17 September 2020
EMA/572529/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trulicity

International non-proprietary name: dulaglutide

Procedure No. EMEA/H/C/002825/X/0045

Note

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

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List of abbreviations

Term	Definition
ADA	American Diabetes Association or anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AV	atrioventricular
BMI	body mass index
Cav,ss	average observed steady-state concentration
CEC	Clinical Endpoint Committee
CI	confidence interval
CL	clearance
Cmax	maximum observed drug concentration
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
F	bioavailability
FDA	United States Food and Drug Administration
FSG	fasting serum glucose
GBGJ	Phase 2 Study H9X-MC-GBGJ
GBGL	Phase 3 Study H9X-MC-GBGL
GBGM	Phase 1 Study H9X-MC-GBGM
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist

HbA1c	glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HOMA2	Homeostasis Model Assessment-2
HOMA2-%B	β-cell function as measured by the HOMA2 method
HOMA2-IR	insulin resistance as measured by the HOMA2 method
HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDF	International Diabetes Federation
ITT	Intent-to-treat
LDL	low-density lipoprotein
Lilly	Eli Lilly and Company
LS	least-squares
MACE	major adverse cardiovascular event(s)
MedDRA	Medical Dictionary for Regulatory Activities: a standard coding terminology for adverse events used globally in compliance with International Conference for Harmonisation (ICH) guidelines.
MTC	medullary thyroid carcinoma
PFS	prefilled syringe
PG	plasma glucose
PK	pharmacokinetic(s)
PKPD	pharmacokinetic/pharmacodynamic
PR interval	the period that extends from the beginning of the P wave (onset of atrial depolarization) until the beginning of the QRS complex (onset of ventricular depolarization), measured on ECG
PT	preferred term
QT interval	the time from the start of the Q wave to the end of the T wave, measured on ECG
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SDP	single-dose pen
SmPC	Summary of Product Characteristics
SMPG	self-monitored plasma glucose

SMQ	Standardised MedDRA Query
$t_{1/2}$	elimination half-life
T2D	type 2 diabetes mellitus
TE	treatment-emergent
TE ADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
V2/F	central volume of distribution
V3/F	peripheral volume of distribution
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein cholesterol
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

Eli Lilly Nederland B.V. submitted on 7 November 2019 an extension of the marketing authorisation. The MAH applied for an addition of two new strengths; 3 mg and 4.5 mg (solution for injection in pre-filled pen).

The MAH applied for the following indication for Trulicity 3 mg and 4.5 mg:

Type 2 Diabetes Mellitus

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

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

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

Furthermore, the PI is brought in line with the latest QRD template.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

Information on Paediatric requirements

Not applicable

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 MAH 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 MAH 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

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	7 November 2019
The procedure started on	28 November 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 March 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	19 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 July 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	23 July 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	1 September 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trulicity on	17 September 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Dulaglutide, a long-acting GLP-1 receptor agonist, is approved at two strengths; 0.75 mg and 1.5 mg solution for injection for subcutaneous use once weekly in the following indication, which remains unchanged with this line extension:

Type 2 Diabetes Mellitus

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

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

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

The purpose of this application is to add two new strengths of dulaglutide; 3.0 mg and 4.5 mg solution for injection for subcutaneous use once weekly for patients in need of additional glycaemic control.

2.1.2. Epidemiology and risk factors

Type 2 diabetes mellitus (T2D) remains a substantial health care challenge that affects the individual patient and the society profoundly. The prevalence of the chronic and progressive metabolic disorder is expected to increase worldwide markedly; projections suggest that around 10% of the global adult population will be affected by 2045. To avoid the microvascular and macrovascular complications associated with the disease, it is a key aim to establish adequate glycaemic control as soon as possible after a T2D diagnosis.

A well-known risk factor for hyperglycaemia, T2D and cardiovascular disease is obesity. A moderate weight loss of 5% improves glycaemic control and CV risk factors in patients with T2D, and thereby provides beneficial effects on T2D and CV disease. Thus, anti-glycaemic drugs that in addition to lowering HbA1c also reduce body weight can provide additional clinical benefits in the treatment of T2D and CV disease.

2.1.3. Aetiology and pathogenesis

T2D is a progressive metabolic disease primarily characterised by abnormal glucose metabolism.

The pathophysiology of T2D is characterised by persistent hyperglycaemia caused by insulin resistance in the peripheral tissue, by reduced insulin production in the pancreatic beta-cells and by increased hepatic glucose release.

The pathogenesis is seemingly heterogeneous and also involves environmental, lifestyle, and genetic components. All of these factors contribute to chronic hyperglycaemia which, if left untreated, is associated with β-cell failure and increased risk of long-term micro- and macrovascular complications.

2.1.4. Clinical presentation, diagnosis

The typical presentation of diabetes includes polyuria and polydipsia. However, many patients with T2D are asymptomatic and are diagnosed with non-specific complaints like fatigue, blurred vision, slow-healing cuts or sores, dry, itchy skin, numbness and tingling feet.

The diagnosis is made by measurement of hyperglycaemia by demonstrating one of the following:

- Fasting plasma glucose level ≥ 126 mg/dl (7.0 mmol/l) on two separate tests
  [A fasting plasma glucose level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes and less than 100 mg/dL (5.6 mmol/L) is normal]
- Oral Glucose Tolerance Test (OGTT): Plasma glucose ≥ 200 mg/dl (11.1 mmol/l) two hours after a 75 gram oral glucose load
  [A reading two hours after a 75 gram oral glucose load between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes and less than 140 mg/dL (7.8 mmol/L) is normal]
- Glycated hemoglobin (HbA1C) ≥ 6.5 % (48 mmol/mol) on two separate tests
  [HbA1C between 5.7 % and 6.4 % indicates prediabetes, below 5.7 % is considered normal]

2.1.5. Management

The guidelines of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) for treatment of T2D have been developed in cooperation and are widely agreed. The major steps recommended for managing type 2 diabetes are lifestyle changes such as diet and exercise. For glycaemic control, primarily metformin, other non-insulin anti-diabetic agents and finally insulin (in various forms) are used.

To avoid the microvascular complications associated with the disease, it is a crucial aim to establish adequate glycaemic control as soon as possible after a T2D diagnosis. Besides anti-glycaemic therapy, antihypertensive, antithrombotic and lipid lowering treatments might be indicated to avoid other associated co-morbidities (e.g. hypertension, obesity, dyslipidemia) and macrovascular complications (MI, stroke).

Recently, SGLT-2 inhibitors and GLP-1 RAs in T2D patients at high CV risk have shown not only improvements in glycaemic control but also a reduction in body weight and CV events.

About the product

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

Dulaglutide is already approved (date of first authorisation: 21 November 2014) at two dose strengths (0.75 mg and 1.5 mg SC injection once weekly) for treatment of type 2 diabetes mellitus.

Type of Application and aspects on development

Preclinical data and clinical experience support the use of dulaglutide as a once-weekly SC injection to improve glycaemic control in adult patients with T2D. As of 31 August 2019, dulaglutide has received marketing authorisation in more than 70 countries worldwide and is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2D. The approved doses of dulaglutide include 0.75 mg and 1.5 mg SC injection once-weekly. Dulaglutide is not approved for any paediatric indication.

The purpose of this application is to add two new higher dose strengths (dulaglutide 3.0 mg and 4.5 mg SC injection once-weekly) for patients who could benefit from additional glycaemic control.

The design of the registration program to investigate higher doses of dulaglutide was informed by available regulatory guidance documents and advice from the EMA/CHMP and FDA.

- FDA 2008: Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.
- ICH 2017: ICH harmonised guideline: estimands and sensitivity analysis in clinical trials, E9(R1), Step 2 version.
- EMA 2018: Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus (draft rev.2).

A pivotal Phase 3 Study (GBGL) provides primary evidence, with supporting data from a Phase 2 study (GBGJ) and a Phase 1 study (GBGM), see Table below.

Overview of Studies Contributing to the Current Marketing Application for Dulaglutide

Study	Primary Objective	Study Design	Study Drug	Number of Treated Participants	Study Population
H9X-MC-GBGL (pivotal)	To demonstrate that once-weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for change from baseline in HbA1c at 36 weeks in patients with inadequately controlled T2D on concomitant metformin therapy	Ongoing, 52-week, Phase 3, multicenter, randomized, double-blind, parallel-group study	Dula 1.5 mg Dula 3.0 mg Dula 4.5 mg	1842	Patients with T2D (HbA1c 7.5% to 11.0% [58 mmol/mol to 97 mmol/mol]), inclusive, and treated with stable doses of metformin
H9X-MC-GBGJ (supportive)	To demonstrate that once-weekly dulaglutide (4.5 mg, 3.0 mg, 1.5 mg) was superior to placebo in HbA1c reduction at 18 weeks in patients with T2D on concomitant metformin monotherapy	Completed, 18-week, Phase 2, randomized, multicenter, placebo-controlled, double-blind study	Placebo Dula 1.5 mg Dula 3.0 mg Dula 4.5 mg	317	Patients with T2D (HbA1c 7.0% to 10.0% [53 mmol/mol to 86 mmol/mol] and treated with stable doses of metformin
H9X-MC-GBGM (supportive)	To evaluate the relative bioavailability of a single dose of dulaglutide 4.5 mg administered SC to healthy subjects as a single injection by SDP (test) compared to 3 injections by PFS (reference)	Completed, Phase 1, single-center, open-label, randomized, 2-period, crossover study	Dula 3×1.5 mg (PFS) Dula 4.5 mg (SDP)	26	Healthy subjects

Abbreviations: Dula = dulaglutide; HbA1c = glycated hemoglobin; PFS = prefilled syringe; SC = subcutaneous; SDP = single-dose pen; T2D = type 2 diabetes mellitus.
Sources: GBGL CSR, GBGJ CSR, and GBGM CSR.

2.2. Quality aspects

2.2.1. Introduction

Eli Lilly Nederland B V. has submitted a line extension application for Trulicity (INN dulaglutide) under Annex I, 2c, of regulation (EC) No 1234/2008 (addition of a new strength). With this line extension two new strengths are added: 3.0 mg and 4.5 mg solution for injection for subcutaneous administration presented in a pre-filled pen (PFP).

The new dulaglutide solution for injection strengths utilise the same active substance, same formulation components, and same container closure system as approved for Trulicity 0.75 mg and 1.5 mg solution for injection in a pre-filled pen.

The new strengths include increases in the active substance concentration and a small increase in stabiliser (Polysorbate 80) to account for the higher concentration of protein. There were no changes to the concentration of the other excipients (sodium citrate, citric acid, mannitol and water for injections) which remains the same for all strengths.

The active substance used for the manufacture of the new strengths is identical to the currently used commercial active substance. Consequently, no new information regarding the active substance has been provided.

However, in the course of the development of the additional strengths, it was found that a slightly higher amount of polysorbate 80 (0.025% instead of 0.02 %) in the product solution is advantageous for the new strengths.

Where applicable, the analytical methods have been revalidated to account for the additional sample matrix. As the analytical methods used for both active substance and finished product are described in the active substance section of the dossier, these changes are described in the active substance section.

2.2.2. Active Substance

General Information

Dulaglutide is a glucagon-like peptide-1 (GLP-1) analog that has been fused to a modified human immunoglobulin G4 (IgG4) Fc domain through a short flexible peptide linker.

Manufacture, process controls and characterisation

N/A (no change)

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications for 3.0 mg and 4.5 mg solution for injection are the same as those used in the approved marketed strengths. The specifications for the active substance include tests for identity, protein content, potency, purity, appearance, purity, bacterial endotoxins, bioburden and pH.

Description and validation of the active substance-related analytical methods used for finished product release are included in section S.4 of the dossier. Thus, the changes introduced in the formulation of the additional finished product strengths and the necessary adaptations in the analytical methods were accounted for in S.4.2 and S.4.3.

Revised descriptions of the analytical procedures have been provided to include deviating sample preparation due to the quantitatively different finished product composition, where applicable.

The MAH repeated analytical method validation for selected methods to account for the increased dulaglutide concentration in the additional strengths of the finished product, and the slightly increased polysorbate 80 concentration in the concentrated finished product formulations. Only selected validation parameters were repeatedly evaluated. For most parameters, the existing data were leveraged.

Deviations concerning the tests on physical appearance, clarity and polysorbate 80 are due to the differences in active substance and polysorbate 80 concentrations and are considered acceptable. The

applied test methods are also the same with respective adaptions concerning the sample preparations. Sufficient method validations/verifications were performed where necessary.

Adequate justifications have been provided for either repeated evaluation or leverage of existing data. These are deemed satisfactory and comprehensible.

The additional validation data provided have adequately addressed the changes introduced by the new (concentrated) finished product formulation.

Stability

N/A

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Dulaglutide injection supplied as either 3.0 mg/ 0.5 mL or 4.5 mg/ 0.5 mL is a clear, colorless, slightly opalescent, essentially free from particles, sterile, and non-pyrogenic parenteral solution for subcutaneous administration. Both dulaglutide finished product strengths are contained in a 1 mL, Type I borosilicate glass syringe with a plunger. Each pre-filled pen contains 0.5 mL of solution.

There are no novel excipients, non-compendial excipients or excipients of human or animal origin used in the manufacture of Trulicity 3.0 mg and 4.5 mg. The qualitative composition of dulaglutide finished product is dulaglutide (active substance), trisodium citrate dihydrate, citric acid, mannitol, polysorbate 80, and water for injections.

The container closure system filled with finished product is referred to as the semi-finished syringe (SFS). Each finished product strength is available to patients as a semi-finished syringe (SFS) assembled into a pre-filled pen for administration.

The same pre-filled pen is used for all strengths of dulaglutide injection. The pre-filled pen is spring-powered and designed to administer the entire contents of the SFS during one injection. After injection, the needle automatically retracts into the device and the device is discarded by the patient. The device is single-dose and is not intended to be refilled or reused.

Pharmaceutical Development

The Quality Target Product Profile (QTPP) and the Critical Quality Attributes (CQAs) for the new strengths of the finished product were defined in accordance with the QTPP and CQAs presented for the already authorised finished product strengths. Development experience with the current strengths was leveraged and design of experiments (DOE) were applied to find the optimised composition of the new finished product strengths. It was found that the polysorbate 80 concentration for the new strengths needed to be increased for the current approved strengths. All other excipients are qualitatively and quantitatively the same in all strengths. The provided information is considered sufficient.

The new finished product strengths of 3.0 mg/0.5 mL and 4.5 mg/0.5 mL were subject to phase 1 and phase 3 clinical studies.

The manufacturing process for dulaglutide injection, 3.0 mg /0.5 mL and 4.5 mg /0.5 mL semi-finished syringes was based on the experience with the manufacturing process of the current dulaglutide injection strengths.

A risk assessment for the manufacturing process unit operations was performed and the results presented. No process steps were ranked as high risk. The risk assessment specifically focused on changes of the manufacturing process compared to that for the 0.75 mg/0.5 mL and 1.5 mg/0.5 mL strengths.

The finished product formulation compounding operation involves a variable batch size and different mixing equipment compared to dulaglutide 0.75 mg/0.5 mL and 1.5 mg/0.5 mL. Therefore, the impact on dulaglutide content uniformity /quantity needed to be evaluated. Peristaltic filling technology is used for the filling of dulaglutide injection, 3.0 mg/0.5 mL and 4.5 mg/0.5 mL. The impact of the filling process has been evaluated to ensure no impact on the product quality attributes and delivery functionality of the semi-finished syringe.

Process characterization studies were performed for the unit operations with medium risks. Extractable and leachable studies for the disposable bags used for buffer and finished product formulation compounding have been provided.

Classification, acceptable ranges, and rationale for process parameters and controls for each unit operation have been presented and are considered comprehensive.

The new strengths of dulaglutide are supplied in the same container closure system used for the currently approved strengths of dulaglutide injection, 0.75 mg/0.5 mL and 1.5 mg/0.5 mL.

Extractable/leachables, compatibility with residual tungsten, needle shield elastomer and silicone oil and drug delivery performance were evaluated for the new strengths and found to be not different to the currently approved finished product strengths.

For transportation of the semi-finished syringes the MAH claims that there is no difference between the current and new finished product strengths. The evaluation that the semi-finished syringes perform as intended after exposure to low-pressure cycling and representative worst-case transportation hazards (e.g. shock, temperature, vibration) can be followed.

A laboratory-based shipping study was conducted to assess the impact of transportation stresses that dulaglutide injection, 3.0 mg /0.5 mL and 4.5 mg /0.5 mL contained in a pre-filled pen may encounter. No adverse effects on quality attributes of the finished product in commercial packaging configurations and exposed to transportation stresses within a temperature range of 1°C to 15°C for 24 days were found.

In addition, to the laboratory-based shipping study a shipping validation study under real transportation conditions was performed. The study results are included in section P.3.5.

Manufacture of the product and process controls

GMP compliance has been demonstrated for the manufacturing sites involved in the production and testing of dulaglutide finished product.

The manufacturing process comprises buffer solution compounding, bulk drug product formulation compounding, bioburden reduction filtration, sterile filtration as part of the filling process and aseptic filling, plungering and inspection.

A flow chart and a narrative description of the finished product manufacturing process have been provided. An adequate control strategy with critical controls and non-critical controls has been established.

Information on the validated single use bags used for compounding with respect to name of supplier, material composition and sterilization procedure has been included. Details on validated filters and filtration conditions used for the bioburden reduction filtration of the bulk finished product solution and the sterile filtration are also available. Furthermore, the sterilization conditions for the packaging, i.e. syringes (vendor ethylene oxide sterilization) and plungers (vendor sterilized via gamma-irradiation) have been adequately characterized.

Processing time limits have been included and sufficiently validated with respect to bioburden, aseptic process simulation (media fill) and microbial retention of the applied filters as applicable.

Process performance qualification has been sufficiently demonstrated with results gained from three batches of each of the new strengths covering lower end and higher end of the batch sizes as defined in section P.3.2.

Satisfactory filter validation has been performed with respect to microbial retention, membrane compatibility, product specific bubble point determination and filter extractables.

Furthermore, satisfactory shipping studies have been performed. The finished product may be shipped at 2-8°C, i.e. the long-term storage conditions or alternatively at 2-15°C for a maximum shipping duration of 24 days.

Product specification, analytical procedures, batch analysis

The specification for the finished product includes tests for identity, quantity, potency, purity, impurities, appearance, osmolality, sterility.

The specifications were adequately justified and are considered acceptable.

Analytical methods

The finished product release and shelf-life specifications for the new strengths are largely the same as for the already approved finished product strengths. Deviations concerning the analytical tests on physical appearance, clarity and polysorbate 80 are due to the differences in active substance and polysorbate 80 concentrations and are considered acceptable. The applied test methods are also the same with respective adaptions concerning the sample preparations. Sufficient methods validations/verifications were performed where necessary.

Batch analyses

Batch analyses for three validation/primary stability batches of each new strengths and for two clinical batches of each new strength have been provided.

The results confirm consistency and uniformity of the product indicating that the manufacturing process for dulaglutide injection, 3.0 mg/0.5 mL and 4.5 mg/0.5 mL is under control. The presented results also show no noticeable differences to the results for dulaglutide injection, 0.75 mg/0.5 mL and 1.5 mg/0.5 mL.

Reference materials

The reference standard used is the same as the one used for the active substance. Reference is made to the currently authorised strengths for further information on the reference standard.

Container Closure System

The primary packaging (glass syringe (type I) encased in a disposable pen) for the new finished product strengths is the same as for the already approved ones.

Stability of the product

The proposed shelf life of 24 months for the finished product when stored at the long term storage condition of 2-8°C with a 14 day patient in-use period at 30°C can be accepted based on the provided stability data and considering the stability data of the already approved finished product strengths which are comparable.

The shelf life is based on the provided stability data for six batches, three 3.0 mg/0.5 mL and three 4.5 mg/0.5 mL finished product batches in pens (primary stability/validation batches) manufactured at the intended commercial scale range. The study has been performed in accordance with ICH requirements over 9 months at 2-8°C and 6 months at 25°C. The applied analytical procedures are those described in section P.5.2 and the primary packaging is that proposed for commercial manufacturing.

The results which are all within specifications and their statistical evaluation demonstrate little inter-batch variability.

In addition, three lots of the validation batches (one 3 mg/0.5 mL and two 4.5 mg/mL) were exposed to temperature cycling. Following the temperature excursions, the samples were tested for stability indicating attributes and then placed on long term (2°C - 8°C) stability for 24 months.

Data after nine months storage have been compared to the nine months stability data for samples that did not undergo temperature cycles. The starting results are different, but the degradation rates are comparable.

Supporting stability data for semi-finished syringe batches (one clinical and one development batch of each strength) stored at 2-8°C for 23.5 months and 24 months respectively followed by 2 weeks at 30°C/65%RH (test at T0, 1 week and 2 weeks storage) have been included with all results within specifications.

In addition, based on in-use stability data Trulicity finished product may be stored unrefrigerated for up to 14 days at a temperature not above 30 ºC. Photostability testing in accordance with ICH Q1B and temperature stress testing confirmed that dulaglutide finished product is sensitive to light and elevated temperatures. The information included in the SmPC and labelling is in accordance with the contents of section P.8.

Sufficient post approval stability commitments have been provided.

Post approval change management protocol

The MAH has provided a post approval change management protocol (PACMP) to introduce a different sterilization method for the sterilizing filters instead of the method included in section P.3. In the current manufacturing process, the finished product solution is sterilized via a single-use, disposable 0.22 µm filter assembly.

The proposed filtration process utilizes a single-use, disposable 0.22 µm filter assembly which is sterilized prior to use. The filter material, pore size and membrane type and supplier remain the same. The potential impact of the change to the critical quality attributes was evaluated.

The change management protocol is acceptable considering that filters were already used for the new finished products strengths (clinical batches) and have been used for the authorized finished product strengths.

Adventitious agents

There were no changes to the information provided for dulaglutide injection 0.75 mg/ 0.5 mL or 1.5 mg/0.5 mL.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The documentation provided is considered adequate and complies with existing guidelines. The control strategy of the finished product is acceptable. The composition of clinical batches and the composition proposed for commercial batches are identical. Sufficient stability data has been provided for the claimed shelf life of 24 months for the finished product when stored at the long-term storage condition of 2-8°C with a 14 day patient in-use period at a temperature not above 30°C.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality documentation provided in this line extension application to introduce the new Trulicity strengths 3.0 mg and 4.5 mg, solution for injection is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Pharmacology

No new studies were performed, which is acceptable.

2.3.2. Pharmacokinetics

No new studies were performed, which is acceptable.

2.3.3. Toxicology

The Applicant has provided a recalculation of the exposure multiples of the toxicology studies previously submitted for the higher doses 3.0 mg and 4.5 mg QW. This approach is acceptable.

2.3.4. Ecotoxicity/environmental risk assessment

The applicant has justified that dulaglutide is exempt from an environmental risk assessment by its protein nature.

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.

2.3.5. Discussion on non-clinical aspects

The applicant did not perform new non-clinical studies. This is considered acceptable since all relevant information for the new doses on PK, PD and toxicology of dulaglutide can be derived from existing studies. Together with the clinical experience, which has accumulated since the approval of the initial MAA, the exposure multiples for the new doses 3.0 and 4,5 mg QW are considered sufficient.

2.3.6. Conclusion on the non-clinical aspects

There are no concerns from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Overview of Studies Contributing to the Current Marketing Application for Dulaglutide

Study	Primary Objective	Study Design	Study Drug	Number of Treated Participants	Study Population
H9X-MC-GBGL (pivotal)	To demonstrate that once-weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for change from baseline in HbA1c at 36 weeks in patients with inadequately controlled T2D on concomitant metformin therapy	Ongoing, 52-week, Phase 3, multicenter, randomized, double-blind, parallel-group study	Dula 1.5 mg Dula 3.0 mg Dula 4.5 mg	1842	Patients with T2D (HbA1c 7.5% to 11.0% [58 mmol/mol to 97 mmol/mol]), inclusive, and treated with stable doses of metformin
H9X-MC-GBGJ (supportive)	To demonstrate that once-weekly dulaglutide (4.5 mg, 3.0 mg, 1.5 mg) was superior to placebo in HbA1c reduction at 18 weeks in patients with T2D on concomitant metformin monotherapy	Completed, 18-week, Phase 2, randomized, multicenter, placebo-controlled, double-blind study	Placebo Dula 1.5 mg Dula 3.0 mg Dula 4.5 mg	317	Patients with T2D (HbA1c 7.0% to 10.0% [53 mmol/mol to 86 mmol/mol] and treated with stable doses of metformin
H9X-MC-GBGM (supportive)	To evaluate the relative bioavailability of a single dose of dulaglutide 4.5 mg administered SC to healthy subjects as a single injection by SDP (test) compared to 3 injections by PFS (reference)	Completed, Phase 1, single-center, open-label, randomized, 2-period, crossover study	Dula 3×1.5 mg (PFS) Dula 4.5 mg (SDP)	26	Healthy subjects

Abbreviations: Dula = dulaglutide; HbA1c = glycated hemoglobin; PFS = prefilled syringe; SC = subcutaneous; SDP = single-dose pen; T2D = type 2 diabetes mellitus.
Sources: GBGL CSR, GBGJ CSR, and GBGM CSR.

2.4.2. Pharmacokinetics

Bioequivalence

Phase I study GBGM comparing 1 x 4.5 mg vs. 3 x 1.5 mg of dulaglutide

Title

Relative Bioavailability of an Investigational Single Dose of Dulaglutide after Subcutaneous Administration by a Single Dose Pen Compared to a Prefilled Syringe in Healthy Subjects

Objectives

In the phase 2 trial GBGJ, dulaglutide doses of 3.0 mg and 4.5 mg were administered as *multiple separate* injections of 2 x 1.5 mg or 3 x 1.5 mg, respectively, using pre-filled syringes. For the phase 3 trial GBGL (for discussion see corresponding section), however, the 3.0 mg or 4.5 mg dose was administered as *one single* injection, using a single-dose pen.

The phase 1 study GBGM was performed to show that administration of 3 x 1.5 mg of dulaglutide with a pre-filled syringe (PFS) results in comparable pharmacokinetics as administration of 1 x 4.5 mg with a single-dose pen (SDP).

Primary objective: relative bioavailability of an s.c. single dose of 4.5 mg dulaglutide; comparison of a single injection (SDP; = study drug) with 3 injections of 1.5 mg each (PFS; = reference drug)

Secondary objective: tolerability of 1 x 4.5 mg injection *vs.* 3 x 1.5 mg injections.

Study design

The study was a single-center, open-label, randomized, 2-period, crossover study in healthy subjects. Subjects were admitted to the clinical research unit (CRU) one day before dosing. Dosing occurred on the morning of day 1 after an overnight fast of ~8 h. Dosing of the subjects occurred according to assigned treatment sequence (either PFS in period 1 and SDP in period 2 or *vice versa*). Standard breakfast was served ~5 min after dosing.

Study drug: Dulaglutide 4.5 mg, s.c. injection into abdomen of 1 x 0.5 ml volume (concentration: 9.0 mg/ml) using a single-dose pen (SDP)

Reference drug: Dulaglutide 4.5 mg, 3 x 1.5 mg s.c. injections into abdomen (3 x 0.5 ml volume; concentration: 3 mg/ml) using a pre-filled syringe (PFS)

The blood samples were collected after 0 h (pre-dose) as well as 24, 48, 72, 96, 120, 144, 168 and 336 hours post-dose. The t_{max} is expected at ~48 h post-dosing (SmPC), which corresponds to the second post-dosing sampling point. The wash-out period between periods 1 and 2 was 28 days, which is sufficiently long (≥5 terminal half-lifes), when a half-life of 4.7 days (SmPC, 1.5 mg dose) is considered.

Assay validation

K_3EDTA plasma samples (n=442) were analysed using a validated radioimmunoassay method. The assay based on the competition between a labeled tracer (^{125}I-GLP-1) and the unlabelled antigen for the GLP-1(Active) antibody. Bound tracer is counted after separation from free tracer in solution. Sample concentrations are determined by interpolation from the standard curve (4-parameter algorithm with 1/ratio^2 weighting). The samples were stored at a nominal temperature of -80°C prior to analysis. The calibration curves range from 1.00 ng/ml to 50 ng/ml. According to the concentration table in the bioanalytical report (Table 5 on p 19-34), the majority of samples had to be diluted (please see also below "*Failed runs and re-analysed samples*").

Pre-study validation:

LLOQ: 5.00 ng/ml; ULOQ: 50.0 ng/ml

Inter-assay accuracy: -6.72% to 2.86%; Inter-assay precision: 6.73% to 22.2%

Intra-assay accuracy: -18.3% to -7.68%; Intra-assay precision: 1.51% to 12.7%

The stability of the analyte was demonstrated for up to 735 d in K_3EDTA-containing human plasma at -70°C and for 25 h in thawed matrix. The sample storage time in the study did not exceed the validated time span of 735 days (first subject enrolled on 07 December 2017; last sample analysed on 01 August 2018).

Freeze/thaw stability was demonstrated over five cycles for quality control samples stored at nominal -20°C and -70°C.

Hook Effect (inhibition of assay response due to excess analyte concentrations) was excluded up to an analyte concentration of ~1000 ng/mL, and haemolysis did not relevantly affect assay results.

Analytical interference with concomitant medications was analysed and excluded for atorvastatin (0.2 µg/ml), lisinopril (0.3 µg/ml), metoprolol (0.3 µg/ml), sitagliptin (1.5 µg/ml), ethinylestradiol (1.0 ng/ml), norgestimate (20 ng/ml), warfarin (10 µg/ml), digoxin (1.5 µg/ml), metformin (15 µg/ml), pioglitazone (5 µg/ml) and insulin lispro (2000 pM).

In-study validation:

Quality controls: QC1: 15.0 ng/ml; QC2: 25.0 ng/ml; QC3: 35.0 ng/ml

Incurred sample re-analysis (ISR) was performed with only 4.5 % of the samples, because one of two ISR runs (16RJFN) was rejected and the ISR samples were inadvertently omitted, when the run was repeated. However, this is of no concern as 100% of these samples fulfilled the criteria

Failed runs and re-analyzed samples:
2 out of 21 bioanalytical runs failed due to unacceptable quality control samples. 39.1% of samples were repeated, mostly (28%) due to "result above upper limit of quantitation", requiring dilution. No sample was repeated because of pharmacokinetic reasons.

Sample size estimation
For sample size calculation, it was assumed that within-subject variability (coefficient of variation) of dulaglutide is 21% for AUC and C_{max} (basing on data from previous studies). To achieve a 90% probability that the half-width of the 90% confidence interval (CI) of the ratio of the geometric means for AUC and C_{max} is ≤14%, a sample size of 18 subjects was calculated. Additional subjects were included to compensate for potential dropouts and withdrawals. In total, 27 subjects were enrolled (23 initially, and 4 additional subjects later due to early withdrawals).

Pharmacokinetic data analysis
Evaluation of log-transformed C_{max}, AUC(0-∞), AUC(0-168h) and AUC(0-336h) was performed using a linear mixed-effects analysis of variance model with fixed effects for treatment (SDP or PFS), period, and sequence, and a random effect for subject within sequence. The ratios of least squares geometric means of SDP compared to PFS, as well as the corresponding 90% CIs were estimated and reported.
T_{max} was analysed non-parametrically using the Wilcoxon signed rank test. Estimates of the median difference and the corresponding 90% CIs were evaluated. The data analysis method used by the applicant corresponds to the recommendations of the EU bioequivalence guideline (90% CIs for ratio of geometric means of test compared to reference, ANOVA analysis with log-transformed parameters).

Results of study GBGM

Characteristics of the dosed study population
The design of study GBGM largely corresponds to the design recommended by the EU bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The study included healthy volunteers (57.7% males and 42.3% females; 26 subjects treated at least once) aged 41.2 ± 10.4 years (from 27 to 59 years). The mean BMI was 30.66 ± 3.95 kg/m^2 (range: 24 - 42.3 kg/m^2) and exceeded the maximum of 30 kg/m^2 recommended by the bioequivalence guideline. However, inclusion of overweight and obese subjects is acceptable, as the target population of dulaglutide (patients with T2DM) is expected to exhibit similar characteristics. Except vitamin/mineral supplements and/or HRT, prescription medications were not permitted from 14 days prior to drug administration and throughout the study. Over-the-counter medications were not allowed from 7 days prior to drug administration and throughout the study, except for acetaminophen (1 g, maximum 4 g per 24 h).

<u>Subject Disposition</u>
- 15 subjects were randomized to receive PFS in period 1 and SDP in period 2.
- 12 subjects were randomized to receive SDP in period 1 and PFS in period 2, but one of these subjects was not dosed.
- Five subjects discontinued due to an adverse event
- Two subjects discontinued due to personal decision
- One subject failed to return for the safety follow-up visit

➔ 19 subjects completed the study

7 of the 8 subjects that withdrew from the study had received at least 1 dose of dulaglutide and were included in the PK dataset. 3 subjects received only PFS dosing (3 x 1.5 mg) and 2 subjects were dosed via SDP only (1 x 4.5 mg). **Table 1** summarizes all PK data. T**able** 2 contains only data from the subjects who received both formulations and shows the statistical analysis of the PK parameters (Wilcoxon signed-rank test). The time-plasma concentration profile is depicted in **Fig. 1**.

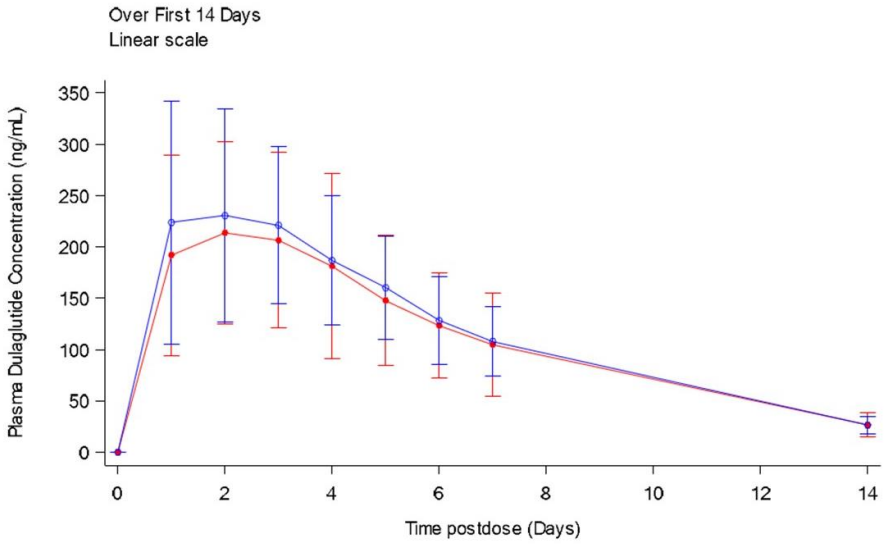
Table 1: Summary of pharmacokinetic results from study GBGM

	4.5 mg Dulaglutide (PFS) (n=24)		**4.5 mg Dulaglutide (SDP) (n=23)**	
Parameter	**Geometric mean (CV%)**	**n**	**Geometric mean (CV%)**	**n**
AUC(0-∞) (ng·h/ml)	37400 (38%)	23	40000 (33%)	22
AUC(0-168h) (ng·h/ml)	24800 (40%)	24	27300 (36%)	22
AUC(0-336h) (ng·h/ml)	33800 (38%)	24	36700 (34%)	22
AUC(0-t_{last}) (ng·h/ml)	33600 (39%)	24	35300 (41%)	23
%AUC(t_{last}-∞) (%)	7.05 (58%)	23	6.85 (59%)	22
C_{max} (ng/ml)	213 (41%)	24	240 (39%)	23
t_{max} (h) (median)	59.61 (23.93-143.95)	24	48.03 (23.23-96.00)	23
$t_{1/2}$ (h) (geometric mean)	82.9 (68.4-105)	23	85.3 (71.6-110)	22
CL/F (L/h)	0.120 (38%)	23	0.113 (33%)	22
V_z/F (L)	14.4 (38%)	23	13.9 (36%)	22
V_{ss}/F (L)	17.6 (39%)	23	16.5 (37%)	22

Table 2: Statistical analysis of the PK parameters of Dulaglutide (Test: 1 x 4.5 mg s.c. with SDP; Reference: 3 x 1.5 mg s.c. with PFS; Wilcoxon signed-rank test)

	Geometric least square (LS) means				**Ratio of geom. LS means**	**90% CI for the ratio**	
Parameter	**SDP**	**n**	**PFS**	**n**	**SDP/PFS**	**(lower, upper)**	**p-value**
AUC(0-∞) (ng·h/ml)	39200	22	37700	23	1.04	(0.949, 1.14)	0.473
AUC(0-168h) (ng·h/ml)	27100	22	24800	24	1.09	(0.970, 1.23)	0.212
AUC(0-336h) (ng·h/ml)	36200	22	34000	24	1.07	(0.963, 1.18)	0.291
AUC(0-t_{last}) (ng·h/ml)	34800	23	34000	24	1.02	(0.906, 1.16)	0.749
C_{max} (ng/ml)	238	23	210	24	1.14	(0.993, 1.30)	0.119
	Medians				**Median of differences**	**~ 90% CI for the difference**	
	SDP	**n**	**PFS**	**n**	**SDP-PFS**	**(lower, upper)**	**p-value**
t_{max} (h)	48.0	21	71.0	21	-23.9	(-24, 0.0167)	0.180

Figure 1: Arithmetic mean (±SD) plasma concentration vs. time profile of dulaglutide (1 x 4.5 mg s.c. with SDP (blue) *vs.* 3 x 1.5 mg s.c. with PFS (red))



AUC(0-∞) was calculated for only 23 subjects and not for 24 subjects (**Table 1** and **2**), because no regression was possible for 1 subject (less than 3 data points after C_{max}).

C_{max} was the first point of the PK curve in a considerable proportion of subjects of the PFS (20.8%) and SDP (30.4%) group.

Protocol deviations

None of the protocol deviations affected the safety of the subjects or the conclusions of the study. There were no significant good clinical practice issues.

Conclusions

No notable differences occurred between SDP and PFS administration with regard to the various measures of AUC. In addition, the individual AUC data provided by the applicant for each subject do not indicate a common trend towards increase or decrease of AUC, when both types of administration are compared.

The value for C_{max} is larger, and T_{max} is reached earlier after administration of 1 x 4.5 mg (SDP) as compared to 3 x 1.5 mg (PFS). The tendency towards a higher incidence of vomiting with SDP as compared to PFS administration may reflect these differences in pharmacokinetics. The 90% CI of the comparison of the C_{max} values (0.993, 1.30) slightly exceeds the range of 0.8 - 1.25 recommended for bioequivalence studies. Moreover, C_{max} was the first point of the PK curve in a considerable proportion of subjects of the PFS (20.8%) and SDP (30.4%) group. However, the dulaglutide PK profile is very flat between day 1 and day 3. Thus, it is expected that there is only a minor contribution of C_{max} to the calculation of overall AUC. In summary, the two methods of administration are considered largely comparable and the purpose of study GBGM (bridging of the forms of administration in study GBGJ and GBGL) is considered fulfilled.

Absorption

Bioavailability

During development of the population PK model for study GBGL (see detailed discussion below), the influence of dose on bioavailability (F1) was considered negligible (mean population F1 values for 1.5

mg, 3.0 mg and 4.5 mg was 0.471, 0.470 and 0.469, respectively). By contrast, for the 0.75 mg and for the 1.5 mg dose a dose-dependency of F1 was reported (Trulicity EPAR EMA/CHMP/524604/2014) with F1 = 44-47% for the 1.5 mg dose and F1 = 65% for the 0.75 mg dose.

Distribution

As shown in study GBGM (Table 1, above), the apparent volume of distribution (Vz/F) was comparable for both forms of administration, 3 x 1.5 mg as well as 1 x 4.5 mg:

PFS (3 x 1.5 mg): Vz/F = 14.4 L and Vss/F = 17.6 L
SDP: (1x 4.5 mg): Vz/F = 13.9 L and Vss/F = 16.5 L

In general, Vz/F determined in study GBGM is lower than previously reported for single dosing of 1.5 mg of Dulaglutide (19.5 L; Trulicity EPAR EMA/CHMP/524604/2014).

Elimination

Classical biotransformation studies are not required for Dulaglutide, which is metabolized through proteolytic degradation into its amino acid components. Elimination of intact substance in the urine is not to be expected (cf. Trulicity EPAR: EMA/CHMP/524604/2014).

Half-life, Metabolism and excretion
For the 4.5 mg dose administered in Study GBGM, the half-life was around 3.5 days (see **Table 1**). Since Dulaglutide is a protein, it is metabolized by general protein catabolism pathways, yielding amino acids. Dulaglutide can be cleaved by dipeptidylpeptidase 4 (DPP-4) to yield the truncated GLP-Fc metabolite 9-37GLP-Fc. *In vitro* assays suggest that this metabolite is an agonist, but with 15,000-fold reduced potency as compared to the parent compound Dulaglutide. Thus, the contribution of 9-37GLP-Fc to the pharmacodynamic response can be considered negligible.

Dose proportionality

Population PK models after multiple dosing of 1.5 mg, 3.0 mg and 4.5 mg of dulaglutide

Study GBGJ:

A total of 1116 PK measurements from 236 patients were used for population PK modelling. The following sampling schedule was used to obtain the PK samples in study GBGJ:
In the following, only the sampling schedule related to PK/PD is discussed.

Venous blood samples (~ 4 ml) were drawn to include a range of sampling time windows (pre-dose, 1-24 h post-dose, 24-96 h post-dose and 120-168 h post-dose):

Visit 3, week 0: 1-24 hours post-injection of study drug
Visit 4, week 2: immediately prior to administration of study drug
Visit 5, week 4: 1-24 hours post-injection of study drug
Visit 6, week 6: 5-7 days (120-168 hours) post-injection of Week 5 study drug or just pre-injection of Visit 6 study drug
Visit 10, week 10: 1-4 days (24-96 hours) post-injection of Visit 10 study drug
Visit 12, week 18: at any time during the visit

Samples were isolated from all patients, but only the samples from patients assigned to one of the dulaglutide study arms were analysed for drug concentrations. Where possible, each PK sample was accompanied by an immunogenicity sample in the same visit. **Fig. 2** shows the visual predictive check to validate the PK model for study GBGJ. The calculated values for C_{max} in steady state ($C_{max,ss}$) and for AUC(0-168)ss are listed in **Table 3**.

Figure 2: Comparison of model-predicted *vs.* observed dulaglutide PK concentrations by treatment. Black circles: measured dulaglutide concentrations; blue solid line: median prediction; blue shaded area: 90% prediction interval. "Algorithm 1" and "Algorithm 2" designate two different up-titration protocols for the 3.0 mg and the 4.5 mg dose.

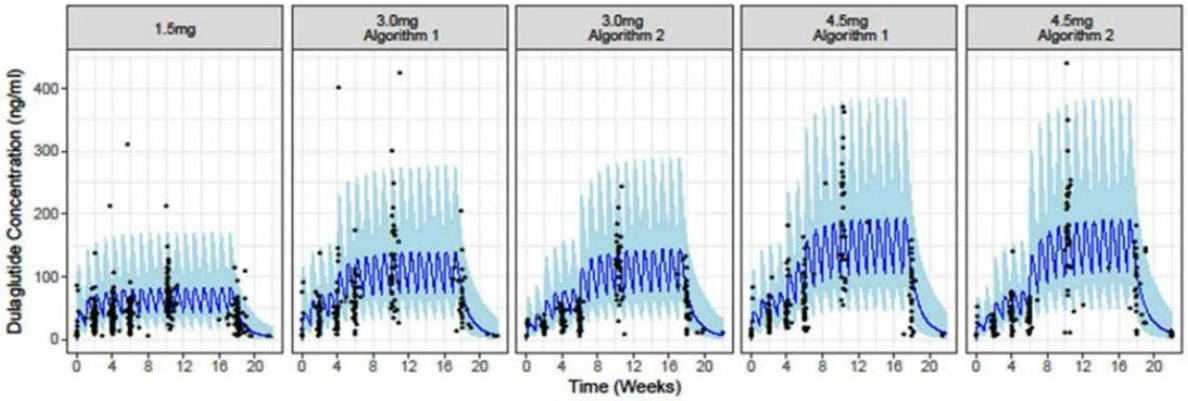


Table 3: C_{max},ss and AUC(0-168)ss for the dulaglutide doses 1.5 mg, 3.0 mg and 4.5 mg

	1.5 mg	**3.0 mg**	**4.5 mg**
c_{max},ss (ng/ml)	90.4	151	204
factor of c_{max},ss increase, related to 1.5 mg	1	1.67	2.26
AUC(0-168)ss (ng · h/ml)	11,800	26,700	36,600
factor of AUC(0-168)ss increase, related to 1.5 mg	1	2.26	3.10

The development of c_{max},ss from the 1.5 mg to 3.0 mg and 4.5 mg dose follows a linear relationship with a proportionality factor of ~0.8. Doubling of the dose from 1.5 mg to 3.0 mg increased c_{max},ss by a factor of ~1.67, which is largely consistent with the factor of 1.8-1.88 derived from the single- and multiple dose-studies reported in the Trulicity EPAR (EMA/CHMP/524604/2014).

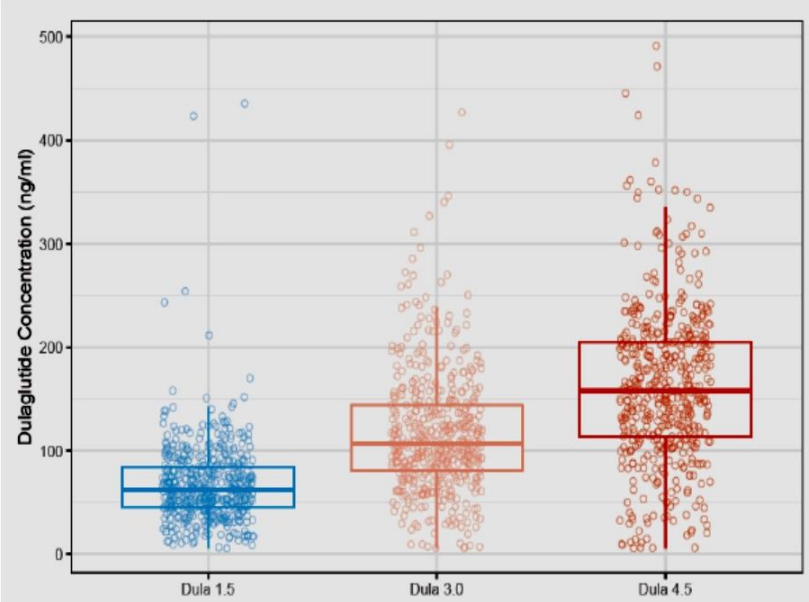
AUC(0-168)ss increases almost proportionally, when the dose is doubled from 1.5 mg to 3.0 mg (factor 2.26) or tripled from 1.5 mg to 4.5 mg (factor 3.10), which is largely consistent with the data previously reported in the Trulicity EPAR (almost proportional increase of AUC(0-∞) by 1.84- to 1.9-fold).

Study GBGL:

A total of 4929 observations from 1843 subjects were used to develop the population PK model. About 96% of these 4929 samples were taken earlier than 350 hours post-dose. More than half of these samples (66%) were taken between 0 and 168 h post-dose, with the majority being collected around 168 h post-dose. One outlier with 1108.7 ng/ml (> 3 x SD) at visit 9 (4.5 mg group) was kept, because no specific reason was identified that would justify exclusion. However, the data point was excluded from the figures.

The observed dulaglutide concentrations at steady state (week 36) demonstrate a clear separation of the 1.5 mg, 3.0 mg and 4.5 mg group as well as a linear increase in plasma concentration with dose (**Fig. 3**). This demonstrates that higher doses are in fact associated with increased exposure.

Figure 3: Boxplot showing observed dulaglutide concentrations at week 36 (visit 9) after s.c. dulaglutide doses of 1.5 mg, 3.0 mg, and 4.5 mg given once weekly.



Base PK model

Since the population PK model developed in study GBGJ (see above) adequately described dulaglutide PK, a structurally similar base model was developed for study GBGL. The model for GBGL did not contain any pre-identified covariates from study GBGJ, but informative priors from model GBGJ were implemented on several PK parameters and on the interindividual variability of several PK parameters.

The population PK model was a two-compartment model, assuming first-order absorption and first-order elimination. The s.c. bioavailability was fixed to the value of 47%, which corresponds to the absolute bioavailability determined for the 1.5 mg dose in study H9X-MC-GBDR. The base model was tested by visual predictive check.

Identification of significant covariates

An effect of the baseline body weight on clearance was identified. The dose seemed to influence bioavailability (F1), but the effect was not meaningful (1.5 mg: F1=0.471; 3.0 mg: F1=0.470 and 4.5 mg: F1=0.469) and therefore excluded from the full model.

Results from the final model

The validity of the model was supported by visual predictive checks (**Fig. 4**). The model revealed that the overall volume of dulaglutide distribution was close to the intravascular blood volume, confirming that dulaglutide does not distribute into the tissue. This is expected, because dulaglutide is a large molecule. A significant effect of baseline body weight on clearance was identified. The other PK parameters were unaffected by baseline BW. The mean AUC(0-168)ss ratio for 70 kg *vs.* 93 kg was 1.25; the corresponding ratio for 120 kg *vs.* 93 kg was 0.808. This indicates that dulaglutide exposure decreases with increasing body weight. This model yielded the steady-state pharmacokinetic results shown in **Table 4**

Figure 4: Visual predictive check of the final population PK model. Circles: observed dulaglutide concentrations; solid red lines: median of the observed concentrations; dotted red lines: 5th and 95th percentiles of the observed concentrations; width of the colored bands: model-simulated 95% confidence intervals of the predicted 5th, 50th, and 95th percentiles

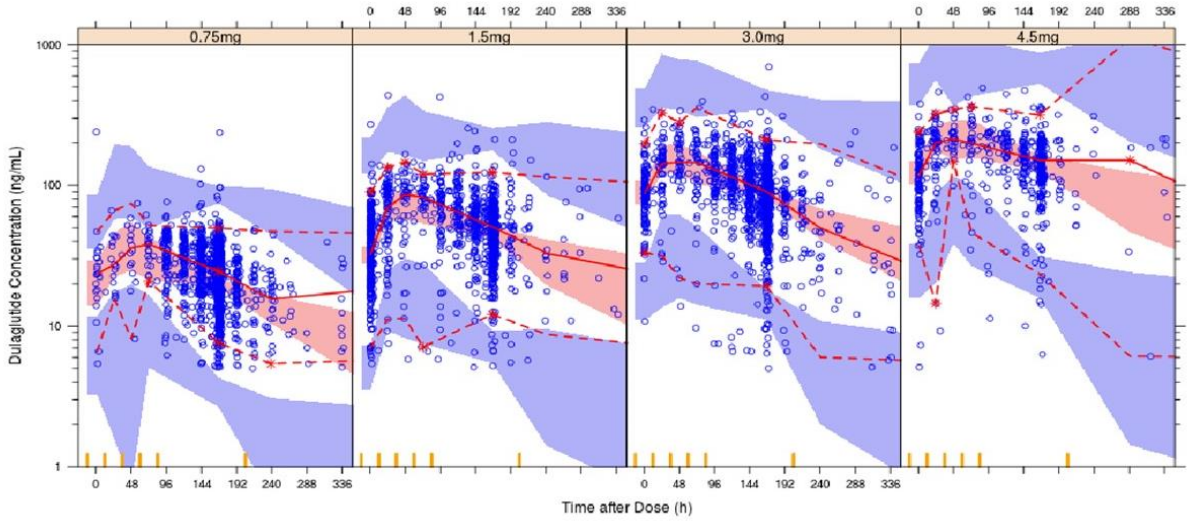


Table 4: C_{max},ss and AUC(0-168)ss for the dulaglutide doses 1.5 mg, 3.0 mg and 4.5 mg

Dose (mg, once weekly)	**1.5 mg**	**3.0 mg**	**4.5 mg**
c_{max},ss (ng/ml) (90% CI)	79.6 (77.7, 81.7)	159 (155, 163)	238 (232, 243)
factor of c_{max},ss increase, related to 1.5 mg	1.00	2.00	2.99
Mean AUC(0-168)ss (ng · h/ml) (90% CI)	11200 (10900, 11500)	22300 (21800, 22900)	33400 (32700, 34200)
factor of AUC(0-168)ss increase, related to 1.5 mg	1.00	1.99	2.98

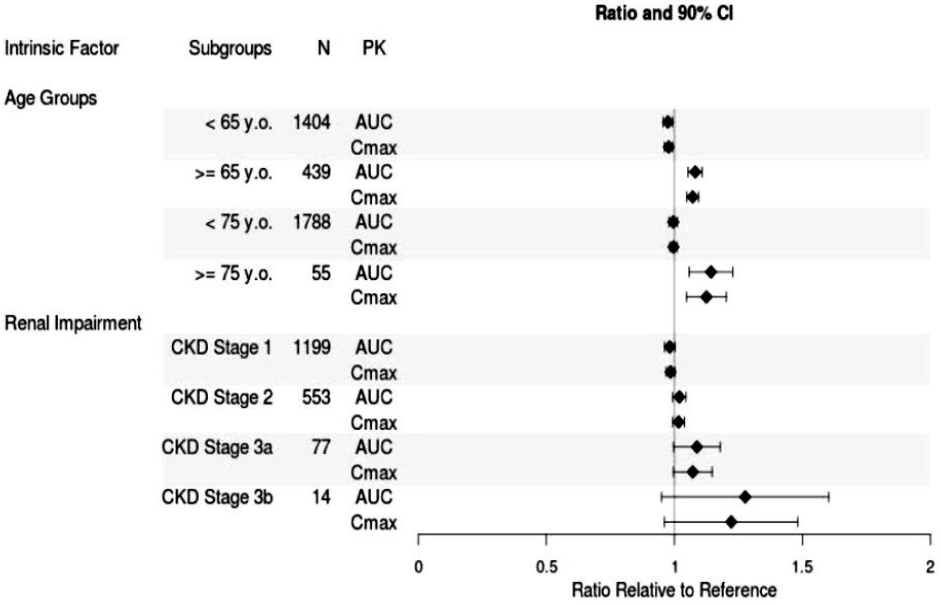
The PK modelling in study GBGL suggests that both AUC(0-168)ss and C_{max},ss develop almost exactly proportional with increasing dose.

Exposure in special populations (pop-PK model from study GBGL)

Age and Impaired renal function

The population mean was predicted using the population PK model detailed above. **Fig. 5** shows the ratios of the predicted post hoc PK exposures in special populations and the predicted population mean.

Figure 5: Forest plot, ratios of predicted *post hoc* PK exposures in study GBGL divided by the mean model predictions at the same dose (AUC: = steady-state $AUC_{0\text{-}168\ h}$)



The CKD stages listed in **Fig. 5** are defined as follows:
Stage 1 = eGFR ≥90 mL/min/1.73 m^2; Stage 2 = 60 mL/min/1.73 m^2 ≤eGFR <90 mL/min/1.73 m^2
Stage 3a = 45 mL/min/1.73 m^2 ≤eGFR <60 mL/min/1.73 m^2; Stage 3b = 30 mL/min/1.73 m^2 ≤eGFR <45 mL/min/1.73 m^2

The mean drug exposure ratios of all special population subgroups shown in **Fig. 5** were between 0.975 and 1.28. The predictions suggest a tendency towards increased dulaglutide exposure with higher age (≥75 years) and more pronounced renal impairment.

Weight
A significant effect of baseline body weight on clearance was observed. **Table 5** shows that $AUC(0\text{-}168)_{ss}$ decreases with increasing body weight.

Table 5: Effect of the body weight covariate on $AUC(0\text{-}168)_{ss}$

Dulaglutide Dose (mg QW)	Mean (5^{th} and 95^{th} Percentile) $AUC(0\text{-}168)_{ss}$ for a 70-kg Patient with T2D (ng.h/mL)	Mean (5^{th} and 95^{th} Percentile) $AUC(0\text{-}168)_{ss}$ for a 93-kg Patient with T2D (ng.h/mL)	Mean (5^{th} and 95^{th} Percentile) $AUC(0\text{-}168)_{ss}$ for a 120-kg Patient with T2D (ng.h/mL)
1.5	13900 (7840, 22300)	11100 (6230, 17800)	8990 (5070, 14400)
3.0	27800 (15700, 44500)	22200 (12500, 35600)	17900 (10100, 28800)
4.5	41700 (23500, 66700)	33300 (18700, 53400)	26900 (15100, 42900)

Abbreviations: $AUC(0\text{-}168)_{ss}$ = simulated steady-state area under the concentration time curve from time 0 to 168 hours; QW = once weekly; T2D = type 2 diabetes.
Values are summarized from simulation of 100 trials, 600 patients per treatment dose and body weight.

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HbA1c efficacy is still preserved and dulaglutide concentrations are still above the EC_{50} required for adequate glycaemic control. There is no significant difference in HbA1c efficacy and overall safety profile between patients with body weight <median or ≥median. Thus, the PK differences between different body weight groups do not translate to clinically relevant differences in efficacy or safety.

Prediction of PK interactions due to dulaglutide-induced delay in gastric emptying

As a GLP-1 receptor agonist, dulaglutide delays gastric emptying and intestinal transit time. This may result in delayed oral absorption of concomitantly administered drugs. Dulaglutide-mediated changes in gastric emptying were simulated in a Pop-PK model (for detailed discussion, please see below), basing on data from the phase 1 studies H9X-MC-GBCH and H9X-MC-GBCD. In this Pop-PK simulation, the effect of the single dulaglutide doses 1 mg, 1.5 mg and 4.5 mg on gastric emptying was estimated based on corresponding changes in acetaminophen pharmacokinetics. Since orally administered acetaminophen is poorly absorbed by the stomach and is instead rapidly absorbed from the small intestine, the rate of appearance of acetaminophen in the circulation reflects the rate of gastric emptying.

The changes in gastric mean residence times for the 1 mg, 1.5 mg and 4.5 mg dose from the pop-PK model were then used in a physiologically-based pharmacokinetic (PBPK) model. The PBPK model was employed to predict the effect of a single dose of 4.5 mg dulaglutide on C_{max}, t_{max} and AUC of various orally administered medications (acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, S-warfarin, ethinylestradiol, and norgestimate/norelgestromin).

In the following, the pop-PK model with Acetaminophen and the final PBPK model are discussed separately.

Pop-PK analysis: Dulaglutide effect on gastric emptying based on the PK of acetaminophen

Datasets used for model development evaluation:
The results of the previously performed studies H9X-MC-GBCD and H9X-MC-GBCH were used to evaluate the model.

Study H9X-MC-GBCD (5 weeks duration) comprised 43 T2DM patients, and the dulaglutide doses 0.05 mg, 0.3 mg, 1,0 mg, 3.0 mg, 5.0 mg and 8.0 mg were administered s.c. on days 1, 8, 15, 22 and 29. Acetaminophen (490 mg) was administered orally on days -1 and 3. PK samples for acetaminophen were drawn on days -1 and 3 (pre-dose, 0.5, 0.75, 1, 2, 3, 4, 6, 9 and 12 hours post-dose). PK samples for dulaglutide were collected on day 1 (pre-dose, 12, 24, 48 and 72 hours post-dose), on days 8, 15, and 22 (only pre-dose) and on day 29 (pre-dose, 24, 48, 72, 144, 168, 264 and 336 hours post-dose).

Study H9X-MC-GBCH (4 weeks duration) comprised 30 healthy subjects. Dulaglutide was administered at the 1 mg and 3 mg dose level on days 1, 8, 15 and 22. Acetaminophen was administered orally on days -1, 3, 24, and 36 with breakfast.

The population PK analysis included 762 observed plasma dulaglutide concentrations from 62 subjects and 1353 observed acetaminophen concentrations from 73 subjects.

PK models for dulaglutide and acetaminophen

Dulaglutide PK model: A model for dulaglutide population PK was previously published as the result of a pop-PK analysis of dulaglutide conducted for phase 2 and 3 studies in T2DM patients [Geiser et al., *Clin Pharmacokinet*. 2016;**55**:625-634]. This model was used to describe the dulaglutide data from the studies GBCD and GBCH. The dulaglutide PK model was linked to the acetaminophen PK model (see

below) through a nonlinear inhibitory effect of dulaglutide concentrations on the gastric emptying rate constant from the stomach to small intestine.

Acetaminophen PK model: The model structure from a previously published [Alskär et al. *J Clin Pharmacol.* (2016) **56**:340-348] semi-mechanistic gastric emptying acetaminophen model was used to describe the acetaminophen concentrations from studies GBCD and GBCH. It is noted that the estimate for k_{GE} (gastric emptying rate at baseline in study GBCD) showed a high inter-individual variability (IIV) of 70.2%, which is, however, similar to the 50% IIV previously published by Alskär et al. (2016) [*J Clin Pharmacol*. (2016) **56**:340-348].

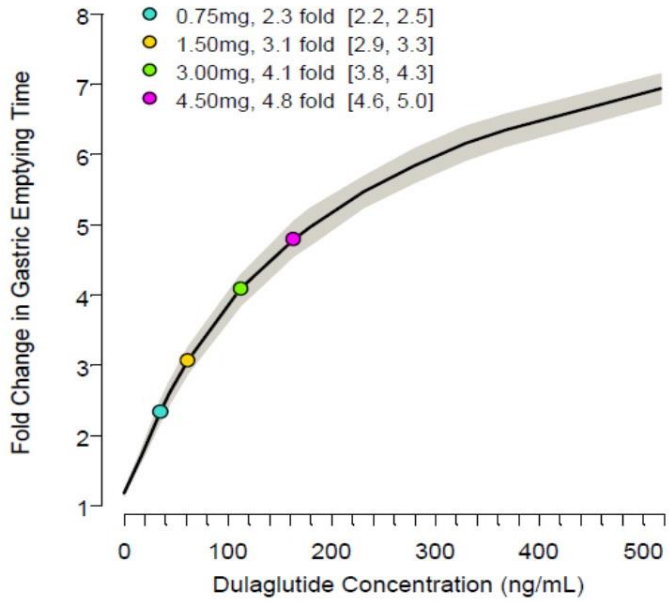
The dulaglutide PK model linked to the semi-mechanistic gastric emptying acetaminophen PK model was evaluated by comparing observed and predicted results from studies GBCD and GBCH. The visual predictive checks for study GBCD and GBCH demonstrated that the model accurately described the development of plasma dulaglutide and acetaminophen concentrations in these studies.

Application of the results

Using the dulaglutide PK model linked to the GE acetaminophen PK model, the fraction of acetaminophen dose remaining in the stomach over time for a range of dulaglutide doses was simulated and a half-life for the gastric acetaminophen dose remnant (GE half-life, GT_{50}) was calculated. Acetaminophen GE half-life in patients with T2DM was calculated to be 11.9 min at baseline and 57.2 min with co-administration of 4.5 mg of dulaglutide. The predictions indicate a clear difference in the baseline GT_{50} between healthy subjects (study GBCH) and patients with T2DM (study GBCD).

However, the fold change (GE time ratio) of acetaminophen co-administered with dulaglutide *vs.* acetaminophen alone (baseline) was similar between healthy subjects and T2DM patients. This ratio term (delayed GE with co-administered dulaglutide/GE prior to dulaglutide exposure) can be used to translate population PK modeling results into the effect of dulaglutide on GE. Thus, the ratio term can be incorporated into a PBPK model that predicts the effect of delayed gastric emptying on the exposure of various orally co-administered drugs for a 4.5 mg dose of dulaglutide. **Fig. 6** shows the model-predicted fold change in gastric emptying time for various dulaglutide doses.

Figure 6: Model-predicted relationship between dulaglutide concentration and fold change in gastric emptying time for acetaminophen in patients with T2D.



PBPK gastric emptying model

The changes in gastric mean residence times for the 1 mg, 1.5 mg and 4.5 mg dose from the pop-PK model (see **Fig. 6**) were then used in a physiologically-based pharmacokinetic (PBPK) model. The PBPK model was employed to predict the effect of a single dose of 4.5 mg dulaglutide on C_{max}, t_{max} and AUC of various orally administered medications (acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, S-warfarin, ethinylestradiol, and norgestimate/norelgestromin).

First, a PBPK model for acetaminophen was developed with the software Simcyp® based on a model described in the literature. This model was modified including a mechanistic absorption model in order to be able to describe the influence of dulaglutide-induced delay in gastric emptying (GED) on the PK of acetaminophen. There are several assumptions underlying the PBPK modelling analyses. The GED ratios applied to the gastric mean residence time in Simcyp® assumed that the fold change was the same between healthy subjects and T2DM patients. Different gastric emptying times were applied for fasted and fed state but it was assumed that the effect of delaying gastric emptying was the same between fasted and fed states. These assumptions was justified by the Applicant .Moreover, observed and predicted concentrations of acetaminophen with and without dulaglutide indicate that high acetaminophen C_{max} values are not well captured by the model. The newly provided pcVPC depicted according to Bergstrand et al (2011) showed that overall, PBPK model performance can be acceptable.

Further, PBPK models for the different potentially comedicated drugs were developed. Existing Simcyp® verified models for digoxin, metformin, metoprolol, S-warfarin, and ethinylestradiol were modified to include a mechanistic absorption model. The PBPK model for metoprolol extended release (Toprol-XL) was built based on the SV-Metoprolol (IR) model built and verified by Simcyp®.

For the other drugs (atorvastatin, lisinopril, sitagliptin and norgestimate/norelgestromin), PBPK models were developed according to literature or were built in based on available data.

Prior observations have indicated that the effect of dulaglutide on acetaminophen t_{max} and C_{max} is highest after the first dose and diminished in steady state after multiple dosing. Therefore, it was assumed that the simulations basing on single-dose data are appropriate for assessing the maximum dulaglutide effect on gastric emptying.

Model validation

The PBPK modeling approach was verified with data from previous drug-drug interaction (DDI) trials with 1 mg of dulaglutide (acetaminophen) and with 1.5 mg of dulaglutide (atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, S-warfarin, ethinylestradiol, and norgestimate/norelgestromin). The baseline metformin PK data from the metformin DDI study (study GBDM) could not be used for verification, because study GBDM did not collect accurate information on the doses of metformin administered. However, the change in metformin exposure before and after dulaglutide dosing was used for verification. Moreover, literature results were used for verification of the PBPK modeling with metformin.

Most of the predicted C_{max} and AUC values before and after administration of dulaglutide were between 80 and 125% of the observed results. The dulaglutide-induced changes in C_{max} and AUC were all predicted by the models in a range between 74 and 100%. The dulaglutide-induced change in t_{max} was under-predicted by >1 hour for atorvastatin, o-hydroxyatorvastatin and metoprolol, while Δt_{max} was over-predicted by 1.81 hours for metformin under fed conditions.

In the responses, additional information supporting model qualification was provided, including justification for the use of the baseline gastric mean residence times in the fed and the fasted state and in healthy volunteers and patients. Additional information on the ability of the model to predict gastric emptying delay of other GLP-1 RA are given. It was clarified that data were available for higher doses of dulaglutide up to 8 mg, thus no extrapolation was needed for the 4.5 mg dose.

Accuracy of prediction of different doses, single and multiple doses and data in the fed and fasted state were provided for the marker substances.

PK changes of co-administered drugs in patients with plasma dulaglutide levels at the upper 5% end of the observed range were given and did not show significant changes for most compounds. For atorvastatin, AUC and Cmax were considerably decreased with delayed gastric emptying, in contrast to behaviour of the other compounds.

And a pcVPC was provided for the acetaminophen data which showed acceptable fit.

Thus, overall with the provided information, the PBPK model is considered acceptable.

Results after application of the PBPK model to predict the effect of 4.5 mg of Dulaglutide

The validated models were used to predict the effect of a single 4.5 mg dose of dulaglutide on the PK of concomitantly administered medications. The corresponding delay of gastric mean residence time was taken from the Pop-PK model developed with acetaminophen (see below, "*in vivo*" section).

For nearly all tested compounds, the predicted AUC ratios of most drugs with and without 4.5 mg dulaglutide were in the range between 0.82 and 1.0 (see **Table 6**). Only metoprolol exhibited an AUC ratio of 1.35 (**Table 6**).

Table 6: Geometric mean C_{max} and AUC ratios (with and without 4.5 mg of dulaglutide) and 90% CI for various drugs co-administered with dulaglutide

Drug	Geometric Mean AUC Ratio (90% CI)[a]	Geometric Mean C_{max} Ratio (90% CI)[a]
Acetaminophen	0.93 (0.86, 1.00)[b]	0.53 (0.50, 0.57)
Digoxin	0.98 (0.93, 1.03)[b]	0.66 (0.64, 0.69)
Lisinopril	0.99 (0.92, 1.06)[b]	0.96 (0.90, 1.03)
Metformin	1.00 (0.94, 1.07)[b]	0.88 (0.83, 0.93)
Metoprolol	1.35 (1.17, 1.55)[b]	1.39 (1.23, 1.57)
Sitagliptin	1.00 (0.95, 1.05)[b]	0.87 (0.83, 0.90)
S-Warfarin	1.00 (0.85, 1.17)[c]	0.78 (0.74, 0.82)
Atorvastatin[d]	0.82 (0.79, 0.85)[c]	0.22 (0.20, 0.24)
Ethinylestradiol	1.00 (0.91, 1.09)[c]	0.56 (0.48, 0.66)
Norelgestromin[e]	0.97 (0.85, 1.11)[c]	0.49 (0.46, 0.53)

Abbreviations: AUC = area under the concentration time curve, CI = confidence interval, C_{max} = maximum concentration.

[a] Ratio calculations are shown in file: Ratios.xlsx.

[b] AUC from time zero to 24-hours.

[c] AUC from time zero to infinity.

[d] Total atorvastatin-related active species.

[e] Metabolite of norgestimate used as clinic marker for efficacy due to rapid conversion of norgestimate.

2.4.3. Pharmacodynamics

PK/PD simulations in studies GBGJ and GBGL

In both studies, GBGJ and GBGL, exposure-response (PK/PD) evaluations were performed for fasting glucose/HbA1c, weight change as well as for adverse events (nausea/vomiting, baseline heart rate/PR interval/QTcF, dulaglutide antibodies).

Primary pharmacology

HbA1c and fasting glucose

No patient factors were retained as covariates in the HbA1c PK/PD model in study GBGJ and GBGL. The PK/PD model for fasting glucose did not identify any covariate in study GBGJ. However, in study GBGL, baseline fasting glucose was associated with increased dulaglutide EC_{50} plasma concentrations. This was considered not to be of clinical concern, because the dulaglutide concentrations after administration of 1.5 mg, 3.0 mg or 4.5 mg are generally expected to remain above the EC_{50} value.

Weight change

The PK/PD model for weight change was the same for study GBGJ and GBGL. Sex was included as covariate to enable differentiation of baseline weight between male and female patients (~10 kg difference). In study GBGJ, a dose-dependent increase in body weight reduction from a common body weight of 92 kg was predicted, confirming a potential additional benefit for the 3.0 mg and the 4.5 mg dose. In study GBGL, body weight reduction was in general more pronounced than in study GBGJ, which is most likely due to the longer duration of study GBGL.

Secondary pharmacology

Nausea and vomiting

Female patients had a higher probability of developing nausea and/or vomiting as compared to male patients. In study GBGJ, a half-life of 5.03 weeks was predicted for maximum tolerance to develop. Based on these results, an up-titration scheme was implemented in the pivotal phase 3 study GBGL.

The PK/PD modelling in study GBGL estimated a "half-life" of 6.2 weeks (43.2 days) for the development of tolerance to nausea. This confirmed the findings from study GBGJ and further justified the up-titration approach in study GBGL. In study GBGL, the model predictions for vomiting were higher than the observed data, probably due to the small number of vomiting events as well as higher variability and lack of consistency of the observed data during the initial 8 weeks. Body weight <93 kg or ≥93 kg was identified as additional covariate in study GBGL and was kept for the final model (higher incidence of nausea and vomiting in patients with lower body weight).

Heart rate, QTcF interval and PR interval
In both studies (GBGJ and GBGL), increased dulaglutide plasma concentrations were significantly correlated with an increased heart rate (ECG and pulse). The variability of changes from baseline HR measurements was considerable, but comparable in dulaglutide *vs.* placebo-treated patients.

In study GBGJ, the model-predicted increase in heart rate for the mean $C_{max,ss}$ of 205 ng/ml (to be expected with the 4.5 mg dose) was more than twice as high as the increase previously predicted for the 1.5 mg dose (2.6 bpm; reported in the EPAR, based on data from phase 3 trials and from study H9X-MC-GBDN). The reduction of QTc interval predicted for the mean $C_{max,ss}$ of 205 ng/ml (to be expected for the 4.5 mg dose) confirmed the observations of study H9X-MC-GBCC (reported in the EPAR), where a dose of 4 mg was administered.

In study GBGL the heart rate increased during the first 18 weeks, followed by a decline until week 36. The dulaglutide plasma concentration correlated with QTcF interval shortening and PR interval prolongation, but only the correlation with PR interval prolongation reached significance in study GBGJ and GBGL ($p<0.05$).

Pancreatic enzymes
In study GBGJ, a significant positive correlation of dulaglutide plasma concentrations with pancreatic amylase and lipase was identified. This initial increase in pancreatic amylase and lipase was followed by a gradual reduction over time, but values did not completely return to baseline at the last measurement in week 22. By contrast, in study GBGL, the correlation was positive for p-amylase and negative for lipase but did not reach statistical significance for any of the parameters. This difference between study GBGJ and GBGL might be due to the different up-titration schemes (faster up-titration in study GBGJ as compared to GBGL). For a detailed discussion on the effect of up-titration on the occurrence of adverse events, please see safety section.

Anti-drug antibodies
Neither in study GBGJ nor in study GBGL, was a visually evident pattern observed that could be used to establish a relationship between dulaglutide plasma concentration and anti-drug antibodies.

2.4.4. Discussion on clinical pharmacology

Phase 1 study GBGM:
The phase 1 clinical study GBGM was conducted to bridge the different ways of dulaglutide administration used in trials GBGJ and GBGL (3 x 1.5 mg with pre-filled syringe in study GBGJ, but 1 x 4.5 mg with single-dose pen in study GBGL). Study GBGM demonstrated that these two ways of administration are

bioequivalent with regard to AUC. With reference to C_{max}, the upper limit of the 90% CI for the SDP/PFS ratio reached 1.30, which slightly exceeds the conventional bioequivalence range of 0.8 - 1.25. The higher C_{max} may be responsible for the more frequent occurrence of vomiting after SDP as compared to PFS administration in study GBGM. However, in clinical reality, a slow up-titration is performed until the maximum dose of 4.5 mg is reached, which minimizes such adverse events. C_{max} was the first point of the PK curve in a considerable proportion of subjects of the PFS (20.8%) and SDP (30.4%) group. However, since the dulaglutide PK profile is very flat between day 1 and day 3, it is expected that there is only a minor contribution of C_{max} to the calculation of overall AUC.

Thus, the two ways of administration compared in study GBGM can be considered bioequivalent, and the results of the phase 2 GBGJ study are able to support the findings of study GBGL.

Studies GBGJ (phase 2) and GBGL (pivotal phase 3):

Pharmacokinetics

According to EPAR EMA/CHMP/524604/2014, the absolute bioavailability (F1) is dose-dependent (F1=44-47% for the 1.5 mg dose and F1=65% for the 0.75 mg dose). By contrast, during development of the final population PK model for study GBGL, the influence of dose on F1 was considered negligible (F1 for 1.5 mg, 3.0 mg and 4.5 mg was 0.471, 0.470 and 0.469, respectively). This suggests that the dose-dependent decrease in bioavailability (F1) reaches a plateau, when the dose exceeds 1.5 mg.

The pop-PK model developed in study GBGL was used to predict changes in exposure in special populations, specifically in older patients and in patients with impaired kidney function. The ratios of the predicted *post hoc* PK exposures in the aforementioned special populations and the predicted population mean reveal a slight effect of higher age (≥75 years) and moderate renal impairment (stage 3b; 30 mL/min/1.73 m^2 ≤ eGFR <45 mL/min/1.73 m^2) on dulaglutide exposure. Due to the limited effect range (0.975 - 1.28), the applicant does not recommend dose adjustments. However, it is unclear, how dulaglutide exposure is affected by very high age, i.e. in patients ≥85 years, as this subgroup was not addressed in the applicant's analysis. Study GBGL included only one patient aged 85 years at baseline, who was randomized to the 3.0 mg dose. As emphasized by the applicant in the response to this issue, only study GBDJ (REWIND, not part of this application) included a considerable number (n=43) of patients aged ≥85 years. However, the REWIND study did not address the 3.0 mg and 4.5 mg dose. Thus, the data is not considered sufficient to exclude a clinically relevant influence of an age ≥85 years on dulaglutide exposure after administration of the high 3.0 and 4.5 mg dose.

The applicant has additionally presented a comparison of observed dulaglutide concentrations and population pharmacokinetics (PK) model-predicted concentrations for the oldest group of patients (aged ≥75 years) throughout the entire course of study GBGL and for each treatment arm. The data confirm that the majority of observed PK concentrations in patients aged ≥75 years are within the 90% PK prediction intervals. Thus, dose adjustment in patients aged ≥75 years is not considered necessary.

With regard to kidney disease, the effect of stage 3b impaired kidney function on dulaglutide exposure is difficult to assess, as the number of patients was very low and consequently, the 90% CI is spanning a wide range from <1.0 to >1.5. However, the mean fold change in exposure from the reference patient across all eGFR categories was within the expected inter-individual dulaglutide PK variability (from 7.69% to 73.0%), suggesting that a potential influence of renal impairment on dulaglutide exposure may not become clinically relevant. Moreover, the subset of CKD stage 3b patients in study GBGL was very small (n=14) and about half of these patients were on the 1.5-mg dose, where no effect of kidney function on dulaglutide exposure is expected. In fact, after combining the stage 3b patients with the larger group of Stage 3a CKD patients from study GBGL, the mean fold change from the reference patient in C_{max} and AUC for the collective group with moderate renal impairment is about the same as observed in the original submission for the 1.5-mg dose across the range of renal impairment.

No patients with stage 4 kidney disease (eGFR of 15 - 30 mL/min/1.73 m^2) were analysed in study GBGL. This population is specifically important as Trulicity is explicitly indicated, when metformin cannot be used, which includes patients with stage 4 renal impairment. Although patients with severe kidney disease and end-stage renal disease have been included in studies GBCM, GBDX and GBDJ (submitted with the original MA application), these studies did not investigate the 3.0 mg and the 4.5 mg dose of dulaglutide. Nevertheless, the applicant presented an analysis, showing that PK in patients with T2DM and Stage 3 or 4 CKD, who received 0.75 mg or 1.5 mg of dulaglutide in study GBDX, ranges within the PK exposure range derived from the general phase 3 T2D patient population from studies GBCF, GBDA and GBDC with less renally impaired patients. It might be assumed that a clinically relevant impact of renal impairment on dulaglutide PK and exposure would have become visible at doses ≤1.5 mg. Although the validity of extrapolating these findings to the 3.0 and 4.5 mg dose strengths may be regarded as somewhat controversial, it is considered unlikely that in renally impaired patients any excess exposure will occur. Based on theoretical considerations, an impact of renal impairment on dulaglutide exposure is not to be expected, because dulaglutide is metabolically degraded into its amino acid components rather than being excreted via the kidneys.

Another subpopulation that was considered in the population PK model of study GBGL, was the group of patients with higher body weight. $AUC(0\text{-}168)_{ss}$ decreases with increasing body weight. In comparison to the $AUC(0\text{-}168)_{ss}$ in a 70 kg-patient, the $AUC(0\text{-}168)_{ss}$ decreases by ~20% and ~35% for persons with 93 kg and 120 kg, respectively. This relationship is similar for all three dulaglutide doses and confirms older findings reported in the initial Trulicity EPAR (EMA/CHMP/524604/2014). The applicant considers dose adjustment because of weight unnecessary, which is acceptable.

Pharmacokinetics/Pharmacodynamics

The PK/PD simulations for study GBGJ and GBGL yield largely consistent results. Regarding HbA1c and fasting glucose, no patient factors were retained as covariates in the HbA1c PK/PD model in study GBGJ and GBGL. In case of fasting glucose, in study GBGL, baseline fasting glucose was associated with increased dulaglutide EC_{50} plasma concentrations. However, this was not considered to be of clinical concern, because the dulaglutide concentrations after administration of 1.5 mg, 3.0 mg or 4.5 mg are generally expected to remain above the EC_{50} value.

The PK/PD model for weight change was the same for study GBGJ and GBGL. Sex was included as covariate to consider the differences in baseline body weight between male and female patients. In study GBGL, body weight reduction was in general more pronounced than in study GBGJ, which is most likely due to the longer duration of study GBGL.

Female patients had a higher probability of developing nausea and/or vomiting as compared to male patients. In study GBGJ, a half-life of 5.03 weeks was predicted for maximum tolerance to develop, which was largely confirmed in study GBGL (6.2 weeks). Based on the results from study GBGJ, an up-titration scheme was implemented in the pivotal phase 3 study GBGL. Body weight <93 kg or ≥93 kg was identified as an additional covariate in study GBGL and was kept for the final model. The incidence of nausea and vomiting was higher in patients with lower body weight, probably due to increased dulaglutide exposure.

In both studies (GBGJ and GBGL), increased dulaglutide plasma concentrations were significantly correlated with an increased heart rate (ECG and pulse). In study GBGJ, the model-predicted increase in heart rate for the mean $C_{max,ss}$ of 205 ng/ml (to be expected with the 4.5 mg dose) was more than twice as high as the increase previously predicted for the 1.5 mg dose (2.6 bpm; reported in the initial EPAR EMA/CHMP/524604/2014). In study GBGL the heart rate increased during the first 18 weeks, followed by a decline until week 36, which indicates development of some tolerance with regard to the effect on heart rate.

The dulaglutide plasma concentrations also correlated with QTcF interval shortening and PR interval prolongation, but only the correlation with PR interval prolongation reached significance in study GBGJ and GBGL ($p<0.05$). It is unclear, whether these cardiovascular effects have long-term consequences on cardiovascular events, as no data from cardiovascular outcome trials with the 3.0 mg and 4.5 mg dose of dulaglutide are available. However, the effects of dulaglutide on heart rate (increase) and PR interval (prolongation) were small so that a relevant increase in CV risk is unlikely. Further reassurance regarding CV safety can be derived from the clinical experience with the substance class.

In study GBGJ, a significant positive correlation of dulaglutide plasma concentrations with pancreatic amylase and lipase was identified. This initial increase in pancreatic amylase and lipase was followed by a gradual reduction over time, but values did not completely return to baseline at the last measurement in week 22. By contrast, in study GBGL, the correlation was positive for p-amylase and negative for lipase but did not reach statistical significance. Possibly, this difference between study GBGJ and GBGL might be due to the different up-titration schemes (faster up-titration in study GBGJ as compared to GBGL).

Interactions of higher dulaglutide doses with concomitantly administered oral medications

The most important mechanism for pharmacokinetic interactions with dulaglutide is the delaying effect of dulaglutide on gastric emptying and small intestinal transit time. The delay in gastric emptying expected for the 4.5 mg dose was calculated by the applicant with data from older studies (GBCD and GBCH), where acetaminophen was concomitantly administered with dulaglutide, and the plasma concentration-time profiles of both substances were determined. For dulaglutide as well as for acetaminophen, pop-PK models were developed based on models previously reported in the literature. Both pop-PK models were linked to predict the influence of various dulaglutide doses on the delay of gastric emptying. This method is acceptable, because acetaminophen shows a PK profile that is largely dependent on gastric emptying and is therefore suitable as a model substance.

After having calculated the expected delay in gastric emptying with the aforementioned acetaminophen model, the applicant has generated a PBPK model to predict dulaglutide-induced changes in PK parameters of selected orally administered drugs. There are several assumptions underlying the PBPK modelling analyses. The GED ratios applied to the gastric mean residence time in Simcyp® assumed that the fold change was the same between healthy subjects and T2DM patients. Different gastric emptying times were applied for fasted and fed state, but it was assumed that the fold-change in gastric emptying was the same between fasted and fed states. As shown in **Fig. 3**, the dulaglutide plasma concentrations after a dose of 4.5 mg show high variability. Specifically, in the few patients that reach very high dulaglutide concentrations, gastric emptying may be delayed by >6-fold, which may result in clinically relevant PK changes of co-administered drugs. Upon request by the CHMP, the applicant reported PK changes assuming a 5.55-fold change in gastric mean residence time. These scenarios were considered unlikely by the Applicant as they were simulated under the assumption of steady state concentrations after 4.5 mg dosing. Treatment will be initiated with lower doses and since effect on gastric emptying is expected to be highest after the first dose and will be attenuated with following doses, the values are likely to have over-estimated the effect of dulaglutide on the exposures of concomitant oral medications. The resulting gastric mean residence time was 6.55 h for the fed state and 1.50 h for the fasted state. This change corresponded to the 95th percentile of the steady-state maximum plasma concentration (C_{max}) of dulaglutide at 243 ng/mL. Predicted changes in PK parameters were provided and did not show significant changes for most compounds. There was an increase in AUC and C_{max} with delayed gastric emptying for metoprolol, which was probably due to the extended release formulation used in this case. For atorvastatin, however, AUC and C_{max} were considerably decreased with delayed gastric emptying, in contrast to the behavior of the other compounds. The strong reduction in atorvastatin C_{max} can be explained by increased conversion of atorvastatin carboxylic acid to its inactive lactone form in the stomach during the prolonged gastric residence time. However, the AUC is less affected than C_{max},

because the lactone form is partially back-converted to the active acid form after absorption. Moreover, if the active metabolite o-hydroxyatorvastatin is additionally considered, the reduction of AUC by dulaglutide is far less pronounced and therefore not considered clinically relevant.

Intestinal transit time was only included in the model for delayed-release metoprolol, but not in the models for the other substances. It can be assumed that PK of delayed-release metoprolol is specifically susceptible to changes in intestinal transit time. Thus, the metoprolol model was adjusted to predict correctly the effect of a given retardation of intestinal transit, which was caused by 1.5 mg dulaglutide. However, it remains uncertain how valid the resulting predictions are. It was not tested whether the model also allows correct prediction for other substances with slow release or poor solubility or other doses of dulaglutide.

Modelling of intestinal absorption appears challenging since it is dependent on many factors (not only transit time) which are difficult to access without invasive methods. It has to be assumed that a given prolongation in transit time affects different drugs in a different way, depending on factors such as absorption rate through the intestinal mucosa and site of absorption within the gut. With this complexity, it is not clear whether existing data (e.g. the degree of prolonging the transit time by liraglutide) are sufficient to inform the model for reliable results. Thus, it is questionable whether the effect of 4.5 mg dulaglutide was predicted correctly and whether the model calculations for metoprolol are representative for other drugs with delayed release or with low solubility/permeability.

It is further noted that gastric emptying delay seems to disappear within 36 days in study GBCH (acetaminophen model), but the prevalence of nausea and vomiting with the 3.0 mg and the 4.5 mg dose in study GBGL does not completely return to baseline and constantly remains higher than with the 1.5 mg dose. Thus, factors other than delayed gastric emptying, e.g. a delay in intestinal transit time, may contribute to these adverse events. Therefore, it cannot be concluded that potential PK interactions resolve within the same period as the interactions caused by delayed gastric emptying.

Both, over- and under-predictions of C_{max} occurred with the applicant's PBPK models. In case of acetaminophen, which had been used to estimate the dulaglutide-induced delay in gastric emptying, a comparison of the observed and predicted concentrations with and without dulaglutide indicates that the model did not well capture the high C_{max} values. Nevertheless, prediction corrected VPCs show that the ability of the PBPK model to describe central tendency and variability of the data is acceptable.

For some of the substances modelled with the applicant's PBPK model, the predicted influence of 4.5 mg dulaglutide is considerably higher than the interactions reported in the current version of the SmPC. For example, for digoxin, the SmPC states that C_{max} is decreased by dulaglutide by up to 22%, but the new predictions for the 4.5 mg dulaglutide dose yield a decrease by 34%. Similarly, the SmPC mentions a reduction of C_{max} of co-administered norelgestromine end ethinylestradiol by -26% and -13%, respectively, while the PBPK model predicts -51% (norelgestromin) and -44% (ethinylestradiol). In case of metoprolol, the SmPC mentions a dulaglutide-induced increase in AUC by 19%, but the predicted increase in AUC for the 4.5 mg dose is 35%.

In summary, interactions between the higher strengths of dulaglutide and several concomitantly administered oral drugs were only predicted based on PBPK modeling, but no clinical drug-drug interaction study was performed. This is sufficiently addressed in section 4.5 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The study GBGM has successfully bridged the two methods of dulaglutide administration in study GBGJ (3x1.5 mg in pre-filled syringe) and GBGL (1x4.5 mg in single-dose pen). Both ways of administration can be considered bioequivalent.

The pop-PK simulations in study GBGJ and GBGL suggest that bioequivalence of dulaglutide is not altered for 3.0 mg and 4.0 mg as compared to the 1.5 mg dose, although a reduction in bioequivalence had been previously reported, when the dose was increased from 0.75 mg to 1.5 mg. An almost proportional increase of AUC and C_{max} was found for increasing doses of dulaglutide.

The pop-PK model in study GBGL suggested increased dulaglutide exposure in patients aged ≥ 75 years and in patients with stage 3B chronic kidney disease. Moreover, the model predicted an inverse relationship between body weight and dulaglutide. As discussed in the preceding section, no dose adjustments for very high age and severe kidney disease are currently recommended.

The PK/PD simulations for study GBGJ and GBGL yielded largely consistent results. In study GBGL, baseline fasting glucose was associated with increased dulaglutide EC_{50} plasma concentrations, but clinical relevance is limited, as the dulaglutide plasma concentrations after administration of 1.5 mg, 3.0 mg or 4.5 mg are generally expected to remain above the EC_{50} value.

Female patients had a higher probability of developing nausea and/or vomiting as compared to male patients. The incidence of nausea and vomiting was higher in patients with lower body weight, probably due to increased dulaglutide exposure. In both studies (GBGJ and GBGL), increased dulaglutide plasma concentrations were significantly correlated with an increased heart rate. This effect declined in study GBGL after week 18. The dulaglutide plasma concentrations were also correlated with QTcF interval shortening and PR interval prolongation, but only the correlation with PR interval prolongation reached significance. It is currently unclear, whether long-term consequences on cardiovascular health may occur with the 3.0 mg and the 4.5 mg dose of dulaglutide. However, the effects of dulaglutide on heart rate (increase) and PR interval (prolongation) were small so that a relevant increase in CV risk is unlikely. Further reassurance regarding CV safety can be derived from the clinical experience with the substance class. The correlation of dulaglutide plasma concentrations with pancreatic amylase and lipase was inconsistent between study GBGJ and GBGL. This may be partially due to different up-titration schemes.

Based on previous data with the model drug acetaminophen, the applicant has developed a PKPB model to predict the interaction of 4.5 mg of dulaglutide with the PK of selected oral drugs. The predicted changes in AUC and/or C_{max} were considered clinically irrelevant.

2.5. Clinical efficacy

A tabulated overview of clinical studies contributing to the current application for the addition of the two new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg s.c. once weekly) are provided above in section 2.4.1 of this report.

2.5.1. Dose response study

Methods

Title of Study

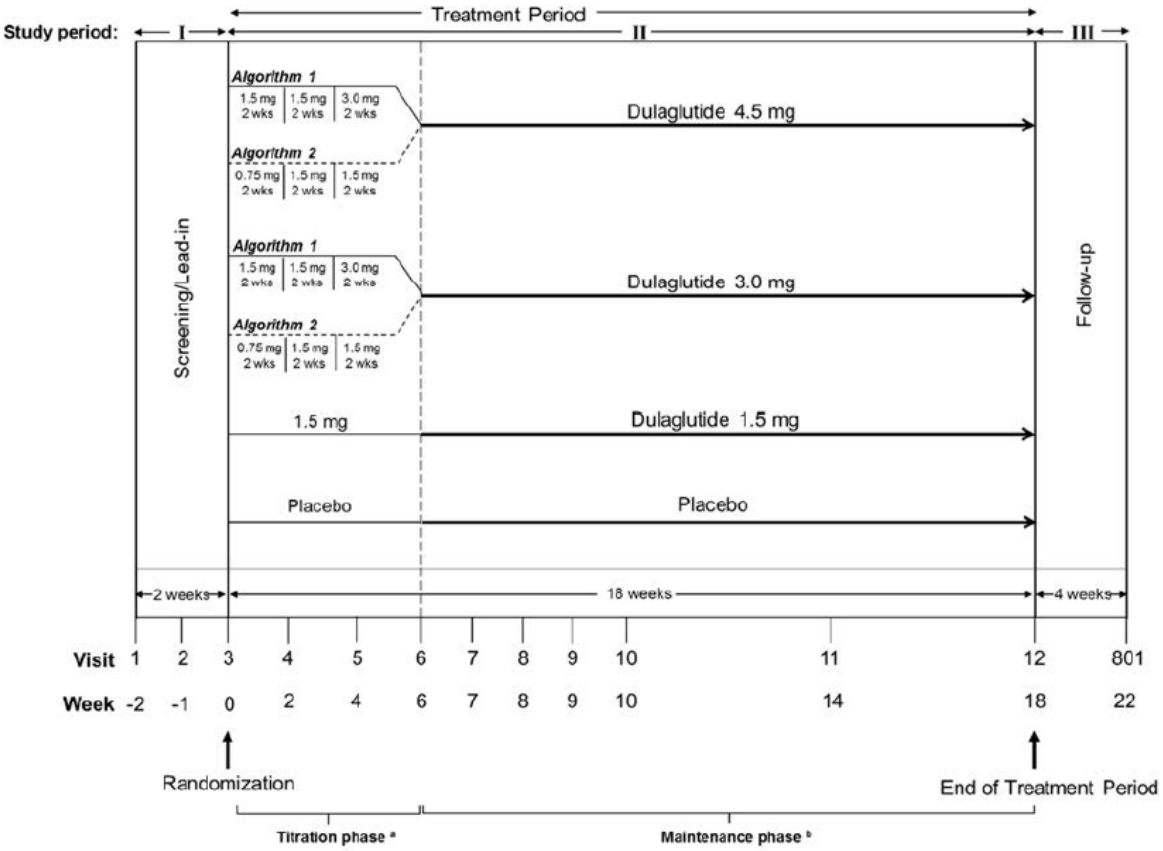
A Phase 2, Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy

Primary Objective

To demonstrate that once weekly dulaglutide (4.5 mg, 3.0 mg, 1.5 mg) is superior to placebo in glycated haemoglobin A1c (HbA1c) reduction from baseline to Week 18 in patients with type 2 diabetes mellitus on concomitant metformin monotherapy.

Study Design

Study H9X-MC-GBGJ (GBGJ) is a randomized, multi-centre, outpatient, placebo-controlled, double-blind Phase 2 trial in patients with T2DM on metformin monotherapy. The study was designed to assess the efficacy and safety of once weekly dulaglutide 1.5 mg, 3.0 mg and 4.5 mg in comparison to placebo. In addition, the trial explored how the two new higher dose strengths dulaglutide 3.0 mg and 4.5 mg compared to the approved dulaglutide 1.5 mg dose. The study consisted of 3 periods: a 2-week screening/lead-in period, an 18-week treatment period (the first 6 weeks were a titration phase for the dulaglutide 3.0 mg and 4.5 mg groups), and a 4-week safety follow-up period. Patients randomized to placebo or dulaglutide 1.5 mg were treated with those doses beginning at Week 0 for all 18 weeks of the treatment phase. Patients randomized to dulaglutide 3.0 mg or 4.5 mg were titrated over the 6 weeks of the titration phase as follows (in each of these groups, patients were randomized in a 1:1 ratio to 1 of the dosing algorithms). Patients randomized to up-titration algorithm A1 received dulaglutide 1.5 mg once weekly for the first 4 weeks followed by dulaglutide 3.0 mg once weekly for the next 2 weeks; patients randomized to up-titration algorithm A2 received dulaglutide 0.75 mg once weekly for the first 2 weeks followed by dulaglutide 1.5 mg once weekly for the next 4 weeks. Thereafter, patients received the full randomized dose for the remaining treatment period of the study.



Main Inclusion Criteria

Eligible patients were male or non-pregnant females ≥18 years of age with T2D for at least 6 months with HbA1c ≥7.0% and ≤10.0%, body mass index (BMI) ≥25 kg/m2 and treated with metformin at stable dose for at least 3 months prior to study entry. Patients were also required to have stable body weight for at least 3 months before screening and were required to agree not to initiate a diet and/or exercise program during the study.

Main Exclusion Criteria

Patients were to be excluded from the study if they met any of the key exclusion criteria:

- had type 1 diabetes mellitus (T1D);

- had used any glucose-lowering medication other than metformin 3 months prior to study entry or during screening/lead-in period or had used any GLP-1 RAs at any time in the past. Short-term use of insulin for acute conditions was allowed (≤14 days);
- had been treated with any other excluded medication (see below) within 3 months prior to screening (Visit 1) and/or between study entry and randomization (Visit 3); excluded glucocorticoids must not have been used for >14 days within 1 month prior to Visit 1 or between Visits 1 and 3;
- had a condition that is a contraindication for use of the GLP-1 RA class or metformin (per country-specific labels) at Visit 1 or developed such condition between Visit 1 and Visit 3;
- had a history of ≥1 episode of ketoacidosis or hyperosmolar state/coma;
- had ≥1 episode of severe hypoglycaemia and/or ≥1 episode of hypoglycaemia unawareness within the 6 months;
- had any of the following CV conditions: acute myocardial infarction (MI), New York Heart Association Class III or Class IV heart failure, or cerebrovascular accident (stroke);
- had a known clinically significant gastric emptying abnormality (e.g. severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (e.g. Lap-Band®);
- had acute or chronic hepatitis, signs and symptoms of any other liver disease other than non-alcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >2.5 times the upper limit of the reference range, as determined by the central laboratory at study entry; patients with NAFLD were eligible for participation in this trial;
- had chronic or acute pancreatitis any time prior to study entry;
- had an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m2, calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation (Levey et al. 2009), as determined by the central laboratory at Visit 1 and confirmed at Visit 2; if any country-specific label for countries involved in this trial requires discontinuation of metformin for eGFR cut-off ≥45 mL/min/1.73 m2, then that requirement must be followed in that country;
- had a personal or family history of medullary thyroid carcinoma (MTC) or personal history of multiple endocrine neoplasia syndrome type 2;
- had serum calcitonin ≥20 ng/L, as determined by the central laboratory at study entry;
- had evidence of significant, active autoimmune abnormality (e.g. lupus, rheumatoid arthritis);
- had active or untreated malignancy, or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years;
- had any serious disease or other condition (e.g. known drug or alcohol abuse) which, in the opinion of the investigator, would pose a significant risk to the patient or interfere with the interpretation of safety, efficacy, or PD data;
- had any hematologic condition that may have interfered with HbA1c measurement (e.g. haemolytic anaemias, sickle-cell disease).

Number of Patients

- **Planned:** Placebo, ~75; dulaglutide 1.5 mg, ~75; dulaglutide 3.0 mg, ~75 (A1, 38; A2, 38); dulaglutide 4.5 mg, ~75 (A1, 39; A2, 37)
- **Randomized:** Placebo, 82; dulaglutide 1.5 mg, 81; dulaglutide 3.0 mg, 79 (A1, 41; A2 2, 38); dulaglutide 4.5 mg, 76 (A1, 39; A2, 37)
- **Treated (at least 1 dose):** Placebo, 81; dulaglutide 1.5 mg, 81; dulaglutide 3.0 mg, 79 (A1, 41; A2, 38); dulaglutide 4.5 mg, 76 (A1, 39; A2, 37)
- **Completed (regardless of duration of treatment):** Placebo, 75; dulaglutide 1.5 mg, 73; dulaglutide 3.0 mg, 75; dulaglutide 4.5 mg, 69

Study Duration

The study consisted of 3 periods: a 2-week screening/lead-in period, an 18-week treatment period (the first 6 weeks were a titration phase for the dulaglutide 3.0 mg and 4.5 mg groups), and a 4-week safety follow-up period.

Study treatments

- **Study Drug:** Dulaglutide 3.0 mg or 4.5 mg given subcutaneously once weekly administered via prefilled syringe
- **Comparator Treatment:** Dulaglutide 1.5 mg given subcutaneously once weekly administered via prefilled syringe; Placebo given subcutaneously once weekly administered via prefilled syringe

Dose selection

The dulaglutide investigational doses of 3.0 mg and 4.5 mg once-weekly were selected for initial evaluation in Phase 2 Study GBGJ based on (a) simulations that included data collected in previous studies (Barrington et al. 2011; Skrivanek et al. 2014) suggesting that these doses may provide incremental clinically relevant reductions in Hb1Ac and body weight in comparison to the 1.5 mg dose, and (b) adequate separation in the PK exposure range between the doses and 1.5 mg to enable evaluation of their efficacy and adverse effect profiles.

Primary and Secondary Outcome Measures

Primary Endpoint

To demonstrate that once weekly dulaglutide (4.5 mg, 3.0 mg, 1.5 mg) is superior to placebo in glycated haemoglobin A1c (HbA1c) reduction from baseline to Week 18 in patients with type 2 diabetes mellitus on concomitant metformin monotherapy. The primary analysis of the primary outcome measure excluded post-rescue data.

A post-hoc supportive sensitivity analysis which excluded data post-rescue and post study drug discontinuation was added to further evaluate the effect of the study drugs on relevant efficacy measures while patients were on treatment.

Secondary Endpoints

Efficacy

Each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) was compared to the placebo arm at 18 weeks for the following secondary efficacy parameters:

• proportion of patients achieving HbA1c target <7.0% (53 mmol/mol);
• change in fasting serum glucose (FSG; central laboratory) from baseline;
• change in body weight from baseline.

Safety

Each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) was compared to the placebo arm at 18 weeks for the following secondary safety parameters:

• treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs);
• discontinuation of study drug due to adverse events (AEs);
• incidence and rate of hypoglycaemia (severe, total, documented symptomatic, and nocturnal).

Pharmacokinetics and Pharmacodynamics

The secondary pharmacokinetic (PK)/pharmacodynamic (PD) objectives were to characterize the PK of dulaglutide and establish the relationships between dose/exposure and key safety and efficacy measures:

• PK parameters (e.g. maximum concentration [Cmax], area under the curve [AUC]);
• PD evaluations included FSG, HbA1c, body weight, Fridericia's corrected QT interval (QTcF), and heart rate (HR).

Tertiary/Exploratory Endpoints

Efficacy

Each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) was compared to the placebo arm at 18 weeks for the following exploratory efficacy parameters:

- proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol);
- change in 6-point self-monitored plasma glucose (SMPG) profiles from baseline.
- change in fasting plasma glucagon from baseline;
- change from baseline in insulin resistance (HOMA-IR) and β-cell function (HOMA-%B) as measured by the HOMA2 Method (Caumo et al. 2006).

Each investigational dulaglutide arm (4.5 mg, 3.0 mg) was compared to the dulaglutide 1.5 mg arm at 18 weeks for the following exploratory efficacy parameters:

- change from baseline in HbA1c;
- proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol);
- change in FSG (by central laboratory) from baseline;
- change in body weight from baseline;
- change in 6-point SMPG profiles from baseline;
- change in fasting plasma glucagon from baseline;
- change in HOMA2-IR and HOMA2-%B from baseline.

Safety

Each investigational dulaglutide arm (4.5 mg, 3.0 mg) was compared to the placebo arm at 18 weeks for the following exploratory safety parameters:

- selected GI tolerability AEs (nausea, vomiting, and diarrhea);
- pancreatic safety assessed by incidence of cases of adjudicated pancreatitis;
- CV safety assessed by the incidence of adjudicated deaths and nonfatal major CV events;
- thyroid-related safety assessed by the incidence of cases of thyroid neoplasms;
- vital signs (HR, BP);
- electrocardiograms (ECG) (HR, QTcF, supraventricular arrhythmias and cardiac conduction abnormalities);
- immune system-related safety, including the incidence of dulaglutide anti-drug antibodies (ADA) and the incidence of allergic and hypersensitivity reactions;
- injection site reactions;
- incidence of rescue therapy initiation due to severe, persistent hyperglycaemia.

Each investigational dulaglutide arm (4.5 mg, 3.0 mg) was compared to the dulaglutide 1.5 mg arm at 18 weeks for the following exploratory safety parameters:

- TEAEs and SAEs;
- discontinuation of study drug due to AEs;
- incidence and rate of hypoglycaemia (severe, total, documented symptomatic, and nocturnal);
- selected GI tolerability AEs (nausea, vomiting, and diarrhoea);
- pancreatic safety assessed by incidence of cases of adjudicated pancreatitis;
- CV safety assessed by the incidence of adjudicated deaths and nonfatal major CV events;
- thyroid-related safety assessed by the incidence of cases of thyroid neoplasms;
- vital signs (HR, BP);
- ECG parameters (HR, QTcF, supraventricular arrhythmias and cardiac conduction abnormalities);
- immune system-related safety, including the incidence of dulaglutide ADA and the incidence of allergic and hypersensitivity reactions;
- injection site reactions;
- incidence of rescue therapy initiation due to severe, persistent hyperglycaemia.

The titration algorithms (Algorithm 1 [A1] versus Algorithm 2 [A2]) were compared within the investigational dose dulaglutide arms (4.5 mg and 3.0 mg) and across the investigational dose arms versus dulaglutide 1.5 mg and placebo at 6 and 18 weeks for the following safety parameters:

- incidence of selected GI AEs (nausea, vomiting, and diarrhoea);
- vital signs (HR, BP).

Concomitant Therapy

Patients were to be permitted to use concomitant medications that they required during the study, except certain medications that may have interfered with the assessment of efficacy and safety characteristics of the study treatments (see table below).

Criteria for Use of Concomitant Medications and Rescue Therapy

Drug Class	Use During Screening/Lead-In	Conditions for Use after Randomization		
		Acute therapy[a]	Rescue therapy	During Safety Follow-Up Period
Drugs with approved weight loss indication[b]	Excluded	N	N/A	Y
Systemic glucocorticoid therapy[c]	Excluded except for acute therapy[a]	Y	N/A	Y
Antihyperglycemia medications				
Other GLP-1 RAs	Excluded	N	N	N
DPP-4 inhibitors	Excluded	N	N	N
SGLT2 inhibitors	Excluded	N	Y	Y
Insulins and insulin mixtures	Excluded except for acute therapy[a]	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors	Excluded	N	Y	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin[d]	Required	N/A	Y[e]	Y

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT2 = sodium-glucose co-transporter 2; Y = yes.

[a] Acute therapy = treatment for up to 14 days.

[b] Included Saxenda® (liraglutide 3.0 mg), Xenical® (orlistat), Meridia® (sibutramine), Sanorex® (mazindol), Apidex® (phentermine), BELVIQ® (lorcaserin), Qsymia® (phentermine/topiramate combination), Contrave® (naltrexone/buproprion), or similar other body weight loss medications including over-the-counter medications (eg, alli®) within 3 months prior to Visit 1 or any time during the trial.

[c] From 1 month prior to Visit 1 or between Visits 1 and 3; did not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

[d] Switching metformin manufacturers was allowed as long as the dosage was the same. Changing to a metformin formulation with a different action profile (ie, from short-acting to long-acting metformin) was not permitted.

[e] For rescue therapy, metformin dose could be increased if the dose was below maximum approved dose per country-specific label.

Statistical methods

Patients were randomly assigned to in a 1:1:1:1 ratio (stratified by country and HbA1c level) to the four treatment arms and within the two higher dose arms 1:1 randomization to two different treatment algorithms was conducted.

A total sample size of 300 patients was planned to achieve a power of provide ≥90% power to demonstrate superiority for the dulaglutide doses to placebo with respect to primary endpoint (assumed treatment effect of -1% HBA1c, standard deviation of 1.2%, alpha=0.05 and 20% dropout).

Efficacy and safety analyses will be conducted in the intent-to-treat (ITT) population (all randomized patients taking at least one dose of study medication) by censoring all post-rescue data. As not all patient directly switched to rescue treatment following treatment discontinuation, post-hoc analyses were conducted excluding data post-rescue or post discontinuation of study drug. As sensitivity analysis, the

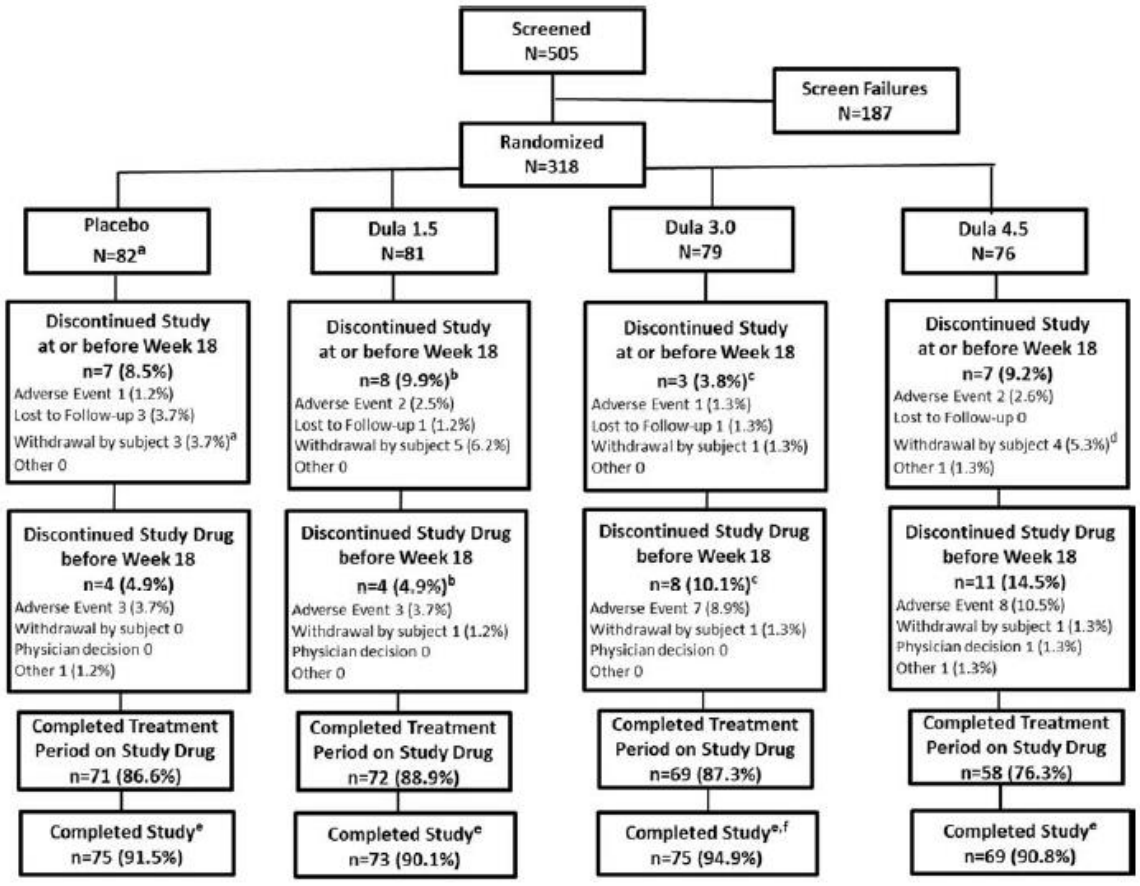
primary endpoint was also evaluated in per protocol population, completer population and the ITT population including post-rescue data.

A mixed model for repeated measures (MMRM) analysis was used to analyze continuous longitudinal variables. The corresponding baseline value will be used as a covariate, and the stratification factors, treatment, visit, and treatment-by-visit interaction will be fixed effects. For HbA1c analyses, the HbA1c strata will be removed. An unstructured covariance matrix will be used to model the within-patient errors. For percentages of patients achieving HbA1c targets, a longitudinal logistic regression with repeated measurements with similar covariates was used. Non-longitudinal endpoints were analyzed by means of an ANCOVA model applying last observation carried forward (LOCF) imputation to handle missing data. Multiplicity control was not conducted. For an exploratory phase 2 study the analyses are overall considered acceptable.

Results

Patient Disposition and Sample Size

A total of 505 patients were screened and 318 patients were randomized to treatment (see Figure below). One patient randomized to placebo withdrew consent to participate in the study prior to receiving study drug. Therefore, 317 patients received at least 1 dose of study drug and comprised the ITT population (placebo, 81; dulaglutide 1.5 mg, 81; dulaglutide 3.0 mg, 79; dulaglutide 4.5 mg, 76).



[a] One patient was randomized but not treated.
[b] Three patients were discontinued from study drug before Week 18 and later from the study (before Week 18).
[c] One patient was discontinued from study drug before Week 18 and from the study at Week 18.
[d] One patient discontinued at the Safety Follow-up visit.
[e] Indicates completed study through Safety Follow-up Period, regardless of duration of study treatment.
[f] One patient completed the treatment period through Week 18 but did not return for Visit 801 at the end of the Safety Follow-up Period.

A total of 318 patients were randomized and 292 (91.8%) completed the study through the Safety Follow-up Period (regardless of duration of treatment with study drug); 48 of 318 randomized patients (15.1%) discontinued from study treatment before Week 18 (patients who stopped study drug before Week 18 with or without stopping the study): Placebo, 11 (13.4%); dulaglutide 1.5 mg, 9 (11.1%); dulaglutide 3.0 mg, 10 (12.7%); dulaglutide 4.5 mg, 18 (23.7%). Adverse event was the most frequent reason for discontinuation of study drug (21 of 318 randomized patients [6.6%]) with more patients discontinuing study drug for AEs at the two higher doses dulaglutide 3.0 mg, 7 (8.9%) and 4.5 mg, 8 (10.5%) and less patients discontinuing study drug for AEs at placebo, 3 (3.7%) and dulaglutide 1.5 mg, 3 (3.7%).

Summary and Analysis of Patient Demographics and Clinical Characteristics at Baseline, Intent-to-Treat Population

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Sex	n*a	81	81	79	76	317
	F	33 (40.7)	42 (51.9)	44 (55.7)	40 (52.6)	159 (50.2)
	M	48 (59.3)	39 (48.1)	35 (44.3)	36 (47.4)	158 (49.8)
Age (yrs)	n*a	81	81	79	76	317
	Mean	56.52	57.65	55.90	57.13	56.80
	Std. Dev.	8.93	9.79	10.74	9.63	9.77
	Median	58.00	58.00	56.00	57.50	57.00
	Min	30.00	34.00	19.00	38.00	19.00
	Max	72.00	76.00	82.00	81.00	82.00

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula_x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Pooled Age Group 1	n*a	81	81	79	76	317
	<65	65 (80.2)	59 (72.8)	62 (78.5)	59 (77.6)	245 (77.3)
	>=65	16 (19.8)	22 (27.2)	17 (21.5)	17 (22.4)	72 (22.7)
Race	n	81	81	79	76	317
	AMERICAN INDIAN OR ALASKA NATIVE	10 (12.3)	6 (7.4)	9 (11.4)	6 (7.9)	31 (9.8)
	ASIAN	0 (0.0)	0 (0.0)	1 (1.3)	3 (3.9)	4 (1.3)
	BLACK OR AFRICAN AMERICAN	6 (7.4)	6 (7.4)	6 (7.6)	6 (7.9)	24 (7.6)
	Missing	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
	WHITE	59 (72.8)	68 (84.0)	58 (73.4)	59 (77.6)	244 (77.0)
	MULTIPLE	5 (6.2)	1 (1.2)	4 (5.1)	2 (2.6)	12 (3.8)

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula_x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Ethnicity	n*a	81	81	79	76	317
	HISPANIC OR LATINO	35 (43.2)	32 (39.5)	38 (48.1)	30 (39.5)	135 (42.6)
	NOT HISPANIC OR LATINO	46 (56.8)	49 (60.5)	40 (50.6)	45 (59.2)	180 (56.8)
	NOT REPORTED	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)	2 (0.6)
Weight (kg)	n*a	81	81	79	76	317
	Mean	94.48	87.90	96.00	89.14	91.90
	Std. Dev.	22.86	17.00	22.69	18.62	20.66
	Median	92.00	84.10	95.20	87.70	88.80
	Min	57.10	58.50	56.60	55.00	55.00
	Max	173.20	129.20	166.60	148.50	173.20

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Height (cm)	n*a	81	81	79	76	317
	Mean	168.04	164.98	166.56	166.07	166.42
	Std. Dev.	10.37	10.68	11.25	9.93	10.58
	Median	166.50	165.10	165.10	166.50	166.00
	Min	147.40	144.70	148.00	144.70	144.70
	Max	195.60	192.00	195.60	189.00	195.60
BMI (kg/m**2)	n*a	81	81	79	76	317
	Mean	33.17	32.20	34.36	32.20	32.99
	Std. Dev.	5.96	4.76	5.98	5.43	5.60
	Median	32.20	31.64	33.24	31.29	32.03
	Min	24.58	25.10	24.63	24.46	24.46
	Max	50.36	43.95	48.85	47.22	50.36

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Country	n*a	81	81	79	76	317
	CZECH REPUBLIC	10 (12.3)	9 (11.1)	10 (12.7)	8 (10.5)	37 (11.7)
	MEXICO	10 (12.3)	10 (12.3)	10 (12.7)	11 (14.5)	41 (12.9)
	POLAND	13 (16.0)	11 (13.6)	10 (12.7)	10 (13.2)	44 (13.9)
	ROMANIA	6 (7.4)	6 (7.4)	5 (6.3)	4 (5.3)	21 (6.6)
	UNITED STATES	42 (51.9)	45 (55.6)	44 (55.7)	43 (56.6)	174 (54.9)
HbA1c at Baseline	n*a	81	81	79	76	317
	Mean	8.08	8.02	8.16	8.12	8.09
	Std. Dev.	0.79	0.80	0.92	0.81	0.83
	Median	7.90	7.90	8.00	8.00	8.00
	Min	7.00	6.80	6.70	6.80	6.70
	Max	10.50	10.10	11.10	10.50	11.10

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Fasting Serum Glucose(mg/dL) at Baseline	n*a	81	81	79	76	317
	Mean	163.06	171.93	173.15	173.77	170.41
	Std. Dev.	39.53	44.66	37.49	50.37	43.23
	Median	160.00	160.33	169.00	165.37	165.74
	Min	86.47	91.00	98.00	109.89	86.47
	Max	310.00	342.00	280.00	477.00	477.00
eGFR (mL/min/1.73 m) at baseline	n*a	81	81	79	76	317
	Mean	93.57	90.15	93.94	90.67	92.09
	Std. Dev.	15.31	18.54	16.81	18.35	17.29
	Median	96.00	92.00	97.00	94.50	96.00
	Min	55.00	47.00	51.00	35.00	35.00
	Max	124.00	128.00	125.00	119.00	128.00

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Diabetes Duration in Years	n*a	81	81	79	76	317
	Mean	7.77	7.88	7.47	9.01	8.02
	Std. Dev.	7.35	5.60	6.04	5.81	6.24
	Median	5.00	7.00	5.00	8.00	6.00
	Min	0.00	1.00	0.00	1.00	0.00
	Max	42.00	27.00	26.00	22.00	42.00
Baseline Systolic Blood Pressure (mmHg)	n*a	81	81	79	76	317
	Mean	133.70	128.69	131.95	131.12	131.36
	Std. Dev.	13.47	16.77	16.55	14.87	15.51
	Median	133.00	129.67	130.33	131.83	131.67
	Min	95.33	86.33	91.00	98.00	86.33
	Max	163.33	177.33	185.00	199.33	199.33

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula_x.x refers to x.x milligrams dulaglutide once weekly.

Demographic Parameter		Placebo (N=81)	Dula_1.5 (N=81)	Dula_3.0 (N=79)	Dula_4.5 (N=76)	Total (N=317)
Baseline Diastolic Blood Pressure (mmHg)	n*a	81	81	79	76	317
	Mean	78.88	77.63	80.29	78.78	78.89
	Std. Dev.	8.93	8.55	9.92	8.69	9.05
	Median	79.67	77.33	81.33	80.00	79.67
	Min	56.00	54.00	60.67	52.67	52.67
	Max	106.33	99.00	109.67	105.67	109.67
Baseline Heart Rate (bpm)	n*a	81	81	79	76	317
	Mean	75.17	76.05	75.01	76.07	75.57
	Std. Dev.	10.16	10.26	11.39	11.74	10.85
	Median	74.33	76.33	74.67	75.67	75.33
	Min	52.00	56.00	42.33	54.67	42.33
	Max	109.67	115.00	108.33	110.33	115.00

Abbreviations: N = number of subjects in At Baseline; n = number of subjects;
NC = not calculable;
*a - number of subjects with non-missing data, used as denominator
*b - p value for overall treatment effect were computed using CHISQ test.
Note 1: Dula_x.x refers to x.x milligrams dulaglutide once weekly.

Demographic and baseline characteristics in the ITT population were comparable between treatment groups. The mean age was 56.8 years. The majority of patients were White 77.0% and 50.2% were female. The mean HbA1c was 8.1% and the mean duration of T2D was 8.0 years. The mean body weight was 91.9 kg. The overall comparison of baseline body weight across the 4 treatment groups was slightly different (p=0.032); the mean body weight was lower in the dulaglutide 1.5 mg and 4.5 mg groups (87.9 and 89.1 kg, respectively) and higher in the placebo and dulaglutide 3.0 mg groups (94.5 and 96.0 kg, respectively). The mean BMI was 33.0 kg/m2; the overall comparison of baseline BMI across the 4 treatment groups was also of borderline significance (p=0.046). The slight differences at baseline observed for body weight and BMI across study groups are not judged as having exerted a meaningful impact on the reliability of the GBGJ study results.

At screening (Visit 1) and at baseline (Visit 3) all patients in the ITT Population were receiving metformin (median dose of 2000 mg/day in all treatment groups) and no patients were receiving oral anti-hyperglycemia agents other than metformin.
A total of 9 patients received rescue medication due to severe, persistent hyperglycemia during the treatment period, as anticipated more patients in the placebo group 6 (7.4%) than in the dulaglutide treatment arms [1.5 mg, 1 (1.2%); 3.0 mg, 1 (1.3%); 4.5 mg, 1 (1.3%)].
The use of concomitant medications after randomization was not significantly different from the use at baseline. The most frequent concomitant medications were antihypertensives (70.3% at baseline and 71.3% after randomization), lipid-lowering agents (45.1% at baseline and 49.5% after randomization) and anti-thrombotic agents (23.7% at baseline and 25.9% after randomization) with comparable use of concomitant medications between treatment groups.

Compliance

Overall, 96.8% of patients were evaluated by the investigator to be compliant with injectable study medication (having received at least 75% of doses of placebo or dulaglutide over at least 75% of visits). Over the entire treatment period through Week 18, overall compliance (mean [SD]) with injectable study medication (placebo or dulaglutide) was 97.3% (10.4%). There were no significant differences in compliance among the 4 treatment groups at any time point.

Protocol Deviations

A total of 33 randomized patients (10.4%) were excluded from the PP Population due to important protocol deviations. The most frequent deviations were not completing the treatment period, Lab/ Imaging Criteria or missing HbA1c at baseline and/or Week 18.

A total of 63 randomized patients (19.8%) had other important deviations which did not result in exclusion from the PP Population; 58 patients had deviations related to study sites being late obtaining reconsent with an Informed Consent Form (ICF) which was amended during the study due to a change in the IB resulting in this most frequently reported protocol deviation.

The protocol deviations were not likely to have significantly affected the analyses of the GBGJ study. This conclusion is supported by results of changes from baseline in HbA1c conducted in the PP Population that were consistent with the results of the analyses in the ITT Population.

Efficacy results

Primary endpoint

The primary objective of the Phase 2 study GBGJ was to demonstrate that once weekly dulaglutide (1.5 mg, 3.0 mg and 4.5 mg) is superior to placebo in HbA1c reduction at Week 18 in patients with T2D on concomitant metformin monotherapy. The mean HbA1c values (SD) at baseline were comparable between dulaglutide and placebo treatment groups.

Primary Analysis: HbA1c (%) from Baseline to Week 18, Intent-to-Treat Population without Post-Rescue Values

Variable Analyzed: BLOOD Hemoglobin A1C HPLC - VARIANT (%)

		Actual Value					Change from Baseline					
Time Point Treatment	n	Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
						LSMean Change Difference	95% CI for Difference			p-value*a		
	Pairwise Comparison											
	Dula_1.5 vs Placebo					-0.80	(-1.07,-0.53)			<.001		
	Dula_3.0 vs Placebo					-0.87	(-1.14,-0.60)			<.001		
	Dula_4.5 vs Placebo					-0.96	(-1.24,-0.69)			<.001		
	Dula_3.0 vs Dula_1.5					-0.08	(-0.34, 0.19)			0.572		
	Dula_4.5 vs Dula_1.5					-0.16	(-0.44, 0.11)			0.235		

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

HbA1c (%) from Baseline to Week 18, Intent-to-Treat Population

Variable Analyzed: BLOOD Hemoglobin A1C HPLC - VARIANT (%)

		Actual Value					Change from Baseline					
Time Point Treatment	n	Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
						LSMean Change Difference	95% CI for Difference			p-value*a		
	Pairwise Comparison											
	Dula_1.5 vs Placebo					-0.80	(-1.06,-0.54)			<.001		
	Dula_3.0 vs Placebo					-0.88	(-1.14,-0.62)			<.001		
	Dula_4.5 vs Placebo					-0.94	(-1.20,-0.67)			<.001		
	Dula_3.0 vs Dula_1.5					-0.08	(-0.34, 0.18)			0.550		
	Dula_4.5 vs Dula_1.5					-0.14	(-0.41, 0.13)			0.308		

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

The primary objective was met as all three doses of dulaglutide (1.5 mg, 3.0 mg and 4.5 mg) reduced HbA1c significantly from baseline to Week 18 compared to placebo ($p<0.001$).

However, the two new higher investigational dose strengths of dulaglutide (3.0 mg and 4.5 mg) did not improve HbA1c significantly from baseline compared to dulaglutide 1.5 mg at Week 18 and the magnitude of the observed HbA1c reductions was small.

In the primary analysis (ITT population without post-rescue values) of study GBGJ, the LSM differences (95% CI) of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg at Week 18 were -0.08%, p=0.572 and -0.16%, p=0.235, respectively.

Sensitivity Analyses for the Primary Endpoint

A post hoc supportive "on-treatment without rescue" analysis which excluded data post-rescue and post study drug discontinuation was added to further evaluate the effect of the study medications on relevant efficacy measures while patients were on treatment.

The Table below presents this supportive "on-treatment analysis" of the primary endpoint (without post-rescue or post discontinued IP values), which is claimed by the applicant as a key prerequisite for understanding the true effect of the various dulaglutide doses on HbA1c.

HbA1c (%) from Baseline to Week 18, On-Treatment Analysis (excluding post-rescue and post discontinued IP values)

Variable Analyzed: BLOOD Hemoglobin A1C HPLC - VARIANT (%)

		Actual Value					Change from Baseline					
Time Point Treatment	n	Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
	Pairwise Comparison					LSMean Change Difference	95% CI for Difference				p-value*a	
	Dula_1.5 vs Placebo					-0.82	(-1.08,-0.56)				<.001	
	Dula_3.0 vs Placebo					-1.04	(-1.31,-0.78)				<.001	
	Dula_4.5 vs Placebo					-1.08	(-1.35,-0.81)				<.001	
	Dula_3.0 vs Dula_1.5					-0.22	(-0.48, 0.03)				0.088	
	Dula_4.5 vs Dula_1.5					-0.26	(-0.52, 0.00)				0.051	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

At Week 18, the differences on HbA1c (%) observed between dulaglutide and placebo were numerically greater in the supportive sensitivity analysis for the primary endpoint excluding data post-rescue and post study drug discontinuation; the LSM differences (95% CI) of dulaglutide 1.5, 3.0 and 4.5 mg versus placebo at 18 weeks were −0.82%, −1.04% and −1.08%, respectively; all p-values < 0.001.

The LSM differences (95% CI) of dulaglutide 3.0 mg and 4.5 mg compared with dulaglutide 1.5 mg at 18 weeks were also more pronounced -0.22%, p=0.088 and -0.26%, p=0.051, but did not reach statistical significance; the observed HbA1c reductions were not >0.3% what is defined by the diabetes guideline (CPMP/EWP/1080/00 Rev. 2) as a clinically meaningful effect size.

Important subgroup analyses of Primary Endpoint: Change in HbA1c (%) from Baseline to Week 18, Intent-to-Treat Population without Post-Rescue Values

Subgroup: < Median BMI 32.03(kg/m^2)

			Change from Baseline			
			LSM diff (95% CI) [p-value]*a*b			
Time/ Visit	Treatment	n	Vs Placebo		Vs Dula_1.5	
Week 18 (Visit 12)	Placebo	32				
	Dula_1.5	39	-0.78 (-1.17, -0.39)	[<.001]		
	Dula_3.0	28	-0.96 (-1.38, -0.55)	[<.001]	-0.18 (-0.58, 0.21)	[0.362]
	Dula_4.5	35	-0.92 (-1.31, -0.52)	[<.001]	-0.14 (-0.51, 0.24)	[0.468]

Subgroup: >= Median BMI 32.03(kg/m^2)

Time/ Visit	Treatment	n	Change from Baseline LSM diff (95% CI) [p-value]*a*b Vs Placebo		Vs Dula_1.5	
Week 18 (Visit 12)	Placebo	38				
	Dula_1.5	34	-0.80 (-1.18, -0.41)	[<.001]		
	Dula_3.0	45	-0.82 (-1.18, -0.46)	[<.001]	-0.02 (-0.40, 0.35)	[0.899]
	Dula_4.5	31	-0.98 (-1.37, -0.59)	[<.001]	-0.18 (-0.59, 0.22)	[0.375]

Subgroup: < Median Body Weight 88.8(kg)

Time/ Visit	Treatment	n	Change from Baseline LSM diff (95% CI) [p-value]*a*b Vs Placebo		Vs Dula_1.5	
Week 18 (Visit 12)	Placebo	27				
	Dula_1.5	44	-1.01 (-1.40, -0.62)	[<.001]		
	Dula_3.0	28	-1.03 (-1.46, -0.60)	[<.001]	-0.02 (-0.41, 0.36)	[0.907]
	Dula_4.5	35	-1.02 (-1.43, -0.61)	[<.001]	-0.01 (-0.37, 0.35)	[0.952]

Subgroup: >= Median Body Weight 88.8(kg)

Time/ Visit	Treatment	n	Change from Baseline LSM diff (95% CI) [p-value]*a*b Vs Placebo		Vs Dula_1.5	
Week 18 (Visit 12)	Placebo	43				
	Dula_1.5	29	-0.52 (-0.92, -0.13)	[0.009]		
	Dula_3.0	45	-0.76 (-1.11, -0.41)	[<.001]	-0.24 (-0.63, 0.15)	[0.231]
	Dula_4.5	31	-0.92 (-1.30, -0.54)	[<.001]	-0.40 (-0.82, 0.02)	[0.062]

Subgroup: < 8%

Time/ Visit	Treatment	n	Change from Baseline LSM diff (95% CI) [p-value]*a*b Vs Placebo		Vs Dula_1.5	
Week 18 (Visit 12)	Placebo	39				
	Dula_1.5	39	-0.71 (-1.08, -0.34)	[<.001]		
	Dula_3.0	35	-0.63 (-1.01, -0.25)	[0.001]	0.08 (-0.30, 0.46)	[0.690]
	Dula_4.5	32	-0.71 (-1.10, -0.33)	[<.001]	-0.00 (-0.39, 0.38)	[0.985]

Subgroup: >= 8%

Time/ Visit	Treatment	n	Change from Baseline LSM diff (95% CI) [p-value]*a*b Vs Placebo		Vs Dula_1.5	
Week 18 (Visit 12)	Placebo	31				
	Dula_1.5	34	-0.83 (-1.23, -0.44)	[<.001]		
	Dula_3.0	38	-1.05 (-1.43, -0.66)	[<.001]	-0.22 (-0.59, 0.16)	[0.259]
	Dula_4.5	34	-1.15 (-1.55, -0.76)	[<.001]	-0.32 (-0.71, 0.06)	[0.101]

The two new investigational dose strengths of dulaglutide (3.0 mg and 4.5 mg) did not significantly improve the primary endpoint [HbA1c (%) change from baseline to Week 18] compared to dulaglutide 1.5 mg across all subgroup analyses (except for the subgroup White, where borderline statistical significance was achieved for dulaglutide 4.5 mg versus placebo, p=0.049).

Secondary Efficacy Objectives

Percentages of Patients Achieving HbA1c <7.0% from Baseline to Week 18, ITT Population Excluding Post-rescue Data

Variable Analyzed: HbA1c <7.0%

Time/Visit	Treatment	n/N (%)	Odds Ratio (95% CI) [p-value] *a*b vs Placebo	Odds Ratio (95% CI) [p-value] *a*b vs 1.5 mg
Baseline (Visit 3)	Placebo	0/ 76		
	Dula_1.5	5/ 80 (6.3)		
	Dula_3.0	2/ 79 (2.5)		
	Dula_4.5	2/ 75 (2.7)		
Week 6 (Visit 6)	Placebo	13/ 74 (17.6)		
	Dula_1.5	33/ 79 (41.8)	5.304 (2.437, 11.543) [<.001]	
	Dula_3.0	37/ 79 (46.8)	7.940 (3.428, 18.392) [<.001]	1.497 (0.774, 2.896) [0.230]
	Dula_4.5	28/ 75 (37.3)	4.219 (1.856, 9.592) [<.001]	0.795 (0.414, 1.528) [0.491]
Week 10 (Visit 10)	Placebo	11/ 72 (15.3)		
	Dula_1.5	47/ 75 (62.7)	23.666 (8.654, 64.717) [<.001]	
	Dula_3.0	48/ 77 (62.3)	24.136 (8.810, 66.122) [<.001]	1.020 (0.402, 2.586) [0.967]
	Dula_4.5	45/ 69 (65.2)	24.103 (9.453, 61.455) [<.001]	1.018 (0.432, 2.400) [0.967]
Week 18 (Visit 12)	Placebo	14/ 70 (20.0)		
	Dula_1.5	52/ 73 (71.2)	24.489 (8.368, 71.667) [<.001]	
	Dula_3.0	52/ 73 (71.2)	27.906 (9.238, 84.300) [<.001]	1.140 (0.396, 3.278) [0.808]
	Dula_4.5	45/ 66 (68.2)	21.852 (7.672, 62.242) [<.001]	0.892 (0.330, 2.411) [0.822]

Abbreviations: CI = confidence interval; HbA1c = hemoglobin a1c; N = number of subjects in the population with baseline and post-baseline value at the specified visit; n = number of subjects in the specified category.

Percentages of Patients Achieving HbA1c <7.0% from Baseline to Week 18, ITT Population

Variable Analyzed: HbA1c <7.0%

Time/Visit	Treatment	n/N (%)	Odds Ratio (95% CI) [p-value] *a*b vs Placebo	Odds Ratio (95% CI) [p-value] *a*b vs 1.5 mg
Baseline (Visit 3)	Placebo	0/ 78		
	Dula_1.5	5/ 80 (6.3)		
	Dula_3.0	2/ 79 (2.5)		
	Dula_4.5	2/ 75 (2.7)		
Week 6 (Visit 6)	Placebo	13/ 76 (17.1)		
	Dula_1.5	33/ 79 (41.8)	5.439 (2.511, 11.780) [<.001]	
	Dula_3.0	37/ 79 (46.8)	8.124 (3.523, 18.735) [<.001]	1.494 (0.772, 2.891) [0.233]
	Dula_4.5	28/ 75 (37.3)	4.306 (1.902, 9.751) [<.001]	0.792 (0.412, 1.522) [0.483]
Week 10 (Visit 10)	Placebo	11/ 77 (14.3)		
	Dula_1.5	47/ 76 (61.8)	23.448 (8.694, 63.240) [<.001]	
	Dula_3.0	48/ 78 (61.5)	24.435 (9.026, 66.148) [<.001]	1.042 (0.416, 2.609) [0.930]
	Dula_4.5	45/ 72 (62.5)	22.516 (8.996, 56.355) [<.001]	0.960 (0.414, 2.226) [0.924]
Week 18 (Visit 12)	Placebo	14/ 75 (18.7)		
	Dula_1.5	52/ 73 (71.2)	24.493 (8.494, 70.629) [<.001]	
	Dula_3.0	52/ 74 (70.3)	27.956 (9.446, 82.738) [<.001]	1.141 (0.404, 3.225) [0.802]
	Dula_4.5	45/ 69 (65.2)	19.768 (7.188, 54.368) [<.001]	0.807 (0.307, 2.121) [0.663]

Abbreviations: CI = confidence interval; HbA1c = hemoglobin a1c; N = number of subjects in the population with baseline and post-baseline value at the specified visit; n = number of subjects in the specified category.

Percentages of Patients Achieving HbA1c <7.0% from Baseline to Week 18, ITT Population without Post-Rescue or Post Discontinued IP Values

Variable Analyzed: HbA1c <7.0%

Time/Visit	Treatment	n/N (%)	Odds Ratio (95% CI) [p-value] *a*b vs Placebo	Odds Ratio (95% CI) [p-value] *a*b vs 1.5 mg
LOCF Week 18	Placebo	12/ 72 (16.7)		
	Dula_1.5	52/ 78 (66.7)	10.977 (4.880, 24.691) [<.001]	
	Dula_3.0	51/ 73 (69.9)	14.854 (6.363, 34.675) [<.001]	1.353 (0.653, 2.802) [0.415]
	Dula_4.5	42/ 73 (57.5)	7.985 (3.554, 17.937) [<.001]	0.727 (0.364, 1.455) [0.368]

The percentages of patients achieving target HbA1c <7.0% at Week 18 were significantly greater in all three dulaglutide groups (1.5 mg, 3.0 mg and 4.5 mg) compared to placebo-treated patients. However, the percentages of patients achieving target HbA1c <7.0% at Week 18 were comparable and not significantly different between the dulaglutide groups.

Fasting Serum Glucose (FSG) mg/dL from Baseline to Week 18, Intent-to-Treat Population Excluding Post-rescue Data

Variable Analyzed: Fasting SERUM Glucose (mg/dL)

Time Point / Treatment	n	Actual Value: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
Pairwise Comparison						LSMean Change Difference	95% CI for Difference				p-value*a	
Dula_1.5 vs Placebo						-23.7	(-36.4,-11.1)				<.001	
Dula_3.0 vs Placebo						-22.1	(-34.5, -9.7)				<.001	
Dula_4.5 vs Placebo						-25.6	(-38.2,-12.9)				<.001	
Dula_3.0 vs Dula_1.5						1.6	(-10.8, 14.1)				0.794	
Dula_4.5 vs Dula_1.5						-1.8	(-14.5, 10.8)				0.776	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

The results of the ITT analysis including all available data regardless of rescue or treatment discontinuation status were consistent with the results excluding post-rescue data.

Fasting Serum Glucose (FSG) mg/dL from Baseline to Week 18, Intent-to-Treat Population

Variable Analyzed: Fasting SERUM Glucose (mg/dL)

Time Point / Treatment	n	Actual Value: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
Pairwise Comparison						LSMean Change Difference	95% CI for Difference				p-value*a	
Dula_1.5 vs Placebo						-22.1	(-34.5, -9.6)				<.001	
Dula_3.0 vs Placebo						-20.5	(-32.6, -8.3)				0.001	
Dula_4.5 vs Placebo						-25.1	(-37.5,-12.7)				<.001	
Dula_3.0 vs Dula_1.5						1.6	(-10.8, 14.1)				0.798	
Dula_4.5 vs Dula_1.5						-3.0	(-15.7, 9.6)				0.636	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

Fasting Serum Glucose (FSG) mg/dL from Baseline to Week 18, ITT Population without Post-Rescue or Post Discontinued IP Values

Variable Analyzed: Fasting SERUM Glucose (mg/dL)

Time Point / Treatment	n	Actual Value: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
Pairwise Comparison						LSMean Change Difference	95% CI for Difference				p-value*b	
Dula_1.5 vs Placebo						-24.4	(-36.7,-12.1)				<.001	
Dula_3.0 vs Placebo						-23.1	(-35.2,-11.0)				<.001	
Dula_4.5 vs Placebo						-27.4	(-39.6,-15.1)				<.001	
Dula_3.0 vs Dula_1.5						1.3	(-10.8, 13.5)				0.829	
Dula_4.5 vs Dula_1.5						-2.9	(-15.2, 9.4)				0.639	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

All three doses of dulaglutide (1.5 mg, 3.0 mg and 4.5 mg) significantly reduced fasting serum glucose from baseline at Week 18 compared to placebo. However, there were no significant changes from baseline at Week 18 between the dulaglutide treatment groups for this parameter.

Body Weight (Kg) from Baseline to Week 18, ITT Population Excluding Post-Rescue Values

Variable Analyzed: Weight (kg)

Time Point / Treatment	n	Actual Value: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
Pairwise Comparison						LSMean Change Difference	95% CI for Difference				p-value*a	
Dula_1.5 vs Placebo						-1.2	(-2.3, -0.2)				0.025	
Dula_3.0 vs Placebo						-2.4	(-3.4, -1.3)				<.001	
Dula_4.5 vs Placebo						-2.6	(-3.7, -1.5)				<.001	
Dula_3.0 vs Dula_1.5						-1.1	(-2.2, 0.0)				0.042	
Dula_4.5 vs Dula_1.5						-1.3	(-2.4, -0.2)				0.017	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

Body Weight (Kg) from Baseline to Week 18, Intent-to-Treat Population

Variable Analyzed: Weight (kg)

Time Point / Treatment	n	Actual Value: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
Pairwise Comparison						LSMean Change Difference	95% CI for Difference				p-value*a	
Dula_1.5 vs Placebo						-1.3	(-2.4, -0.2)				0.019	
Dula_3.0 vs Placebo						-2.5	(-3.5, -1.4)				<.001	
Dula_4.5 vs Placebo						-2.5	(-3.6, -1.4)				<.001	
Dula_3.0 vs Dula_1.5						-1.2	(-2.2, -0.1)				0.034	
Dula_4.5 vs Dula_1.5						-1.2	(-2.3, -0.1)				0.033	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

Body Weight (Kg) from Baseline to Week 18, ITT Population without Post-Rescue or Post Discontinued IP Values

Variable Analyzed: Weight (kg)

Time Point / Treatment	n	Actual Value: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline: Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Within treatment p-value *a*b
Pairwise Comparison						LSMean Change Difference	95% CI for Difference				p-value*a	
Dula_1.5 vs Placebo						-1.3	(-2.4, -0.2)				0.022	
Dula_3.0 vs Placebo						-2.6	(-3.8, -1.5)				<.001	
Dula_4.5 vs Placebo						-2.8	(-3.9, -1.6)				<.001	
Dula_3.0 vs Dula_1.5						-1.3	(-2.4, -0.2)				0.020	
Dula_4.5 vs Dula_1.5						-1.5	(-2.6, -0.3)				0.011	

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

All three doses of dulaglutide (1.5 mg, 3.0 mg and 4.5 mg) significantly reduced body weight from baseline compared to placebo at Week 18.

In addition, both new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg) also reduced body weight significantly compared to dulaglutide 1.5 mg at Week 18.

2.5.2. Main Study

Methods

Title of Study

A Randomized, Double-Blind, Parallel Arm Phase 3 Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus

Primary objective

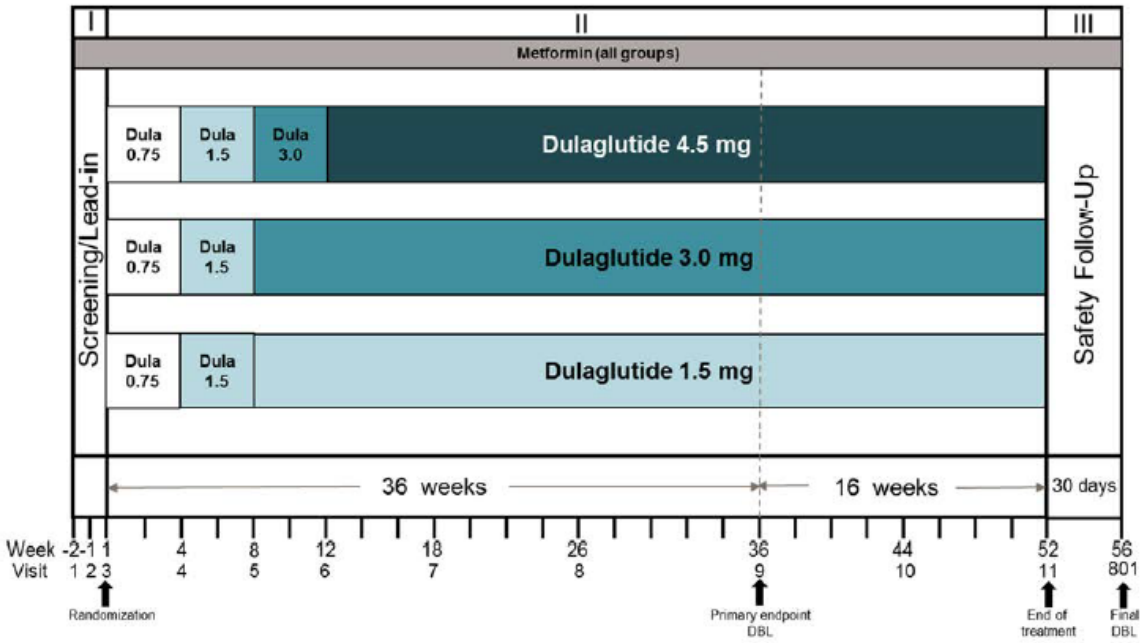
The primary objective of the study was to demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both compared to dulaglutide 1.5 mg on HbA1c change from baseline to Week 36 in patients with inadequately controlled T2D on concomitant metformin therapy.

The primary objective was separately assessed using two estimands, termed an "efficacy estimand" and a "treatment-regimen estimand". For the efficacy estimand, analyses excluded data after premature treatment discontinuation or initiation of new antihyperglycemic therapy for more than 14 days (whichever occurred first). For the treatment-regimen estimand, the analyses included all data collected before and after initiation of new antihyperglycemic therapy, premature treatment discontinuation (or both), with Week 36 missing data imputed using a retrieved drop-out approach.

Study Design

Design of Phase 3 Study GBGL

An overview of the study design is given in the following table:



Abbreviations: DBL = database lock; Dula = dulaglutide.

Main Inclusion Criteria

Patients were eligible for inclusion in the study only if they met all of the inclusion criteria.

A summary of key inclusion criteria is provided below. Eligible patients:

- were men and nonpregnant women aged ≥18 years;
- had T2D for ≥6 months according to the WHO classification or other locally applicable diagnostic standards;
- had HbA1c ≥7.5% and ≤11.0%, inclusive, as assessed by the central laboratory;
- were treated with stable doses of metformin for at least 3 months prior to Visit 1 and between Visit 1 and Visit 3:
    - o The metformin dose was considered stable for this period if all prescribed daily doses were in the range between the minimum required dose (≥1500 mg/day) and the maximum approved dose per country-specific label.
    - o Lower doses were allowed only with documented GI intolerability in the required dose range or a documented eGFR (measured by CKD-EPI) or other renal function measure which requires lower doses per country-specific labelling.
- had stable body weight for at least 3 months prior to Visit 1 (not changed by more than 5% in the past 3 months); and
- had BMI ≥25 kg/m2.

Main Exclusion Criteria

A summary of key exclusion criteria is provided below. Ineligible patients:

- had T1D;
- had used

  - o any glucose-lowering medication other than metformin 3 months prior to study entry or during the Screening and Lead-In Period, or
  - o any GLP-1 RA at any time in the past, or
  - o insulin for chronic conditions (>14 days);
- had been treated with prescription or OTC drugs that promote weight loss:
  - o within 3 months prior to screening (Visit 1), or
  - o between study entry and randomization (Visit 3), or
  - o both; or
  - o was currently (or within the last 3 months) participating in, or planned to initiate within the timeframe of the study, an organized diet and/or exercise weight reduction program other than the lifestyle and dietary measures for diabetes treatment;
- had been treated with any other excluded medication (see below):
  - o within 3 months prior to screening (Visit 1), or
  - o between study entry and randomization (Visit 3), or
  - o both;
  - o Excluded glucocorticoids must not have been used for >14 days within 1 month prior to Visit 1 or between Visits 1 and 3;
- had discontinued metformin therapy, or changed metformin dose or formulation, between Visit 1 and Visit 3;
- had ≥1 episode of severe hypoglycaemia, ≥1 episode of hypoglycaemia unawareness within the 6 months, or both;
- had any of the following CV conditions within 2 months prior to Visit 1:
  - o acute MI, or
  - o NYHA Class III or Class IV heart failure, or
  - o cerebrovascular accident (stroke);
- had chronic or acute pancreatitis any time prior to study entry;
- had known proliferative retinopathy;
- had an eGFR <30 mL/min/1.73 m2 (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by CKD-EPI, as determined by the central laboratory at Visit 1 and confirmed at Visit 2.

Number of Patients

- **Planned:** 1800: dulaglutide 1.5 mg, 600; dulaglutide 3.0 mg, 600; dulaglutide 4.5 mg, 600.
- **Randomized:** 1842: dulaglutide 1.5 mg, 612; dulaglutide 3.0 mg, 616; dulaglutide 4.5 mg, 614.
- **Treated (at least 1 dose):** 1842: dulaglutide 1.5 mg, 612; dulaglutide 3.0 mg, 616; dulaglutide 4.5 mg, 614.

Completed Week 36: 1717: dulaglutide 1.5 mg, 568; dulaglutide 3.0 mg, 571; dulaglutide 4.5 mg, 578.

- **Completed Week 36 on study drug:** 1645: dulaglutide 1.5 mg, 549; dulaglutide 3.0 mg, 544; dulaglutide 4.5 mg, 552.

Study Drug, Dose, and Mode of Administration

The two new higher dose strengths of dulaglutide (3.0 mg or 4.5 mg s.c. once-weekly) were administered via single-dose pen. All patients randomized to one of the investigational dose groups initiated treatment with dulaglutide 0.75 mg once-weekly for 4 weeks followed by 1.5 mg once-weekly for 4 weeks and then 3.0 mg once-weekly for 4 weeks. Thereafter, patients randomized to the 3.0 mg group were maintained

on this dose for the remainder of the treatment period whereas patient randomized to the 4.5 mg group had their dose increased to 4.5 mg once-weekly after 4 weeks of treatment with 3.0 mg once-weekly.

Reference Therapy, Dose, and Mode of Administration

The approved dose strength of dulaglutide (1.5 mg s.c. once-weekly) was administered via single-dose pen. All patients were initiated on treatment with dulaglutide 0.75 mg once-weekly for 4 weeks. Thereafter, the dose of dulaglutide was increased to 1.5 mg once-weekly and maintained for the remainder of the treatment period.

Duration of Treatment

36 weeks for primary endpoint database lock; 52 weeks for final database lock.

Primary and Secondary Outcome Measures

Primary Endpoint

The primary endpoint of this study was to demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both versus dulaglutide 1.5 mg on HbA1c change from baseline to Week 36 in patients with inadequately controlled T2D on concomitant metformin therapy.

The primary and all secondary efficacy outcome measures were separately assessed using two estimands, termed an "*efficacy estimand*" and a "*treatment-regimen estimand*" (for details please refer to statistical methods).

Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary Efficacy Objectives To demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both compared to dulaglutide 1.5 mg for the following secondary efficacy parameters at 36 weeks (controlled for Type 1 error)	• change from baseline in body weight • proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) • change from baseline in FSG
Safety Objectives To compare each investigational dulaglutide dose (4.5 mg, 3.0 mg) to dulaglutide 1.5 mg for the following safety parameters through 36 weeks and 52 weeks	• incidence of TEAEs and discontinuation of study drug due to AEs • adjudicated and confirmed CV and pancreatic AEs • incidence of thyroid neoplasm AEs • incidence of TE dulaglutide ADA and systemic hypersensitivity reactions • change from baseline in PR • ECG parameters • occurrence of hypoglycemic episodes
Pharmacokinetic and Pharmacodynamic Objectives To characterize dulaglutide PK and the dose and/or exposure-response relationships for key efficacy and safety measures	• PK parameters (for example, C_{max}, AUC) at steady state • PD evaluations may include changes from baseline in HbA1c, body weight, and heart rate at Weeks 36 and 52

Abbreviations: ADA = antidrug antibodies; AEs = adverse events; AUC = area under the concentration-time curve; C_{max} = maximum concentration; CV = cardiovascular; ECG = electrocardiogram; FSG = fasting serum glucose;

HbA1c = glycated hemoglobin; PD = pharmacodynamic; PK = pharmacokinetic; PR = pulse rate; TE = treatment emergent; TEAEs = treatment-emergent adverse events.

Exploratory Objectives and Endpoints

Objectives	Endpoints

To compare once-weekly dulaglutide 4.5 mg and 3.0 mg to dulaglutide 1.5 mg for the following exploratory measures through 36 and 52 weeks (unless noted otherwise)	• proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol)
	• change from baseline in 6-point SMPG profile
	• proportion of patients achieving ≥5% body weight loss
	• proportion of patients achieving ≥10% body weight loss
	• proportion of patients meeting the composite endpoint comprised of
	  ○ HbA1c <7.0% (53 mmol/mol), and
	  ○ no weight gain, and
	  ○ no documented symptomatic or severe hypoglycemia
	• proportion of patients meeting the composite endpoint comprised of
	  ○ HbA1c <7.0% (53 mmol/mol), and
	  ○ body weight loss ≥5%, and
	  ○ no documented symptomatic or severe hypoglycemia
	• changes from baseline in
	  ○ fasting plasma glucagon,
	  ○ HOMA2-%B,
	  ○ HOMA2-IR, and
	  ○ C-peptide
	• changes from baseline in
	  ○ serum cystatin C, and
	  ○ cystatin C-based assessment of eGFR
	• incidence of initiation of rescue therapy for severe, persistent hyperglycemia
	• changes from baseline in SBP, DBP, and RPP
	• changes from baseline in serum lipid parameters:
	  ○ total cholesterol,
	  ○ HDL,
	  ○ LDL,
	  ○ VLDL, and
	  ○ triglycerides
	• DID-EQ scores at Week 12
	• changes from baseline in EQ-5D-5L scores
	• changes from baseline in IW-SP scores
	• changes from baseline in APPADL scores

Abbreviations: APPADL = Ability to Perform Physical Activities of Daily Living; DBP = diastolic blood pressure; DID-EQ = Diabetes Injection Device Experience Questionnaire; eGFR = estimated glomerular function; EQ-5D-5L = European Quality of Life 5-Dimension 5-Level; HbA1c = glycated hemoglobin; HDL = highdensity lipoprotein; HOMA2 = Homeostasis Model Assessment-2; HOMA2-%B = β-cell function as measured by the Homeostasis Model Assesment-2 method; HOMA2-IR = insulin resistance as measured by the HOMA2 method; IW-SP = Impact of Weight on Self-Perceptions Questionnaire; LDL = low-density lipoprotein; RPP = rate pressure product; SBP = systolic blood pressure; SMPG = self-monitored plasma glucose; VLDL = very-low-density lipoprotein.

Randomization
Patients will be randomized in a 1:1:1 ratio to dulaglutide 4.5 mg, dulaglutide 3.0 mg and dulaglutide 1.5 mg. Randomization will be stratified by country and HbA1c (<8.5% [69 mmol/mol], ≥8.5% [69 mmol/mol]).

Blinding
This is a double-blind study. Investigators, site staff, clinical monitors and patients will remain blinded to the treatment assignments until the study is complete. To preserve the blinding of the study, the Sponsor will be blinded to treatment assignments until after the primary endpoint (Week 36) database lock.

Target of estimation (Estimand)
Two different strategies (estimands) to handle intercurrent events are specified. Relevant intercurrent events are premature treatment discontinuation (untreated afterwards), initiation of new antihyperglycemic agent (with discontinuation of study treatment) and use of rescue medication/new antihyperglycemic agent on top of study treatment. [Only few patients (14.7%) had an intercurrent event up until week 36 and distribution was similar across treatment arms. 8.7%, 4.0% and 2.0% discontinued treatment completely, initiated new antihyperglycemic medications without discontinuing treatment and switched from study treatment to new anti-hyperglycaemic medications, respectively.]

The 'efficacy estimand' (primary estimand for EU; also referred to as ''on-treatment without initiation of new antihyperglycemic medications") is based on a hypothetical strategy targeting the effect if all patients had continued study treatment as planned and rescue medication/other antihyperglycemic agents had not been available. For this estimand, data collected after initiation of any new antihyperglycemic medication for more than 14 days or premature treatment discontinuation are excluded.

The 'treatment regimen estimand' (primary for US FDA), is based on a treatment policy strategy targeting the effect regardless of treatment discontinuation and use of rescue medication/other antihyperglycemic agents. Data collected after initiation of other antihyperglycemic therapy and/or after premature treatment discontinuation will be used.

While it is agreed that both estimands can be tested at the full alpha level of 0.05 (efficacy estimand is specified as primary for EU), the treatment regimen estimand is considered of less regulatory relevance due to being blurred by the effect of alternative antihyperglycemic agents/rescue medication.

Definition of the primary estimand (the 'efficacy estimand') is in part agreed. While targeting the effect if rescue medication/other antihyperglycemic agents had not been available is considered reasonable, use of a treatment policy strategy is considered of higher relevance for discontinuation of study treatment (in particular if treatment is discontinued due to adverse events). Hence, the estimand targeting the effect regardless of treatment discontinuation and had rescue medication or other antihyperglycemic agents not been available is considered of higher relevance as it takes the issue of drug tolerability into account. This estimand is in line with the draft guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2), and it is similar to the pre-specified primary 'efficacy estimand', but differs in the handling of true treatment discontinuation and switching from study treatment to new antihyperglycemic agent due to AEs. Additional analyses targeting the newly described estimand were provided. However, (1) as results for all three estimands are consistent (similar dose-relating effects for all) and in line with incremental effect of other antidiabetic medications for which several doses are approved , (2) as the newly proposed estimand may actually overestimate the effect of drug tolerability (because all treatment discontinuations regardless of reason are accounted for) and (3) as there are some issues with estimation of the newly proposed estimand (see below), it is agreed to primarily report results of the pre-specified primary efficacy estimand. Therefore, also no detailed results of the newly proposed estimand are reported in this document.

Sample size

A sample size of 600 patients per group will provided ≥80% power to demonstrate superiority of at least one of the investigational dulaglutide doses (4.5 mg or 3.0 mg) to dulaglutide 1.5 mg with respect to the primary endpoint, assuming a 15% dropout rate and a treatment effect of -0.22% (standard deviation of 1.1%) for either of the investigational doses (two-sided alpha of 0.05).

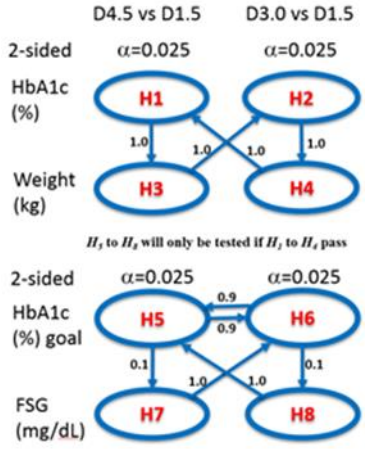
Statistical methods

Efficacy analysis were based on the ITT population (all randomized patients receiving at least one dose of study treatment). Still, patients without baseline assessment were excluded from analyses using the treatment-regimen estimand and patients without baseline or without post-baseline assessments will be excluded from analysis using the efficacy estimand. This is generally not agreed. However, additional analyses were provided that support the conclusion that no relevant bias was introduced by the exclusions.

The pre-specified efficacy estimand analysis for the primary endpoint and other longitudinal continuous endpoints (change from baseline to week 36 in HbA1c, body weight and FSG) employed a mixed-model repeated measurements (MMRM) included factors for treatment, pooled country, visit, treatment-by-visit interaction, and baseline as a covariate. An unstructured covariance structure will be used to model the within-patient errors. For analyses of body weight and FSG, the baseline HbA1c stratum (≥8.5% [69 mmol/mol] and <8.5%) was added to this model as a fixed effect. The proportion of patients achieving target HbA1c <7.0% at Week 36 was analyzed using a longitudinal logistic regression with repeated measurements using the same covariates as for the MMRM analysis. While the covariates included and the data included (only on-treatment data) are acceptable for the efficacy estimand, , further sensitivity analyses were requested (in addition to the ones listed below) to assess robustness of results with regard to deviations from the missing-at-random (MAR) assumption underlying the MMRM and the longitudinal logistic regression. As a potentially conservative missing data handling approach analyses using reference-based imputations (jump to reference and copy reference) were conducted for the efficacy estimand. These analyses yield smaller effect estimates as compared to the primary analysis but overall support the robustness of results. Such analyses can also be interpreted as addressing the above discussed estimand of higher regulatory interest if data collected after true treatment discontinuation are included. Corresponding analyses for the newly proposed estimand were provided and results were overall consistent with results for the other estimands. Still, it has to be considered that jump-to-reference (J2R) imputation is usually applied in placebo-controlled trials and then aligned to the newly proposed estimand, as imputations following treatment discontinuation reflect the effect of 'no treatment' (mimicked by the placebo arm). Nevertheless, J2R-based imputation was considered as a potentially conservative approach to estimate treatment effects (i.e. difference between treatment arms) for the newly proposed estimand in this active controlled trial, although estimated average changes from baseline within each treatment arm can be difficult to interpret. The treatment-regimen estimand analysis for the primary endpoint and other longitudinal continuous endpoints employed an analysis of covariance (ANCOVA) model applied to multiply imputed data (1000 imputations). Missing Week 36 data were imputed based on measurements from patients with the same treatment group, the same status of premature treatment discontinuation (yes, no) and measured (primary) Week 36 endpoint data. The ANCOVA included pooled country and treatment as fixed effects, and baseline as a covariate and inference was based on pooled estimates. For analyses of body weight and FSG, the baseline HbA1c stratum was added to this model as a fixed effect. There are some issues with this analysis (not completely pre-specified and status 'other antihyperglycemic medication (yes/no)' is not considered), which are not considered of further concern, as the treatment regimen estimand is considered of less regulatory relevance. For the treatment-regimen estimand and the HbA1c target <7.0% endpoint, a logistic regression model was fit to the complete data (missing data imputed as non-response). Pooled country and treatment were included as fixed effects, and baseline HbA1c as a covariate.

In order to assess the robustness of results for the primary/secondary endpoints, several sensitivity/supplementary analyses were conducted. Per-protocol and completers populations were evaluated separately using the same MMRM model as described above. Data collected after initiation of new antihyperglycemic medications, treatment discontinuation, or both was excluded. Primary/secondary endpoints were analyzed using an analysis of covariance model (continuous endpoints) or logistic regression (binary endpoints) using on-treatment data and last observation carried forward (LOCF) imputation. The logistic regression model was also applied (1) counting patients who initiated new antihyperglycemic medications, discontinued, or both prior to Week 36 as not achieving HbA1c target and (2) to the multiply imputed complete dataset (see above).

Multiplicity was properly controlled across the primary and secondary endpoints based on the following graphical procedure. Adjusted p-values and simultaneous confidence intervals in line with the graphical procedure were provided for the pre-specified MMRM analysis of the primary efficacy estimand, and adjusted p-value information is reported in the SmPC.



Abbreviations: D1.5 = once-weekly dulaglutide 1.5 mg; D3.0 = once-weekly dulaglutide 3.0 mg; D4.5 = once-weekly dulaglutide 4.5 mg; FSG = fasting serum glucose; H = hypothesis; HbA1c = glycated hemoglobin.

H_1: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in mean change from baseline in HbA1c at 36 weeks
H_2: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in mean change from baseline in HbA1c at 36 weeks
H_3: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in mean change from baseline in body weight at 36 weeks
H_4: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in mean change from baseline in body weight at 36 weeks
H_5: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in proportion of patients achieving an HbA1c <7.0% at 36 weeks
H_6: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in proportion of patients achieving an HbA1c <7.0% at 36 weeks
H_7: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in mean change from baseline in FSG at 36 weeks
H_8: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in mean change from baseline in FSG at 36 weeks

Results

Patient Disposition and Sample Size

The GBGL study was conducted at 203 study centers in 15 countries. Date of first patient enrolled (assigned to therapy) was 19 April 2018 and date of last patient completed Week 36 was 28 May 2019.

A total of 2739 patients were screened and 1842 patients were randomly assigned to treatment, received at least 1 dose of study drug, and were included in the ITT population (dulaglutide 1.5 mg, N=612; dulaglutide 3.0 mg, N=616; dulaglutide 4.5 mg, N=614). Of the 897 patients not randomized, the majority (93.1%) were screen failures because they did not meet protocol entry criteria.

A total of 1842 patients were randomized and 1717 (93.2%) completed the Week 36 primary endpoint visit; 1645 of 1842 randomized patients (89.3%) completed the Week 36 primary endpoint visit on study drug. There were no significant differences across dulaglutide dose groups in the proportion of patients discontinuing the study (p=0.533) or study drug (p=0.623) prior to Week 36. The most frequent reason for premature discontinuation of study drug was due to AE (4.9%) and was similar for dulaglutide 1.5 mg (4.2%), dulaglutide 3.0 mg (5.5%) and dulaglutide 4.5 mg (5.0%) (p=0.593).

Baseline characteristics

Summary and Analysis of Patient Demographics and Clinical Characteristics at Baseline, Intent-to-Treat Population

Parameter	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)	Total (N=1842)
Age (years), mean ± SD	57.8 ± 9.7	56.9 ± 10.2	56.6 ± 10.2	57.1 ± 10.0
≥65 years, n (%)	156 (25.5)	150 (24.4)	132 (21.5)	438 (23.8)
≥75 years, n (%)	20 (3.3)	14 (2.3)	21 (3.4)	55 (3.0)
Duration of diabetes (years), mean ± SD	7.6 ± 5.8	7.6 ± 5.5	7.7 ± 5.8	7.6 ± 5.7
Female, n (%)	314 (51.3)	288 (46.8)	296 (48.2)	898 (48.8)
Race, n (%)				
American Indian or Alaska Native	30 (4.9)	26 (4.2)	32 (5.2)	88 (4.8)
Asian	13 (2.1)	18 (2.9)	14 (2.3)	45 (2.4)
Black or African American	28 (4.6)	31 (5.0)	23 (3.7)	82 (4.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.2)	3 (0.5)	5 (0.3)
White	529 (86.4)	521 (84.6)	530 (86.3)	1580 (85.8)
Multiple	11 (1.8)	19 (3.1)	12 (2.0)	42 (2.3)
eGFR (mL/min/1.73 m^2), mean ± SD	93.4 ± 18.2	93.3 ± 17.8	93.7 ± 18.3	93.5 ± 18.1
HbA1c (%), mean ± SD	8.6 ± 0.9	8.6 ± 1.0	8.6 ± 0.9	8.6 ± 1.0
BMI (kg/m^2), mean ± SD	34.4 ± 6.4	34.3 ± 6.2	34.0 ± 6.2	34.2 ± 6.3
Weight (kg), mean ± SD	95.5 ± 20.2	96.3 ± 20.1	95.4 ± 20.6	95.7 ± 20.3
Systolic Blood Pressure (mmHg), mean ± SD	132.1 ± 14.2	131.1 ± 14.1	132.1 ± 14.0	131.8 ±14.1
Diastolic Blood Pressure, (mmHg), mean ± SD	78.8 ± 9.3	78.4 ± 8.7	79.0 ± 9.0	78.7 ± 9.0
Heart Rate (bpm), mean ± SD	75.6 ± 10.1	75.3 ± 9.5	75.5 ± 10.3	75.5 ± 10.0
Fasting Serum Glucose (mg/dL), mean ± SD	185.0 ± 52.0	184.0 ± 54.4	183.4 ± 48.0	184.1 ± 51.5

Abbreviations: BMI = body mass index; Dula = dulaglutide; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; N = number of patients randomized and treated; n = number of patients in the specified category; SD = standard deviation.

The distribution of patients by age group and dulaglutide dose is presented in the following table:

Table 5.113. Distribution of Patients by Age Category and Dulaglutide Dose

Dulaglutide Dose Group	Age <65 Years (N=1404) n (%)	Age 65-74 Years (N=383) n (%)	Age 75-84 Years (N=54) n (%)	Age ≥85 Years (N=1) n (%)
1.5 mg	456 (32.5)	136 (35.5)	20 (37.0)	0
3.0 mg	466 (33.2)	136 (35.5)	13 (24.1)	1 (100)
4.5 mg	482 (34.3)	111 (29.0)	21 (38.9)	0

Abbreviations: n = number of patients in the specified category; N = number of patients randomized and treated.

Per protocol, all patients were taking metformin at baseline. Metformin dose was similar across the three dulaglutide dose groups (median daily dose, 2000 mg). Only 1 patient was receiving any other antihyperglycaemic medication at baseline. This patient was treated with insulin for hyperglycemia

considered by the investigator to require emergent treatment (allowed per protocol), beginning

3 days prior to randomization and ending on the day of randomization.

The most common antihyperglycemic medications (other than metformin) reported during the 36-week treatment period (Visit 3 to Visit 9) were SGLT-2 inhibitors (3.9%), sulfonylureas (2.0%), and insulin (1.6%).

A total of 91 patients (4.9%) received rescue medication due to severe, persistent hyperglycemia during the treatment period with no significant difference in the dulaglutide treatment arms [1.5 mg, 31 (5.1%); 3.0 mg, 29 (4.7%); 4.5 mg, 31 (5.0%)].

The use of concomitant medications after randomization was similar to the use at baseline. The most frequent concomitant medications were antihypertensives (70.7% at baseline and 72.1% after randomization), lipid-lowering agents (55.0% at baseline and 58.0% after randomization) and anti-thrombotic agents (27.6% at baseline and 29.6% after randomization).

Compliance

Patients were allowed under the protocol to temporarily interrupt and then resume study drug.
The number of patients with at least 1 study drug interruption reported due to an AE was similar across the dulaglutide dose groups (1.5 mg, 17 patients [2.8%]; 3.0 mg, 21 patients [3.4%]; 4.5 mg, 18 patients [2.9%]). Over the entire treatment period through Week 36, 95.4% of patients in the ITT population were evaluated by the investigator to be compliant with injectable study medication (having received at least 75% of doses of dulaglutide for at least 75% of visits).

Protocol Deviations

The most common category of protocol deviation was related to informed consent (6.7%). Protocol deviations related to informed consent were primarily categorized as "lost or late consent" which was most often caused by patients not signing an updated ICF on the next scheduled study visit. All patients eventually signed the most recent, approved version of the ICF.

Efficacy results

Primary endpoint

The primary endpoint of this study was to demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both versus dulaglutide 1.5 mg on HbA1c change from baseline to Week 36 in patients with inadequately controlled T2D on concomitant metformin therapy.

The primary and all secondary efficacy outcome measures were separately assessed using two estimands, termed an "*efficacy estimand*" and a "*treatment-regimen estimand*":

- For the *efficacy estimand*, analyses excluded data after premature treatment discontinuation or initiation of new antihyperglycemic therapy for more than 14 days (whichever occurred first).
- For the *treatment-regimen estimand*, the analyses included all data collected before and after initiation of new antihyperglycemic therapy, premature treatment discontinuation (or both), with Week 36 missing data imputed using a retrieved drop-out approach.

Primary Efficacy Endpoint: Change from Baseline in HbA1c at Week 36, ITT Population

	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)
Primary Objective			
HbA1c (%)			
Efficacy Estimand[a]			
LS mean change from baseline at Week 36	-1.53	-1.71	-1.87
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.17* (-0.29, -0.06)	-0.34** (-0.45, -0.22)
Treatment-Regimen Estimand[b]			
LS mean change from baseline at Week 36	-1.54	-1.64	-1.77
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.10 (-0.23, 0.02)	-0.24** (-0.36, -0.11)

Abbreviations:
ANCOVA = analysis of covariance; CI = confidence interval; Dula = dulaglutide; HbA1c = glycated hemoglobin; LS = least-squares; N=number of patients randomized and treated; N/A=not applicable.

Notes: The treatment-regimen included only patients with a non-missing baseline value; the efficacy estimand included only patients with a non-missing baseline value and at least 1 non-missing post-baseline value of the response variable. Analyses for treatment-regimen estimand included data after treatment discontinuation or initiation of new antihyperglycemic medications; analyses for efficacy estimand excluded data after treatment discontinuation or initiation of new antihyperglycemic medications.

a Mixed-model repeated measures analysis.
b ANCOVA with multiple imputation.
c Longitudinal logistic regression.
d Logistic regression with missing Week 36 HbA1c classified as not achieving HbA1c target.
Note: p-values are only indicated when statistical significance was met under graphical testing procedure.
* The p-value <0.05 versus dulaglutide 1.5 mg.
** The p-value <0.001 versus dulaglutide 1.5 mg.

Using the *efficacy estimand*, the least squares mean HbA1c changes from baseline to Week 36 were for dulaglutide 1.5 mg: -1.53%, for dulaglutide 3.0 mg: -1.71%, and for dulaglutide 4.5 mg: -1.87%.

The mean treatment difference in HbA1c reduction versus the dulaglutide 1.5 mg group was -0.34% in the dulaglutide 4.5 mg group (p<0.001), and -0.17% in the dulaglutide 3.0 mg group (p=0.003).

Using the *treatment-regimen estimand*, the least squares mean HbA1c changes from to Week 36 were for dulaglutide 1.5 mg: -1.54%, for dulaglutide 3.0 mg: -1.64%, and for dulaglutide 4.5 mg: -1.77%. The mean treatment difference in HbA1c reduction versus the dulaglutide 1.5 mg group was -0.24% in the dulaglutide 4.5 mg group (p<0.001), and -0.10% in the dulaglutide 3.0 mg group (ns; p=0.096).

Supportive Analyses of the Primary Endpoint

Summary and Analysis of HbA1c (%) from Baseline to Week 36, Per Protocol Population*

Variable Analyzed: BLOOD Hemoglobin A1C HPLC - VARIANT (%)

Time Point Treatment	n	Actual Value Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline Mean (SD)	Min	Median	Max	LSMean (SE) *a*b	Within treatment p-value *a*b
Week 36 (Visit 9)												
Dula 1.5	540	7.00 (0.988)	4.90	6.80	12.30	7.00 (0.040)	-1.63 (1.058)	-4.50	-1.60	4.10	-1.62 (0.040)	<.001
Dula 3.0	529	6.86 (1.026)	4.90	6.60	12.40	6.86 (0.040)	-1.77 (1.079)	-5.10	-1.70	3.00	-1.76 (0.040)	<.001
Dula 4.5	528	6.69 (0.947)	4.90	6.50	13.50	6.70 (0.040)	-1.91 (1.107)	-5.40	-1.90	3.80	-1.92 (0.040)	<.001

Pairwise Comparison	LSMean Change Difference *a*b*c	95% CI for Difference *a*b*c	p-value *a*b*c
Dula 3.0 vs Dula 1.5	-0.14	(-0.25,-0.03)	0.014
Dula 4.5 vs Dula 1.5	-0.29	(-0.41,-0.18)	<.001
Dula 4.5 vs Dula 3.0	-0.16	(-0.27,-0.04)	0.006

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

*Per-Protocol (PP) Population included all patients of the ITT population who met all of the following criteria:

- had no important protocol deviation that impacted the assessment of the primary endpoint;
- completed the Treatment Period through 36 weeks (Visit 9);
- had a value of the primary efficacy measure (HbA1c) at Week 36 (Visit 9).

Summary and Analysis of HbA1c (%) from Baseline to Week 36, Completers Population**

Variable Analyzed: BLOOD Hemoglobin A1C HPLC - VARIANT (%)

Time Point Treatment	n	Actual Value Mean (SD)	Min	Median	Max	LSMean (SE) *a*b*c	Change from Baseline Mean (SD)	Min	Median	Max	LSMean (SE) *a*b	Within treatment p-value *a*b
Week 36 (Visit 9)												
Dula 1.5	567	7.03 (1.004)	4.90	6.90	12.30	7.03 (0.040)	-1.60 (1.065)	-4.50	-1.50	4.10	-1.60 (0.040)	<.001
Dula 3.0	572	6.92 (1.062)	4.90	6.70	12.40	6.92 (0.040)	-1.70 (1.102)	-5.10	-1.65	3.00	-1.71 (0.040)	<.001
Dula 4.5	575	6.79 (1.017)	4.90	6.60	13.50	6.79 (0.040)	-1.84 (1.136)	-5.40	-1.80	3.80	-1.84 (0.040)	<.001

Pairwise Comparison	LSMean Change Difference *a*b*c	95% CI for Difference *a*b*c	p-value *a*b*c
Dula 3.0 vs Dula 1.5	-0.11	(-0.22, 0.00)	0.053
Dula 4.5 vs Dula 1.5	-0.25	(-0.36,-0.14)	<.001
Dula 4.5 vs Dula 3.0	-0.14	(-0.25,-0.03)	0.015

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LSMean = least squares mean; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

**Completers Population included all patients in the ITT population who had an HbA1c measure at Week 36 (Visit 9), regardless of compliance with the protocol, initiation of new antihyperglycemic medications, or treatment discontinuation.

Supportive analyses of the primary endpoint (changes from baseline to Week 36 in HbA1c) were conducted in the PP Population and Completers Population. Results of each of the supportive analyses were consistent with the primary analysis.

Secondary Efficacy Measures

Secondary efficacy measures were to demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both compared to dulaglutide 1.5 mg at 36 weeks for change from baseline in body weight, proportion of patients achieving HbA1c target <7.0%, and change from baseline in fasting serum glucose (mg/dL). As for the primary endpoint, two estimands were used to compare the dulaglutide dose groups for the secondary efficacy measures: an efficacy estimand and a treatment-regimen estimand.

	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)
Secondary Objectives			
Body Weight (kg)			

Efficacy Estimand[a]			
LS mean change from baseline at Week 36	-3.1	-4.0	-4.7
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.9* (-1.4, -0.4)	-1.6** (-2.1, -1.1)
Treatment-Regimen Estimand[b]			
LS mean change from baseline at Week 36	-3.0	-3.8	-4.6
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.9 (-1.4, -0.4)	-1.6** (-2.2, -1.1)
Percentage of patients with HbA1c <7.0% (53 mmol/mol) at Week 36 (%)			
Efficacy Estimand[c]	57.0	64.7*	71.5**
Treatment-Regimen Estimand[d]	49.7	55.8	62.2
Fasting Serum Glucose (mg/dL)			
Efficacy Estimand[a]			
LS mean change from baseline at Week 36	-44.2	-47.9	-52.3
LS mean difference from dula 1.5 mg (95% CI)	N/A	-3.7 (-7.8, 0.5)	- 8.1** (-12.3, -3.9)
Treatment-Regimen Estimand[b]			
LS mean change from baseline at Week 36	-44.9	-46.4	-51.2
LS mean difference from dula 1.5 mg (95% CI)	N/A	- 1.6 (-6.6, 3.5)	-6.4 (-11.2, -1.6)

Abbreviations:

ANCOVA = analysis of covariance; CI = confidence interval; Dula = dulaglutide; HbA1c = glycated hemoglobin; LS = least-squares; N=number of patients randomized and treated; N/A=not applicable.

Notes: The treatment-regimen included only patients with a non-missing baseline value; the efficacy estimand included only patients with a non-missing baseline value and at least 1 non-missing post-baseline value of the response variable. Analyses for treatment-regimen estimand included data after treatment discontinuation or initiation of new antihyperglycemic medications; analyses for efficacy estimand excluded data after treatment discontinuation or initiation of new antihyperglycemic medications.

a Mixed-model repeated measures analysis.

b ANCOVA with multiple imputation.

c Longitudinal logistic regression.

d Logistic regression with missing Week 36 HbA1c classified as not achieving HbA1c target.

Note: p-values are only indicated when statistical significance was met under graphical testing procedure.

* The p-value <0.05 versus dulaglutide 1.5 mg.

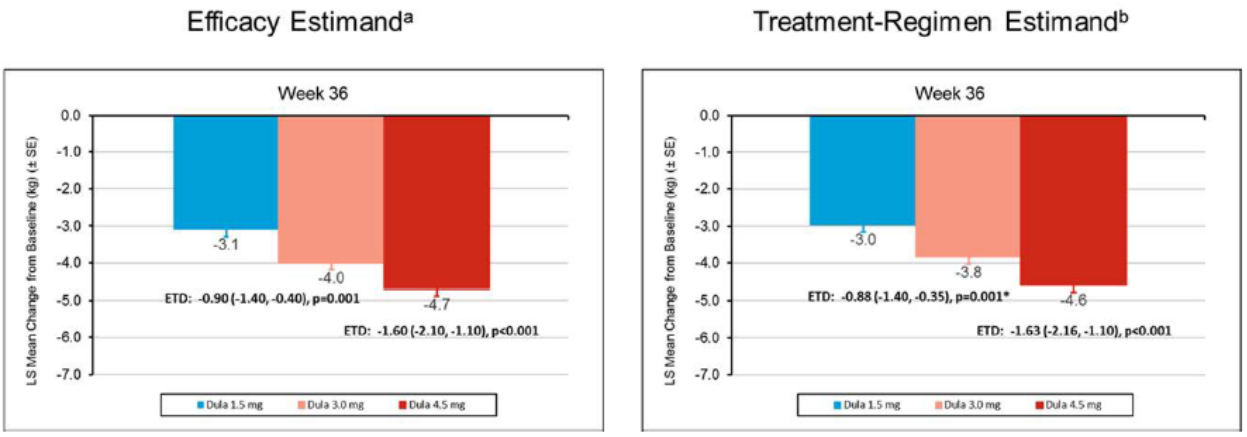
** The p-value <0.001 versus dulaglutide 1.5 mg.

Change in Body Weight from Baseline to Week 36

Using the efficacy estimand, the least squares mean changes in body weight from baseline to Week 36 were for dulaglutide 1.5 mg: -3.1 kg, for dulaglutide 3.0 mg: -4.0 kg, and for dulaglutide 4.5 mg: -4.7 kg. The mean treatment difference in change in body weight versus dulaglutide 1.5 mg was -1.60 kg in the dulaglutide 4.5 mg group (p<0.001) and -0.90 kg in the dulaglutide 3.0 mg group (p=0.001).

Using the treatment-regimen estimand, the least squares mean changes in body weight from baseline to Week 36 were for dulaglutide 1.5 mg: -3.0 kg, for dulaglutide 3.0 mg: -3.8 kg, and for dulaglutide 4.5 mg: -4.6 kg. The mean treatment difference in change in body weight versus dulaglutide 1.5 mg

was -1.63 kg in the dulaglutide 4.5 mg group (p<0.001) and -0.88 kg in the dulaglutide 3.0 mg group (nominal p=0.001).

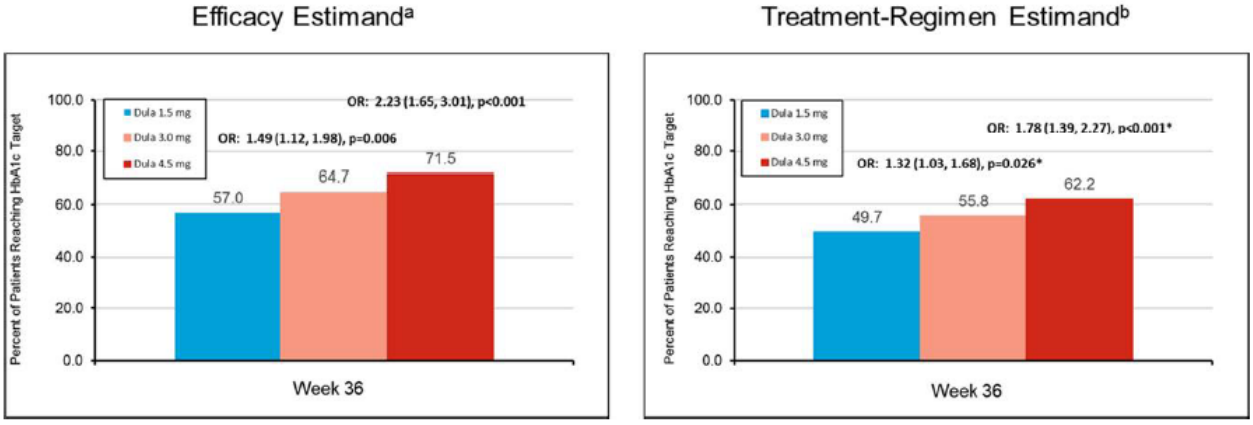


Abbreviations:
Dula = dulaglutide; ETD = estimated treatment difference; LS = least-squares; SE = standard error.
a Only patients with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in this analysis. The analysis includes data collected up to either early treatment discontinuation or initiation of new antihyperglycemic therapy.
b Only patients with non-missing baseline values were included in the analysis. Missing values were imputed by treatment and by the same status of premature treatment discontinuation (yes, no) using multiple imputation method.
* Nominal p-value, not adjusted for multiplicity.
Note: ETD = LS Mean Difference (95% confidence interval).

Proportion of Patients Achieving HbA1c Target <7.0% at Week 36

Using the efficacy estimand, the percent of patients achieving an HbA1c <7% by dulaglutide dose group were for dulaglutide 1.5 mg: 57.0%, for dulaglutide 3.0 mg: 64.7% (odds ratio [95% CI] versus 1.5 mg=1.49 [1.12, 1.98], p=0.006), and for dulaglutide 4.5 mg: 71.5% (odds ratio [95% CI] versus 1.5 mg=2.23 [1.65, 3.01], p<0.001).

Using the treatment-regimen estimand, the percent of patients achieving an HbA1c <7% by dulaglutide dose group were for dulaglutide 1.5 mg: 49.7%, for dulaglutide 3.0 mg: 55.8% (odds ratio [95% CI] versus 1.5 mg=1.32 [1.03, 1.68], nominal p=0.026*), and for dulaglutide 4.5 mg: 62.2% (odds ratio [95% CI] versus 1.5 mg=1.78 [1.39, 2.27], nominal p<0.001*).



Abbreviations: Dula = dulaglutide; HbA1c = glycated hemoglobin; OR = odds ratio.

a Only patients with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in this analysis. The analysis includes data collected up to either early treatment discontinuation or initiation of new antihyperglycemic therapy.
b Only patients with non-missing baseline values were included in the analysis. Missing Week 36 HbA1c was classified as not achieving HbA1c target.
* Nominal p-value, not adjusted for multiplicity.
Note: OR = Odds Ratio (95% confidence interval).

Both investigational doses of dulaglutide (3.0 mg and 4.5 mg) were superior to the 1.5 mg dose in the secondary efficacy objective of percent of patients achieving HbA1c <7% using the efficacy estimand: More patients achieved an HbA1c<7% at Week 36 with dulaglutide 4.5 mg 71.5% (odds ratio [95% CI] versus 1.5 mg=2.23 [1.65, 3.01]; p<0.001) and dulaglutide 3.0 mg 64.7% (odds ratio [95% CI] versus 1.5 mg=1.49 [1.12, 1.98], p=0.006) compared to the 1.5 mg dose (57%).

Using the treatment-regimen estimand, percent of patients achieving an HbA1c <7% at Week 36 were 62.2%, 55.8% and 49.7% for dulaglutide 4.5 mg, 3.0 mg and 1.5 mg, respectively.

Although the nominal p-value (not adjusted for multiplicity) was <0.001 for dulaglutide 4.5 mg vs 1.5 mg and 0.026 for the 3.0 mg vs 1.5 mg comparison, these results were not statistically significant based on the graphical testing approach used to control for type I error.

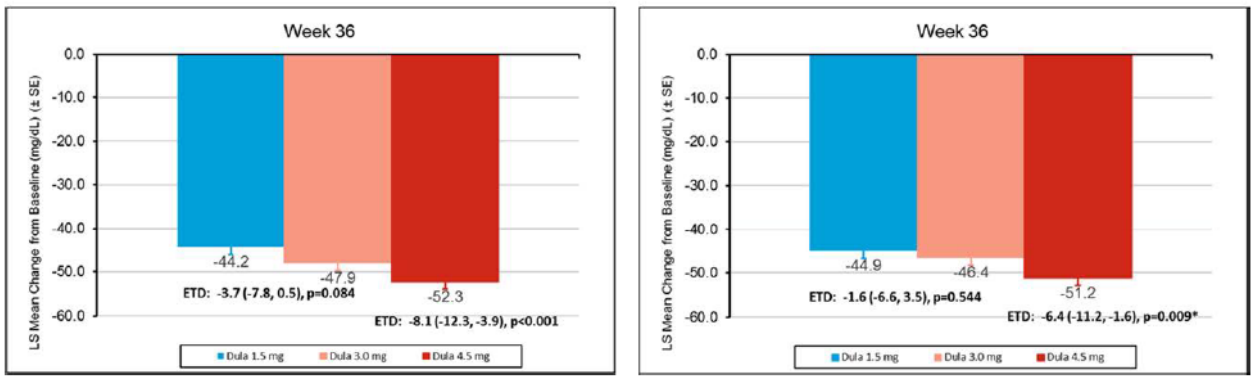
Change in Fasting Serum Glucose (mg/dL) from Baseline to Week 36

Using the efficacy estimand, the LS mean changes in fasting serum glucose from baseline to Week 36 were -44.2 mg/dL, -47.9 mg/dL, and -52.3 mg/dL for dulaglutide 1.5 mg, 3.0 mg and 4.5 mg.

The mean treatment difference was -8.1 mg/dL (p<0.001) between dulaglutide 4.5 mg and 1.5 mg and -3.7 md/dL (p=0.084, not significant) between dulaglutide 3.0 mg and 1.5 mg.

Using the treatment-regimen estimand, the LS mean changes in fasting serum glucose from baseline to Week 36 were -44.9 mg/dL, -46.4 mg/dL, and -51.2 mg/dL for dulaglutide 1.5 mg, 3.0 mg and 4.5 mg. The mean treatment difference was -6.4 mg/dL (nominal p=0.009) between dulaglutide 4.5 mg and 1.5 mg and -1.6 mg/dL (p=0.544, not significant) between dulaglutide 3.0 mg and 1.5 mg.

Efficacy Estimand[a] | Treatment-Regimen Estimand[b]



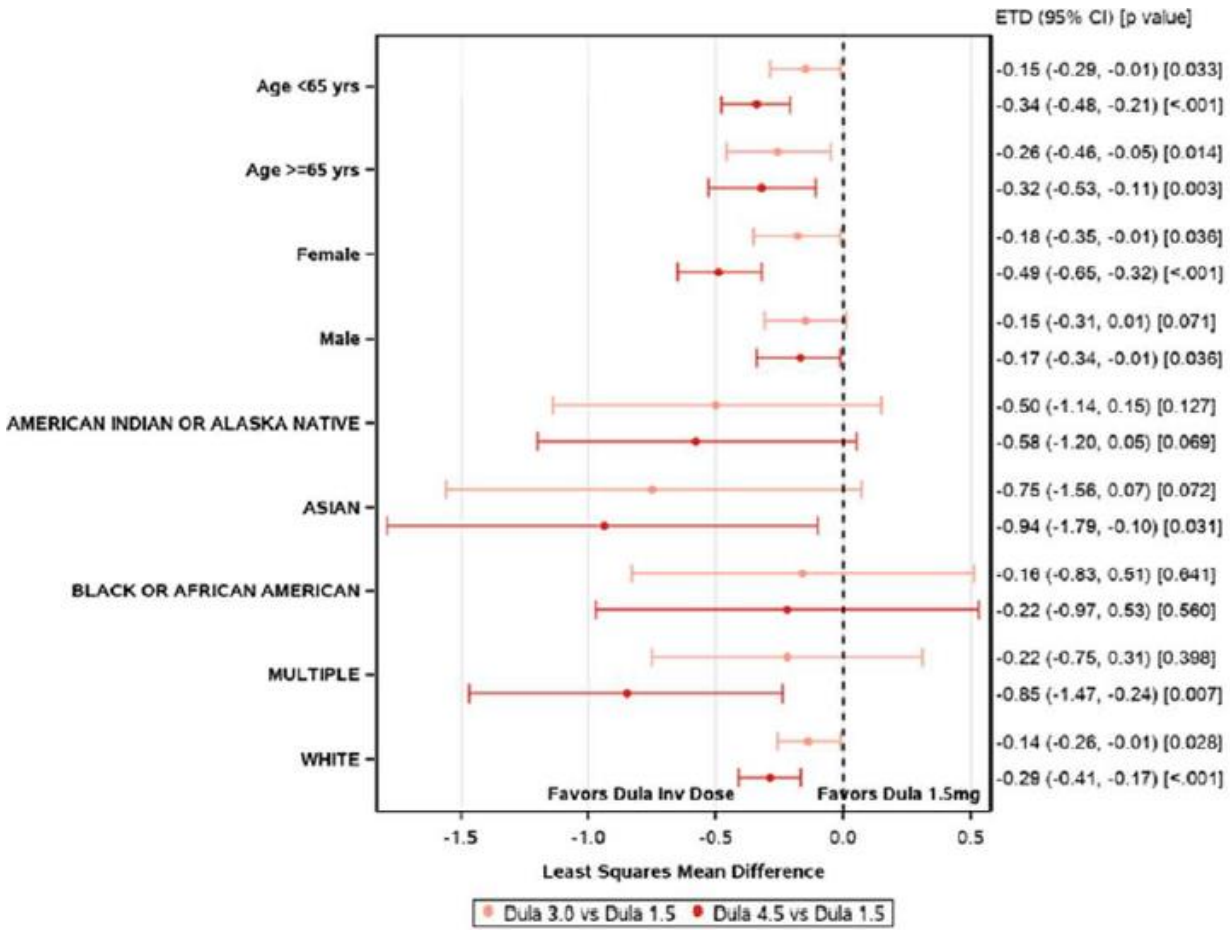
Abbreviations: Dula = dulaglutide; ETD = estimated treatment difference; LS = least-squares; SE = standard error.
a Only patients with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in this analysis. The analysis includes data collected up to either early treatment discontinuation or initiation of new antihyperglycemic therapy.
b Missing values were imputed by treatment and by the same status of premature treatment discontinuation (yes, no) using multiple imputation method.

* Nominal p-value, not adjusted for multiplicity.
Note: ETD = LS Mean Difference (95% confidence interval).

The secondary efficacy measure of superiority over dulaglutide 1.5 mg for change in fasting serum glucose from baseline to Week 36 was met with the dulaglutide 4.5 mg dose for the efficacy estimand (-8.1 mg/dL, p<0.001) but not the treatment-regimen estimand (-6.4 mg/dL, nominal p=0.009, not adjusted for multiplicity). For dulaglutide 3.0 mg, superiority for the secondary efficacy measure of fasting serum glucose was not met for the efficacy estimand (-3.7 mg/dL, p=0.084) and the treatment-regimen estimand (-1.6 mg/dL, p=0.544).

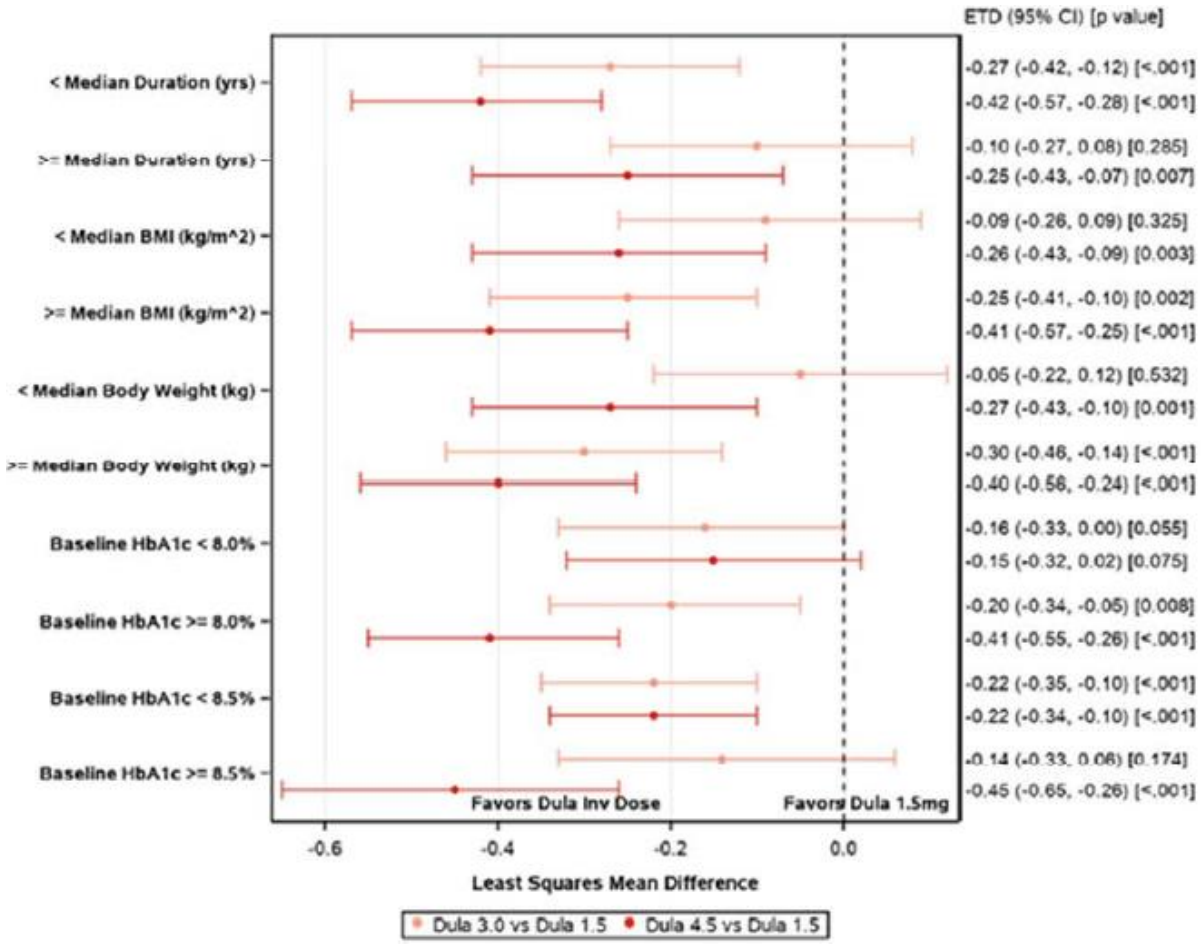
Subgroup Analyses on Primary Endpoint
A forest plot for treatment differences between investigational doses (dulaglutide 3.0 mg and 4.5 mg) versus the 1.5 mg dose in HbA1c changes from baseline to Week 36 by subgroup is provided below.

Forest plot for subgroup analyses of changes from baseline in HbA1c (%), by treatment group at Week 36, intent-to-treat population on-treatment without new antihyperglycemic medications.



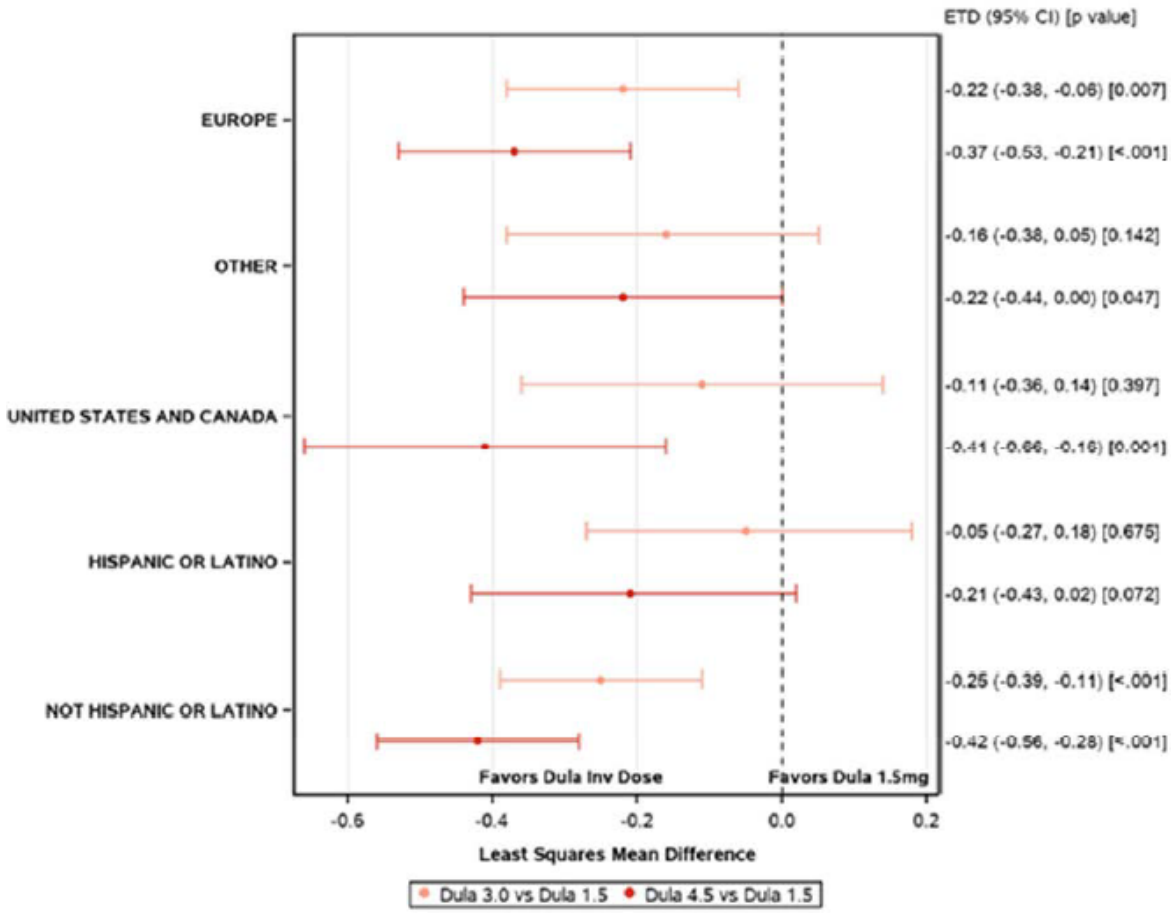
A significant treatment-by-sex interaction was observed for the primary endpoint of change in HbA1c using the efficacy estimand. For female patients, the LS mean changes in HbA1c from baseline to Week 36 were:

-1.52%, -1.70% and -2.01% for dulaglutide 1.5 mg, 3.0 mg and 4.5 mg, respectively and for male patients: -1.56%, -1.71% and -1.73%.The treatment-by-sex interaction was due primarily to a greater LS mean decrease in HbA1c in the dulaglutide 4.5 mg group in females versus males, whereas change in HbA1c was comparable between females and males for both the 1.5 mg and 3.0 mg dose groups. According to the applicant, this interaction may have been a chance finding, as there was no significant treatment-by-sex interaction effect on the change in HbA1c in any of the AWARD studies included in the original dulaglutide submission, and there is no known biological mechanism by which GLP-1 RA would be expected to have inherently different efficacy in females versus males with T2D.



For patients with baseline HbA1c <8.5%, the LS mean changes in HbA1c from baseline to Week 36 were: -1.16%, -1.38% and -1.38% for dulaglutide 1.5 mg, 3.0 mg and 4.5 mg, respectively and for patients with baseline HbA1c ≥8.5%: -1.89%, -2.02% and -2.34%.

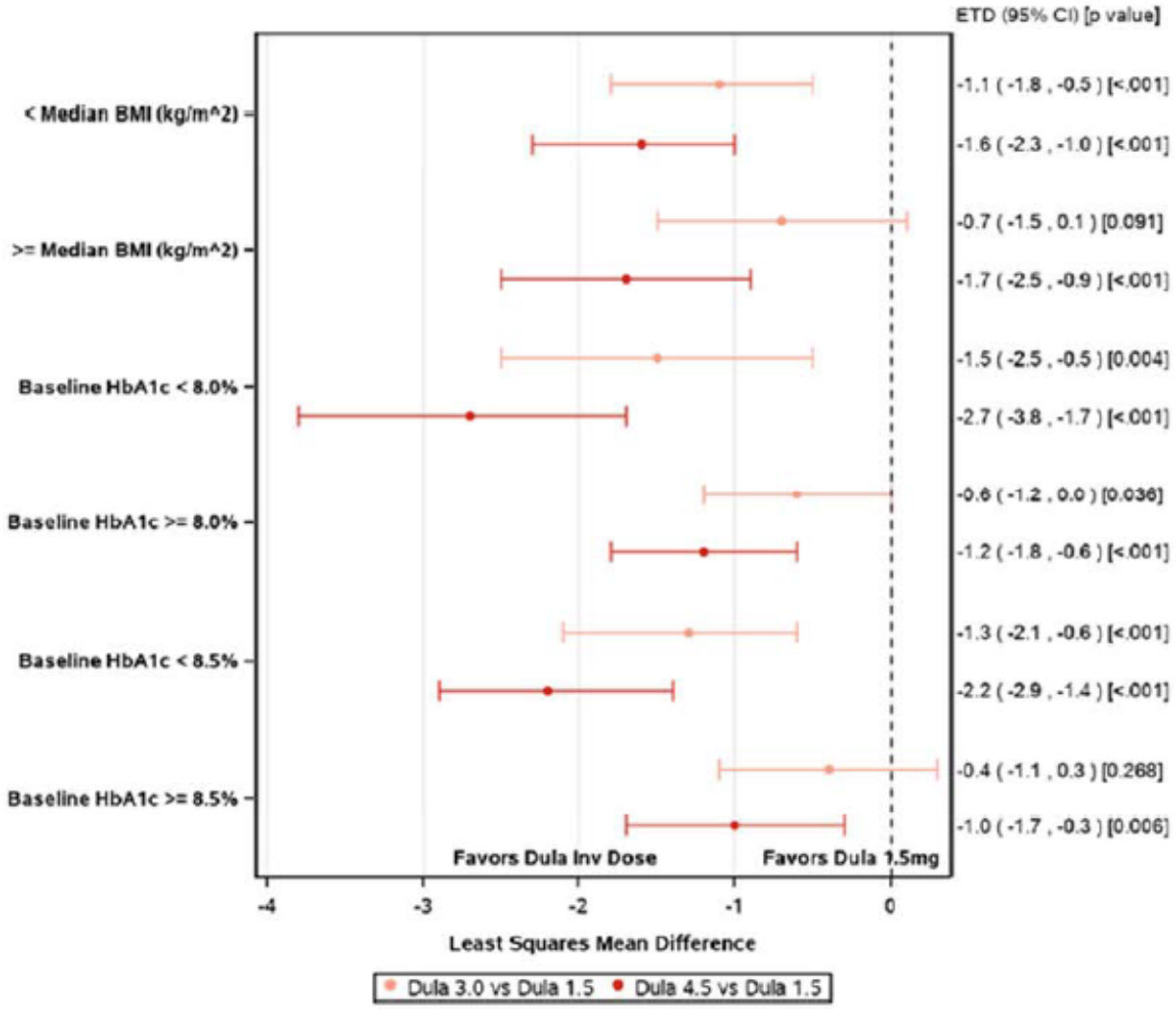
The treatment-by-subgroup interaction for the primary endpoint of HbA1c was significant (p=0.020) for baseline HbA1c (<8.5% or ≥8.5%). The significant interaction appeared largely driven by the greater LS mean change from baseline in HbA1c in the 4.5 mg dose groups versus 1.5 mg dose in patients with baseline HbA1c ≥8.5%. Although the treatment-by-subgroup interaction for the primary endpoint of HbA1c was not significant (p=0.116) for baseline HbA1c <8% or ≥8%, a similar pattern was observed: the LS mean change from baseline in HbA1c was greater in the 4.5 mg dose group versus the 1.5 mg dose in patients with baseline HbA1c ≥8% versus those with baseline HbA1c <8%.



Overall, analyses of changes in HbA1c across patient subgroups were consistent in favour of the two new investigational doses of dulaglutide (3.0 mg and 4.5 mg) compared to the approved dulaglutide 1.5 mg dose strength using the efficacy estimand.

Subgroup Analyses on Body Weight

Forest plot for subgroup analyses of changes from baseline in body weight (kg), by treatment group at Week 36, intent-to-treat population on-treatment without new antihyperglycemic medications.



Analyses of changes in body weight across subgroups using the efficacy estimand were generally consistent with the subgroup analysis of the primary endpoint.

A significant reduction in body weight from baseline to Week 36 was achieved with dulaglutide 4.5 mg versus 1.5 mg across all subgroups except for some countries or regions (for details it is referred to the CSR).

The reduction in body weight from baseline to Week 36 was less pronounced for dulaglutide 3.0 mg versus 1.5 mg and a significant weight loss was not achieved in subgroups of patients with baseline BMI ≥median [-0.7 kg (-1.5, 0.1); p=0.091], in patients with baseline HbA1c ≥8.5% [-0.4 kg (-1.1, 0.3); p=0.268].

Modelling and Simulation (M&S) analyses

With regard to Modelling and Simulation (M&S) analyses (e.g. POP-PK & PD) reference is made to Clinical Pharmacology Section 2.2 Pharmacodynamics and PK/PD.

Exploratory Endpoints Analyses

All analyses of exploratory endpoints were performed in the ITT population, using data collected up to initiation of new antihyperglycemic medication or premature treatment discontinuation (efficacy estimand).

Proportion of Patients Achieving ≥5% or ≥10% Body Weight Loss at Week 36

Using the efficacy estimand, significantly more patients in the dulaglutide 3.0 mg and 4.5 mg dose groups achieved the exploratory endpoint of ≥5% or ≥10% body weight loss at Week 36:

For ≥5% reduction:

- dulaglutide 1.5 mg: 172 patients (32.95%),
- dulaglutide 3.0 mg: 215 patients (41.35%); p=0.004 versus 1.5 mg, and
- dulaglutide 4.5 mg: 267 patients (50.76%); p<0.001 versus 1.5 mg.

For ≥10% reduction:

- dulaglutide 1.5 mg: 33 patients (6.32%),
- dulaglutide 3.0 mg: 64 patients (12.31%); p<0.001 versus 1.5 mg, and
- dulaglutide 4.5 mg: 72 patients (13.69%); p<0.001 versus 1.5 mg.

Proportion of Patients Achieving HbA1c Target ≤6.5% at Week 36

At Week 36, a significantly greater proportion of patients who escalated to the higher dulaglutide doses achieved an HbA1c ≤6.5% compared to patients maintained on the 1.5-mg dose (1.5 mg: 38.05%; 3.0 mg: 48.37%; 4.5 mg: 51.71%; p<0.001 for 3.0 mg and 4.5 mg versus 1.5 mg).

Patients escalating to dulaglutide 3.0 mg or 4.5 mg were significantly more likely to achieve an HbA1c target of ≤6.5% compared to those maintained on dulaglutide 1.5 mg at Week 36 (odds ratios [95% CI] of 1.62 [1.24; 2.13] and 1.95 [1.48; 2.57] for 3.0 mg and 4.5 mg, respectively).

Variable Analyzed: HbA1c <= 6.5%

Time Point Treatment	N	n	(%)
Week 36 (Visit 9)			
Dula 1.5	523	199	38.05
Dula 3.0	521	252	48.37
Dula 4.5	526	272	51.71

Pairwise Comparison (A vs B)	Odds Ratio (Treatment A/B) *a*b*c	95% CI for Odds Ratio *a*b*c	p-value *a*b*c
Dula 3.0 vs Dula 1.5	1.62	(1.24, 2.13)	<.001
Dula 4.5 vs Dula 1.5	1.95	(1.48, 2.57)	<.001
Dula 4.5 vs Dula 3.0	1.20	(0.91, 1.58)	0.194

Abbreviations: CI = confidence interval; N = number of subjects in the population with baseline and post-baseline value at the specified time point; n = number of subjects in the specified category.

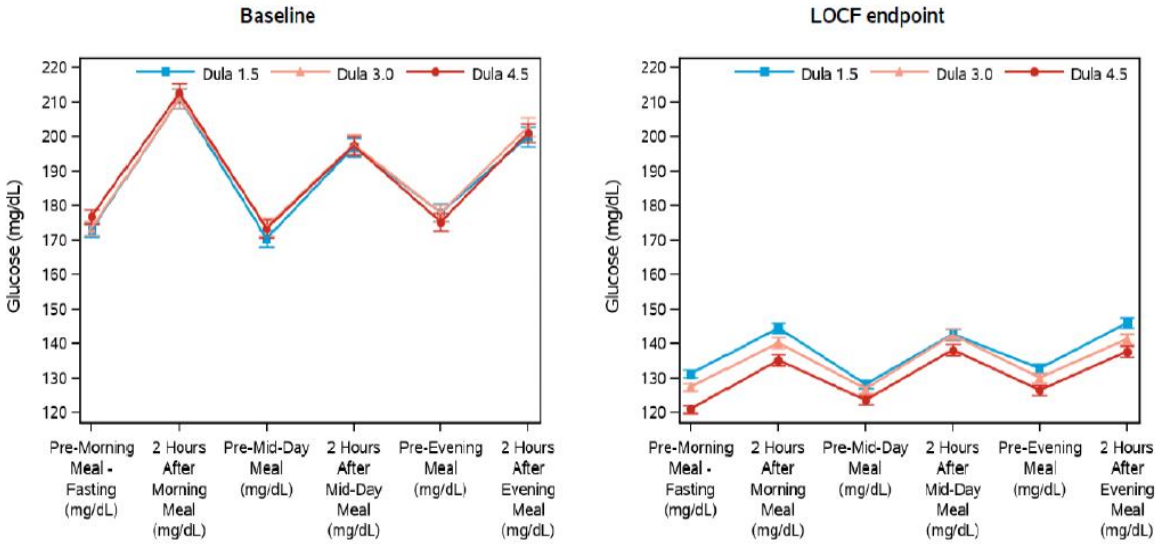
Change from Baseline in 6-Point Self-Monitored Plasma Glucose (SMPG) Profile

The SMPG data were collected at the following 6 time points:

- pre-morning meal,
- 2 hours post-morning meal,
- pre-midday meal,
- 2 hours post-midday meal,
- pre-evening meal, and
- 2 hours post-evening meal.

The Figure below shows the LS mean time profile of SMPG for the three dulaglutide dose groups at baseline and Week 36 (LOCF).

Plot for LS mean time profile of SMPG (mg/dL), ITT population, on-treatment without new antihyperglycemic medications (efficacy estimand).



Abbreviations: Dula = dulaglutide; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; SMPG = self-monitored plasma glucose.

Changes from Baseline in Markers of Glucose Metabolism and Beta-Cell Function

Key results included:

- Small decreases in fasting insulin were observed in all three dulaglutide groups as measured by the geometric LS mean ratio, with no significant differences between the higher dulaglutide dose groups and dulaglutide 1.5 mg.

- Small decreases in insulin resistance as measured by HOMA2-IR were observed across the three dulaglutide dose groups with no significant differences between the higher dose dulaglutide groups and dulaglutide 1.5 mg.

- Mean percent increases in indices of pancreatic beta-cell function (HOMA2-%B) were observed in all three dulaglutide groups (range, 88.2% to 122.2%). Dulaglutide 4.5 mg significantly increased HOMA2-%B from baseline compared to dulaglutide 1.5 mg ($p<0.001$).

- Small decreases in fasting C-peptide as measured by geometric LS mean ratios were observed across the three dulaglutide groups with no significant differences between the higher dose dulaglutide groups and dulaglutide 1.5 mg.

- Mean percent decreases were observed in all three dulaglutide groups in indices of alpha-cell function, measured both by fasting plasma glucagon (range, -8.8% to -18.0%) and fasting plasma glucagon corrected for fasting glucose (range, -27.5% to -38.2%). Dulaglutide 4.5 mg decreased fasting plasma glucagon and adjusted glucagon from baseline significantly more than dulaglutide 1.5 mg ($p<0.001$ for both).

Health Outcomes/Quality-of-Life Evaluation

<u>Changes from Baseline in Impact of Weight on Self Perception Questionnaire Scores (IW-SP)</u>

- At Week 36, there was a significant improvement in the IW-SP total score from baseline for all three dulaglutide dose groups ($p<0.001$ for all).
- There was a significant difference in the IW-SP total score between both the dulaglutide 4.5-mg and 3.0-mg dose groups compared with the 1.5-mg dose group at Week 36 ($p=0.025$ and

p=0.040, respectively), with larger improvements in total score with each investigational dose versus the 1.5-mg dose.

Changes from Baseline in Ability to Perform Physical Activities of Daily Living Scores (APPADL)

- At Week 36, there was a significant improvement in the APPADL total score from baseline for all 3 dulaglutide dose groups (1.5 mg: p=0.002; 4.5 mg and 3.0 mg: p<0.001).
- There was a significantly greater improvement in APPADL total score for the dulaglutide 4.5-mg group versus the 1.5-mg group at Week 36 (p=0.025).

Changes from Baseline in European Quality of Life-5 Dimension 5 Level Scores (EQ-5D-5L)

- At Week 36, there was a significant improvement in the EQ-5D-5L UK index score and VAS score from baseline for all three dulaglutide dose groups.
- There were no significant differences across the 3 dulaglutide dose groups in the EQ-5D- 5L UK index score and VAS score at Week 36.

Diabetes Injection Device Experience Questionnaire Scores at Week 12 (DID-EQ)

- Mean scores for the three dulaglutide dose groups on the 3 global items ranged from 3.76 to 3.79 for overall satisfaction, 3.78 to 3.80 for ease of use, and from 3.76 to 3.80 for convenience on a 4-point scale.
- There were no significant differences between the dulaglutide higher dose groups compared with the 1.5-mg group for the 3 global item scores of overall satisfaction, ease of use, and convenience.

Efficacy results at 52 weeks

Improvements in glycaemic control measures and body weight were sustained from Week 36 to Week 52 for all dulaglutide doses.

Using the efficacy estimand (considered primary for purposes of these exploratory 52-week analyses), the change from baseline in HbA1c at Week 52 was significantly greater in the dulaglutide 3.0 mg (estimated treatment difference, -0.19%; p=0.002) and 4.5-mg (estimated treatment difference, -0.31%; p<0.001) dose groups compared to the 1.5-mg group, consistent with the differences observed at the primary 36-week endpoint (Table GBGL.9.1). Likewise, a significantly higher proportion of patients in the 3.0 mg (65%) and 4.5 mg (72%) dose group achieved an HbA1c <7% compared to those on 1.5 mg (59%) through 52 weeks. Dose-related effects of dulaglutide on FSG, as well as on exploratory measures of glycemic control (6-point SMBG) and markers of dulaglutide pharmacological action relevant to glucose control, were also observed at the final 52-week endpoint, similar to the effects observed at the 36-week primary endpoint. These exploratory analyses support sustainability in glycemic control across dulaglutide doses through at least 52 weeks of treatment.

Mean body weight continued to decline in all the dulaglutide dose groups from Week 36 to Week 52, culminating in a mean weight loss of 5 kg at the highest 4.5mg dose using the efficacy estimand (Table GBGL.9.1). Change from baseline in body weight at Week 52 was significantly greater in the dulaglutide 3.0 mg (estimated treatment difference, -0.8 kg; p=0.006) and 4.5 mg (estimated treatment difference, -1.6 kg; p<0.001) dose groups compared to the 1.5 mg group, consistent with the differences observed at the primary 36-week endpoint (see table below). Significantly more patients in both the dulaglutide 3.0 mg and 4.5mg dose groups achieved the clinically relevant weight loss threshold of ≥5% at 52 weeks than those maintained on dulaglutide 1.5 mg, and the proportion of patients meeting weight loss thresholds at Week 52 was consistently larger than at Week 36. Thus, continued treatment with dulaglutide beyond 36 weeks results in additional mean weight loss across doses, with maintenance of greater weight reduction in the 3.0-mg and 4.5-mg groups versus the 1.5-mg dose group.

Table GBGL.9.1. **Summary of Efficacy Measures at 36-Week Primary Endpoint and Exploratory 52-Week Endpoint, Intent-to-Treat Population, Efficacy Estimand and Treatment-Regimen Estimand**

	Efficacy Estimand			Treatment-Regimen Estimand		
	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)
HbA1c change from baseline (%)						
36 weeks	-1.53	-1.71	-1.87	-1.54	-1.64	-1.77
52 weeks	-1.52	-1.71	-1.83	-1.55	-1.61	-1.72
% patients with HbA1c<7%						
36 weeks	57.0	64.7	71.5	49.7	55.8	62.2
52 weeks	58.6	65.4	71.7	49.3	54.1	59.4
Fasting Serum Glucose change from baseline (mg/dL)						
36 weeks	-44.2	-47.9	-52.3	-44.9	-46.4	-51.2
52 weeks	-43.1	-48.7	-52.7	-44.3	-45.6	-50.1
Body Weight (kg) change from baseline						
36 weeks	-3.1	-4.0	-4.7	-3.0	-3.8	-4.6
52 weeks	-3.5	-4.3	-5.0	-3.4	-4.0	-4.9

Abbreviations: Dula = dulaglutide; HbA1c = glycated hemoglobin; N = number of patients randomized and treated.
Sources: GBGL primary 36-week CSR (36-week data); Table GBGL.7.6.

Although the treatment-regimen estimand was only specified as primary for purposes of testing the primary and secondary efficacy endpoints at 36 weeks at the request of the FDA, this estimand was also used in the 52-week exploratory analyses of HbA1c change from baseline, proportion of patients achieving HbA1c <7%, FSG change from baseline, and body weight change from baseline. Consistent with the efficacy estimand results, the improvements in glycaemic control measures were largely sustained while reductions in body weight were numerically greater across all dulaglutide dose groups at Week 52 versus Week 36 using the treatment-regimen estimand.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy Phase 3 Trial (H9X-MC-GBGL)

Title of Study: A Randomized, Double-Blind, Parallel Arm Phase 3 Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus			
Study identifier	H9X-MC-GBGL		
Design	Study H9X-MC-GBGL (GBGL) is a 52-week, Phase 3, randomized, double-blind, parallel-arm study designed to assess the efficacy and safety of once-weekly investigational dulaglutide doses (4.5 mg or 3.0 mg) compared to dulaglutide 1.5 mg in patients with T2D on metformin monotherapy. The prespecified primary efficacy endpoint was the Week 36 time point.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		36 weeks for primary endpoint database lock; 52 weeks for final database lock. 2-week Run-In period 4-week Safety Follow-Up Period
Hypothesis	To demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both compared to dulaglutide 1.5 mg on HbA1c change from baseline to Week 36 in patients with inadequately controlled T2D on concomitant metformin therapy.		
Treatments groups	Study Drug		Dulaglutide 4.5 mg s.c. once-weekly administered via single-dose pen (n=614).
	Study Drug		Dulaglutide 3.0 mg s.c. once-weekly administered via single-dose pen (n=616).
	Reference Therapy		Dulaglutide 1.5 mg s.c. once-weekly administered via single-dose pen (n=612).
Endpoints and definitions	Primary endpoint	HbA1c change from baseline to Week 36	To demonstrate superiority of once-weekly dulaglutide 4.5 mg, dulaglutide 3.0 mg, or both compared to dulaglutide 1.5 mg on HbA1c change from baseline to Week 36 in patients with inadequately controlled T2D on concomitant metformin therapy.
	Secondary Efficacy Endpoints	Body weight, Proportion of patients with HbA1c <7.0%, fasting serum glucose at Week 36	To demonstrate that once-weekly dulaglutide 4.5 mg, 3.0 mg, or both was superior to dulaglutide 1.5 mg at 36 weeks: -Change in body weight from baseline -Proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) -Change in fasting serum glucose (FSG) from baseline
	Secondary PK endpoints	Cmax, AUC	To characterize dulaglutide PK and the dose-response relationship, exposure-response relationship, or both for key efficacy and safety measures: -PK parameters (for example, maximum concentration [Cmax], area under the concentration-time curve [AUC]) at steady state
Database lock	Primary endpoint database lock at Week 36; final database lock at Week 52. Treatment Period (between Weeks 36 and 52) and the Safety Follow-Up Period are currently still ongoing.		

Results and Analysis			
Analysis description	**Primary and Secondary Efficacy Endpoints, Intent-to-Treat Population**		
	Dula 1.5 mg (N=612)	**Dula 3.0 mg (N=616)**	**Dula 4.5 mg (N=614)**
Primary Objective			
HbA1c (%)			
Efficacy Estimand[a]			
LS mean change from baseline at Week 36	-1.53	-1.71	-1.87
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.17* (-0.29, -0.06)	-0.34** (-0.45, -0.22)
Treatment-Regimen Estimand[b]			
LS mean change from baseline at Week 36	-1.54	-1.64	-1.77
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.10 (-0.23, 0.02)	-0.24** (-0.36, -0.11)
Secondary Objectives			
Body Weight (kg)			
Efficacy Estimand[a]			
LS mean change from baseline at Week 36	-3.1	-4.0	-4.7
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.9* (-1.4, -0.4)	-1.6** (-2.1, -1.1)
Treatment-Regimen Estimand[b]			
LS mean change from baseline at Week 36	-3.0	-3.8	-4.6
LS mean difference from dula 1.5 mg (95% CI)	N/A	-0.9 (-1.4, -0.4)	-1.6** (-2.2, -1.1)
Proportion of patients with HbA1c <7.0% (53 mmol/mol) at Week 36 (%)			
Efficacy Estimand[c]	57.0	64.7*	71.5**
Treatment-Regimen Estimand[d]	49.7	55.8	62.2
Fasting Serum Glucose (mg/dL)			
Efficacy Estimand[a]			
LS mean change from baseline at Week 36	-44.2	-47.9	-52.3
LS mean difference from dula 1.5 mg (95% CI)	N/A	-3.7 (-7.8, 0.5)	- 8.1** (-12.3, -3.9)
Treatment-Regimen Estimand[b]			
LS mean change from baseline at Week 36	-44.9	-46.4	-51.2
LS mean difference from dula 1.5 mg (95% CI)	N/A	- 1.6 (-6.6, 3.5)	-6.4 (-11.2, -1.6)

Abbreviations:

ANCOVA = analysis of covariance; CI = confidence interval; Dula = dulaglutide; HbA1c = glycated hemoglobin; LS = least-squares; N=number of patients randomized and treated; N/A=not applicable.

Notes: The treatment-regimen included only patients with a non-missing baseline value; the efficacy estimand included only patients with a non-missing baseline value and at least 1 non-missing post-baseline value of the response variable. Analyses for treatment-regimen estimand included data after treatment discontinuation or initiation of new antihyperglycemic medications; analyses for efficacy estimand excluded data after treatment discontinuation or initiation of new antihyperglycemic medications.

a Mixed-model repeated measures analysis.

b ANCOVA with multiple imputation.

c Longitudinal logistic regression.

d Logistic regression with missing Week 36 HbA1c classified as not achieving HbA1c target.

Note: p-values are only indicated when statistical significance was met under graphical testing procedure.

* The p-value <0.05 versus dulaglutide 1.5 mg.

** The p-value <0.001 versus dulaglutide 1.5 mg.

Analysis performed across trials (pooled analyses and meta-analysis)

Only one pivotal Phase 3 Study (GBGL) that provides primary evidence was submitted and therefore pooled analyses and/or a meta-analysis were not conducted.

Clinical studies in special populations

As this application does not concern a new indication, new pharmaceutical form or new route of administration, no additional new studies in special populations e.g. in children, in the elderly and in patients with renal or hepatic impairment have been submitted and reference is made to Section 4.2 and Section 5.2 of the approved SmPC.

Supportive studies

Supportive studies included a Phase 2 study (GBGJ) and a Phase 1 study (GBGM) which are described in detail in the respective sections of this assessment report.

Previous Conclusions of EPAR Trulicity (Procedure No. EMEA/H/C/002825) on Study GBCF

Study GBCF was a 104-week, adaptive, dose-finding and confirmatory, inferentially seamless, Phase 2/3, placebo-controlled, safety, and efficacy study and investigated 7 doses of dulaglutide (0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 3.0 mg s.c. once weekly) compared to sitagliptin and placebo in patients with T2DM on metformin background therapy. An optimal dose was to be selected based on efficacy (HbA1c and weight) and safety (DBP and heart rate) measures. At the completion of the dose-finding portion of the study, the dulaglutide 1.5 mg dose was selected as the dose with the optimal benefit-risk profile. Of note, randomization to the dulaglutide 3.0 mg dose was stopped prematurely based on the recommendation of an independent Data Monitoring Committee (DMC) following observations of increased heart rate and concerns related to pancreatic safety.

Table 13 Summary of HbA1c (%), Fasting Serum Glucose, Body Weight, Sitting Pulse Rate, Sitting Systolic Blood Pressure, and Sitting Diastolic Blood Pressure for Dose Assessment at Decision Point – ITT Patients in All 9 Treatment Arms Randomized during Stage 1; Study GBCF

Variable[b] (Units)	Mean (Standard Deviation)[a] Change from Baseline								
	PL/Sit (N=38)	Sit (N=42)	Dula_0.25 (N=24)	Dula_0.5 (N=25)	Dula_0.75 (N=21)	Dula_1.0 (N=10)	Dula_1.5 (N=25)	Dula_2.0 (N=30)	Dula_3.0 (N=15)
HbA1c (%)	-0.06 (0.64)	-0.76 (0.86)	-0.70 (0.49)	-0.94 (0.65)	-1.02 (0.99)	-0.98 (0.47)	-1.49 (1.12)	-1.25 (0.68)	-1.09 (0.77)
Body weight (kg)	-0.56 (1.69)	-0.43 (1.78)	-0.85 (1.47)	-1.53 (1.88)	-1.17 (2.30)	-2.23 (1.63)	-2.12 (1.93)	-2.15 (1.97)	-3.32 (3.37)
Fasting glucose (mmol/L)	0.14 (2.00)	-1.52 (2.36)	-1.19 (1.06)	-1.90 (1.96)	-2.63 (1.99)	-2.03 (1.85)	-4.16 (3.78)	-3.18 (2.11)	-2.17 (2.74)
Pulse rate (bpm)	1.81 (7.90)	-0.16 (8.07)	1.05 (9.44)	1.91 (6.18)	-1.63 (8.03)	3.34 (9.88)	2.39 (7.88)	3.43 (10.14)	6.63 (7.28)
DBP (mm Hg)	-0.22 (7.94)	-1.11 (6.65)	1.28 (4.06)	-0.75 (7.99)	-3.18 (10.13)	-0.08 (8.00)	-1.20 (4.67)	-1.17 (6.32)	-1.21 (7.47)
SBP (mm Hg)	-0.61 (14.75)	-2.16 (10.62)	1.67 (10.18)	0.40 (11.51)	-6.21 (19.13)	-2.00 (9.94)	-4.77 (11.37)	-4.63 (15.28)	-8.85 (12.92)

2.5.3 Discussion on clinical efficacy

Design and conduct of clinical studies

The purpose of this application is to add two dose strengths of dulaglutide (3.0 mg and 4.5 mg s.c. once-weekly). The application is supported by one pivotal phase 3 study (GBGL) and two supportive studies (bioequivalence study GBGM and phase 2 study GBGJ).

Study GBGJ was a randomized, placebo-controlled, double-blind phase 2 study in patients with T2DM on metformin monotherapy. The primary objective of this trial was to show superiority of three dulaglutide doses (1.5 mg, 3.0 mg and 4.5 mg) *to placebo* in change in HbA1c at 18 weeks in T2DM patients. In addition, effects on body weight, number of responders (HbA1c<7%) and fasting serum glucose were investigated. The study consisted of 3 periods: an approximate 2-week lead-in period, an 18-week treatment period, and a 4-week safety follow-up period. A total of 317 patients were randomized to one of four treatment arms: placebo n=81, dulaglutide 1.5 mg n=81, dulaglutide 3.0 mg n=79, dulaglutide 4.5 mg n=76. To explore the effect on gastrointestinal tolerability two stepwise dose escalation algorithms were applied in patients assigned to dulaglutide 3.0 mg and 4.5 mg.

Efficacy and safety analyses were conducted in the intent-to-treat (ITT) population (all randomized patients taking at least one dose of study medication) by censoring all post-rescue data. It was intended that patients who stopped study drug would immediately start rescue therapy, and thus analyses excluding post-rescue data would also exclude any data obtained post discontinuation of study drug. However, there were patients who stopped study drug and did not begin rescue therapy; thus, post-hoc analyses were also done excluding data obtained post-rescue or post discontinuation of study drug (the "on-treatment without rescue" analyses). For comparison of dose/response in this phase 2 study this approach seems acceptable.

Concomitant medications and demographic baseline characteristics were generally comparable between the treatment groups. A high percentage of patients (91.8%) completed the study through the safety follow-up period; 48 of 318 randomized patients (15.1%) discontinued from study treatment before week 18: Placebo, 11 (13.4%); dulaglutide 1.5 mg, 9 (11.1%); dulaglutide 3.0 mg, 10 (12.7%) and dulaglutide 4.5 mg, 18 (23.7%). Adverse events as the most frequent reason for discontinuation of study drug occurred in a dose related fashion with more patients discontinuing study drug for AEs at the two higher doses dulaglutide: placebo, 4 (4.9%) and dulaglutide 1.5 mg, 5 (6.2%), dulaglutide 3.0 mg, 8 (10.1%) and dulaglutide 4.5 mg, 10 (13.2%).

The primary objective of the *ongoing* **phase 3 study GBGL** was to show superiority of dulaglutide 3.0 mg, 4.5 mg, or both *to dulaglutide 1.5 mg* for change in HbA1c from baseline to week 36. Secondary objectives were to compare 3.0 mg and 4.5 mg dulaglutide to dulaglutide 1.5 mg with respect to the

effect on body weight, the proportion of patients reaching HbA1c target <7.0%, and the effect on fasting serum glucose. The study consisted of 3 periods: an approximately 2-week screening/lead-in period followed by a 52-week double-blind treatment period, and a 4-week safety follow-up period.

The primary and secondary efficacy endpoints were separately assessed using two estimands termed an "efficacy estimand" and a "treatment-regimen estimand". For the *efficacy estimand*, analyses excluded data after premature treatment discontinuation or initiation of new antihyperglycemic therapy for more than 14 days (whichever occurred first). For these patients, data were implicitly imputed by data from comparable patients who are on-treatment using an MMRM model (missing-at-random assumption). It may provide a representative estimate of the treatment differences expected with dose escalation from dulaglutide 1.5 mg once-weekly to 3.0 mg and 4.5 mg once-weekly attributable to the pharmacological action of dulaglutide. Further sensitivity analyses were provided for the efficacy estimand. These support the robustness of results with regard to deviations from the primarily applied missing data handling approach (MAR assumption). For the *treatment-regimen estimand*, the analyses included all data collected before and after initiation of new antihyperglycemic therapy, premature treatment discontinuation (or both), with week 36 missing data imputed using a retrieved drop-out approach. Hence, it provides a conservative estimate of the overall treatment effect in the general population where patients may not adhere to treatment, may initiate other glucose lowering therapies, or both.

In addition, and in line with the draft guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2), an additional estimand addressed targeting the effect regardless of treatment discontinuation and had rescue medication or other antihyperglycemic agents not been available. This estimand may be considered of higher relevance as compared to the efficacy estimand as it takes drug tolerability issues into account. Still, overall results for the additional estimand support results for the efficacy and treatment regimen estimand. Effects for all estimands are consistent, similar dose-relating effects are seen for all three investigated estimands, and for all estimands observed effects are in line within the range of incremental effects that have been accepted for other antihyperglycemic agents for which different dose strengths have been approved. Furthermore, the additional estimand may in fact overestimate the impact of drug tolerability (as all discontinuations are accounted for regardless of reason). Hence, all in all it is agreed to primarily report results of the pre-specified primary efficacy estimand.

A dose-escalation period of 4 weeks at each dose was employed to reduce the occurrence of GI AEs: all patients began the trial with 4 weeks of treatment with dulaglutide 0.75 mg once-weekly followed by 4 weeks of treatment with dulaglutide 1.5 mg once-weekly. After 8 weeks, patients assigned to the 1.5 mg group continued on 1.5 mg once-weekly. Patients assigned to the 3.0 mg group escalated to 3.0 mg once-weekly and maintained this dose for the remainder of the treatment period. Patients assigned to the 4.5 mg group escalated to 3.0 mg once-weekly for 4 weeks followed by escalation to their final assigned dose of 4.5 mg once-weekly at week 12 and beyond.

A total of 1842 patients were randomized and included in the analysis (dula 1.5 mg n=612, dula 3.0 mg n=616, dula 4.5 mg n=614).

The population studied included adult patients with T2D who were overweight and inadequately controlled on concomitant metformin therapy. The mean age of patients was 57 years, mean duration of T2D was almost 8 years, mean HbA1c at baseline was 8.6% and the mean BMI 34.2 kg/m^2. When comparing these patients with the population included in one of the 5 phase 3 studies (assessed in the initial MAA), baseline variables for glycemic control were modestly higher (mean baseline HbA1c mean value in phase 3 studies 7.6 to 8.5%), duration of diabetes was longer, and body weight was in the upper range of the one in the initial studies. These differences were primarily by design, with study GBGL requiring an HbA1c at screening between 7.5% and 11%, whereas the lower limit of HbA1c for inclusion in the original efficacy studies was generally 7.0% and 6.5% for the dulaglutide monotherapy study H9X-

MC-GBDC. The rationale for the HbA1c range in Study GBGL was to enroll patients who might require treatment intensification and may therefore benefit from treatment with higher dulaglutide doses. This is generally accepted.

Demographic and clinical baseline characteristics were representative for the (European) target population and comparable across the 3 dulaglutide dose groups. Metformin dose (median 2000 mg daily) was similar across the three dulaglutide dose groups, and the majority of patients continued on metformin with no changes in dose reported up to the week 36 primary endpoint. Metformin was the sole additional antihyperglycemic medication. In the initial phase 3 studies, the efficacy of dulaglutide 1.5 mg once-weekly has been established on a wide variety of antihyperglycemic background medications. In general, one could expect that any effects observed for the higher doses are preserved when used in combination with other glucose-lowering medications (and no restricted label would be necessary in this regard for the higher dose strengths).

Reassuringly, the number of patients who completed the study and were adherent to study drug was high: 93.1% of randomized patients completed the week 36 primary endpoint visit (89% on study drug). This result is consistent with the disposition in the five phase 3 studies submitted for initial MAA (performed with 0.75 mg and 1.5 mg dulaglutide) where 81.3% to 97.2% were on study drug at the end of the studies. This may serve a rough indicator of a comparable adherence to study drug between the lower and the higher dose ranges of dulaglutide.

The occurrence of protocol deviations was balanced across dulaglutide dose groups. There were no significant differences across the 3 dose groups in the proportions of patients initiating new antihyperglycemic therapy for any reason during the treatment period (1.5 mg, 7.0%; 3.0 mg, 5.5%; 4.5 mg, 6.8%; p=0.491). Overall, 93.5% of patients had no new antihyperglycemic therapy initiated through 36 weeks. Of the 119 patients who initiated new antihyperglycemic therapy for any reason, 91 of them received this new therapy as rescue for severe, persistent hyperglycaemia.

Overall, the number of treatment discontinuations and applications of rescue medication is considered low; this led to very similar results between the a. m. estimands. Therefore, except for the primary endpoint of the pivotal study, results will be presented for the efficacy estimand only (for detailed results for the treatment-regimen estimand please refer to section 3.3.5 of this report).

The clinical assessment of the pivotal Phase 3 study GBGL and the supportive studies (GBGM, GBGJ) submitted for this application did not reveal concerns regarding GCP non-compliance.

Efficacy data and additional analyses

In the **phase 2 study GBGJ** all three doses of dulaglutide (1.5 mg, 3.0 mg and 4.5 mg) reduced HbA1c significantly from baseline *compared to placebo* (all p-values <0.001; dulaglutide 1.5 mg vs plc -0.80, dulaglutide 3.0 mg vs plc -0.87, dulaglutide 4.5 mg vs plc -0.96). However, *compared to the 1.5 mg dose*, only very small numerical improvements in HbA1c were shown after 18 weeks for the two higher dose strenghts: -0.08% (-0.34%, 0.19%) for 3.0 mg, p=0.572 and -0.16% (-0.44%, 0.11%) for 4.5 mg, p=0.235. The HbA1c lowering effect over and above that exerted by 1.5 mg dulaglutide is small and of questionable clinical relevance for the study population as a whole.

All three doses of dulaglutide significantly reduced **body weight** from baseline compared to placebo at week 18 (dula 1.5 mg vs plc -1.2kg, dula 3.0 mg vs plc -2.4 kg, dula 4.5 mg -2.6 kg). In addition, both of the two new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg) also reduced body weight significantly compared to dulaglutide 1.5 mg at week 18. Body weight was reduced in a dose-related fashion after 18 weeks of treatment. The effect size, even for the 4.5 mg strength, is moderate (2.6 kg correspond to 2.7% from the mean BL body weight of 95.7 kg). A more pronounced effect on body weight may have been expected with a study duration exceeding 18 weeks.

Significantly greater percentages of patients in all three dulaglutide groups achieved **HbA1c<7.0%** at week 18 than placebo-treated patients (placebo 16.7%, dulaglutide 1.5 mg 66.7%, dulaglutide 3.0 mg 69.9%, dulaglutide 4.5 mg 57.5%; all p-values <0.001). There was no dose-related increase in responders. This likewise applied for **fasting serum glucose**, which was significantly reduced compared to placebo by all dulaglutide doses, but without a significant differences between doses. As the MoA of dulaglutide is glucose-dependent, FSG is not considered the ideal pharmacodynamic marker; hence, these results are less important in this context.

Efficacy results of the **phase 3 study GBGL** (which had no placebo control) were as follows: using the *efficacy estimand*, the LS mean changes in HbA1c from baseline to week 36 were: -1.53%, -1.71% and -1.87% for dulaglutide 1.5 mg, 3.0 mg, 4.5 mg, respectively. Using the *treatment-regimen estimand*, the LS mean changes in HbA1c from to week 36 were: -1.54%, -1.64%, and -1.77% for dulaglutide 1.5 mg, 3.0 mg, 4.5 mg, respectively. HbA1c changes from baseline to week 36 showed that the primary efficacy measure of superiority was met with dulaglutide 4.5 mg compared to dulaglutide 1.5 mg for both the efficacy estimand (-0.34%, p<0.001) and the treatment-regimen estimand (-0.24%, p<0.001). For dulaglutide 3.0 mg superiority for the primary efficacy measure was met for the efficacy estimand (-0.17%, p=0.003) but not the treatment-regimen estimand (-0.10%, p=0.096).

Overall, the incremental effects on glycaemic control of the higher dose strengths of dulaglutide were rather small but are within the additional effects observed for different doses strengths of other approved antihyperglycemic agents.

Results of subgroup analyses of the primary outcome

Analyses of change from baseline in HbA1c across patient characteristic subgroups were generally consistent with the primary results. There were no significant treatment-by-subgroup interactions based on age, race, country, ethnicity, region or duration of diabetes.
The treatment-by-subgroup interaction effect for the primary efficacy measure of HbA1c was significant for sex (female versus male) and baseline HbA1c (<8.5% versus ≥8.5%). The subgroup interaction for sex is considered unlikely to have clinical relevance (no such finding in previous studies with dulaglutide, no plausible biological mechanism). In line with the well-known effect of a greater magnitude of HbA1c reduction with higher baseline HbA1c, dose-response relationship was shown to be more pronounced for patients with higher baseline HbA1c: for patients with baseline HbA1c <8.5%, the LS mean changes in HbA1c from baseline to week 36 were: -1.16%, -1.38% and -1.38% for dulaglutide 1.5 mg, 3.0 mg and 4.5 mg, respectively, and for patients with baseline HbA1c ≥8.5%: -1.89%, -2.02% and -2.34%. Thus, the mean difference between the 4.5 mg dose and the 1.5 mg was higher for the patient group with HbA1c >8.5% (-0.45% [-0.65, -0.26]) than for the patient group with HbA1c < 8.5% (-0.22 [--0.34,-0.10]).

Results of secondary outcome measures

The LS mean changes in **body weight** from baseline to week 36 were for dulaglutide 1.5 mg: -3.1 kg, for dulaglutide 3.0 mg: -4.0 kg, and for dulaglutide 4.5 mg: -4.7 kg. The mean treatment difference in change in body weight versus dulaglutide 1.5 mg was -0.90 kg in the dulaglutide 3.0 mg group (p=0.001) and -1.60 kg in the dulaglutide 4.5 mg group (p<0.001).

Overall, the two new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg) resulted in greater body weight reduction at week 36 compared to the approved 1.5 mg dose. As outlined above, this likewise applied for the *placebo-corrected* body weight reductions attained in the shorter term 18-week study GBGJ (-2.4 kg and -2.6 kg for 3 and 4.5 mg dulaglutide, respectively). Although the incremental effect on weight is modest, this is an additional benefit in the usually overweight patients with T2DM.

Both investigational doses of dulaglutide (3.0 mg and 4.5 mg) were superior to the 1.5 mg dose in the secondary efficacy objective of percent of **patients achieving HbA1c <7%**: more patients achieved an HbA1c<7% at week 36 with dulaglutide 4.5 mg 71.5% (odds ratio [95% CI] versus 1.5 mg=2.23 [1.65, 3.01]; p<0.001) and dulaglutide 3.0 mg 64.7% (odds ratio [95% CI] versus 1.5 mg=1.49 [1.12, 1.98], p=0.006) compared to the 1.5 mg dose (57%). The secondary efficacy measure of superiority over dulaglutide 1.5 mg for change in **fasting serum glucose** from baseline to week 36 was met with the dulaglutide 4.5 mg dose (-8.1 mg/dL, p<0.001).

Results of important exploratory endpoints

The proportion of patients achieving a HbA1c goal of ≤6.5% as well as improvements in 6-point self-monitored plasma glucose (SMPG) and daily average SMPG measures showed an incremental improvement in patients treated with 3.0 mg or 4.5mg dula doses compared with those maintained on the dula 1.5 mg dose. In addition, there were also dose-related changes in markers of glucose metabolism, alpha-cell function, and beta-cell function that were consistent with the known pharmacological profile and mechanism of action of dulaglutide.

Health Outcomes/Quality-of-Life Evaluation

Two health outcomes questionnaires were included to assess the potential impact of dulaglutide treatment on a patient's perception of health and well-being related to body weight: the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) assesses patients' self-perception related to weight (Hayes and DeLozier 2015), and the Ability to Perform Physical Activities of Daily Living (APPADL) Questionnaire assesses how difficult it is for patients to engage in various physical activities such as walking, standing, and climbing stairs (Hayes et al. 2011; Hayes et al. 2012). At week 36, there was a significant improvement in the IW-SP and APPADL total scores from baseline for all three dulaglutide dose groups. The improvement in IW-SP total score at Week 36 was significantly greater in patients escalated to dulaglutide 3.0 mg or 4.5 mg compared to patients maintained on dulaglutide 1.5 mg. The improvement in APPADL total score was significantly greater with 4.5 mg versus the 1.5 mg group.

Generic health-related quality of life assessed using the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) UK index score and VAS score significantly improved from baseline to week 36 for all three dulaglutide dose groups, with no significant difference between doses. This is not unexpected given the more general nature of the assessment and heterogeneity of the domains included in the composite scores (mobility, selfcare, anxiety or depression, usual activities, and pain or discomfort).

These results based on the patients' self-perception underpin the clinical relevance of the greater weight loss achieved with the investigational dulaglutide doses compared to the 1.5 mg dose.

Exploratory efficacy results at week 52

Exploratory efficacy analyses at week 52 showed that dose-related improvements in glycaemic measures (HbA1c, FSG), proportion of patients achieving HbA1c targets of <7% and ≤6.5%, and body weight reduction were maintained from 36 weeks to 52 weeks. HbA1c was reduced at week 52 in a dose-related fashion (1.5 mg dula -1.52%, 3mg dula -1.71%, 4.5 mg dula -1.83%). Additionally, effects of dula to improve other measures of glycaemic control (SMPG), markers of glucose metabolism, body weight control (proportion of patients achieving clinically relevant weight loss thresholds), exploratory composite endpoints, and health outcomes measures (APPADL and IW-SP) at 52 weeks were all largely maintained relative to the effects observed at the primary 36-week endpoint.

2.5.4 Conclusions on the clinical efficacy

The design and conduct of the clinical studies are acceptable. The pivotal study GBGL showed that treatment with dulaglutide 3 mg and 4.5 mg was associated with a dose-related improvement in glycemic measures and body weight, partly demonstrating significant superiority towards the 1.5 mg dose. Efficacy was maintained throughout week 52.

Although the anti-hyperglycemic effect size brought about by the two higher strengths is considered rather small, it is within the range of incremental effects that have been accepted for other antihyperglycemic agents for which different dose strengths have been approved. The incremental effect on weight-reduction over the dose range of dulaglutide 1.5 mg to 4.5 mg was moderate but is an additional benefit for the usually overweight patients with T2DM, which was perceived as such according to the health outcome evaluation. Other measures of glycemic control consistently showed small-sized dose-related improvements.

Of note, a prior phase 2 study (study GBCF, submitted during initial MAA) did not show any incremental benefit in HbA1c reduction with higher doses (2.0 mg and 3.0 mg) compared to 1.5 mg but the results from the considerably larger pivotal study are considered more important.

Overall, in the overweight study population investigated the benefit of the higher doses over and above the one afforded by the 1.5 mg dose was rather small but acceptable. According to SmPC section 4.2, up-titration should be performed after a minimum duration of 4 weeks in patients in need of additional glycaemic control, which is considered appropriate. The decision to up-titrate after the minimum duration of 4 weeks should be based on patient measured blood glucose since the full effect on HbA1c takes longer to show than just 4 weeks.

2.6 Clinical safety

The safety profile of dulaglutide (1.5 mg QW) in adult patients with T2D has been characterized based upon data from the original marketing application and post-marketing data. The most common adverse events (AEs) are gastrointestinal (GI) symptom related (for example, nausea, vomiting, and diarrhoea), and are generally consistent with findings in the GLP-1 RA class.

The following presentation of the safety profile of higher once weekly doses of dulaglutide (3.0 mg and 4.5 mg) for treatment of patients with T2D focuses on the Phase 3 Study H9X-MC-GBGL (GBGL), an ongoing 52-week study designed to assess the safety and efficacy of once-weekly dulaglutide 3.0 mg and 4.5 mg in comparison to dulaglutide 1.5 mg. Previously, a safety evaluation based on the 36-week results of the phase 3 study GBGL was provided. The safety evaluation was updated and now focuses on the 52-week data.

Since the safety profile of dulaglutide is already known in general, in Study GBGL not all AEs but only deaths, SAEs, TEAEs, and discontinuations from study or study drug due to AEs were collected.

Two additional studies were performed as part of the development program for these investigational dulaglutide doses: A Phase 2 study (H9X-MC-GBGJ [GBGJ]) in 318 adult patients with T2D to provide initial safety and efficacy data for dulaglutide 4.5 mg and 3.0 mg once-weekly, and a Phase 1 clinical pharmacology study (H9X-MC-GBGM [GBGM]), which confirmed equivalent bioavailability and similar tolerability of dulaglutide 4.5 mg administered as a single injection via single-dose pen (SDP) (used for the Phase 3 study) versus an equivalent dose administered as three 1.5-mg injections using prefilled syringes (PFS) (used for the Phase 2 study).

Compared to the phase 2 study, another, more prolonged, scheme of up-titration was used to reduce the incidence of nausea and other GI side effects.

Patient exposure

In the phase 3 study GBGL, 612 to 616 patients per dose group were exposed to dulaglutide for 331 to 334 days (mean). Total exposure to dulaglutide over the 52 weeks of treatment was 1678.5 patient-years. In the phase 2 study GBGJ, around 80 patients per dose group were exposed for 110 days (mean).

Adverse events

In study GBGL, the fraction of patients per treatment group experienced at least one treatment-emergent AE was slightly increasing with dula dose, from 62.1% (1.5 mg dula) to 66.4% (4.5 mg dula). For details see table below. A placebo group was not included in this study.

Overview of Deaths and Adverse Events Reported through Week 52 of Completed Study GBGL Safety Population

Event[a]	Treatment Group Assigned				p-Value[d]
	Dula 1.5 (N=612) n (%)	Dula 3.0 (N=616) n (%)	Dula 4.5 (N=614) n (%)	Total (N=1842) n (%)	
Deaths[b]	3 (0.5)	4 (0.6)	4 (0.7)	11 (0.6)	>0.999
SAEs	51 (8.3)	42 (6.8)	38 (6.2)	131 (7.1)	0.333
Discontinuation from study due to an AE	8 (1.3)	11 (1.8)	14 (2.3)	33 (1.8)	0.434
Discontinuation from study drug due to an AE	37 (6.0)	43 (7.0)	52 (8.5)	132 (7.2)	0.256
Treatment-emergent Adverse Events (TEAEs)	380 (62.1)	384 (62.3)	408 (66.4)	1172 (63.6)	0.204
TEAEs related to study drug[c]	159 (26.0)	194 (31.5)	197 (32.1)	550 (29.9)	0.035

a Patients may be counted in more than 1 category.
b Deaths are also included as SAEs and discontinuations due to AE.
c Includes events that were considered related to study drug as judged by the investigator.
d P-values for overall treatment effect were computed using Fisher's exact test

In Study GBGJ, the percentage of patients with at least one TEAE in the dula groups was somewhat higher than in Study GBGL, ranging from 66.7% to 83.5%; in the placebo group, 58.0% of patients experienced at least one TEAE.

Reassuringly, the percentage of subjects experiencing at least one serious AE (SAE) was fairly balanced across the treatment groups in both studies and no dose-dependent increase was observed. The percentages in the dula groups was comparable to the percentage observed in the placebo group of Study GBGJ.

A dose-dependent increase in events of discontinuation of study medication was observed in both trials.

Regarding the nature of the AEs, expressed according to system organ class and preferred term, it turned out that most of them were gastrointestinal disorders, e.g. nausea, vomiting, dyspepsia, diarrhoea and constipation (see the following two tables). This finding was consistent across both studies, GBGJ and GBGL, and is expected for a GLP1 receptor agonist. The percentage of patients suffering one or more GI events was markedly higher in Study GBGJ than in GBGL (e.g. 27.8% vs. 43.2% in the dula 1.5 mg group of Study GBGL and GBGJ, respectively). This is most likely due to the faster dose-up-titration in the (shorter) study GBGJ.

Summary of TEAEs in at Least 2% of Patients in Any Treatment Group by SOC, PT, and Treatment Group through Week 52 in Study GBGL Safety Population

System Organ Class Preferred Term	Dula 1.5 mg (N=612) n (%)	Dula 3.0 mg (N=616) n (%)	Dula 4.5 mg (N=614) n (%)	Total (N=1842) n (%)	p-Value Overall
Patients reporting ≥1 TEAE	**380 (62.1)**	**384 (62.3)**	**408 (66.4)**	**1172 (63.6)**	**0.204**
Gastrointestinal Disorders	170 (27.8)	209 (33.9)	219 (35.7)	598 (32.5)	0.008
Nausea	87 (14.2)	99 (16.1)	106 (17.3)	292 (15.9)	0.336
Diarrhea	47 (7.7)	74 (12.0)	71 (11.6)	192 (10.4)	0.021
Vomiting	39 (6.4)	56 (9.1)	62 (10.1)	157 (8.5)	0.048
Constipation	19 (3.1)	26 (4.2)	24 (3.9)	69 (3.7)	0.574
Dyspepsia	17 (2.8)	31 (5.0)	17 (2.8)	65 (3.5)	0.060
Abdominal pain upper	18 (2.9)	21 (3.4)	16 (2.6)	55 (3.0)	0.714
Abdominal pain	17 (2.8)	15 (2.4)	17 (2.8)	49 (2.7)	0.918
Gastroesophageal reflux disease	12 (2.0)	15 (2.4)	18 (2.9)	45 (2.4)	0.540
Abdominal distension	9 (1.5)	11 (1.8)	22 (3.6)	42 (2.3)	0.033
Flatulence	7 (1.1)	12 (1.9)	12 (2.0)	31 (1.7)	0.482
General Disorders andAdministration Site Conditions	42 (6.9)	40 (6.5)	50 (8.1)	132 (7.2)	0.507
Fatigue	10 (1.6)	9 (1.5)	12 (2.0)	31 (1.7)	0.788
Infections and Infestations	147 (24.0)	137 (22.2)	150 (24.4)	434 (23.6)	0.629
Nasopharyngitis	28 (4.6)	32 (5.2)	38 (6.2)	98 (5.3)	0.458
Urinary tract infection	14 (2.3)	12 (1.9)	25 (4.1)	51 (2.8)	0.058
Upper respiratory tract infection	15 (2.5)	17 (2.8)	16 (2.6)	48 (2.6)	0.983
Influenza	19 (3.1)	9 (1.5)	19 (3.1)	47 (2.6)	0.097
Bronchitis	12 (2.0)	8 (1.3)	14 (2.3)	34 (1.8)	0.416
Gastroenteritis	8 (1.3)	14 (2.3)	10 (1.6)	32 (1.7)	0.458
Sinusitis	6 (1.0)	9 (1.5)	12 (2.0)	27 (1.5)	0.362
Investigations	50 (8.2)	40 (6.5)	53 (8.6)	143 (7.8)	0.332
Lipase Increased	13 (2.1)	8 (1.3)	14 (2.3)	35 (1.9)	0.385
Metabolism and NutritionDisorders	58 (9.5)	52 (8.4)	59 (9.6)	169 (9.2)	0.744
Hyperglycemia	19 (3.1)	19 (3.1)	24 (3.9)	62 (3.4)	0.681
Decreased appetite	15 (2.5)	13 (2.1)	18 (2.9)	46 (2.5)	0.645
Musculoskeletal and ConnectiveTissue Disorders	57 (9.3)	55 (8.9)	60 (9.8)	172 (9.3)	0.881
Back pain	16 (2.6)	15 (2.4)	12 (2.0)	43 (2.3)	0.748
Nervous System Disorders	60 (9.8)	61 (9.9)	62 (10.1)	183 (9.9)	0.990
Headache	28 (4.6)	25 (4.1)	21 (3.4)	74 (4.0)	0.594
Dizziness	18 (2.9)	10 (1.6)	12 (2.0)	40 (2.2)	0.243
Vascular Disorders	21 (3.4)	22 (3.6)	23 (3.7)	66 (3.6)	0.975
Hypertension	12 (2.0)	12 (1.9)	13 (2.1)	37 (2.0)	0.978

The applicant also provided a table (see below) showing the types of AEs which were markedly different (p-value <0.05) between the dosage groups. A dose-dependent increase was observed with abdominal distension and decreased weight. These are established effects of GLP1-receptor agonists. The relevance of the other imbalances, which did not show dose dependence, is not known.

Summary of Other Treatment-Emergent Adverse Events Through Week 52 of Completed Phase 3 Study GBGL that were Significantly Different among the Dulaglutide Dose Groups Safety Population

Preferred Term	**Treatment Group Assigned**			**Total (N=1842) n (%)**	**Overall p-Value***
	Dula 1.5 mg (N=612) n (%)	**Dula 3.0 mg (N=616) n (%)**	**Dula 4.5 mg (N=614) n (%)**		
Higher in One or Both Investigational Dose Groups Compared to the 1.5-mg Dose					
Abdominal Distension	9 (1.5)	11 (1.8)	22 (3.6)	42 (2.3)	0.033
Weight Decreased	1 (0.2)	2 (0.3)	8 (1.3)	11 (0.6)	0.047

Blood Calcitonin Increased	2 (0.3)	0 (0)	5 (0.8)	7 (0.4)	0.049
Cellulitis	1 (0.2)	0 (0)	5 (0.8)	6 (0.3)	0.028
Lower in the Investigational Dose Groups Compared to the 1.5-mg Dose					
Hiatus Hernia	6 (1.0)	0 (0)	1 (0.2)	7 (0.4)	0.004
Subcutaneous Abscess	4 (0.7)	0 (0)	1 (0.2)	5 (0.3)	0.032
Duodenitis	4 (0.7)	0 (0)	0 (0)	4 (0.2)	0.012
Arteriosclerosis	3 (0.5)	0 (0)	0 (0)	3 (0.2)	0.037
Discomfort	3 (0.5)	0 (0)	0 (0)	3 (0.2)	0.037
Gastric Polyps	3 (0.5)	0 (0)	0 (0)	3 (0.2)	0.037

Abbreviations: Dula = dulaglutide; n = number of patients in the specified category; N = number of patients randomized and treated.
* P-values for overall treatment effect were computed using Fisher's Exact test.

AEs of special interest

Gastrointestinal effects

The applicant provided more detailed analyses of the GI side effects, diarrhoea, vomiting, abdominal pain and constipation, in the phase 3 study GBGL, see table below. Despite a rather high frequency of GI side effects, the percentage of patients discontinuing study drug due to GI AE was low, in the range of 1% to 2%; see section on discontinuations due to AEs for details.

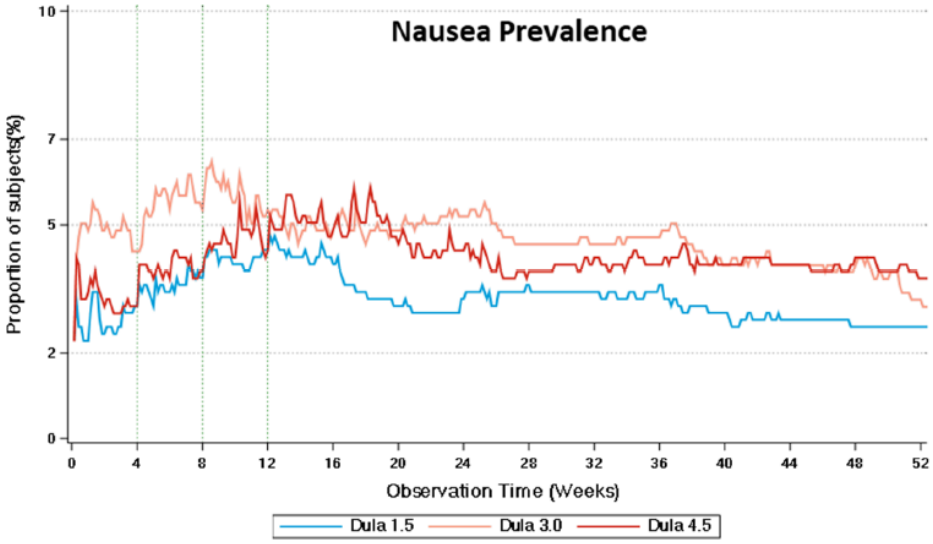
Summary of GI-Related TEAE Clusters through Week 52 Study GBGL

TEAE Cluster Term	Dula 1.5 mg (N=612) n (%)	Dula 3.0 mg (N=616) n (%)	Dula 4.5 mg (N=614) n (%)	Total (N=1842) n (%)	p-Value Overall
Diarrhea	47 (7.7)	74 (12.0)	71 (11.6)	192 (10.4)	0.021
Vomiting	39 (6.4)	56 (9.1)	62 (10.1)	157 (8.5)	0.048
Abdominal pain	38 (6.2)	39 (6.3)	40 (6.5)	117 (6.4)	0.985
Constipation	19 (3.1%)	26 (4.2)	24 (3.9)	69 (3.7)	0.574

GI side effects are expected mainly to occur at the beginning of the treatment with GLP1 receptor agonists. Therefore, the applicant analysed occurrence of nausea, vomiting and diarrhoea over time during the course of the study. For better comprehension, the figure below displays the dose up-titration scheme used in Study GBGL. Dose is increased every four weeks. Thus, in the highest dose group (4.5 mg QW), it lasts 12 weeks until the intended dose level is reached.

The prevalence of nausea is shown in the following figure. As expected from the dose up-titration scheme presented above, the percentage of patients experiencing nausea increases over the first 12 weeks in the 4.5 mg group. It decreases again later and appears to reach a steady state at Week 28 with around 3% to 5% of patients suffering nausea. Also, the other dose groups seem to be in steady state at this time, i.e. with no further change in nausea prevalence.

Prevalence of nausea in Study GBGL by dulaglutide dosage.



For vomiting and diarrhoea the prevalence was overall lower than for nausea. It was highest around 12 to 16 weeks after start of treatment and reached a steady state after around 28 weeks. In steady state, the prevalence was nearly identical in the 3.0 mg and 4.5 mg group.

According to the dose up-titration scheme shown above, all patients were treated equally in the first eight weeks of the study (dula 0.75 mg for four weeks and dula 1.5 mg for another four weeks). Nevertheless, the group finally ending up at 3 mg QW displayed a higher frequency of nausea and diarrhoea than the other groups in the first eight weeks for unknown reasons. This may indicate that variability of the GI findings was high in the first weeks. It is reassuring that the prevalence of the main GI effects (nausea, vomiting and diarrhoea) was very similar in the low and high dose group, demonstrating that the high dose (4.5 mg QW) does not lead to undue increase in GI side effects with the up-titration scheme used in Study GBGL.

On the other hand, it also becomes obvious from the above figures that at steady state (around Week 28 onwards) the prevalence of adverse GI effects is consistently higher with the new doses (3.0 and 4.5 mg) than with the established dose of 1.5 mg. Reassuringly, also with the new doses the prevalence was rather low (around 1% for vomiting, 2% for diarrhoea and nearly 5% for nausea). In respect to safety it should be noted that these GI effects are hardly hazardous to the patient; if a patient does not tolerate higher dulaglutide doses, dose reduction is possible.

Hypoglycaemia

Events of hypoglycaemia were no more frequent in the higher dula dose groups than in the 1.5 mg group.

Cardiovascular events

In Study GBGL, deaths and nonfatal CV AEs were adjudicated by the CEC. The following nonfatal CV AEs were adjudicated: MI, hospitalization for unstable angina; hospitalization for heart failure, coronary interventions (such as coronary artery bypass graft or PCI); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack (TIA).

There were two CV deaths in the 3.0 mg dula group, one in the 1.5 mg group and one in the 4.5 mg group. There were also some non-fatal CV events, but no dose-dependency was observed.

Summary of Patients with CEC-Confirmed Cardiovascular Events through Safety Follow-Up Period; Safety Population

Event	Dula 1.5 mg (N=612) n (%)	Dula 3.0 mg (N=616) n (%)	Dula 4.5 mg (N=614) n (%)	Total (N=1842) n (%)
Patients with ≥1 CEC-confirmed CV events[a]	2 (0.3)	8 (1.3)	5 (0.8)	15 (0.8)
Cardiovascular death	1 (0.2)	2 (0.3)	1 (0.2)	4 (0.2)
Sudden cardiac death	0 (0)	1 (0.2)	1 (0.2)	2 (0.1)
Acute myocardial infarction	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Stroke	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Acute coronary syndrome events	1 (0.2)	3 (0.5)	1 (0.2)	5 (0.3)
Myocardial infarction	1 (0.2)	2 (0.3)	1 0.2)	4 (0.2)
Hospitalized unstable angina	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Coronary revascularization[b]	1 (0.2)	4 (0.6)	1 (0.2)	6 (0.3)
Hospitalization for heart failure	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Cerebrovascular events	0 (0)	3 (0.5)	2 (0.3)	5 (0.3)
Ischemic stroke	0 (0)	2 (0.3)	2 (0.3)	4 (0.2)
Transient ischemic attack	0 (0)	1 (0.2)	0 (0)	1 (0.1)

The number of confirmed CV events was low in Study GBGL so that firm conclusions are not possible. The applicant noted that a CV outcome study (REWIND) did not indicate increased CV risk by dula at the 1.5 mg QW dose. Although it is acknowledged that the mechanism of action of dula gives no hint for adverse effects that could increase CV risk, it is uncertain whether extrapolation of the REWIND results to higher dula doses is possible. The processes triggered by GLP1 agonists are complex so that undesired CV effects of higher doses cannot fully be excluded.

Pancreatitis

Pancreatitis has been reported with the use of GLP-1 RAs, including dulaglutide.

It is known from GLP1 receptor agonist that they can increase pancreatic enzymes in the absence of other signs for pancreatitis, i.e. in case of therapy with GLP1 agonist, increase in pancreatic enzymes in plasm does not necessarily indicate pancreatitis. Alterations of pancreatic enzymes in Study GBGL are discussed in the section on laboratory findings.

In Study GBGL, pancreatitis was analysed based on adjudicated events. A total of 6 events in 6 patients were confirmed by the CEC to be pancreatitis, 1 event in the dula 1.5 mg group, 2 events in the dula 3.0 mg and 3 events in the dula 4.5 mg group. All 6 confirmed events were adjudicated as acute pancreatitis and occurred when patients were taking their final maintenance dose of dulaglutide. All events were mild in severity, and no pancreatic complications were reported.

Summary of Adjudicated Pancreatic Events from Baseline through Week 52 in Study GBGL; Safety Population

Events	Dula 1.5 mg (N=612) m, n (%)	Dula 3.0 mg (N=616) m, n (%)	Dula 4.5 mg (N=614) m, n (%)	Total (N=1842) m, n (%)
CEC-Assessed Pancreatitis				
Yes	**1, 1 (0.2)**	**2, 2 (0.3)**	**3,3 (0.5)**	**6, 6**
Acute pancreatitis	1, 1 (0.2)	2, 2 (0.3)	3, 3 (0.5)	6, 6 (0.3)
Diagnostic criteria used to confirm acute pancreatitis				

Symptoms and elevated enzymes	0	0	3, 3 (0.5)	3, 3 (0.2)
Symptoms and imaging	1, 1 (0.2)	1, 1 (0.2)	0	2, 2 (0.1)
Symptoms, imaging, and elevated enzymes	0	1, 1 (0.2)	0	1, 1

Abbreviations: CEC = Clinical Endpoint Committee; Dula = dulaglutide; m = number of events in each treatment arm; n = number of unique patients with the event in each treatment group; N = number of patients randomized and treated.

Gallbladder disease

An association between the GLP-1 RA therapeutic class and risk of biliary tract events has been reported. In Study GBGL, a total of 30 patients (1.6%) had at least 1 event related to acute gallbladder disease, with similar proportions across the 3 dulaglutide dose groups. The most frequent TE event in the Gallbladder-related disorders SMQ was cholelithiasis, which occurred in a total of 16 patients (0.9%): 4 (0.7%) in the 1.5-mg group, 5 (0.8%) in the 3.0-mg group, and 7 (1.1%) in the 4.5-mg group.

Serum calcitonin and C-cell hyperplasia/neoplasia

No events of C-cell hyperplasia or tumour were reported.

Two patients had a postbaseline serum calcitonin value that was ≥35 ng/L and a ≥50% increase from the baseline value. The applicant provided narratives of these patients. One patient was diagnosed with multiple myeloma and osteolytic changes. For the other patient no reason for calcitonin elevation was found.

Serious adverse events and deaths

Deaths

A total of 11 patients died during the study from baseline through Week 52 (see tables below); all 11 deaths were adjudicated by the CEC.

Four deaths were confirmed as CV-related upon adjudication; two patients experienced this event while receiving 1.5 mg dula (one patient of them was assigned to the 3.0 mg group and was in the up-titration phase). One patient received 3.0 mg dula prior to the event and one 4.5 mg. Hence, there was no dose-dependency.

Listing of Adjudicated Deaths Through Week 36 All Randomized Population

Unique Subject ID	Treatment	Study Day*	PI Event
H9X-MC-GBGL-114-02458	Dula 0.75	44	Metastases to abdominal cavity
H9X-MC-GBGL-102-02698	Dula 1.5	251	Metastatic uterine cancer
H9X-MC-GBGL-703-03623	Dula 1.5	61	Ischaemic stroke
H9X-MC-GBGL-608-03833	Dula 3.0	239	Cardio-respiratory arrest
H9X-MC-GBGL-560-02133	Dula 3.0	78	Death
H9X-MC-GBGL-356-03579	Dula 4.5[c]	187	Sudden death

* - Day derived relative to first day of dosing with study drug.
c Dulaglutide 4.5 mg had been permanently discontinued due to diarrhea approximately 3 months and 4 days before death.
Note: The actual dose at the time of death is indicated, not the group the patient was assigned to

Listing of Adjudicated Deaths After Week 36 All Randomized Population

Unique Subject ID	Treatment	Study Day*	PI Event
H9X-MC-GBGL-947-2050	Dula 1.5	366	Acute Myocardial Infarction
H9X-MC-GBGL-558-2004	Dula 3.0	296	Malignancy

H9X-MC-GBGL-703-2587	Dula 3.0	324	Sudden death
H9X-MC-GBGL-103-3183	Dula 4.5	265	Sudden death
H9X-MC-GBGL-614-3510	Dula 4.5	309	Cardio-respiratory arrest

SAEs

Reassuringly, the number and percentage of patients with at least one serious AE decreased with increasing dula dose. The frequency of each individual SAE type was low, and no pattern of functionally related SAEs was observed. None of the individual SAE types showed a clear dose-dependency. The following table lists all SAE types which occurred in at least 2 patients of a dose group.

Serious Adverse Events in Study GBGL Occurring in at Least 2 Patients in Any Dulaglutide Dose Group through Week 52 by Descending Order of Frequency by PT Safety Population

Preferred Term	Dula 1.5 mg (N=612) n (%)	Dula 3.0 mg (N=616) n (%)	Dula 4.5 mg (N=614) n (%)	Total (N=1842) n (%)
Patients with ≥1 SAE	**51 (8.3)**	**42 (6.8)**	**38 (6.2)**	**131 (7.1)**
Pneumonia	2 (0.3)	2 (0.3)	1 (0.2)	5 (0.3)
Atrial fibrillation	3 (0.5)	0	1 (0.2)	4 (0.2)
Cholecystitis acute	0	2 (0.3)	2 (0.3)	4 (0.2)
Abdominal Pain	1 (0.2)	0	2 (0.3)	3 (0.2)
Acute Myocardial Infarction	2 (0.3)	1 (0.2)	0	3 (0.2)
Acute respiratory failure	1 (0.2)	2 (0.3)	0	3 (0.2)
Ischaemic Stroke	0	2 (0.3)	1 (0.2)	3 (0.2)
Lipase increased	2 (0.3)	0	1 (0.2)	3 (0.2)
Myocardial Infarction	1 (0.2)	2 (0.3)	0	3 (0.2)
Non-cardiac chest pain	2 (0.3)	1 (0.2)	0	3 (0.2)
Sudden Death	0	1 (0.2)	2 (0.3)	3 (0.2)
Pregnancy[a]	0	2 (0.7)	0	2 (0.2)

a Denominator adjusted because gender-specific event for females: N = 314 (Dula 1.5), N = 288 (Dula 3.0), N = 296 (Dula 4.5)

Laboratory findings

Serum chemistry

Serum lipids

LDL- and HDL-cholesterol remained essentially unchanged in all treatment groups during the course of Study GBGL. Statistically significant changes from baseline to Week 52 were observed for total cholesterol, HDL-cholesterol (increase), triglycerides and VLDL-cholesterol (decrease). There was a weak dose-dependencyl.

Baseline Means and Mean Change from Baseline to Week 52 in Serum Lipid Parameters, Safety Population

Parameter/ Statistic	Dula 1.5 mg	Dula 3.0 mg (N=616)	Dula 4.5 mg	Overall p-Value
Total cholesterol				
Baseline mean (mg/dL)	177.36	176.65	178.58	-
Mean change from baseline (mg/dL) to Week 52	-3.27*	-4.89*	-7.87*	0.088
HDL-C				
Baseline mean (mg/dL)	46.35	45.44	45.05	-
Mean change from baseline (mg/dL) to Week 52	0.27	0.32	0.68*	0.470

LDL-C[a]				
Baseline mean (mg/dL)	91.91	93.25	95.12	-
Mean change from baseline (mg/dL) to Week 52	2.15	0.00	-1.78	0.331
VLDL-C[a]				
Baseline mean (mg/dL)	33.95	34.22	35.34	-
Mean change from baseline (mg/dL) to Week 52	-3.22*	-3.77*	-6.04*§	0.001
Triglycerides				
Baseline mean (pg/mL)	207.22	198.11	201.78	-
Mean change from baseline (mg/dL) to Week 52	-33.47*	-29.71*	-40.48*§	0.005

a Calculated value based on Friedwald equation.
* The p-value <0.05 for within treatment comparison of Week 52 to baseline.
§ The p-value <0.05 for comparison of dulaglutide 3.0 mg or 4.5 mg vs. 1.5 mg.

Baseline Means and Mean Change from Baseline to Week 52 in Serum Lipid Parameters, Safety Population

Parameter/ Statistic	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)	Overall p-Value
Total cholesterol				
Baseline mean (mg/dL)	177.36	176.65	178.58	-
Mean change from baseline (mg/dL) to Week 52	-3.27*	-4.89*	-7.87*	0.088
VLDL-C[a]				
Baseline mean (mg/dL)	33.95	34.22	35.34	-
Mean change from baseline (mg/dL) to Week 52	-3.22*	-3.77*	-6.04*§	0.001
Triglycerides				
Baseline mean (pg/mL)	207.22	198.11	201.78	-
Mean change from baseline (mg/dL) to Week 52	-33.47*	-29.71*	-40.48*§	0.005

a Calculated value based on Friedwald equation.
* The p-value <0.05 for within treatment comparison of Week 52 to baseline.
§ The p-value <0.05 for comparison of dulaglutide 3.0 mg or 4.5 mg vs. 1.5 mg.

Besides cholesterol, VLDL particles carry large amounts of triglycerides so that the decrease in VLDL may reflect the decrease in triglycerides. Notably, VLDL-C is not measured directly but calculated using the triglyceride level. Hence, a similar behaviour of VLDL-c and triglycerides is expected.

As for LDL-C, decrease in plasma VLDL-C is considered beneficial so that the above findings are not considered a safety concern. They may reflect the dula-induced loss in body fat mass.

Pancreatic enzymes

It was observed that GLP1 receptor agonists can increase pancreatic enzymes (lipase, amylase) in serum without further signs of pancreatitis. A mean increase in serum lipase and amylase was also observed in the participants of Study GBGL, see table below. Pancreatic amylase increased from baseline by 22% during the course of the study without relevant differences between the treatment groups. Lipase increased in mean by 19% with slight dependency from the dula dose.

P-amylase and Lipase Values (IU/L) at Baseline and Mean Values, Changes, and Geometric Mean Change from Baseline at Week 52 by Treatment, MMRM Safety Population

Enzyme/ Time Point/ Parameter	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)
Pancreatic Amylase			
Baseline			
n	584	590	595
Median, IU/L	22	22	23
Mean (SD), IU/L	27.5 (28.3)	27.0 (19.9)	26.7 (19.2)

Week 52			
Median, IU/L	27	26	28
Mean (SD), IU/L	31.6 (25.6)	32.6 (25.5)	32.5 (23.2)
Mean change (SD), IU/L	4.6 (18.5)	6.0 (22.7)	6.3 (18.4)
Geometric LS mean ratio	**1.19**	**1.20**	**1.22**
Lipase			
Baseline			
n	584	590	595
Median, IU/L	37	36	36
Mean (SD), IU/L	45.9 (44.3)	45.1 (36.9)	46.4 (44.2)
Week 52			
Median, IU/L	41	42	44
Mean (SD), IU/L	50.3 (34.3)	55.7 (63.0)	55.4 (50.0)
Mean change (SD), IU/L	5.3 (45.5)	11.0 (60.6)	9.6 (52.9)
Geometric LS mean ratio	**1.12**	**1.17**	**1.19**

Abbreviations: Dula = dulaglutide; LS = least-squares; MMRM = mixed-model repeated measure; N = number of patients randomized and treated; n= number of patients with baseline and at least 1 post-baseline value; N/A = not applicable; SD = standard deviation.
*The p-value <0.05 for dulaglutide investigational dose (3.0 mg or 4.5 mg) versus 1.5-mg dose.
Geometric LS mean ratio = Week 52 value / baseline value estimated from MMRM model.

Others

Apart from serum lipids and pancreatic enzymes no meaningful changes in clinical chemistry parameters were observed.

Haematology

There were no significant or clinically meaningful differences across the dulaglutide dose groups in change from baseline to Week 36 for any haematology parameter.

Vital signs

There was an increase in heart rate (HR) during treatment with dual as compared to baseline. This effect is known for GLP1 receptor agonists. The increase over baseline was 1.9 bpm at Week 52 with the two new doses, 3.0 and 4.5 mg QW. Simultaneously, there was a small decrease from baseline in systolic blood pressure (SBP), up to -4.1 mmHg. Changes in HR and SBP were more pronounced with the new, higher doses of dula than with the established dose of 1.5 mg QW.

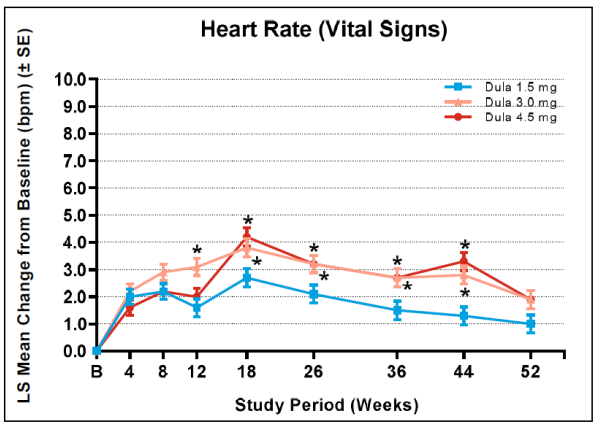
Summary and Analysis of Vital Signs Baseline Values and Change from Baseline at Week 52, MMRM Safety Population

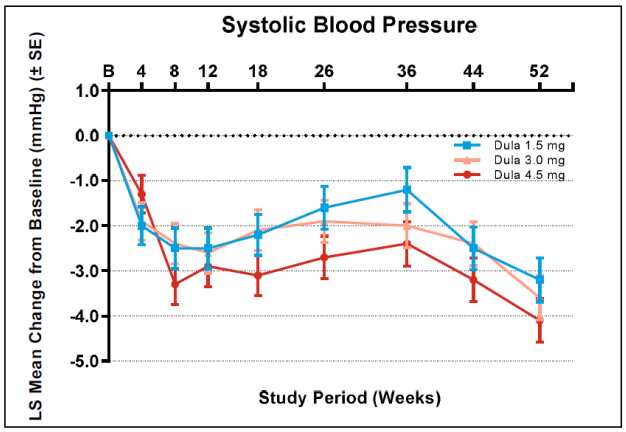
Parameter/ Time Point	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)
Heart Rate (bpm)			
LS mean at baseline	75.7	75.3	75.4
LS mean change at Week 52	1.0*	1.9*	1.9*
LS mean difference vs. Dula 1.5 mg	N/A	0.9	0.9
Systolic Blood Pressure (mmHg)			
LS mean at baseline	132.0	131.1	132.1
LS mean change at Week 52	-3.2*	-3.6*	-4.1*
LS mean difference vs. Dula 1.5 mg	N/A	-0.3	-0.8
Diastolic Blood Pressure (mmHg)			
LS mean at baseline	78.7	78.5	79.0
LS mean change at Week 52	-1.1*	-1.0*	-1.1*
LS mean difference vs. Dula 1.5 mg	N/A	0.1	-0.1

Abbreviations: bpm = beats per minute; Dula = dulaglutide; LS = least-squares; MMRM = mixed-model repeated measures; N = number of patients randomized and treated; N/A = not applicable; vs. = versus.
* The p-value <0.05 for within treatment comparison of Week 52 to baseline.

The following figures display the course of HR and SBP over time. Most pronounced effects were observed at Week 18 for HR, with increase up to around 4 bpm, and at Week 8 for SBP with decrease of around 3.2 mmHg for the highest dose. A more pronounced decrease was observed from Week 36 onwards.

LS mean changes from baseline in heart rate (left) and SBP (right), safety population



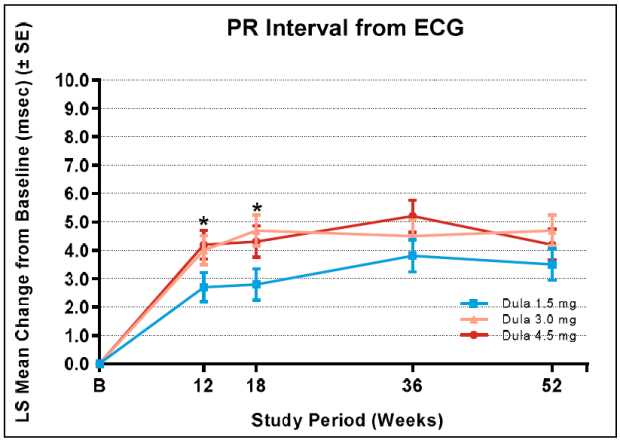


ECG

Dose-dependent shortening of the QTcF interval was observed, the effect being maximal at around 18 weeks after start of treatment. The time-course was similar to the time course of HR increase so that the QTcF shortening could be due to over-correction by the Fridericia formula.

Furthermore, dula prolonged the PR interval. The effect size was similar for the 3.0 and 4.5 mg dose and was larger with the new doses than with the established dose of 1.5 mg. The time course of the PR elongation is depicted in the following figure. In contrast to HR, PR prolongation was highest at Week 36 (around 5 ms with the highest dula dose). No further increase was observed thereafter.

LS mean change from baseline in PR interval from ECG, safety population



In accordance with the PR prolongation, AV block first degree was reported as an AE in 6 to 7 patients and second degree in 1 to 2 patients per dose group (see table below). No dependence on dula dose was

observed. For all cardiac conduction disorders a slight numerical increase with the higher doses compared to the established dose (1.5 mg) was observed (14 vs. 12).

Most Commonly Reported PTs Based on Cardiac conduction disorder (SMQ) Reported as TEAEs through Week 52 Study GBGL Safety Population

SMQ (Narrow) Preferred Term	Dula 1.5 mg (N=612)	Dula 3.0 mg (N=616)	Dula 4.5 mg (N=614)	Total (N=1842) n
Cardiac conduction disorder TEAEs	***12 (2.0)***	***14 (2.3)***	***14 (2.3)***	***40 (2.2)***
AV block first degree	6 (1.0)	7 (1.1)	6 (1.0)	19 (1.0)
AV block second degree	1 (0.2)	2 (0.3)	2 (0.3)	5 (0.3)
Bundle branch block left	1 (0.2)	1 (0.2)	3 (0.5)	5 (0.3)
Bundle branch block right	1 (0.2)	2 (0.3)	1 (0.2)	4 (0.2)

No obvious explanation can be provided for the PR prolongation. Notably, a higher heart rate is expected to shorten the PR interval so that dula's effect on PR interval is probably even larger. The underlying mechanism is unclear. Due the small effect size, PR prolongation is not considered a concern *per se*. However, this finding indicates that dula has some (unexpected) effects on the CV system.

Safety in special populations

The applicant evaluated the safety profile of dulaglutide in Study GBGL for the most frequently reported TEAEs (occurring in ≥5% patients in any treatment group) based on the following intrinsic baseline factors: age, race, sex, baseline body mass index (BMI), ethnicity, duration of diabetes, and baseline eGFR.

There was a significant treatment-by-sex interaction for nausea and diarrhoea which was driven primarily by the higher overall incidence of nausea and diarrhoea in females, with a similar incidence across the dulaglutide dose groups.

AE incidence by age is shown in the table below. In subjects ≥75 years of age AEs were numerically more frequent, but the number of study participants is very low in this age group so that firm conclusions are not possible.

Summary of Safety through Week 52 by Age Group Safety Population (Study GBGL)

MedDRA Terms	Age <65 N = 1404 n (%)	Age 65-74 N = 383 n (%)	Age 75-84 N = 54 n (%)	Age ≥85 N=1[a]
Total AEs	**933 (66.5)**	**248 (64.8)**	**41 (75.9)**	**0**
Dula 1.5 mg	292 (64.0)	91 (66.9)	14 (70.0)	
Dula 3.0 mg	307 (65.9)	87 (64.0)	9 (69.2)	
Dula 4.5 mg	334 (69.3)	70 (63.1)	18 (85.7)	
Serious AEs – Total	**93 (6.6)**	**33 (8.6)**	**5 (9.3)**	**0**
Dula 1.5 mg	34 (7.5)	16 (11.8)	1 (5.0)	
Dula 3.0 mg	35 (7.5)	7 (5.1)	0	
Dula 4.5 mg	24 (5.0)	10 (9.0)	4 (19.0)	
Fatal	*5 (0.4)*	*4 (1.0)*	*2 (3.7)*	
Dula 1.5 mg	1 (0.2)	2 (1.5)	0	
Dula 3.0 mg	3 (0.6)	1 (0.7)	0	
Dula 4.5 mg	1 (0.2)	1 (0.9)	2 (9.5)	

Immunological events

Hypersensitivity reactions

A total of 52 patients (2.8%) experienced a TEAE under the Hypersensitivity SMQ, with similar proportions of patients across the 3 dose groups. The most frequent hypersensitivity PTs were rash (12 patients [0.7%]) and urticaria (11 patients [0.6%]), with similar proportions of patients across the 3 dose groups. Of the 52 patients with a TEAE of hypersensitivity reaction, 5 were TE ADA+: 1.5 mg, 3 patients (0.5%); 3.0 mg, 1 patient (0.2%); 4.5 mg, 1 patient (0.2%).

Injection site reactions

A total of 24 patients (1.3%) experienced injection site reaction TEAEs per the LSC during the 52-week Treatment Period; 11 (0.6%) patients experienced at least 1 potentially immune-mediated injection site reaction. The most frequent injection site reaction PTs were injection site pruritus (7 patients [0.4%]) and injection site reaction (5 patients [0.3%]). Only 1 patient experienced a new injection site reaction after the primary 36-week endpoint. A numerically higher percentage of patients assigned to the dulaglutide 4.5-mg group (13 patients, 2.1%) experienced any injection site reactions compared to those assigned to the dulaglutide 1.5-mg (5 patients, 0.8%) and 3.0-mg (6 patients, 1.0%) groups. Of the 24 patients with a TEAE of injection site reaction, 5 were TE ADA+: 1.5 mg, 0 patients; 3.0 mg, 1 patient (0.2%); 4.5 mg, 4 patients (0.7%).

Anti-drug-antibodies (ADA)

A patient was considered to have TE dulaglutide ADA if the patient had at least 1 titer that was TE relative to baseline, defined as a 4-fold increase in titer from baseline when dulaglutide ADA were detected at baseline, or 2-fold greater than the MRD of the screening assay (MRD 1:2) if no dulaglutide ADA were detected at baseline.

Samples were analysed using a 4-tiered approach in validated ADA assays. All samples were assessed in Tier 1 (screening). Samples at or above the screening assay cut point were assessed in Tier 2a (confirmation). Any samples confirmed as positive for ADA in Tier 2a were reported as "detected." All samples below the screening assay cut point, Tier 1, or not confirmed in Tier 2a were reported as "not detected." Any "detected" sample in Tier 2a was assessed in Tier 2b (cross-reactive binding to native GLP-1), Tier 3 (titer assessment), and Tier 4a (dulaglutide neutralizing ADA assay). Any "detected" sample in Tier 2b was assessed in Tier 4b (native GLP-1 neutralising assay).

The ADA results are summarised in the table below. The proportion of patients with TE ADA was similar in all dula dose groups and was around 4%.

Summary of Patients With Treatment-Emergent Dulaglutide Antidrug Antibodies, All Post-Baseline; Observations up to Week 52; Safety Population

	Dula 1.5 (N=612) n (%)	Dula 3.0 (N=616) n (%)	Dula 4.5 (N=614) n (%)	Total (N=1842) n (%)	p-value overall *c
Patients Evaluable for TE ADA *a	595	607	604	1806	
Evaluable Patients with ADA Present **at Baseline**	59(9.9)	71(11.7)	81(13.4)	211(11.7)	0.170
Neutralizing LY for GLP-1-R at Baseline	3(0.5)	2(0.3)	1(0.2)	6(0.3)	0.544
GLP-1 Cross-Reactive at Baseline	26(4.4)	25(4.1)	34(5.6)	85(4.7)	0.426
Neutralizing nsGLP-1 at Baseline	3(0.5)	0	2(0.3)	5(0.3)	0.175
Patients Postbaseline TE ADA+ *b	**26 (4.4)**	**20 (3.3)**	**24 (4.1)**	**71 (3.9)**	**0.596**
Neutralizing LY for GLP-1-R	3(0.5)	0	4(0.7)	7(0.4)	0.124
GLP-1 Cross-Reactive	21(3.5)	16(2.6)	19(3.1)	56(3.1)	0.675
Neutralizing nsGLP-1	0	0	0	0	-

*a A subject is TE ADA evaluable if there is at least one non-missing test result for LY ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA evaluable subjects in each treatment group
*b If ADA is DETECTED with no titer available, baseline titer is imputed as 1:2 and postbaseline titer is imputed as 1:4. A TE ADA evaluable subject is considered to be TE ADA+ if the subject has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA Not Present, then the subject is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 1: 4 (treatment-induced). A TE ADA evaluable subject is TE ADA Inconclusive if >=20% of the subject's postbaseline samples, drawn pre-dose, are ADA Inconclusive and the subject is not otherwise TE ADA+. A TE ADA evaluable subject is TE ADA- if not TE ADA+ and not TE ADA Inconclusive.
*c P-values are from Fisher's exact test

In search for neutralising antibodies, the applicant also addressed potential clinical signs of decreasing therapeutic effect of dula, thereby considering HbA1c and body weight. Changes of these two parameters were similar for all patients and the patients with TE ADA, indicating absence of neutralising antibodies.

The applicant did not show the changes in titre from pre- to post-treatment. This information was only included in the definition of "treatment emergent", but detailed titre results were not provided. For a complete picture this information should be provided. For some subjects, titres were imputed.

Safety related to drug-drug interactions and other interactions

GLP1 receptor agonists are known to retard gastric emptying. This can affect the absorption of other drugs and is discussed in the PK/PD section of this report.

Discontinuation due to AEs

In total, 7.2% of study participants discontinued due to AE up to Week 52. discontinuation rate increased with dula dose from 6.0% to 8.5%, see table below. The predominant reason for discontinuation was a GI-related AE.

Summary of Study Treatment Discontinuation Due to Adverse Events or Death by Descending Frequency of Preferred Term through Week 52, Safety Population

	Dula 1.5 (N=612)		**Dula 3.0 (N=616)**		**Dula 4.5 (N=614)**		**Total (N=1842)**		**p-value**
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	Overall
Subjects Discontinued Study Treatment due to AE	**37**	**(6.0)**	**43**	**(7.0)**	**52**	**(8.5)**	**132**	**(7.2)**	**0.256**
Nausea	8	(1.3)	8	(1.3)	9	(1.5)	25	(1.4)	0.968
Diarrhoea	1	(0.2)	6	(1.0)	6	(1.0)	13	(0.7)	0.122
Vomiting	0		5	(0.8)	8	(1.3)	13	(0.7)	0.011
Abdominal Pain	2	(0.3)	1	(0.2)	2	(0.3)	5	(0.3)	0.752
Abdominal Pain Upper	1	(0.2)	3	(0.5)	1	(0.2)	5	(0.3)	0.629
Constipation	1	(0.2)	0		2	(0.3)	3	(0.2)	0.443
Dyspepsia	0		2	(0.3)	1	(0.2)	3	(0.2)	0.777
Weight Decreased	0		0		3	(0.5)	3	(0.2)	0.073
Abdominal Distension	0		1	(0.2)	1	(0.2)	2	(0.1)	1.000
Amylase Increased	1	(0.2)	0		1	(0.2)	2	(0.1)	0.555
Blood Calcitonin Increased	0		0		2	(0.3)	2	(0.1)	0.221
Cardio-Respiratory Arrest	0		1	(0.2)	1	(0.2)	2	(0.1)	1.000
Decreased Appetite	0		2	(0.3)	0		2	(0.1)	0.333
Dizziness	0		1	(0.2)	1	(0.2)	2	(0.1)	1.000
Gastrooesophageal Reflux Disease	2	(0.3)	0		0		2	(0.1)	0.110

Hepatic Enzyme Increased	1	(0.2)	0		1	(0.2)	2	(0.1)	0.555
Ischaemic Stroke	0		2	(0.3)	0		2	(0.1)	0.333
Lipase Increased	2	(0.3)	0		0		2	(0.1)	0.110
Pancreatitis Acute	1	(0.2)	1	(0.2)	0		2	(0.1)	0.777
Sudden Death	0		1	(0.2)	1	(0.2)	2	(0.1)	1.000
Angioedema	1	(0.2)	0		0		1	(0.1)	0.332
Asthenia	0		0		1	(0.2)	1	(0.1)	0.666

Abbreviations: N = number of subjects in the analysis population; n = number of subjects with events meeting specified criteria.

Post-marketing experience

Post-marketing experience exists for the 1.5 mg QW dose but not for the new, higher doses of 3.0 and 4.5 mg QW.

2.6.1. Discussion on clinical safety

The main safety information on 3.0 mg and 4.5 mg dula QW came from the phase 3 study GBGL, providing comparison to the 1.5 mg QW dose. The safety profile of 1.5 mg QW dula is well established from marketing authorisation studies and post-marketing experience. The applicant also conducted a phase 2 trial with the new doses, Study GBGJ. The safety outcome of the latter was in line with the results from Study GBGL with the exception that GI side effects were more pronounced in Study GBGJ since a faster dose up-titration scheme was used. This is not relevant for clinical use since in the SmPC the slow up-titration (dose increase after at least four weeks) as used in the phase 3 study GBGL is recommended.

Since the safety profile of dulaglutide is already known in general, not all AEs were collected in the pivotal study GBGL but only serious AES, AEs leading to discontinuation and AEs of special interest. Reassuringly, the percentage of patients suffering a serious AE was not higher in the 3.0 mg and 4.5 mg groups than in the 1.5 mg group. The number of deaths was balanced between the treatment groups.

As expected for a GLP1 receptor agonist, the most frequent AEs were related to gastrointestinal symptoms such as nausea, diarrhoea and vomiting. Most events occurred in the first weeks after start of treatment. The frequency of GI side effects was somewhat higher with the 3.0 mg and 4.5 mg doses than with the 1.5 mg dose, but this is not regarded as a safety concern since dose reduction is possible if a subject does not tolerate the higher doses due to GI effects. Comparison of the frequency of GI events in Study GBGL (phase 3) vs. Study GBGJ (phase 2) revealed that not the absolute dose of dula but the dose escalation scheme mainly determines the rate of GI effects.

A potentially serious side effect of GLP1 receptor agonists is pancreatitis. Diagnosis of the latter is complicated by the fact that GLP1R agonists increase the level of pancreatic enzymes in plasma independent of pancreatitis (e.g. by triggering increased synthesis). Potential pancreatitis cases were adjudicated by an expert committee. In the 1.5 mg dula group of Study GBGL, 1 confirmed pancreatitis event occurred, and in the 3.0 mg and 4.5 mg groups 2 and 3 events, respectively, per group. Due to the small number of events, firm conclusions are not possible. On the other hand, it is reassuring in respect to safety that the number of events was low. Additional reassurance can be derived from wide clinical experience with the substance class. Pancreatitis is an important identified risk in the RMP and is appropriately addressed in the SmPC, section 4.4.

The most important safety aspect when increasing the dula dose for diabetes treatment is the effect on cardiovascular (CV) risk. A CV outcome trial was conducted with dula 1.5 mg which did not indicate an increased risk, but the situation for higher doses is unclear. There is a previous example of increasing

the dose of a GLP1R agonist, i.e. liraglutide. This compound was developed for treatment of diabetes at a lower dose, and thereafter the indication obesity was sought with a higher dose. In this case, information on CV safety was derived from a meta-analysis of the 4 clinical studies conducted to support the obesity indication (Saxenda EPAR). In the case of dula, performing a meta-analysis is not possible because only one study was conducted. In addition, the number of CV events was rather low so that firm conclusions are not possible. In the absence of a CV outcome study with the higher doses applied for, assessment of CV risk has to rely on the CVOT conducted with the 1.5 mg dose, on mechanistic considerations and on the clinical experience with the substance class. A known CV effect of GLP1R agonist is increase in heart rate. This was also observed for dula, but the magnitude of the effect was rather small (increase by 1.9 bpm from baseline at Week 52 in the mid- and high-dose group). Simultaneously, there was a slight decrease in systolic blood pressure. The applicant considered the increase in HR too small for constituting a CV risk. This is generally agreed but ECG recordings revealed that dula had additional, partly unexplained effects on cardiac function. There was shortening of the Fridericia-corrected QTc interval which could be due to over-correction of the increased HR by the Fridericia formula although other effects cannot be excluded. And there was a consistent prolongation of the PR interval over the whole study duration, accompanied by a slight increase in cardiac conduction disorders. Notably, a higher heart rate is expected to shorten the PR interval so that dula's effect on PR interval is probably somewhat larger. The underlying mechanism is unclear. However, this effect was also small so that no relevant increase in events of higher-degree AV block is expected.

Notably, the dulaglutide dose of 3.0 mg was tested previously in the seamless phase 2 / phase 3 study GBCF which had been submitted with the original MAA for dula. In this study, the 3.0 mg arm was prematurely stopped, among others because of a marked mean increase in heart rate by 6.6 bpm. In the present phase 3 study GBGL, HR increase peaked at Week 18 and reached a peak increase from baseline of around 4 to 5 bpm in the 3.0 mg and 4.5 mg group, respectively. The peak coincided with the peak in the intensity of GI side effects so that the latter may have contributed to the HR increase. Reassuringly, HR decreased during the further course of Study GBGL, ending up at 1.9 bpm above baseline at Week 52 in the 3.0 mg and 4.5 mg group; for comparison, in the 1.5 mg group HR was 1.0 bpm above baseline at this time point.

The applicant has investigated the formation of anti-drug antibodies (ADA). Around 4% of the subjects in each dose group showed treatment-emergent antibodies. Reassuringly there was no dose dependence, i.e. the higher doses did not display increased immunogenicity. Also, injection site reactions and systemic hypersensitivity reaction were not more frequent with the new 3.0 and 4.5 mg doses than with the established 1.5 mg dose.

2.6.2. Conclusions on the clinical safety

No new safety signals appeared with the higher doses 3.0 mg and 4.5 mg as compared to the established dose of 1.5 mg. Also, the most prominent side effects of treatment with incretin mimetics, nausea, vomiting, diarrhoea and other GI symptoms, were not relevantly increased with the new doses due to a careful dose up-titration regimen.

The most relevant safety aspect is CV safety of the higher doses since a CV outcome trial was performed with the 1.5 mg dose only. In Study GBGL, submitted to support use of the higher doses, the rate of CV events was very low. The studied population was at slightly higher risk for adverse cardiovascular outcomes compared to the population included in the five phase 3 studies submitted with the initial MAA (higher inclusion threshold for HbA1c, longer duration of diabetes, all patients overweight or obese). However, firm conclusions on CV safety of the 3.0 mg and 4.5 mg dose are not possible to draw on the basis of the submitted data but additional experience with the substance class provides sufficient reassurance. Dulaglutide slightly increased HR, which is a known effect of GLP1 receptor agonists, but

also prolonged the PR interval. The underlying mechanism is unknown. However, this effect was also small so that no safety concerns arise.

2.7. Risk Management Plan

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 studies in the Post-authorisation Pharmacovigilance Development Plan

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 **Error! Reference source not found.** of this RMP
			Final Report: Estimated submission of study report	31/03/2032
Utilisation of Dulaglutide in European Countries (H9X-MC-B010) Ongoing		• Diagnosed with severe renal failure • Patients with congestive heart failure	Protocol Submission:	Provided in **Error! Reference source not found.** of this RMP

	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.	• 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	Final Report: Estimated submission of study report	31/12/2019 *(SR provided: assessment ongoing as part of variation II-48)*
Category 3 - Required additional pharmacovigilance activities				
Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009) Ongoing	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	Protocol Submission:	Provided in **Error! Reference source not found.** of this RMP

		• 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.	Final Report: Estimated submission of study report	31/03/2020 *(SR provided: assessment ongoing as part of variation II-51)*
Dulaglutide Retrospective Study (H9X-MC-B013) Planned	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 *(Assessment ongoing as part of MEA 006.1 and MRA 006.2)*
			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.

Risk minimisation measures

Safety Concern	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.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
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.
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.

Safety Concern	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.
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	Risk Minimisation Measures	Pharmacovigilance Activities
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; CV = cardiovascular; EU = European Union; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; PL = package leaflet; RA = receptor agonist; RMP = risk management plan; SmPC = summary of product characteristics; T2DM = type 2 diabetes mellitus; US = United States.

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1 Therapeutic Context

3.1.1. Disease or condition

Dulaglutide, a long-acting GLP-1 receptor agonist, is approved at two doses (0.75 mg and 1.5 mg s.c. once weekly) for treatment of type 2 diabetes mellitus. The purpose of this application is to add two new dose strengths (dulaglutide 3.0 mg and 4.5 mg s. c. once-weekly) for patients who need additional glycaemic control.

The present indication *remains unchanged* by this line extension. The proposed update of the posology reads as follows:

4.2 Posology and method of administration

"…

For additional glycaemic control,

1. *the 1.5 mg dose may be increased after at least 4 weeks to 3.0 mg once weekly.*
2. *the 3.0 mg dose may be increased after at least 4 weeks to 4.5 mg once weekly.*

The maximum dose is 4.5 mg once weekly.

3.2.2. Available therapies and unmet medical need

There are several classes of medicinal products for the treatment of T2D. All products have been shown to reduce blood glucose level and to improve HbA1c. Based on the extensive therapeutic experience, metformin is currently recommended as first-line treatment for all patients with T2D, unless contraindications apply (most notably, GFR <30 ml/min). Recently, SGLT2-inhibitors and GLP-1 receptor agonists have shown to be superior compared to placebo in reducing 3-point MACE in patients with established CV disease in CV outcomes trials.

Because T2D is a progressive disease, treatment intensification is often required to maintain glycaemic control over time. There may be advantages to increase the dose of one drug before adding another, for instance, the complexity of treatment would be reduced and the risk of new side effects would be avoided.

3.1.3. Main clinical studies

Study GBGL assessed the efficacy and safety of dulaglutide 3.0 mg or 4.5 mg compared to dulaglutide 1.5 mg in patients with T2D on metformin monotherapy. Efficacy and safety endpoints were evaluated at week 36, as predefined. The primary objective of this study was to demonstrate that once-weekly dulaglutide 4.5 mg, 3.0 mg, or both, was superior to dulaglutide 1.5 mg for change from baseline HbA1c. Key secondary endpoints were other measures of glycaemic control (responder analysis and FSG) and body weight reduction. The study enrolled overweight or obese patients (BMI ≥25 kg/m2) with HbA1c of 7.5% (58 mmol/mol) to 11% (97 mmol/mol), inclusive, despite a stable dose of metformin monotherapy.

The phase 2 study GBGJ (n=317) is supportive for the assessment of efficacy. It was a randomized, placebo-controlled, double-blind study in patients with T2DM on metformin monotherapy. The primary

objective of this trial was to show superiority of three dulaglutide doses (1.5 mg, 3.0 mg and 4.5 mg) to placebo as regards change in HbA1c at 18 weeks in T2DM patients. Secondary endpoints were in line with those in study GBGL.

3.2. Favourable effects

Within this line extension, the PK data provided evidence to support dulaglutide 3.0 mg and 4.5 mg once-weekly as distinct doses from an exposure perspective.

HbA1c changes from baseline to week 36 showed that the primary efficacy measure of superiority was met with dulaglutide 4.5 mg compared to dulaglutide 1.5 mg for both the efficacy estimand (-0.34%, p<0.001) and treatment-regimen estimand (-0.24%, p<0.001). For dulaglutide 3.0 mg superiority for the primary efficacy measure was met for the efficacy estimand (-0.17%, p=0.003), but not the treatment-regimen estimand (-0.10%, p=0.096).

Both investigational doses of dulaglutide (3.0 mg and 4.5 mg) were superior to the 1.5 mg dose in the secondary efficacy objective of percentage of patients achieving HbA1c <7%. The percentages of patients achieving an HbA1c <7% were 57.0% for dulaglutide 1.5 mg, 64.7% for dulaglutide 3.0 mg (odds ratio [95% CI] versus 1.5 mg: 1.49 [1.12, 1.98], p=0.006), and 71.5% for dulaglutide 4.5 mg (odds ratio [95% CI] versus 1.5 mg: 2.23 [1.65, 3.01], p<0.001).

The secondary efficacy measure of superiority over dulaglutide 1.5 mg for change in fasting serum glucose from baseline to week 36 was met with the dulaglutide 4.5 mg dose for the efficacy estimand (-8.1 mg/dL, p<0.001). For dulaglutide 3.0 mg, superiority was not met for FSG (-3.7 mg/dL, p=0.084).

The least squares mean changes in **body weight** from baseline to week 36 were for dulaglutide 1.5 mg: -3.1 kg, for dulaglutide 3.0 mg: -4.0 kg, and for dulaglutide 4.5 mg: -4.7 kg. The mean treatment difference in change in body weight versus dulaglutide 1.5 mg was -1.60 kg in the dulaglutide 4.5 mg group (p<0.001) and -0.90 kg in the dulaglutide 3.0 mg group (p=0.001).

Two validated **health outcomes questionnaires** were included to assess the potential impact of dulaglutide treatment on a patient's perception of health and well-being related to body weight: the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) and the Ability to Perform Physical Activities of Daily Living Questionnaire (APPADL). At week 36, there were statistically significant improvements in the IW-SP and the APPADL total scores from baseline for all three dulaglutide dose groups. The improvement in IW-SP total score at Week 36 was statistically significantly greater in patients escalated to dulaglutide 3.0 mg or 4.5 mg compared to patients maintained on dulaglutide 1.5 mg. The improvement in APPADL total score was statistically significantly greater with 4.5 mg versus the 1.5 mg group.

Supportive benefits from study GBGJ (valuable for evaluation of the effect size due to placebo control):

All three doses of dulaglutide (1.5 mg, 3.0 mg and 4.5 mg) reduced **HbA1c** significantly from baseline *compared to placebo* (all p-values <0.001; dulaglutide 1.5 mg vs plc -0.80, dulaglutide 3.0 mg vs plc -0.87, dulaglutide 4.5 mg vs plc -0.96). *Compared to the 1.5 mg dose*, a numerical improvement was shown in glucose control after 18 weeks: -0.08% (-0.34%, 0.19%) for 3.0 mg, p=0.572 and -0.16% (-0.44%, 0.11%) for 4.5 mg, p=0.235.

All three doses of dulaglutide significantly reduced **body weight** from baseline compared to placebo at week 18 (dula 1.5 mg vs placebo -1.2 kg, dula 3.0 mg vs placebo -2.4 kg, dula 4.5 mg vs placebo -2.6 kg). In addition, both of the two new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg) also reduced body weight significantly compared to dulaglutide 1.5 mg at week 18.

Exploratory efficacy results at week 52 showed that efficacy was maintained throughout week 52.

3.3. Uncertainties and limitations about favourable effects

The magnitude of the observed changes in HbA1c in study GBGL for the two new higher dose strengths versus dulaglutide 1.5 mg is considered rather small but within the range of incremental effects that have been accepted for other antihyperglycemic agents for which different dose strengths have been approved.

Strengths of dulaglutide higher than 1.5 mg were not supported by the dose-finding study GBCF submitted during the initial marketing authorization procedure in 2014 (EMEA/H/C/002825). In this study dula 2.0 mg and 3.0 mg had a numerically smaller effect on HbA1c-reduction compared to dula 1.5 mg. However, results have to be seen in the light of the small patient number per dose group and are considered less important compared to the data from study GBGL.

In studies GBGJ and GBGL dulaglutide was studied as add-on to metformin but not in combination with other antihyperglycemic agents (in contrast to the phase 3 studies where dula was tested add-on various background medications). However, this is not considered a relevant limitation, as any incremental benefit of the higher doses is likely to be maintained when used in combination with other glucose-lowering medications.

3.4. Unfavourable effects

The most prominent side effects of GLP1 receptor agonists are gastrointestinal (GI) symptoms such as nausea, vomiting, diarrhoea and abdominal pain. These mainly occur upon commencement of treatment and can be ameliorated by starting with a low dose and increasing it slowly. Besides of being a tolerance issue, the possibility exists that the accompanying alteration of gastrointestinal motility, e.g. delayed gastric emptying, may affect bioavailability of concomitantly taken oral medication. Prevalence of GI side effects was somewhat higher with the new doses of 3.0 mg and 4.5 mg dulaglutide than with the established dose of 1.5 mg.

GLP1 receptor agonists are also known to increase heart rate, most likely via action on CNS. Dulaglutide 3.0 mg and 4.5 mg increased the heart rate by around 4 bpm from baseline at Week 18 and around 3 bpm at Week 36, compared to 1.5 bpm with 1.5 mg dula. Furthermore, there was a small but consistent elongation of the PR interval in the ECG; the underlying mechanism is unclear.

Otherwise no new undesired effects of dulaglutide became obvious during the newly submitted studies GBGJ and GBGL.

3.5. Uncertainties and limitations about unfavourable effects

GLP1 receptor agonists are known to increase pancreas enzymes (lipase, amylase) in the serum, but it is unclear whether this GLP1-related increase is indicative for pancreatitis. Both lipase and amylase levels increased from baseline in study participants by – on average - 20% to 25% with weak dose-dependency. Potential events of pancreatitis were adjudicated by an expert board. Confirmed cases of pancreatitis were rare (one case in the 1.5 mg group and two cases each in the 3.0 mg and 4.5 mg group). The risk of pancreatitis is included in the RMP as important identified risk and appropriately labelled.

Cardiovascular safety was established for 1.5 mg QW dulaglutide in a CV outcome trial. It is unclear whether the results of this trial can be extrapolated to the higher doses. However, the effects of dula on heart rate were very small so that a relevant increase in CV risk is unlikely. Furthermore, prolongation of the PR interval was observed in the ECG, but this effect was also small so that no relevant increase in events of higher-degree AV block is expected. Further reassurance regarding CV safety can be derived from the clinical experience with the substance class.

Notably, the dulaglutide dose of 3.0 mg was tested previously in the phase 2 / phase 3 study GBCF which had been submitted with the original MAA for dula. In this study, the 3.0 mg arm was prematurely stopped, among other things because of a marked increase in heart rate by 6.6 bpm. In the present phase 3 study GBGL, HR increase peaked at Week 18 and reached a peak increase from baseline of around 4 to 5 bpm in the 3.0 mg and 4.5 mg group. HR decreased during the further course of Study GBGL, ending up at 1.9 bpm above baseline at Week 52 in the 3.0 mg and 4.5 mg group; for comparison, in the 1.5 mg group HR was 1.0 bpm above baseline at this time point.

The GBGL data suggest a trend towards increased exposure in patients aged ≥75 years or with declining renal function. However, a clinical relevance is considered unlikely, because the majority of observed PK concentrations in patients aged ≥75 in study GBGL are within the 90% PK prediction intervals. Moreover, based on clinical data for the lower dulaglutide doses (0.75 mg and 1.5 mg) in patients with impaired renal function, and based on theoretical considerations about the elimination mechanism of dulaglutide, no clinically relevant impact of impaired renal function on dulaglutide exposure is to be expected.

Potential interactions of concomitantly administered oral drugs with the 4.5 mg dose of dulaglutide were predicted based on a PBPK modelling approach that included some simplifications (e.g. in most cases, potential changes of intestinal transit times were not considered in the model), but no distinct drug-drug interaction studies were performed with the higher dose strengths. Thus, it is clearly stated in SmPC section 4.5 that the interactions with the higher dulaglutide strengths were predicted by a modelling approach.

3.6. Effects Table

Table: **Effects Table for dulaglutide s.c. once weekly in treatment of type 2 diabetes.**

Effect	Short Description	Unit	Dula 3.0 mg 4.5 mg	Dula 1.5 mg	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary Endpoint Efficacy Estimand	HbA1c reduction from baseline to Week 36	%-points	-1.71 -1.87	-1.53	LS mean difference from dula 1.5 mg (95% CI) -0.17%; p=0.003 (-0.29, -0.06) -0.34%; p<0.001 (-0.45, -0.22)	Study GBGL
Primary Endpoint Treatment-Regimen Estimand	HbA1c reduction from baseline to Week 36	%-points	-1.64 -1.77	-1.54	LS mean difference from dula 1.5 mg (95% CI) -0.10%; not significant (-0.23, 0.02) -0.24%; p<0.001 (-0.36, -0.11)	Study GBGL
Secondary Endpoint Efficacy Estimand	Body Weight reduction from baseline to Week 36	kg	-4.0 -4.7	-3.1	LS mean difference from dula 1.5 mg (95% CI) -0.9 kg; p=0.001 (-1.4, -0.4) -1.6 kg; p<0.001 (-2.1, -1.1)	Study GBGL

Effect	Short Description	Unit	Dula 3.0 mg 4.5 mg	Dula 1.5 mg	Uncertainties/ Strength of evidence	References
Secondary Endpoint Treatment-Regimen Estimand	Body Weight reduction from baseline to Week 36	kg	-3.8 -4.6	-3.0	LS mean difference from dula 1.5 mg (95% CI) -0.9 kg; nominal p=0.001 (-1.4, -0.4) -1.6 kg; p<0.001 (-2.2, -1.1)	Study GBGL
Secondary Endpoint Efficacy Estimand	Percent of patients with HbA1c<7.0 % at Week 36	%	64.7% 71.5%	57.0%	odds ratio [95% CI] versus 1.5 mg=1.49 [1.12, 1.98], p=0.006 odds ratio [95% CI] versus 1.5 mg=2.23 [1.65, 3.01], p<0.001	Study GBGL
Secondary Endpoint Treatment-Regimen Estimand	Percent of patients with HbA1c<7.0 % at Week 36	%	55.8% 62.2%	49.7%	odds ratio [95% CI] versus 1.5 mg=1.32 [1.03, 1.68], nominal p=0.026 odds ratio [95% CI] versus 1.5 mg=1.78 [1.39, 2.27], nominal p<0.001	Study GBGL
Unfavourable Effects						
Treatm.-emergent AEs		n(%)	351 (57.0) 378 (61.6)	346 (56.5)		Study GBGL
All SAEs		n(%)	30 (4.9) 26 (4.2)	39 (6.4)		Study GBGL
AEs leading to discont.		n(%)	8 (1.3) 11 (1.8)	6 (1.0)		Study GBGL
Deaths		n(%)	2 (0.3) 2 (0.3)	2 (0.3)		Study GBGL
GI effects						Study GBGL
All		n(%)	198 (32.1) 200 (32.6)	161 (26.3)		Study GBGL
CV para-meters						Study GBGL
HR	change from baseline at Week 52	bpm	1.9 1.9	1.0		Study GBGL
SBP	change from baseline at Week 52	mmHg	-3.6 -4.1	-3.2		Study GBGL
Pancreas						Study GBGL
Serum lipase	fold change from baseline at Week 52		1.12 1.17	1.19		Study GBGL

Effect	Short Description	Unit	Dula 3.0 mg 4.5 mg	Dula 1.5 mg	Uncertainties/ Strength of evidence	References
Serum amylase	fold change from baseline at Week 52		1.19 1.20	1.22		Study GBGL
Adj. events of pancreatitis		n(%)	2 (0.3) 3 (0.5)	1 (0.2)		Study GBGL

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Studies GBGL and GBGJ in overweight patients with T2DM showed overall small-sized but still relevant incremental reductions in HbA1c for dulaglutide 3.0 mg and 4.5 mg compared to the approved 1.5 mg dose strength. In study GBGL, additional measures of glycaemic control (number of patients achieving HbA1c<7%, FSG) showed dose-related numerical improvements.
The two new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg) led to greater body weight reductions at week 36 compared to the approved 1.5 mg dose. This likewise applied for the placebo-corrected body weight reductions attained in the shorter 18-week phase 2 study GBGJ (-2.4 kg and -2.6 kg for 3 and 4.5 mg dulaglutide, respectively). Despite the moderate effect size, additional weight reduction is an additional benefit in the mostly overweight T2DM population. Subgroup analyses suggest that patients with higher BMI experienced greater weight loss compared to those with lower BMI. According to the results of the patient-reported outcome measure questionnaires (Impact of Weight on Self-Perceptions Questionnaire (IW-SP) and the Ability to Perform Physical Activities of Daily Living Questionnaire (APPADL)), patients perceived weight reduction and associated effects as beneficial.

Overall, the safety data for the two new doses do not indicate an unacceptable risk or tolerability issue. Prevalence of GI side effects was somewhat higher with the new doses of 3.0 and 4.5 mg dulaglutide than with the established dose of 1.5 mg. This is not considered an important issue since dose reduction would be possible if an individual subject does not tolerate the higher doses.

A recent CV outcome study with the established dulaglutide dose of 1.5 mg s.c. QW did not indicate a CV risk but it is not clear whether this result can be extrapolated to higher doses. However, the effects of the higher doses of dulaglutide on heart rate (increase) and PR interval (prolongation) were so small that an increase in CV risk is highly unlikely. Further reassurance regarding CV safety can be derived from the clinical experience with the substance class.

Pancreatitis is an identified risk of GLP-1 receptor analogues. In Study GBGL, pancreatitis was analysed based on adjudicated events. A total of 5 events in 5 patients were confirmed by the Clinical Endpoint Committee (CEC) to be pancreatitis, 1 event in the dulaglutide 1.5 mg group, 2 events in the dulaglutide 3.0 mg and 3 events in the 4.5 mg group. All 6 confirmed events were adjudicated as acute pancreatitis and occurred when patients were taking their final maintenance dose of dulaglutide. Due to the small number of events, firm conclusions are not possible. The risk of pancreatitis is included in the RMP as important identified risk and appropriately labelled.

3.7.2. Balance of benefits and risks

The additional antihyperglycemic effects of the higher doses applied for are considered beneficial in patients who are insufficiently controlled with lower doses. These benefits need to be balanced against a potential increase in adverse events, e.g. nausea, vomiting, diarrhoea, and some cardiac effects such as increase in heart rate, PR prolongation, and concerns related to pancreatic safety. Overall, the tolerability and safety issues are considered manageable and not prohibitive for the approval of the higher dose strengths.
Albeit only overweight patients had been included in study GBGL, extrapolation of the benefit/ risk to patients with BMI<25 kg/m^2 seems justified, as it was demonstrated that neither efficacy (HbA1c reduction) nor tolerability depended on baseline BMI.

3.8. Conclusions

The B/R of the two new higher dose strengths of dulaglutide (3.0 mg and 4.5 mg) is positive.

The overall B/R of Trulicity is positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the benefit-risk balance of Trulicity 3.0 mg and 4.5 mg (solution of injection in pre-filled pen) is favourable in the following 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.*

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.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Trulicity subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.