type 2 diabetes mellitus with established cardiovascular disease (see section 5.1).

The efficacy and safety data supporting the new indication are derived from the recently completed cardiovascular outcome trial [Study H9X-MC-GBDJ (REWIND)].

3.1.2. Available therapies and unmet medical need

As cardiovascular disease is the leading cause of morbidity and mortality for individuals with diabetes (Davies et al. 2018; ADA 2019b), therapeutic agents that not only promote glycemic control but also reduce CV risk in patients with T2D are needed.

Recent cardiovascular outcome studies with the SGLT-2 inhibitors (empagliflozin in EMPA-REG, canagliflozin in CANVAS, dapagliflozin in DECLARE) and GLP-1 RA (liraglutide in LEADER, semaglutide in SUSTAIN-6) have shown a (modest) superior effect compared to placebo in the prevention of CV events while other antidiabetic agents e.g. DPP4-inhibitors (Sitagliptin in TECOS, Saxagliptin in SAVOR, Alogliptin in EXAMINE and Linagliptin in CAROLINA and CARMELINA) have reported a neutral, non-inferior effect on cardiovascular outcomes.

The proportion of patients with established cardiovascular disease at baseline is lower in the REWIND study (31.5%) as compared to other CV outcome studies (established cardiovascular disease: 100% in ELIXA, 81.3% in LEADER, 58.8% in SUSTAIN-6 and 73.1% in EXSCEL). However, definitions of CVD differed between studies. For instance, in SUSTAIN-6 and LEADER patients with heart failure and chronic kidney disease stage 3 were included. Thus, it is not possible to conclude at present whether treatment effect on composite MACE is independent of cv disease status.

3.1.3. Main clinical studies

Study H9X-MC-GBDJ (REWIND) was a well-designed double-blind cardiovascular outcome trial (CVOT) conducted in 9901 patients (randomized in a 1:1 ratio to dulaglutide 1.5 mg s.c. once weekly or placebo). The patients included in this study had a wide range of T2D disease severity with relatively good glycemic control at baseline and a majority did not have established CVD. The median follow-up time of this study was 5.4 years.

3.2. Favourable effects

The key benefit demonstrated in the REWIND study was the reduction of 3-component MACE compared to placebo (death from CV causes, nonfatal MI, or nonfatal stroke) in adult patients with T2D and either with or without established CVD. Dulaglutide significantly reduced the risk for 3-component MACE by 12% compared with placebo (hazard ratio [95.33% CI]: 0.88 [0.79, 0.99], p=0.026). The Kaplan-Meier curve showed that the incidence of the composite primary endpoint was consistently lower for the dulaglutide group over time compared to placebo. The curves appeared to separate early, with clear divergence by 6 months from randomization, which was maintained through the end of the study.

Consistent effects were demonstrated for each monocomponent of the primary endpoint (albeit formally statistical significance has not be shown for any of the monocomponents) and across the majority of subgroups. Of note, no treatment by subgroup interaction could be found for the subgroups defined by pre-existing prior cardiovascular disease (yes/no). The HR for all-cause mortality was 0.90 (0.80-1.01) which was in line with the result of the primary analysis.

Dulaglutide also demonstrated a beneficial effect on the composite endpoint for microvascular outcomes. The point estimate for the composite microvascular endpoint was driven by the effect of dulaglutide on diabetic nephropathy. Fewer dulaglutide-treated patients compared with placebo-treated patients reported worsening of diabetic nephropathy during the study (hazard ratio [95% CI]: 0.84 [0.77, 0.91]), primarily driven by a lower incidence of clinical proteinuria (UACR >300 mg/g). Although the effect cannot be considered statistically significant (nominal p-value), patients treated with dulaglutide appeared 16% less likely to experience worsening of diabetic nephropathy.

Furthermore, known antihyperglycemic and antihypertensive effects of dulaglutide were confirmed in REWIND: the effects on HbA1c at month 60 (-0.51% [-0.57, -0.45], p<0.001) were significant but modest, which might be explained by the intended low baseline HbA1c (7.3%), a higher use of additional antidiabetic agents in the placebo group over the study duration and a considerable longer observational period. The effects of dulaglutide on blood pressure are consistent with previous dulaglutide studies and are reflected in the descriptions of the current labelling (Trulicity SmPC 2019).

3.3. Uncertainties and limitations about favourable effects

Assessment of the individual components of the primary composite 3-point MACE were not statistically significant since the p-values were all greater than their final corresponding significance levels based on the hierarchical testing scheme. However, all of the three single MACE components (death from CV causes, nonfatal MI, or nonfatal stroke) favored dulaglutide (hazard ratios <1).

A nominally significant treatment-by-subgroup interaction was observed in the a-priori-defined regional subgroups, multiplicity adjustments were not made for the large number of pre-specified subgroups interactions tested (n=21). However, this limitation was alleviated by additional analyses of US or Europe versus the respective remainder of the study population as well as assessment of the primary endpoint by country support a consistency in treatment effect across international geographies.

3.4. Unfavourable effects

The safety profile for dulaglutide is well characterized, as described in the original dulaglutide application and in current labeling; the most frequently reported TEAEs are GI-related events (e.g., nausea, vomiting, and diarrhea). The data from Study H9X-MC-GBDJ (REWIND) provide more extensive information on the dulaglutide safety profile, including CV safety in a population of patients who were at higher CV risk than patients in the original marketing application. Reflective of the original application, acute pancreatitis is considered a key risk of dulaglutide. In Study H9X-MC-GBDJ (REWIND) the risk for

acute pancreatitis was numerically increased with dulaglutide (dulaglutide: 26 events in 23 patients [0.5%]; placebo: 14 events in 13 patients [0.3%]). However, it is known that dulaglutide, like other GLP1-RAs, increases pancreatic enzymes in the blood by a mechanism unrelated to pancreatitis and causes GI side effects so that confirmation of pancreatitis without imaging is difficult in patients treated with dulaglutide. The number of patients with pancreatitis confirmed by imaging was very low so that this is not considered a concern.

Increases in heart rate from baseline to Month 60 were significantly larger in the dulaglutide group compared to the placebo group [+1.37 beats/min (0.96, 1.78), p<0.001], however the effect size was smaller than the one observed in the studies submitted with the initial MAA.

Overall, the safety results of Study H9X-MC-GBDJ (REWIND) are consistent with the known safety profile for dulaglutide, and no new safety concerns were identified. No changes to safety labelling and no new pharmacovigilance or risk minimization activities are proposed.

3.5. Uncertainties and limitations about unfavourable effects

While none are considered key risks for this benefit-risk assessment of dulaglutide, some AEs remain of particular interest for the GLP-1 RA class. In Study H9X-MC-GBDJ, thyroid cancer and diabetic retinopathy requiring treatment with laser therapy, vitrectomy, or anti-VEGF therapy were secondary safety and efficacy endpoints, respectively. Numerical differences were observed for papillary thyroid cancer and diabetic retinopathy requiring treatment; the treatment differences were small and not significant.

No thyroid events were adjudicated as medullary thyroid carcinoma (MTC), and 1 event was adjudicated as C-cell hyperplasia in the dulaglutide group. A total of 7 patients were adjudicated with papillary thyroid cancer (dulaglutide: 6; placebo: 1). The data from Study H9X-MC-GBDJ (REWIND) do not support causal relationships between dulaglutide treatment and papillary thyroid cancers, C-cell hyperplasia or MTC. C-cell hyperplasia and neoplasia is a consistent finding in rodents, but the mechanism responsible for this species-specific effect is largely understood. To date there a no hints that GLP1-RAs affect C-cells in humans. Due to the rare occurrence of C-cell tumours in humans and the long latency period, a small effect cannot be excluded from existing clinical study data, but such a small effect would not be regarded as a relevant concern.

Diabetic retinopathy requiring treatment with laser therapy, vitrectomy, or anti-VEGF therapy was a component of the composite microvascular efficacy endpoint. The events for this composite endpoint of diabetic retinopathy requiring treatment were limited to procedural endpoints; these were reported by investigators but were not adjudicated. In Study H9X-MC-GBDJ, the occurrences of diabetic retinopathy that required the procedures of laser therapy, vitrectomy, or anti-VEGF therapy were numerically larger for the dulaglutide group (95 [1.9%]) compared with the placebo group (76 [1.5%]). Increased risk of diabetic retinopathy was also observed in the CV outcome trial of semaglutide (SUSTAIN-6) but was not observed in published database studies. Further information is needed to confirm or exclude an effect of GLP1-RAs on the progression of retinopathy. In case of dulaglutide, the effect – if true – was small so that it is not considered a concern.

3.6. Effects Table

Effects Table for Dulaglutide (data cut-off: April 2019)

Effect	Short description	Unit	Dulaglutide N=4949	Placebo N=4952	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Dulaglutide N=4949	Placebo N=4952	Uncertainties / Strength of evidence	References
Primary 3-point MACE	Death from CV causes, nonfatal MI, or nonfatal stroke	n (%)	594 (12.0)	663 (13.4)	hazard ratio (CI) 0.88 (0.79, 0.99), p=0.026	REWIND
Death from CV Causes	Component of Primary CV Endpoint	n (%)	317 (6.4)	346 (7.0)	hazard ratio (CI) 0.91 (0.78, 1.06) Nominal P-Value: 0.211	REWIND
Nonfatal MI	Component of Primary CV Endpoint	n (%)	205 (4.1)	212 (4.3)	hazard ratio (CI) 0.96 (0.79, 1.16) Nominal P-Value: 0.652	REWIND
Nonfatal Stroke	Component of Primary CV Endpoint	n (%)	135 (2.7)	175 (3.5)	hazard ratio (CI) 0.76 (0.61, 0.95) Nominal P-Value: 0.017	REWIND
All-Cause Mortality	Other Endpoints	n (%)	536 (10.8)	592 (12.0)	hazard ratio (CI) 0.90 (0.80, 1.01) Nominal P-Value: 0.067	REWIND
Microvascular endpoint	Composite microvascular endpoint	n (%)	1099 (22.2)	1241 (25.1)	hazard ratio (CI) 0.86 (0.79, 0.93) Nominal P-Value: <0.001	REWIND
Diabetic Retinopathy	Component of microvascular endpoint	n (%)	95 (1.9)	76 (1.5)	hazard ratio (CI) 1.24 (0.92, 1.68) Nominal P-Value: 0.156	REWIND
Diabetic Nephropathy	Component of microvascular endpoint	n (%)	1042 (21.1)	1200 (24.2)	hazard ratio (CI) 0.84 (0.77, 0.91) Nominal P-Value: <0.001	REWIND
HF requiring Hospitalization	Heart failure requiring Hospitalization	n (%)	213 (4.3)	226 (4.6)	hazard ratio (CI) 0.93 (0.77, 1.12) Nominal P-Value: 0.456	REWIND
HUA	hospitalization for unstable angina	n (%)	88 (1.8)	77 (1.6)	hazard ratio (CI) 1.14 (0.84, 1.54) Nominal P-Value: 0.413	REWIND
Unfavourable Effects						
Nausea	Treatment-Emergent AE	n (%)	737 (14.9)	271 (5.5)	p<0.001	REWIND
Diarrhea	Treatment-Emergent AE	n (%)	671 (13.6)	442 (8.9)	p<0.001	REWIND
Vomiting	Treatment-Emergent AE	n (%)	330 (6.7)	159 (3.2)	p<0.001	REWIND
Decreased Appetite	Treatment-Emergent AE	n (%)	326 (6.6)	105 (2.1)	p<0.001	REWIND
Acute Pancreatitis	AE of Special Interest	n (%)	23 (0.5)	13 (0.3)	Not significant	REWIND
Thyroid Neoplasms	AE of Special Interest	n (%)	10 (0.2)	2 (0.0)	Not significant	REWIND
Severe Hypoglycemia	AE of Special Interest	n (%)	64 (1.3)	74 (1.5)	Not significant	REWIND
Allergic and Hypersensitivity Reactions	AE of Special Interest	n (%)	39 (0.8)	12 (0.2)	Not significant	REWIND

Effect	Short description	Unit	Dulaglutide N=4949	Placebo N=4952	Uncertainties / Strength of evidence	References
SAEs of Supraventricular Arrhythmias or CV Conduction Disorders	AE of Special Interest	n (%)	217 (4.4)	192 (3.9)	Not significant	REWIND
Serious GI Events	AE of Special Interest	n (%)	120 (2.4)	117 (2.4)	Not significant	REWIND
Serious Hepatic Events	AE of Special Interest	n (%)	25 (0.5)	40 (0.8)	Not significant	REWIND
Serious Renal Events	AE of Special Interest	n (%)	84 (1.7)	93 (1.9)	Not significant	REWIND
Benign and Malignant Neoplasms, excluding basal or squamous cell skin cancer	AE of Special Interest	n (%)	540 (10.9)	521 (10.5)	Not significant	REWIND
Any Cancer (malignant neoplasms, excluding basal or squamous cell skin cancer)	AE of Special Interest	n (%)	377 (7.6)	360 (7.3)	Not significant	REWIND
Pancreatic Cancer	AE of Special Interest	n (%)	16 (0.3)	11 (0.2)	Not significant	REWIND
Permanent Discontinuation from Study Drug for Any Reason	AE of Special Interest	n (%)	1621 (32.8)	1697 (34.3)	Not significant	REWIND

3.7. Benefit-risk assessment and discussion

Study H9X-MC-GBDJ (REWIND), the CVOT of dulaglutide in adults with T2D, demonstrated that dulaglutide 1.5 mg s. c. once weekly was superior to placebo as regards reduction of MACE (hazard ratio [95.33% CI]: 0.88 [0.79, 0.99], p=0.026).

The safety profile for patients treated with dulaglutide in Study H9X-MC-GBDJ (REWIND) was consistent with the safety profile reflected in current labelling, as established by the clinical trials for the original and subsequent marketing applications for dulaglutide, and postmarketing data. No new safety concerns were identified in Study H9X-MC-GBDJ (REWIND).

Based on the results from Study H9X-MC-GBDJ (REWIND), which demonstrated CV benefit together with the consistent safety profile, the benefit-risk balance of once-weekly dulaglutide 1.5 mg s.c. remains positive. However, the CHMP did not agree with the MAH's proposed to include an additional indication in section 4.1 of the SmPC but the CHMP considered the strengthening of the wording of the indication in section 4.1 of the SmPC by deleting "improvement of glycaemic control" from section 4.1 of the SmPC (as this restriction does no longer adequately reflect the demonstrated effects for dulaglutide) together with the description of the benefits with dulaglutide regarding macrovascular and microvascular events, as assessed in this application, in section 5.1 of the SmPC (see discussion below).

3.7.1. Importance of favourable and unfavourable effects

The most important effect is that superiority was shown for dulaglutide compared to placebo: the hazard ratio (0.88 [0.79, 0.99]); p=0.026) for the primary 3-component MACE (death from CV causes, nonfatal MI, or nonfatal stroke) was significantly lower for patients in the dulaglutide group compared to the placebo group. Several sensitivity and subgroup analyses were conducted to evaluate the consistency of effect on the primary endpoint in different study populations including the PP population and on-treatment population, or when adjusting for baseline factors or concomitant medications, also in different subgroups based on baseline characteristics. Results from all of these sensitivity and subgroup analyses were consistent with the primary analysis showing that superiority was achieved for dulaglutide compared to placebo.

All of the three monocomponents contributed to the overall effect on the primary composite 3-component MACE since the estimated hazard ratios for all 3 monocomponents were <1. Furthermore, the incidence rate of nonfatal stroke was lower for the dulaglutide group compared to the placebo group (hazard ratio 0.76, p=0.017), albeit statistical significance was not achieved for the time to first event analysis for nonfatal stroke when controlling for Type 1 error.

Further important secondary endpoints, which showed favourable effects in line with the primary analysis, included all-cause mortality, MI (fatal and nonfatal), stroke (fatal and nonfatal), hospitalization for heart failure, or hospitalization for unstable angina, albeit none of these secondary endpoints achieved statistical significance when controlled for Type I error.

Safety findings for patients treated with dulaglutide in the REWIND study were consistent with previously reported safety data from Phase 2 and Phase 3 dulaglutide studies in patients with T2D and other GLP-1 RAs; the most frequently reported TEAEs were GI-related events (e.g. nausea, vomiting, and diarrhea).

The most important unfavorable effects that were reported as adverse events of special interest (AESI) included pancreatitis and thyroid neoplams. The number of patients with adjudicated acute pancreatitis events was higher in the dulaglutide group (0.5%) compared to placebo (0.3%).
No thyroid events were adjudicated as medullary thyroid carcinoma (MTC), and 1 event was adjudicated as C-cell hyperplasia in the dulaglutide group. A total of 7 patients were adjudicated with papillary thyroid cancer (dulaglutide: 6; placebo: 1). The data from REWIND study do not support a causal relationship between dulaglutide treatment and papillary thyroid cancers, C-cell hyperplasia or MTC. Uncertainties remain for thyroid C-cell hyperplasia and MTC due to the long latency period and very rare occurrence.

The overall incidence of severe hypoglycemia was small and no meaningful differences between the treatment groups were observed. Small differences in the incidence rates over time were likely related to adjustments in other antihyperglycemic concomitant medications during this double-blinded study. The incidence of allergic and hypersensitivity reactions prospectively collected on the specific eCRFs was higher in the dulaglutide group compared to placebo. This difference is mainly due to the higher number of GI events that were reported as allergic and hypersensitivity reactions for the dulaglutide group. The incidence of the investigator-reported immune-mediated reactions including serious allergic and hypersensitivity reactions was lower in the dulaglutide group compared to placebo. No significant differences between treatment groups were observed in incidence of serious renal AEs potentially related to acute renal failure or in the progression to ESRD. In general, these renal events occurred in numerically fewer patients in the dulaglutide group compared to the placebo group. No differences between the treatment groups were observed in the incidence of other AEs of interest including serious GI AEs, serious hepatic AEs, or serious supraventricular arrhythmias or CV conduction disorders.

3.7.2. Balance of benefits and risks

Study H9X-MC-GBDJ (REWIND) was designed and powered as a superiority study to test the hypothesis that a once-weekly s.c. injection of dulaglutide 1.5 mg reduces the occurrence of the composite primary 3-component MACE of death from CV causes, nonfatal MI, or nonfatal stroke when added to glucose-lowering regimen of patients with T2D, compared to the addition of a once-weekly placebo injection.

The results showed that patients treated with dulaglutide had significantly lower risk for experiencing a 3-component MACE (first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke). The dulaglutide group has 12% lower risk for 3-component MACE and approximately 60 patients would need to be treated over a period of 5.4 years to prevent an event of death from CV causes, MI, or stroke.

Based on Study H9X-MC-GBDJ (REWIND), which provided important information concerning the effect of dulaglutide on cardiovascular outcomes and its long term safety, the MAH proposed an extension of indication to include within section 4.1 of the SmPC:

"Trulicity is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)

· in adults with type 2 diabetes mellitus who have multiple cardiovascular risk factors without established cardiovascular disease

• in adults with type 2 diabetes mellitus with established cardiovascular disease (see section 5.1)."

With regard to the indication claimed by the MAH, the CHMP is of the view that the patient population eligible for treatment with dulaglutide should be mentioned, i.e. patients with T2DM, without mentioning any goal of treatment, i.e. neither improvement of glycaemic control, nor prevention of MACE. This means that the wording of the indication will refer to the patient population for whom treatment with dulaglutide is intended, i.e. patients with T2DM, and the information on the REWIND study, will be included in section 5.1. The CHMP considers both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of T2DM, which could best be expressed in a single indication for the "treatment of T2DM". Therefore, a separate cardiovascular prevention indication was not considered approvable. However, the CHMP considered the strengthening of the wording of the indication in section 4.1 of the SmPC by deleting "improvement of glycaemic control" from section 4.1 of the SmPC (as this restriction does no longer adequately reflect the demonstrated effects for dulaglutide) together with the description of the benefits with dulaglutide regarding cardiovascular events, as assessed in this application, in section 5.1 of the SmPC. The wording " treatment of T2DM" is considered more relevant as it encompasses both glycaemic control and results on clinical outcomes such as CV complications, with a reference to section 5.1 of the SmPC.

With respect to the target population, the CHMP was of the view that the population studied in the REWIND trial (i.e. patients with T2DM and either with or without established CVD), is covered by the T2DM population already approved for Trulicity. Therefore CHMP considered it not justified to include a separate reference in section 4.1 of the SmPC as applied by the MAH. However the CHMP acknowledges the benefit in terms of cardiovascular outcome demonstrated in the REWIND study and is therefore of the view that the current wording of the indication which only makes reference to the treatment goal " improvement of glycaemic control" does not fully reflect the demonstrated effects with dulaglutide. The wording "treatment of T2DM" was therefore considered more relevant in section 4.1 of the SmPC, as it

encompasses both glycaemic control and results on clinical outcomes such as cardiovascular complications, and a cross-reference to section 5.1 of the SmPC where the study results of the REWIND are reflected
All patients that would benefit from the treatment with dulaglutide are covered by the indication as worded in the section 4.1 of the SmPC that resulted from this variation procedure.

Thus, consistent with previous EMA decisions on CVOTs for other antidiabetic agents, the claimed new indication is not acceptable (since reduction of cardiovascular events is seen as a treatment goal of the underlying type 2 diabetes disease). But the indication wording in section 4.1 has been strengthened by removing the surrogate goal "to improve glycaemic control" to reflect the full demonstrated effect of dulaglutide together with a reflection of the results of the REWIND in section 5.1 of the SmPC. Following the outcome of the CHMP assessment, the MAH withdrew the initially claimed Extension of Indication and modified the wording of section 4.1 of the SmPC as requested by the CHMP.

3.7.3. Additional considerations on the benefit-risk balance

The final wording for the modified indication in SmPC section 4.1 as agreed by the CHMP is as follows:

"**Type 2 Diabetes Mellitus**

Trulicity is indicated **for the treatment of** ~~in~~ adults with **insufficiently controlled** type 2 diabetes mellitus **as an adjunct** to **diet and exercise** ~~improve glycaemic control as:~~

- **As** ~~M~~**m**onotherapy ~~W~~**w**hen ~~diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of~~ metformin is considered inappropriate due to intolerance or contraindications

- **In addition to other** ~~Add-on therapy In combination with other glucose lowering~~ medicinal products **for the treatment of diabetes.** ~~including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for data with respect to different combinations).~~

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."

Further, sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have all been updated based on the data obtained with the Study H9X-MC-GBDJ (REWIND), and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes and to align the annexes with the latest QRD template. These amendments to the product information are all acceptable.

An updated RMP version 3.4 was agreed during the procedure.

3.8. Conclusions

The overall B/R of Trulicity (dulaglutide) in the treatment of T2DM remains positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Update of sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC based on the data from Study H9X-MC-GBDJ (Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)); a single pivotal Phase 3 long-term cardiovascular outcomes study, which assessed the efficacy and safety of treatment with once-weekly injection of dulaglutide 1.5 mg when added to glucose-lowering regimen of patients with type 2 diabetes (T2D), compared to the addition of a once weekly placebo injection. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a minor correction in section 5.1 of the SmPC, to implement editorial changes and to align the annexes with the latest QRD template.

An updated RMP version 3.4 was agreed during the procedure.