25 September 2014
EMA/CHMP/524604/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trulicity

International non-proprietary name: dulaglutide

Procedure No. EMEA/H/C/002825/0000

Note

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

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Administrative information

Name of the medicinal product:	Trulicity
Applicant:	Eli Lilly Nederland B.V. Grootslag 1-5 3991 RA Houten NETHERLANDS
Active substance:	dulaglutide
International Nonproprietary Name/Common Name:	dulaglutide
Pharmaco-therapeutic group (ATC Code):	Not assigned yet
Therapeutic indication(s):	Trulicity is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as: Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. Add-on therapy In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for data with respect to different combinations).
Pharmaceutical form:	Solution for injection

Strength:	0.75 mg and 1.5 mg
Route of administration:	Subcutaneous use
Packaging:	Glass syringe in pre-filled pen
Package size(s):	2 pens, 4 pens, multipack 3 packs of 4 pens, 4 syringes and multipack 3 packs of 4 syringes

Table of contents

List of abbreviations

ABPM	Ambulatory blood pressure monitoring
ADA	Anti-drug antibody
2-AB	2-aminobenzamide
ACN	Acetonitrile
ADCC	antibody dependent cell mediated cytotoxicity
ALT	Alanine transaminase
AS1	Analysis Set 1
AS3	Analysis Set 3
AST	Aspartate transaminase
AUC	Area under the concentration versus time curve
$AUC_{(0-12)}$	Area under the concentration versus time curve from time zero to 12 hours
$AUC_{(0-168)}$	Area under the concentration versus time curve from time zero to 168 hours
$AUC_{(0-\infty)}$	Area under the concentration versus time curve from zero to infinity
AUC(0-x)	Area under the concentration versus time curve from time zero to **x** hours
AUC_{τ}	Area under the concentration versus time curve during one dosing interval
AVB	Atrioventricular block
BID	Twice daily injection
BMI	Body mass index
bpm	Beats per minute
C_{ave}	Average plasma concentration
CD	Circular dichroism
CDC	Complement-dependent cytotoxicity
CE	Capillary Electrophoresis
CEC	Clinical endpoint committee
CE-LIF	Capillary electrophoresis with laser-induced fluorescence detection
CHMP	Committee for Medicinal Products for Human Use
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
CID	collision-induced dissociation
CIOMS	The Council for International Organizations of Medical Sciences
CIPC	Critical In-Process Control
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CPP	Critical Process Parameter
CSR	Clinical study report
CT	Clinical Trial
CTD	Common technical document
CUI	Clinical Utility Index
CV	Cardiovascular
CYP	Cytochrome P450
CZE	Capillary Zone Electrophoresis
DBP	Diastolic blood pressure
Des H	desHis1 variant of N-terminus
Des H/G	desHis1Gly2 variant of N-terminus
DoE	Design of Experiments
DPP-4	Dipeptidyl peptidase-4
DS	drug substance
DSC	Differential scanning calorimetry
DTSQ	Diabetes Treatment Satisfaction Questionnaire

DTSQc	Diabetes Treatment Satisfaction Questionnaire change
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
DTT	Dithiothreito
DURATION	Diabetes Therapy Utilization: Researching Changes in A1c, Weight and Other Factors Through Intervention with Exenatide Once Weekly
ECB	Extended Cell Bank
ECG	Electrocardiogram
EE	Ethynilestradiol
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FBG	Fasting blood glucose
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
GI	Gastrointestinal
GIP	gastric inhibitory polypeptide, or glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like Peptide 1
GLP1R	GLP-1 receptor
GPCR	G-protein coupled receptor
HbA1c	Glycosylated haemoglobin A1c
HEK293 cells	human embryonic kidney cells
hERG	Human ether-à-go-go-related gene
HILIC	Hydrophilic Interaction liquid chromatography
HPAEC	High pH Anion-Exchange Chromatography
HR	Hazard ratio
HR	Heart rate
i.v.	Intravenous
ICH	International conference on harmonization
IDF	International Diabetes Federation
IFU	Instructions for use
IgG	Immunoglobulin
IgG4	Immunoglobulin G4
INR_{max}	Maximum international normalized ratio response
IPC	In-Process Control
IPS	In-Process Specification
ITT	Intent to treat
IVGTT	Intravenous glucose tolerance test
K_i	affinity constant
KLH	Keyhole Limpet Haemocyanin
LEAD	The liraglutide effect and action in diabetes studies
LIVCA	Limit of In Vitro Cell Age
LRF	Log Reduction Factor
LS	Least squares
MACE	Major adverse cardiovascular events
MCB	Master Cell Bank
MCV	Mean corpuscular volume
MET	Metformin
MI	Myocardial infarction
MMV	Mouse Minute Virus
MRHD	Maximum recommended human dose
MTC	Medullary thyroid carcinoma
MTD	Maximum tolerated dose
MuLV	Murine Leukemia Virus
NeuAc	N-acetylneuraminic acid
NGMN	Norelgestromin
NI	Noninferiority
NLT	Not less than

NMT	Not more than
NOAEL	No observed adverse effect level
NOEL	No observed effect level
nsGLP-1	Native sequence glucagon-like peptide 1
OAM	Oral antihyperglycemic medication
OPP	Operational Process Parameter
PAD	Pulsed Amperometric Detection
PBMC	Human peripheral blood mononuclear cell
PCB	Parental Cell Bank
PD	Pharmacodynamics
pI	Isoelectric point
PK	Pharmacokinetics
PPV	Porcine Parvovirus
PRO	Patient-reported outcome questionnaire
PRS	primary reference standard
PRV	Pseudorabies Virus
PSIG	Pounds-force per Square Inch Gauge
PVAC	Process validation acceptance criteria
QT	Standard cardiovascular ECG interval between Q and T waves
QTc	Corrected QT interval
QW	Once weekly injection
REMS	Risk Evaluation and Mitigation Strategy
Reo-3	Reovirus Type 3
REWIND	REsearching cardiovascular events with a Weekly INcretin in Diabetes
RMP	Risk management plan
RP-HPLC	Reversed Phase High Performance Liquid Chromatography
RS	Reference Standard
RVLP	Retrovirus-like Particles
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SDS	Sodiumdodecyl Sulfate
SEC-HPLC	Size exclusion High Performance Liquid Chromatography
SEM	standard error of the mean
SGI	Stepped glucose infusion
SLS	Static light scattering
SOC	System Organ Class
SU	Sulfonylurea
SV-AUC	Sedimentation velocity analytical ultracentrifugation
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TEM	Transmission Electron Microscopy
TFA	Trifluoracetic acid
$tINR_{max}$	Time of maximum observed INR response
TK	Toxicokinetics
t_{max}	Time of maximum observed drug concentration
TQT	Thorough QT
Trp-FL	Tryptophan fluorescence
TZD	Thiazolidinedione
UACR	Urine albumin to creatinine ratio
UBH	Unprocessed Bulk Harvest
ULN	Upper limit of normal
USPI	United States Package Insert
Vz/F	Apparent volume of distribution

WCB	Working Cell Bank
WHO	World Health Organization
ZDF rats	Zucker diabetic fatty rats

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 27 September 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Trulicity, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied initially for the following indication:

"Trulicity is indicated for the treatment of adults with type 2 diabetes mellitus in combination with glucose-lowering medicinal products together with diet and exercise, to improve glycaemic control (see section 5.1 for available data on the different combinations)."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that dulaglutide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/37/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/37/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance dulaglutide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advicefrom the CHMP in January 2008 and November 2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Eli Lilly Italia S.p.A.
Via Gramsci 731/733
50019, Sesto Fiorentino
Firenze (FI)
Italy

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Greg Markey Co-Rapporteur: Martina Weise

- The application was received by the EMA on 27 September 2013.
- The procedure started on 23 October 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 5 February 2014.
- During the meeting on 20 February 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 February 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 June 2014.
- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2014.
- PRAC RMP Advice and assessment overview, adopted on 11 September 2014
- During the meeting on 25 September 2014, 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.

2. Scientific discussion

2.1. Introduction

Problem statement

Type 2 diabetes mellitus is one of the most common non-communicable diseases and is a global health problem. In 2011, the estimated number of people with T2DM was 366 million (8.3% of total world population), with an estimated increase to 552 million (9.9% of total world population) by 2030. Patients with type 2 diabetes are at increased risk of macro- and microvascular complications including increased cardiovascular morbidity and mortality. The main purpose of antidiabetic therapy is to reduce these risks.

There exist several types of antihyperglycaemic agents targeting one or more of the pathophysiologic deficiencies associated with T2DM, including metformin (MET), sulphonylureas (SU), thiazolidinediones (TZD), and insulins. However, they can have undesirable side effects and/or limited usefulness in certain populations. For example, MET is contraindicated in patients with renal insufficiency, while TZDs are known to exacerbate congestive heart failure in some patients. Insulin and insulin analogs as well as SUs are often associated with hypoglycaemia and weight gain. More recently, incretin-based therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have become available for patients with T2DM. Among the available GLP-1 agonists, there are differences in duration of action, frequency and timing of dosing, ease of administration, effectiveness, tolerability and immunogenicity.

Despite the currently available agents, a substantial proportion of patients with T2DM remain poorly controlled suggesting that there continues to be a medical need for additional treatment options in these patients. Furthermore, there is still potential for a better benefit:risk profile within the GLP-1 receptor agonist class.

About the product:

The endogenous circulating form of GLP-1 has a very short half-life (90 to 120 seconds) mainly because of rapid N-terminal cleavage and inactivation by the DPP-4 enzyme. To take advantage of the multidimensional effects of GLP-1 on glycaemic control, two different approaches have been used towards incretin-based therapies: inhibition of DPP-4 enzyme (by DPP-4 inhibitors) and the development of human GLP-1 analogs resistant to the action of DPP-4 enzyme (GLP-1 receptor agonists). The injectable GLP-1 receptor agonists are designed to mimic the effect of endogenous GLP-1, thereby stimulating pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying, and decreasing appetite which may also result in weight loss.

Dulaglutide is a new long acting human GLP-1 receptor agonist. Dulaglutide molecule consists of 2 identical, disulfide-linked chains, each containing a human GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small peptide linker. The GLP-1 analog portion of dulaglutide is approximately 90% homologous to native human GLP-1 with amino acid substitutions aiming at optimizing its clinical profile, including protection from DPP-4 inactivation and reduced immunogenicity. The IgG-Fc increases the size of the molecule therefore reducing the rate of clearance. The IgG4 Fc portion of the molecule was also modified to prevent half-antibody formation and to reduce the potential for interaction with high affinity Fc receptors that may result in immunologic cytotoxicity. The pharmacokinetic profile of dulaglutide

suggests a plasma half-life (t1/2) of approximately 4.7 days, which makes it suitable for once weekly administration.

The applicant applied for the following indication:

> *"Trulicity is indicated for the treatment of adults with type 2 diabetes mellitus in combination with glucose-lowering medicinal products together with diet and exercise, to improve glycaemic control (see section 5.1 for available data on the different combinations)."*

As part of their responses to the Day 120 LoQ, the Applicant requested an amendment of the indications to also include a monotherapy indication as follows:

> *Trulicity is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:*
> *Monotherapy*
> *When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.*
> *Add-on therapy*
> *In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for data with respect to different combinations).*

Initially the application concerned only one formulation, 1.5mg solution for injection recommended to be administered subcutaneously once weekly. At a later stage (Day 180), in response to a CHMP request, a lower strength formulation 0.75mg was introduced. At Day 181, the proposed posology for monotherapy was 0.75 mg once weekly. For add-on therapy the 1.5 mg once weekly dose was recommended. For potentially vulnerable populations, like patients ≥ 75 years or patients with severe heart failure, 0.75 mg once weekly was proposed for consideration as a starting dose.Dulaglutide can be given at any time of day, with or without meals.

The dulaglutide clinical program includes 30 completed clinical studies (21 clinical pharmacology studies, 4 Phase 2 studies, and 5 Phase 3 studies). As of April 2013, a total of 680 subjects were exposed to dulaglutide in the 21 completed clinical pharmacology trials. In the completed Phase 2 and Phase 3 studies, T2DM patients received dulaglutide once weekly from 1 week to 104 weeks: 4006 received dulaglutide, 703 received placebo, and 1541 received active comparator. An additional 10 studies are ongoing.

The clinical pharmacology and biopharmaceutics studies were designed primarily to assess PK, pharmacodynamics (PD), the effect of extrinsic and intrinsic factors on dulaglutide PK and/or PD, the effects of dulaglutide on PK of other drugs, important drug-drug interactions, and safety and tolerability, including the effect of dulaglutide on corrected QT (QTc) interval. Single doses of dulaglutide were administered over a range of 0.1 mg to 12 mg, and multiple doses of 0.05 mg to 8 mg were administered once weekly for up to 6 weeks. Assessment of efficacy and safety of the initial submission was based on 4 Phase 2 (12-26 weeks) and 5 long-term Phase 3 (52-104 weeks) clinical studies. Efficacy was primarily evaluated based on the dulaglutide effect on glycosylated haemoglobin (HbA1c).

General guidance about antidiabetic therapies is provided by the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1). The clinical program is generally in line with the Guideline's recommendations.

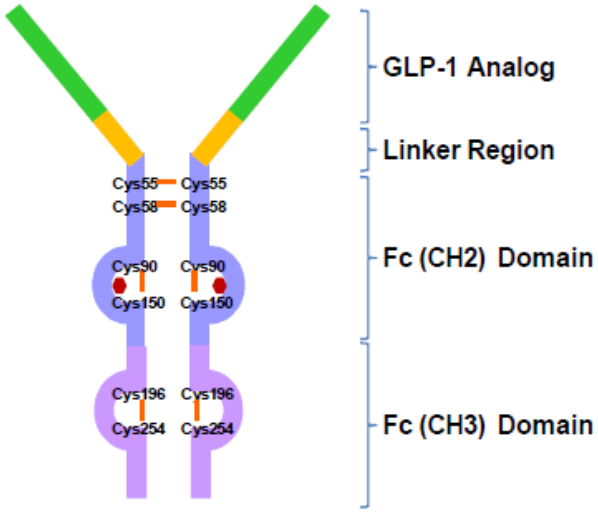
2.2. Quality aspects

2.2.1. Introduction

The chemical name of dulaglutide is: 7-37-Glucagon-like peptide I [8-glycine,22-glutamic acid,36-glycine] (synthetic human) fusion protein with peptide (synthetic 16-amino acid linker) fusion protein with immunoglobulin G4 (synthetic human Fc fragment), dimer [Gly^{8},Glu^{22},Gly^{36}]human glucagon-like peptide 1-(7-37)-peptidyltetraglycyl-Lseryltetraglycyl- L-seryltetraglycyl-L-seryl-L-alanyldes-Lys^{229}-[Pro^{10},Ala^{16},Ala^{17}] human immunoglobulin heavy constant γ4 chain H-CH2-CH3 fragment, (55-55':58-58')- bisdisulfide dimer. The company's compound number during development was LY2189265 (this name is used in the initial phases of the clinical program; LY2189265 and dulaglutide are used interchangeably at different parts of this report).

Dulaglutide is a homodimer that consists of two identical polypeptide chains. Its structure is shown schematically in the Figure below 1 Each chain has a molecular mass of 29,841 Da. Since dulaglutide is produced as a disulfide-linked two-chain molecule, its molecular mass is 59,671 Da (all 12 Cys residues are involved in disulfide bonds). In addition, each polypeptide chain contains an N-linked glycosylation site at Asn126.

Figure 1 A Schematic Diagram of Dulaglutide. The GLP-1 analog, linker region, and IgG4 Fc CH2 and CH3 domains are depicted. The 12 Cys residues that are involved in the inter-chain and intra-chain disulfide bonding are also shown. The hexagonal symbol represents the N-linked glycosylation at Asn126 in each polypeptide chain.



2.2.2. Active substance

General information

Dulaglutide drug substance is manufactured at the Eli Lilly, Kinsale site, located in Ireland.

Origin, source and history of the cells, characterisation and testing

A proprietary cell line that has been adapted to suspension, serum-free chemically defined medium, is used as the parental host cell line.

Dulaglutide is a disulfide-bonded covalent homodimer fusion protein encoded by a single synthetic gene. The gene for dulaglutide contains the GLP-1 analogue, linker and an engineered human IgG4 Fc domain.

The host cells were transfected by electroporation and cultivated in the presence of methionine sulfoximide (MSX). A lead clone was selected, used to establish a research cell bank (RCB) and subsequently a pre-master cell bank (pmRCB). The pmRCB was found to be free adventitious agents and then utilised to generate the MCB.

The MCB was tested for cell line identity by isoenzyme analysis and for adventitious agents. The genetic integrity was proven by dulaglutide gene sequence verification, restriction endonuclease mapping and Southern Blot. The gene copy number was determined using both an IgG4 specific probe and a GLP-1 specific probe.

The WCB was created based on one vial of the MCB. A protocol for the generation of a new working cell bank is included in the dossier.

The cell line has been demonstrated to be genetically stable as the results of the characterisation of the LIVCA cells and the MCB were comparable. Data regarding the viable cell density and cell viability at the LIVCA have been provided and substantiate the claimed cell line stability.

Manufacture, characterisation and process controls

Manufacturing process

Cell culture process

The manufacturing process comprises a straight-forward cell culture process starting with WCB or MCB vial thaw, cell expansion phase for inoculum build-up using progressively larger bioreactors and ending with the production bioreactor that is run in a fed-batch mode. The bioreactor is fed with a nutrient feed to provide nutrient supplements for cell growth and product formation. The whole harvest of one cell culture run is processed downstream and defines one batch.

Downstream Purification

Dulaglutide purification multiple chromatography steps and addresses viral clearance, including nanofiltration for physical removal of potential viral particles. Final ultrafiltration is employed prior to the dispensing operation.

The company provided a manufacturing process description including the ranges of critical process parameters and controls. The updated flowchart and process description now includes also the normal operating ranges for the parameters investigated in the process characterisation studies. Sufficient details regarding the downstream purification are included.

Control of Materials

A list of raw materials used per unit operation has been provided. Media and buffer compositions are included in the dossier. Materials of animal or human origin are not directly used for the manufacturing process. Materials

of animal or human origin used in the production of starting materials are sufficiently qualified and EDQM certificates have been provided. The specifications of non-compendial raw materials are given.

Control of Critical Steps and Intermediates

Process characterization studies were performed to establish ranges for the process parameters and acceptable limits for (critical) in-process controls or in-process specifications.

Following the addition of further detail to S.2.2, the applicant has also set out the deviation management procedure, and overall the process is considered to be sufficiently controlled. An additional CPP was implemented and one of the IPC was moved to a more relevant control point downstream.

Process validation

Data from full scale cell culture/ primary recovery validation runs and of three full scale purification runs were provided, supporting that the dulaglutide manufacturing process is able to produce material of consistent quality. Additional data for all unit operations were provided.

The Applicant has provided the monitoring data of the process validation runs regarding the depletion of process impurities. The data show reduction of these impurities to low levels. These studies have been supplemented with spiking studies.

Sufficient validation data for resin reuse for chromatography steps has now been provided.

Manufacturing Process Development

The manufacturing process history is adequately described and rationales for process changes provided. A cell line change was made during development and a site change was introduced to transition from the development to the commercial manufacturing site. The data provided demonstrated comparability for the changes.

The single unit operations were characterised by designed experiments either at small or at full scale. Nevertheless, the process validation was traditional.

The assessment of the criticality of dulaglutide quality attributes is considered reasonable. Modifications in the molecule not impacting on the bioactivity, efficacy and safety are considered non-CQA which is considered justified.

A scaled-down model of the production bioreactor was used to characterise the production process. The suitability of the model was shown. The small scale models of the downstream process are considered representative of the full scale unit operations based on the data provided.

The comprehensive process characterisation studies following ICH Q principles built the basis for the criticality assessment of process parameters. The applicant has provided additional justification for non-critical designations.

The applicant has further clarified the approach to deviation management.

Characterisation

The elucidation of the structure of the dulaglutide molecule is adequate, and the applicant has used a range of orthogonal analytical techniques to confirm results. Oligosaccharide structure, charge heterogeneity and higher order structure were included in the analysis. The results demonstrate that the molecule conforms to the predicted sequence and structure.

Biological assays used to confirm the function of the fusion protein are overall adequately chosen and include

receptor binding studies for both functional elements and determination of potency.

The applicant has identified a large spectrum of dulaglutide modifications, determined their proportion in the DS and listed methods of identification. The process related impurities are also adequately identified, and described.

Specification

The drug substance specification comprises testing of identity, quantity, potency using a cell-based bioassay, purity and charge heterogeneity.DS specification also includes determination of physical appearance, colour, clarity, bacterial endotoxins, bioburden and pH. In addition appropriate controls for process-related impurities DNA, protein A and host cell proteins have been introduced.

Several specifications have now been tightened for the DS purity tests.

Analytical procedures overall are sufficiently described. Validation summaries and reports have been provided.

Batch data are available for the commercial, phase 3 and phase 2 manufacturing process. All batches used for clinical phases and DS stability studies are included. In addition, data for batches manufactured with the phase 1 manufacturing process are provided. Overall the batches show a good degree of consistency, even when earlier phases of process development are considered.

The applicant has given a rationale for the specifications, which is based on historical batches, but also using tolerance intervals. For a number of specifications, the calculated limits have been tightened.

Reference Standard

Qualification data for the reference material used to date including release as well as characterisation data have been submitted. All characterisation studies are within the proposed specifications and comparability between the original and current reference standard was sufficiently shown. Satisfactory analytical results on the current working reference standard were also submitted. The protocol for preparation/establishment and qualification of future reference standards is provided.

Stability

The Applicant claims 36 months stability for dulaglutide when stored at ≤ -65°C. All results of the 36 month stability study performed at ≤ -65°C storage with three phase 3 commercial scale batches (primary stability batches) in the commercial container closure system are found within the proposed acceptance criteria. The primary stability data have not been manufactured at the DS manufacturing facility in Kinsale, however, this has been supplemented by 36 months data for batches from the Kinsale facility.

Studies have been carried out to allow several freeze/thaw cycles to the DS, however, stability for freeze thaw batches has not been carried out to the full DS shelf life of 36 months as insufficient material is available from the study to test beyond 24 months. The applicant has committed to carry out additional tests when any previously freeze thawed DS is used after 24 months and will proposea suitable testing regimen for this.

2.2.3. Finished Medicinal product

Description of the product and Pharmaceutical Development

Dulaglutide for injection is supplied as 0.75mg/0.5ml and 1.5 mg/0.5 mL solution for subcutaneous administration in a 1 mL glass syringe barrel with a bromobutyl plunger (semi-finished syringe, SFS). Dulaglutide for injection contains trisodium citrate dihydrate, citric acid anhydrous, mannitol, polysorbate 80 and water for injection. The semi-finished syringe is assembled into either a single-use pen (SUP) or a prefilled syringe (PFS).

Pharmaceutical development

Multivariate experiments were performed to further investigate the criticality of quality attributes and to define the commercial formulation composition. The Applicant does not claim real-time release or a design space.

The composition of the drug product solution corresponds to the drug substance solution except for the addition of the tonicity agent mannitol. The impact of mannitol was studied in the solution formulation DOE study. Stability data for the dulaglutide drug product show the final composition containing mannitol is stable over the intended shelf-life.

Manufacturing process development is sufficiently described. The same site, scale and process were used for Phase 3 clinical supplies, primary stability and validation. All process parameters have been defined either as a Critical Process Parameter (CPP) or Operational Process Parameter (OPP).

The results of the manufacturing process DoE studies combined with clinical development and manufacturing experience were used to define the proven acceptable ranges (PARs). PARs are provided for both the CPPs and OPPs. Critical In-process Controls (CIPC), In-process Controls (IPC), and In-process Specifications (IPS) with the respective control ranges are described. The overall drug product critical quality attribute control strategy and the analytical control strategy for low risk quality attributes are presented which is acceptable. Comparability studies were performed demonstrating that drug product used in clinical studies and drug product manufactured with the commercial process is comparable.

The suitability of the semi-finished syringe was appropriately studied in terms of container closure integrity, safety of the components (extractables, leachables studies), compatibility with the DP solution, and performance when assembled in the single-use pen and prefilled syringe.

Manufacture of the product and process controls

Manufacture

The semi-finished syringe is assembled with the respective components to the single-use pen.

The manufacture of dulaglutide DP employs a standard formulation and aseptic filling process. The batch composition is given and the manufacturing process is adequately described.

Consistency and reproducibility of the manufacturing process is demonstrated by the validation exercises. For process validation validation batches each at commercial scale of the 1.5 mg/0.5 mL strength and the 0.75

mg/0.5 mL strength (supportive data) have been manufactured. Process parameter data considering all PARs, in-process control results and release testing results are provided. Also included are processing time limit challenge studies and results of aseptic process simulation. Furthermore, sterile filter validation has been performed.

The applicant has conducted a large range of studies to ensure transportation does not adversely impact product quality.

Product Specifications

The specifications for the semi-finished syringe, the pre-filled syringe and the single-use pen cover all tests expected for these kinds of products.

The specification limits consider the quality of dulaglutide used in clinical and non-clinical studies, manufacturing experience, analytical variability, and the stability of the drug product as well as the purity of the drug substance where applicable.

The chosen specification categories for the SFS, PFS and SUP are accepted.

The lower/higher shelf-life specification limits for quantity, the purity tests, charge heterogeneity and polysorbate compared to the release limits are not justified by the provided stability data. All results are well within the limits defined for release. The shelf-life specification limits have been further tightened in accordance with the provided stability data.

The description and validation of the analytical methods used for DP release and stability testing is considered adequate. For identity, quantity, purity, potency, charge heterogeneity in the drug product the same analytical methods are used as indicated for the drug substance. Comprehensive information has been provided for validation of in-house methods. All specified validation acceptance criteria were met for these methods.

The batch results confirm consistency and uniformity of drug product lots for pivotal clinical studies and process validation lots. The results further indicate that the process is under control to produce the product of the intended quality.

Container closure

The primary packaging consisting of Type I clear glass 1 mL-long syringe barrel with small round flange, staked needle, rigid needle shield and bromobutyl plunger is adequately described.

The list of quality control tests for the primary packaging components has been updated and respective limits/criteria have been added where applicable.

The applicant has also given an overview over the attributes, development rationale, in use parameter etc. for both the SUP and the PFS. Both devices comply with European directives and relevant ISO standards.

The applicant has undertaken shipping studies and investigated the product mainly for mechanical functionality. The assembly process was validated at each manufacturing line for at least two batches, and relevant characteristics such as glide force and injection timing were investigated.

Stability of the product

An expiry period of 24 months for the drug 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.

The shelf-life is primarily based on the provided stability data for 0.75 mg/0.5 mL and 1.5 mg/0.5 mL drug product batches (primary stability batches) manufactured at the intended commercial scale (semi-finished syringes). The results which are all within specifications and their statistical evaluation demonstrate little intra- and inter-batch variability.

Additional stability data for twelve semi-finished syringe batches manufactured for process validation show a comparable trend to the data of the primary stability batches. Therefore, it can be concluded that the expiry period of 24 months at 2-8°C with a 14 day in-use period at 30°C is also applicable for semi-finished syringes.

Based on the provided stability data it is not expected that assembly alters the stability profile of the dulaglutide drug product. Therefore, the expiry period and storage conditions of the semi-finished syringe are also applicable for the assembled single-use pen and pre-filled syringe.

Facilities and equipment.

Sufficient information is provided on facilities and equipment. GMP certificates for the manufacturing sites are included in the dossier, although one site has not received a GMP inspection for the area where DP will be produced. This inspection will be carried out during the next scheduled inspection for the overall site.

Adventitious Agents

The virus safety of the dulaglutide manufacturing process is controlled by a complementary strategy comprising testing of cell banks, raw materials and the unprocessed bulk harvest for adventitious/endogenous agents as well as validation of the virus removal/inactivation capacity of the manufacturing process.

Production cell culture is performed under serum-free.

Four process steps have been characterized by Design of Experiments methodology and further investigated in virus validations studies. The filter charge capacity has now been adequately tightened.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No major objections were raised during the assessment of the quality part of the dossier. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of product quality characteristics.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In general, the quality dossier for Trulicity is considered to be of good quality. In Module 3 the development, characterisation, manufacture and control of the dulaglutide drug substance and drug product are adequately described, including the dossier updates in made to include the 0.75mg/0.5ml presentation. The proposed control strategy has been sufficiently described. Sufficient process validation data have now been provided ensuring a robust and well controlled manufacturing process. .

The CHMP recommendation to carry out additional tests on the DS where previously freeze/thawed drug substance is used beyond the 24 month has been agreed by applicant. The applicant's proposal to submit a suitable testing plan is acceptable.

Area	Number	Description	Classification*	Due date
Quality	1	*Where previously freeze/thawed drug substance (DS) is used beyond the 24 months' time point, the applicant has agreed to carry out additional tests on the DS and will submit a proposal for a suitable testing regimen for this as recommended by the CHMP.*	REC	

On the basis of the Quality data submitted, a positive CHMP opinion can be granted. The active substance status on the 'new active substance' status was discussed by BWP at d.120 (Ref. BWP EMA/CHMP/BWP/66318/2014, February 2014).

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

Dulaglutide binds to the GLP-1 receptor with high affinity (Ki 0.45 nM) when compared to the human glucagon and human gastric inhibitory peptide receptors (Ki > 697 nM). In human embryonic kidney cells expressing the human GLP-1 receptor, dulaglutide stimulates cAMP production, with an EC_{50} of 12.5 pM. The EC_{50} was said to be comparable to that of native GLP-1 and was shown to be 2-fold higher than the reference peptide, Val8 GLP-1 (7-37)-OH.

In the INS-1 832/3 rat insulinoma cell line, dulaglutide stimulates insulin secretion under high glucose conditions only (16.8 nM glucose) with EC_{50} values of 8.3 to 34 nM. Dulaglutide also dose-dependently enhanced insulin secretion at high glucose concentrations in rat islet cells with EC_{50} values of 4.9 nM and at > 100 nM in cynomolgus monkey islets. At low glucose concentrations, dulaglutide was unable to increase insulin secretion from either INS-1 832/3 cells, rat, or monkey islet cells, which confirms the glucose-dependent insulinotropic activity of dulaglutide. Close examination of the data generated in rat islet cells reveals that dulaglutide (3 to 30 nM) enhanced insulin secretion from isolated rat islets by 2.5- to 3-fold, while native human GLP-1 (3 nM) produced a 4-fold increase in insulin secretion, which seems to suggest that native GLP-1 is slightly more potent at glucose independent insulin secretion than dulaglutide.

Overall, the Applicant has evaluated the effects of dulaglutide *in vitro* in rat, human and monkey cells but different methods have been used to assess functional activity. Therefore, the in vitro data provided did not allow for a direct comparison of the activity at the rat, human and monkey GLP-1 receptors.

The Applicant has used 2 *in vivo* models: the intravenous glucose tolerance test (IVGTT) and the stepped glucose infusion (SGI) model to demonstrate the ability of dulaglutide to stimulate insulin secretion. For the IVGTT studies, in the rat the insulin AUC within the dulaglutide group was not always significantly higher than that observed for the vehicle group and in the monkey, the effect on insulin AUC appeared to be short lived; however, the data provided some evidence of insulinotropic activity following a single dose of dulaglutide (up to

0.179 mg/kg in the rat and 0.1 mg/kg in the monkey). Using the SGI model, where glucose was infused to produce serum glucose levels within a given range, in the rat, dulaglutide at 0.0179 to 1.79 mg/kg caused a significant dose-dependent increase in the serum levels of insulin. Likewise, in the monkey, subcutaneous administration of 0.1 mg/kg dulaglutide increased serum levels of insulin for up to 7 days post-dose. In a 4-week study, significant insulinotropic activity was also observed following repeated weekly administration, which supports chronic use of the proposed product.

Secondary pharmacodynamic studies

No secondary pharmacology studies have been performed, which is acceptable for products of this nature.

Safety pharmacology programme

Single subcutaneous administration of dulaglutide at 1 and 10 mg/kg resulted in dose-related increases in HR and dP/dtmax. Although increased HR is consistent with GLP-1 agonists, the elevations in HR and dP/dtmax were prolonged and resulted in the lack of normal hemodynamic changes during the dark cycles. In addition, exposure to dulaglutide at a dose of 10 mg/kg resulted in an increase in QTc at a single time point, potentially indicative of a delay in ventricular repolarization. A no-observed-effect level (NOEL) could not be established due to prolonged increases in HR and dP/dtmax at 1 mg/kg.

Following repeated administration of dulaglutide at 1, 3 and 10 mg/kg twice weekly for 1 month, there was an increase in QTc interval at all doses; this was shown to be statistically significant prior to dosing on Day 4 (all doses) and Day 28 (at 3 and 10 mg/kg) and at 2 hours post-dose on Day 28. No significant changes in HR were observed. Following repeated administration twice weekly for 3 and 9 months, there was a trend towards an increase in heart rate; however, the Applicant did not consider the observed increase to be adverse. During these studies there were small increases in QTc which were not considered to be clinically significant (3 month study) and a sporadic increase in QTc noted on Day 29 only (prior to dosing during the 9 month study). No other electrocardiographic abnormalities were observed and the NOAEL for cardiovascular effects during this study was considered to be 8.15 mg/kg. Overall, the studies of a longer duration suggest that the potential for QTc prolongation is less likely. Taking all of the data into consideration, it is apparent that effects on HR and QTc interval have been observed at doses as low as 1 mg/kg which corresponds to exposures that are ~45-fold higher than that proposed clinically.

Given the observed effects on the cardiovascular system, the Applicant conducted an experiment to investigate the effects of dulaglutide on the human ether-a-go-go-related gene (hERG) channel current. The CHMP note that it is considered unlikely that dulaglutide would block the hERG channel, as the relatively small pore size would exclude access to proteins of this size. Nevertheless, the study was conducted, was not performed to GLP and was fundamentally flawed as the effects of the vehicle were not evaluated. The maximum observed reduction in hERG amplitude of 33% at a concentration of 15.2 µg/mL could have therefore been due to the effects of the test article or the vehicle itself.

The 1 month repeated dose study performed in the monkey suggests that the potential for effects on the respiratory and central nervous systems is low.

Dulaglutide was designed to minimize the risk of potential effector functions of the molecule: the *in vitro* studies performed as well as the repeat-dose toxicity studies demonstrate that dulaglutide does not exhibit effector

function activity. In addition, the potential for antibody formation against foreign epitopes was considered to be low.

2.3.2. Pharmacokinetics

Dose-related increases in systemic exposure were observed in mice, rats, rabbits and monkeys.

In general, repeated dosing was associated with a modest increase in systemic exposure in rats (6-month repeat dose toxicity study) and monkeys consistent with accumulation associated with the twice weekly dosing frequency of dulaglutide. Lower exposure after repeat dosing was observed in mice (6-month carcinogenicity study), rats (12-month mechanistic study) and rabbits potentially due to the formation of anti-drug antibodies. It should also be noted that anti-drug antibodies were not detected in monkeys following twice weekly subcutaneous administration of dulaglutide for 9 months.

The half-life of elimination of dulaglutide was determined to be approximately 7 days in monkeys. Time to achieve the observed peak plasma concentrations (T_{max}) appeared to be unaffected by dose or duration. There were no apparent sex-related differences in dulaglutide plasma concentrations or resulting TK parameters.

The Applicant has provided exposure multiples for the pivotal studies, in order to demonstrate how the exposures observed compare to those proposed clinically. However, further clarification was sought with respect to the safety margins provided.

As outlined in the ICH S6 (R1) guideline, classical biotransformation studies are not required for proteins as it is expected that dulaglutide will be degraded to smaller proteins and amino acids. Hence, the absence of metabolism and excretion studies is justified. However, the CHMP notes that the excretion of dulaglutide in breast milk was not determined during the reprotoxicity studies conducted to date and further clarification was sought.

2.3.3. Toxicology

Repeat dose toxicity

During the repeated dose studies, important outcomes included reduction in food consumption with secondary decreases in weight gain in rodents and monkeys. There was no dose-limiting target organ toxicity. No pancreatic inflammation, necrosis, hyperplasia, or neoplasia in rats was observed at 58-fold the maximum recommended human dose of 1.5 mg/week (MRHD) based on AUC. No thyroid C-cell neoplasia or pancreatic inflammation, necrosis, hyperplasia, or neoplasia was observed in monkeys at 474-fold the MRHD based on AUC.

Carcinogenicity

In the carcinogenicity studies, non-fatal, thyroid C-cell tumors in rats occurred at $\geq$ 7-fold the MRHD based on AUC. C-cell carcinomas were noted in rats, but no pancreatic inflammation, necrosis, hyperplasia, or neoplasia at 58-fold the MRHD based on AUC. No thyroid C-cell or pancreatic inflammation, necrosis, hyperplasia, or neoplasia was observed in transgenic mice at 4-fold the MRHD based on AUC. In non-diabetic rats, chronic dulaglutide treatment (58-fold the MRHD, based on AUC) increased focal thyroid C-cell hyperplasia in

non-diabetic rats, but focal thyroid C-cell hyperplasia was not preceded by increased thyroid C-cell volume. Consistent with the lack of morphometric changes in thyroid C-cell volume in non-diabetic rats, dulaglutide did not increase diffuse C-cell hyperplasia or basal or calcium chloride-stimulated plasma calcitonin. Dulaglutide produced effects typically associated with other marketed long acting GLP-1 receptor agonists such as Victoza (liraglutide) and Bydureon (exenatide once-weekly). The human relevance of thyroid C-cell tumors from the GLP-1 receptor agonist class is unknown and at this time a potential to cause carcinogenicity in man cannot be completely ruled out. The findings have been included in Section 5.3 of the SmPC, which is acceptable and no further non-clinical study is required at this time.

Reproduction Toxicity

During the embryofetal development studies, as observed for other GLP-1 receptor agonists, in the rat and rabbit, skeletal effects were noted at 44- and 11-fold the MRHD, respectively, based on AUC. Memory deficits in Biel swimming maze of F1 female offspring was observed at 16-fold the MRHD, based on AUC, in association with reduced maternal food consumption and weight gain.

2.3.4. Ecotoxicity/environmental risk assessment

Dulaglutide is a recombinant protein. No risk to the environment from the use of dulaglutide is expected.

2.3.5. Discussion on non-clinical aspects

Overall, the Applicant has evaluated the effects of dulaglutide *in vitro* in rat, human and monkey cells but different methods have been used to assess functional activity. The data provided did not allow for a direct comparison of the activity at the rat, human and monkey GLP-1 receptors. The Applicant has clarified that at the GLP-1 receptor, all of the residues involved in direct ligand interaction are fully conserved between human and cynomolgus monkey receptors and between human and rat receptors. This therefore confirms the suitability of the species used for the *in vivo* toxicology studies. During the procedure the Applicant has clarified that *in vitro* pharmacology studies have been performed with earlier batches of dulaglutide (generated in NSO and HEK293 cells) and batches that are considered to be representative of the commercial product (generated in CHO cells). In addition, it was confirmed that studies which evaluated the activity at the GLP-1 receptor and the potential to mediate antibody-dependent cell mediated cytotoxicity (ADCC) with material that is representative of the final product.

Given that QTc prolongation was observed in the monkey (at doses higher than that proposed clinically), the Applicant conducted an experiment to investigate the effects of dulaglutide on the human ether-a-go-go-related gene (hERG) channel current. The CHMP noted that it is considered unlikely that dulaglutide would block the hERG channel, as the relatively small pore size would exclude access to proteins of this size. Nevertheless, the study was conducted, was not performed to GLP and was fundamentally flawed as the effects of the vehicle were not evaluated and there is evidence to suggest that similar vehicles have the potential for hERG inhibition. Hence, the maximum observed reduction in hERG amplitude of 33% at a concentration of 15.2 µg/mL; may have been due to the effects of the test article or the vehicle [10 mM (1.92 mg/mL) citrate and 0.02% (w/v) polysorbate 80 at pH 6.5]. The Applicant subsequently submitted a report demonstrating the effects of a citrate buffer. This study was conducted to GLP and it is evident that citrate (at 5 mg/mL) inhibits the hERG channel current. The data generated would suggest that citrate causes a concentration-related reduction in hERG channel current. It is acknowledged that a vehicle group should have been included in the earlier study.

However, upon review of the results of the subsequent study, CHMP agreed that an additional hERG study to verify the effects of the vehicle and dulaglutide is not warranted.

It was concluded that the sporadic effects on QT interval which occurred in a number of the non-clinical studies may not be of clinical relevance as the findings occurred at exposures considered sufficiently in excess of the maximum human exposure. Given the observed effects on the cardiovascular system, upon request for scientific advice, the CHMP suggested that additional cardiovascular studies should be carried out in the dog [EMEA/CHMP/SAWP/629115/2009]. The Applicant provided justification for not adhering to the CHMP Scientific advice and it is agreed that no further *in vivo* studies are required in the dog, given the clinical data available. Although, the thorough QT study was terminated prematurely and the supratherapeutic dose of 7 mg was actually reduced to 4 mg in some instances, the clinical data available to date do not indicate a risk for QT prolongation in man, if the product is used as proposed.

The Applicant was also asked to discuss whether the model used (with respect to the time course of placental transfer and the extent to which the fetus is exposed) was truly representative of the clinical situation, as dulaglutide (which carries an IgG4 Fc moiety) is expected to be transported across the placenta via the FcRn receptor mainly during the last trimester of pregnancy. The Applicant has clarified that the rabbit model used to determine the potential effects of dulaglutide on embryofetal development has some clinical relevance as it is believed that transfer of dulaglutide via the FcRn receptor occurs in both the rabbit and man. In addition, the Applicant re-iterated that the study and its design are in line with the current regulatory guidance.

The toxicology package submitted in support of this application was generally adequate. Clarification was sought with respect to the nature of the test article used during the toxicology studies and how it compares to the proposed product. The responses provided confirmed that the majority of the pivotal studies were conducted using test material generated in the CHO cell line, which is used for the final commercial process. Moreover, the process used to generate batches used for the carcinogenicity some of the reproductive toxicity and the 52-week mechanistic study in the monkey was generated using a process deemed comparable to the commercial process.

Toxicokinetic analysis was performed during all pivotal studies. Within the non-clinical dossier, the Applicant provided calculations for exposure multiples for these studies, however, clarification was sought as to whether the calculated safety margins were correct. The Applicant confirmed that the duration of the dosing regimens used during the non-clinical studies (0-72 hour or 96 hour) were different to those used in man (0-168 hour). Therefore, it was necessary to normalize the reported AUC based on the dosing interval (τ) to obtain similar information in animals and humans to compare for calculation of the safety margins.

Finally, the CHMP noted that the excretion of dulaglutide in breast milk was not determined during the reprotoxicity studies conducted to date. It is to be expected that a child would be exposed to dulaglutide during the last trimester of pregnancy, and the first milk gift. The applicant has indicated that the structure of dulaglutide resembles the structure of an antibody. These are known to be excreted in milk and therefore excretion in milk is to be assumed. Although absorption via the gut in neonates is considered to be minimal, breast feeding has been contraindicated; the wording within Section 4.6 of the SmPC is considered to be acceptable and is similar to that used for other members of this pharmacological class.

2.3.6. Conclusion on the non-clinical aspects

Given the data provided during the course of the procedure, from a non-clinical perspective, this application was considered to be approvable by CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

The dulaglutide clinical development program included 30 completed studies (21 clinical pharmacology studies and 9 Phase 2 and 3 studies (Table 1) with an additional 10 studies ongoing (Table 2).

The Phase 2 and 3 studies included patients with T2DM treated with a range of therapies at the time of random assignment to study treatment: diet and exercise, single or dual oral antihyperglycemic medications (OAMs), or conventional insulin therapy with or without metformin. Treatment durations ranged from 12 to 26 weeks in the Phase 2 studies and from 52 to 104 weeks in the Phase 3 studies. Dulaglutide was examined against a placebo comparator in the 4 Phase 2 studies (H9X-MC-**GBCJ**, H9X-MC-**GBCK,** H9X-JE-**GBCZ** and H9X-MC-**GBDN**) and 2 of the Phase 3 Studies (H9X-MC-**GBCF**) and H9X-MC-**GBDA**). Active comparators in the Phase 3 studies included sitagliptin (H9X-MC-**GBCF**), exenatide BID (H9X-MC-**GBDA**), metformin (H9X-MC-**GBDC**), and insulin glargine (H9X-MC-**GBDB** and H9X-MC-**GBDD**).

Table 1 Completed Clinical Pharmacology/Biopharmaceutic, Phase 2 and 3 Clinical, and Device Studies Contributing to Safety Assessments in the Dulaglutide Marketing Application

Clinical Pharmacology and Biopharmaceutic Studies	**Device Studies** [a]
Healthy Subject PK, PD, and Tolerability GBCA – Single-dose safety, PK, and PD ***Studies Providing Patient PK and/or PD Information*** GBCD – Multiple-dose safety, PK, and PD GBCB – Single-dose safety, PK, and PD in Japanese patients with T2DM GBCL – Multiple-dose safety, PK, and PD in Japanese patients with T2DM ***Effect of Intrinsic Factors*** GBCM -Renal impairment (subjects with normal/impaired renal function) GBCT -Elderly (≥65 years of age) patients with T2DM GBDO -Hepatic impairment (subjects with normal/impaired hepatic function) GBCN -Effect of injection site on BA; effect of BMI (subjects with high/low BMI) ***Effect of Dulaglutide on PK and/or PD of other Drugs*** GBCO -Lisinopril/metoprolol in subjects with hypertension (with/without T2DM) and healthy subjects	IQBA -safety/tolerability of single-use pen vs. prefilled syringe IQBE – summative human factors study for the single-use pen **Phase 2 Studies** GBCJ – 16-week, placebo-controlled, dulaglutide dose titration (background: 2 OAMs -MET, SU, TZD, or DPP-4 inhibitor) GBCK – 12-week, placebo-controlled, dose-dependent effects on glycemic control (background: diet/exercise) GBCZ – 12-week, placebo-controlled, dose-dependent effects on glycemic control, Japanese patients with T2DM (background: diet/exercise) GBDN – 26-week, placebo-controlled, BP/HR with ABPM (background: OAM(s) -MET, SU, TZD, glinides, α-glucosidase inhibitors) **Phase 3 Studies**

GBCP -Atorvastatin in healthy subjects GBCQ -Oral contraceptives in healthy women taking OC GBCR -Digoxin in healthy subjects GBCS -Warfarin in healthy subjects GBDM[b] – MET in patients with T2DM GBDW -Sitagliptin in patients with T2DM ***Special Studies*** GBCI -Restoration of first/second phase insulin (healthy subjects/T2DM) GBCH -Gastric emptying (healthy subjects) ***Thorough QT Interval Study*** GBCC -Thorough QT study ***Bioavailability (Healthy Subjects)*** GBDR -Absolute BA of SC; relative BA of IM vs. SC GBDT -Comparative PK of single-use pen vs. prefilled syringe	GBCF[c] – 104-week, placebo-and sitagliptin-controlled, HbA1c noninferiority vs. sitagliptin (background: MET) GBDA – 52-week, placebo-and exenatide BID-controlled, HbA1c superiority vs. placebo (background: MET+TZD) GBDB – 78-week, insulin glargine-controlled, HbA1c noninferiority vs. comparator (background: MET+SU) GBDC – 52-week, MET-controlled, HbA1c noninferiority vs. comparator (background: diet/exercise) GBDD – 52-week, insulin glargine-controlled, HbA1c noninferiority vs. comparator (background: insulin lispro±MET)
Completed Clinical Pharmacology/Biopharmaceutic, Phase 2 and 3 Clinical, and Device Studies Contributing to Safety Assessments in the Dulaglutide Marketing Application a Study IQBA was a clinical pharmacology study using the prefilled syringe and single-use pen, and Study IQBE was a summative human factors using the single-use pen alone. Study H8L-MC-IQBF was a summative human factors study with the prefilled syringe. Study H8L-MC-IQBD was a formative human factors study for the single-use pen. Because neither Study IQBD not IQBF contributed to the safety assessments presented in this safety summary, they are not included in this table. b Study GBDM is also considered as Special Study as it assessed gastric emptying using scintigraphy in patients with T2DM. c Study GBCF was an adaptive dose-finding, inferentially seamless Phase 2/3, placebo-controlled study in patients with T2DM on metformin.	

Table 2 Dulaglutide Ongoing Clinical Studies as of 19 April 2013

Study	Protocol Title
Phase 1	
GBDL	Pharmacokinetics of a Single LY2189265 Dose in Healthy Chinese Subjects and of Multiple LY2189265 Doses in Chinese Patients with T2DM
Phase 3	
GBCG[a]	The Efficacy and Safety of Once-Weekly, Subcutaneous Dulaglutide Monotherapy Compared to Glimepiride in Patients with Type 2 Diabetes Mellitus
GBDE	A Randomized, Open-Label, Parallel-Arm Study Comparing the Effect of Once-Weekly Dulaglutide with Once-Daily Liraglutide in Patients with Type 2 Diabetes
GBDG	A Randomized, Parallel-Arm, Double-Blinded Study Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Patients with Type 2 Diabetes Mellitus on Sulphonylurea Therapy
GBDJ	The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly Incretin in Diabetes
GBDK[a]	The Efficacy and Safety of Once-Weekly, Subcutaneous Dulaglutide Compared to Once-Daily Insulin Glargine in Patients with Type 2 Diabetes Mellitus on Metformin and/or a Sulphonylurea
GBDP[b]	A Phase 3 Study of LY2189265 Monotherapy Compared to Placebo and Liraglutide in Patients with Type 2 Diabetes Mellitus
GBDQ[b]	A 52-Week, Open-Label, Long-Term Safety Study of LY2189265 in Combination with Monotherapy of Oral Antihyperglycaemic Medications in Patients with Type 2 Diabetes Mellitus
GBDX	A Randomized, Open-Label, Parallel-Arm Study Comparing the Effect of Once-Weekly Dulaglutide With Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease
GBDY[b]	A Phase 3 Study of LY2189265 Compared to Insulin Glargine in Patients with Type 2 Diabetes Mellitus on a Sulphonylurea and/or Biguanide
a Predominantly Asian subjects. b Japanese subjects. Note: An ongoing study is defined as any study that had achieved a first patient visit but had not achieved any database lock (including interim locks) as of 19 April 2013, the data cutoff date for this submission.	

Clinical Pharmacology

The clinical pharmacology of dulaglutide was evaluated in 21 clinical pharmacology studies, 4 Phase 2 studies, and 3 additional Phase 3 studies, including an adaptive seamless Phase 2/3 study. Single doses of dulaglutide over a range of 0.1 to 12 mg and once weekly multiple doses over a range of 0.05 to 8 mg for up to 6 weeks were studied. The studies included 535 healthy subjects and 229 patients with T2DM. Special population studies included subjects with renal and hepatic impairment, elderly, and subjects with hypertension. Two clinical

pharmacology studies were conducted in Japanese patients with T2DM. Intrinsic and extrinsic factors that could affect the PK and PD of dulaglutide, as well as the potential effect of dulaglutide on the PK of commonly co-administered medications, were evaluated in individual studies. The program also included PD mechanistic studies that assessed the effects of dulaglutide on first and second phase insulin secretion and gastric emptying.

Population PK and PK/PD analyses were also performed throughout the program to provide: (1) an assessment of dulaglutide PK in the target population, (2) an assessment of intrinsic and extrinsic factors that could significantly influence dulaglutide PK and PD, (3) a characterization of PK and PD between-patient variability, and (4) an assessment of dulaglutide exposure-response relationships for efficacy (FPG-HbA1c, and body weight) and safety measures (ECG, heart rate, BP, amylase [pancreatic and total], lipase, calcitonin) to inform the dose range for Phase 2, dose selection for Phase 3, and the final recommended commercial dose. An outline of the clinical pharmacology studies is presented in Table 3 below.

Table 3 Clinical Pharmacology Studies

Study	Description	Population	SC Dosing Regimen
Healthy Subject PK, PD, and Tolerability			
GBCA	Single dose safety, PK, PD	Healthy subjects	0.1, 0.3, 1, 3, 6, and 12 mg single dose
Patient PK and/or PD			
GBCD	Multiple dose safety, PK, PD	T2DM	0.05, 0.3, 1, 3, 5, and 8 mg QW/5 weeks
GBCB	Single dose safety, PK, PD	Japanese T2DM	0.3, 1, 3, and 6 mg single dose
GBCL	Multiple dose safety, PK, PD	Japanese T2DM	1 or 1.5 mg QW/5 weeks
Effect of Intrinsic Factors			
GBCT	Effect of age	Elderly (≥65 years of age) T2DM	0.5, 0.75 and 1.5 mg QW/6 weeks
GBCM	Effect of renal impairment	Normal or impaired renal function	Single 1.5 mg dose
GBDO	Effect of hepatic impairment	Normal or impaired hepatic function	Single 1.5 mg dose
GBCN	Effect of BMI	Healthy subjects: low and high BMI	Single 1.5 mg dose
Effect of Other Drugs on dulaglutide PK			
GBDW	Effect of sitagliptin	T2DM	3 single 1.5 mg doses
Effect of Dulaglutide on PK and/or PD of other Drugs			
GBCO	Effect on lisinopril and metoprolol	Patients with hypertension, with and without T2DM; healthy subjects	1.5 mg QW for 4 weeks or 2 single 1.5 mg doses
GBCP	Effect on atorvastatin	Healthy subjects	Single 1.5 mg dose
GBCQ	Effect on oral contraceptives	Healthy women taking OC	Single 1.5 mg dose
GBCR	Effect on digoxin	Healthy subjects	2 single 1.5 mg doses
GBCS	Effect on warfarin	Healthy subjects	Single 1.5 mg dose
GBDW	Effect on sitagliptin	T2DM	3 single 1.5 mg doses
GBDM	Effect on metformin	T2DM	Patients with T2DM
Mechanistic Pharmacodynamic Studies			
GBCI	Effect on 1st and 2nd phase insulin	Healthy subjects; T2DM	Single 1.5 mg dose
GBCH	Effect on gastric emptying using acetaminophen	Healthy subjects	1 or 3 mg QW for 4 weeks
GBDM	Effect on gastric emptying scintigraphy	T2DM	1.5 mg QW for 4 weeks
Thorough QT Study			
GBCC	Thorough QT study	Healthy subjects	Single 4 or 7 mg dose

Studies Providing Population PK/PD Information			
GBCJ	Population PK/PD, Phase 2	Overweight and obese T2DM	1 mg and dose titration: 0.5 to 1 mg, 1 to 2 mg
GBCK	Population PK/PD, Phase 2	T2DM	0.1, 0.5, 1, 1.5 mg
GBCZ	Population PK/PD, Phase 2	Japanese T2DM	0.25, 0.5, 0.75 mg
GBDN	Population PK/PD, Phase 2	T2DM	0.75, 1.5 mg
GBCF	Population PK/PD, Phase 2/3	T2DM	0.25, 0.5, 0.75, 1, 1.5, 2, 3 mg
GBDA	Population PK/PD, Phase 3	T2DM	0.75, 1.5 mg
GBDC	Population PK/PD, Phase 3	T2DM	0.75, 1.5 mg
Device Study			
IQBA	Safety and tolerability of device	Healthy subjects	Single injection, placebo only

Abbreviations: BA = bioavailability; BMI = body mass index; IM = intramuscular; IV = intravenous; OC = oral contraceptives; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; SC = subcutaneous; T2DM = type 2 diabetes mellitus; vs. = versus.

2.4.2. Pharmacokinetics

Development of the dulaglutide involved modification of the molecule to improve the solubility of the peptide, and increase the duration of its pharmacological activity by making the GLP-1 analog portion more stable against DPP-4 inactivation, and by decreasing the rate of clearance of the molecule via fusion to the Fc fragment of IgG4.

The PK characteristics of dulaglutide were assessed in a number of studies as shown in Table 3 above. PK parameters after single and multiple-dose administration were then summarized in a meta-analysis of 8 clinical pharmacology studies that included healthy subjects and patients with T2DM. Population PK analyses were used to evaluate the dulaglutide PK in the target population, the effect of intrinsic and extrinsic factors and PK inter-patient variability.

Two formulations supported the clinical development program. The initial lyophilized formulation was used only in the Phase 1 single-dose safety study and multiple-dose safety study. The final commercial solution formulation was used in subsequent Phase 1 studies as well as the Phase 2 and 3 therapeutic studies.

Transferability of data was mainly demonstrated by a bioequivalence study comparing the PK of the prefilled syringe and the single use pen (PK; Study GBDT). In addition, a validation (summative human factors study) using simulated use, a human factors study with the prefilled syringe and the single-use pen devices using a simulated injection, a validation (summative human factors) study (Study IQEB) in patients with T2DM using actual placebo injections, a phase 1 non-inferiority study in healthy subjects (Study IQBQ) comparing pain intensity at the injection site for single-use pen compared to the prefilled syringe were conducted to support the use of both, the prefilled syringe and the single-use pen.

Plasma samples from the clinical studies were analyzed for dulaglutide using validated radioimmunoassay (RIA) methods.

Absorption and Bioavailability

Information on the absorption of dulaglutide is based on single dose PK data in healthy volunteers (H9X-MC-**GBCA**), and multiple dose studies in T2DM patients (H9X-MC-**GBCD**). The absolute bioavailability was examined after single subcutaneous (SC) 1.5mg administration in healthy volunteers (H9X-MC-**GBDR**). The

relative bioavailability of dulaglutide 1.5 mg was also examined after SC injection into the arm and thigh compared to the abdominal wall (H9X-MC-**GBCN**).

Dulaglutide is slowly absorbed after SC administration with maximum concentrations reached between 48 and 72 hours. Steady state appears to be reached after two weeks of once weekly dosing.

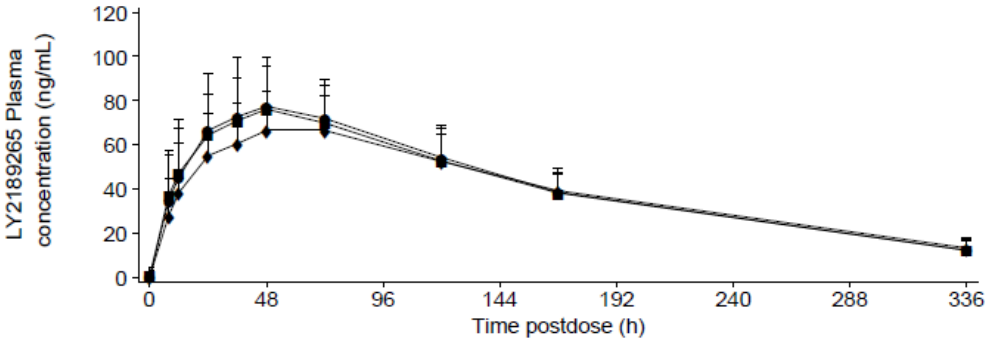
The absolute bioavailability of dulaglutide following a 1.5 mg SC dose was found to be approximately 44% probably due to metabolism/degradation at the site of injection. Bioavailability does not appear to be significantly affected by the site the administration as no significant effect on the exposure of dulaglutide was found after a 1.5 mg dose was SC injected into the arm or thigh compared to the abdominal wall (Table 4 and Figure 2). A slightly lower Cmax was observed after administration in the thigh compared to the abdomen but is unlikely to be clinically relevant. The Applicant suggests that all three injection sites can be used interchangeably without dose-adjustment and this is agreed. The relative bioavailability of an IM dose was found similar to an SC dose (although this was calculated based on a 0.75mg dosing) which is reassuring in case of errors during self-injection.

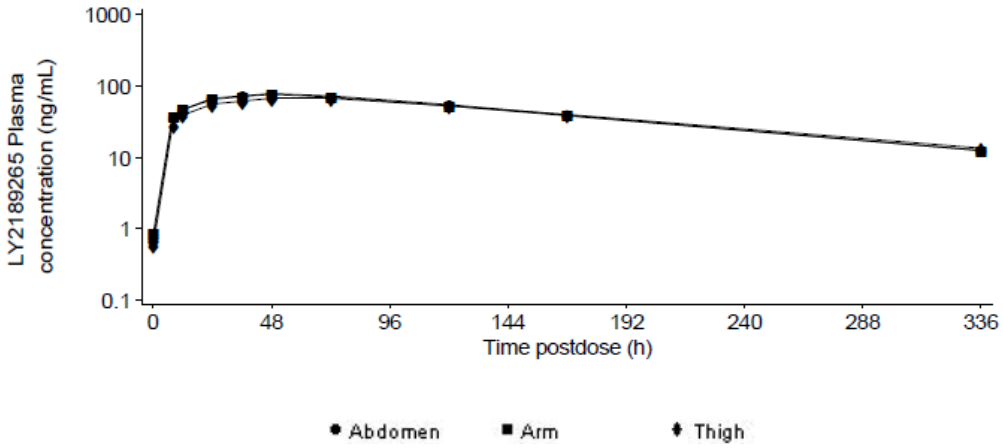
In contrast to the administration site, BMI was found to be a significant factor inversely affecting bioavailability (this is further discussed in the Special Populations section below).

Table 4 Summary of Dulaglutide Pharmacokinetics from a Relative Bioavailability of Injection at different Sites in Healthy Subjects (Low and High Body Mass Indices); Study H9X-MC-GBCN.

Injection site	**Abdomen**	**Arm**	**Thigh**
N	43	40	44
$AUC_{(0\text{-tlast})}$ (ng•h/mL)	13200 (24)	13000 (24)	12600 (21)
$AUC_{(0\text{-}\infty)}$ (ng•h/mL)	15100 (24)	14800 (25)	14600 (18)
$AUC_{(0\text{-}168)}$ (ng•h/mL)	9410 (26)	9270 (24)	8660 (24)
Cmax (ng/mL)	76.9 (30)	76.1 (25)	68.5 (27)
tmax (h)	48.0 (24.0-72.0)	48.0 (12.0-72.0)	48.0 (12.0-120)
t1/2 (h)	102 (80.7-155)	103 (75.0-146)	107 (75.6-194)
CL/F (L/h)	0.0996 (24)	0.101 (25)	0.101 (20)
Vz/F (L)	14.6 (28)	15.0 (26)	15.5 (25)
F_{rel} (Arm/Abdomen)	NA	96.6 (14)	NA
F_{rel} (Thigh/Abdomen)	NA	NA	99.0 (13)

Figure 2 Arithmetic mean (+SD) plasma concentration versus time profiles of LY2189265 (dulaglutide) across BMI groups and administration sites following single dose administration of 1.5 mg dulaglutide by SC injection (upper panel: linear scale; lower panel: semi-logarithmic scale); Study H9X-MC-GBCN





Distribution

The mean apparent volumes of distribution (Vz/F) after single and multiple 1.5 mg SC dosing were calculated as 19.5 L (40.5% CV) and 17.4 L (range 9.3 to 33) respectively, based on the findings of the PK meta-analysis combining data from single and multiple dose Studies (H9X-MC-**GBCT** and H9X-JE-**GBCL**). After a single 0.75 mg dose, mean Vz/F was calculated 11.3 L. After 0.1 mg IV administration, mean volume of distribution (Vz) was 5.32 L (17% CV) (Study H9X-MC-**GBDR**), indicating that dulaglutide distributes primarily in the blood volume. Protein binding was not reported for dulaglutide. The IgG Fc drives the time action profile and this clearance mechanism is independent of protein binding. In addition, dulaglutide was not designed to bind to serum albumin and has a large molecular weight with inclusion of the IgG Fc component for half-life extension (molecular weight of 59,671 Daltons).

Elimination

Data from the PK meta-analysis indicate an apparent clearance (CL/F) in patients with T2DM after multiple 1.5 mg dosing of 0.107 L/hr. Mean terminal half-life (t1/2) after multiple 1.5 mg dosing was 4.7 days. Following single doses of dulaglutide 1 mg and higher, mean plasma concentrations were quantifiable up to 336 hours (14 days) (Study H9X-JE-**GBCB** in Japanese T2DM patients). Model-derived PK parameter estimates were similar to non-compartmental estimations from individual studies.

Native GLP-1 (amino acid sequence 7-37) is susceptible to proteolysis by DPP-4 and other enzymes. The cleavage of native GLP-1 by DPP-4 results in the loss of the dipeptide off the N-terminal end, generating inactive GLP-1 metabolites (amino acid sequence 9-36 or 9-37). Dulaglutide was engineered to be less susceptible to cleavage by DPP-4, but due to the extended exposure profile, dulaglutide may still undergo cleavage on the N-terminal end to form a truncated GLP-Fc metabolite (9-37GLP-Fc) in vivo.

To investigate if 9-37GLP-Fc is present in circulation after administration of dulaglutide, a directed liquid chromatographic/tandem mass spectrometric (LC/MS/MS) method was developed to detect dulaglutide and the 9-37GLP-Fc metabolite in human plasma. This non-validated method was used to conduct an exploratory analysis of pooled human plasma samples following SC administration of 1.5 mg dulaglutide from Study H9X-MC-**GBCT**. The 9-37GLP-Fc metabolite was detected over the course of the dulaglutide concentration-time profile following a single or weekly subcutaneous administration of 1.5 mg for 6 weeks. By the last collection timepoint, 9-37GLP-Fc had a plasma concentration that exceeded the parent dulaglutide compound. The activity of 9-37GLP-Fc was assessed using a recombinant cell-based reporter gene assay system. This assay was used to test the potential of 9-37GLP-Fc to activate the human GLP-1 receptor. The in vitro system used human

embryonic kidney cells (HEK-293) stably expressing the human GLP-1 receptor at the cell surface and an intracellular reporter gene whose expression was coupled to GLP-1 receptor signalling through cyclic AMP production (cyclic AMP responsive CRE-4-Luciferase system). In this test system, 9-37GLP-Fc was determined to be a weak but full agonist with about 7400-fold less potency than the control peptide (7-37GLP-1 analogue). A direct comparison of dulaglutide to control peptide in a similar assay system indicated that 9-37GLP-Fc would be about 15,000-fold less potent compared to dulaglutide. Thus, despite the higher concentrations of 9-37GLP-Fc, the contribution of 9-37GLP-Fc to the PD response of dulaglutide is negligible.

Dose proportionality

Dose proportionality was examined in studies H9X-MC-**GBCA** and H9X-MC-**GBCD** (see also Absorption section above), as well as the PK meta-analysis. Study H9X-MC-**GBCA** in healthy volunteers single dose SC administration of dulaglutide over a range from 1.0 mg to 12.0 mg showed that Cmax and AUC(0-∞) increased less than proportionally. With each doubling of dose, Cmax increased by 1.88 (90% CI: 1.76 to 2.01) and AUC(0-∞) increased by 1.84 (90% CI:1.76 to 1.93). However, it was concluded that this was not a clinically meaningful difference.

The multiple dose study H9X-MC-**GBCD** in T2DM patients showed that at steady state (following the fifth dulaglutide dose) increases in exposure (Cmax, AUC) less than proportional over the dose range of 0.05 mg to 8 mg. With each doubling dose, there was an approximately 1.8-fold increase in Cmax and a 1.9-fold increase in AUC, which were again considered not likely to be clinically relevant.

Time dependency

This topic was not specifically discussed by the applicant. However, given that multiple dose pharmacokinetics are predicable from single dose data, there is no evidence of time dependency

Variability

Data from the single dose H9X-MC-**GBCA** study in healthy volunteers suggest a relatively low inter- and intra-subject variability.

Table 5 Estimates of Inter-subject and Intra-subject Variability of Pharmacokinetic Parameters for dulaglutide following Single Doses of 1 to 12 mg; Study H9X-MC-GBCA

	CV% (90% CI)	
Pharmacokinetic Parameter	**Intersubject**	**Intrasubject**
C_{max} (ng/mL)	17.5 (10.6, 61.2)	18.7 (12.6, 39.8)
$AUC_{(0\text{-last})}$ (ng*h/mL)	19.0 (14.2, 29.7)	8.3 (5.5, 18.4)
$AUC_{(0\text{-}\infty)}$ (ng*h/mL)	19.5 (14.4, 31.2)	8.2 (5.1, 24.2)

The estimates of intersubject variability from the meta-analysis of clinical pharmacology studies were higher (Table 6), with values of 30% for AUC and 28-35% for Cmax. Intra-subject variability estimates were 12 and 16% for AUC and Cmax, respectively.

Table 6 Dulaglutide pharmacokinetic parameters from the meta-analysis of clinical pharmacology studies.

	Mean (Inter-subject CV%)	
Parameter	**0.75 mg single dose**	**1.5 mg multiple dose**
Number of subjects	19	15
$AUC_{(0-168)}$	5240 ng.hr/mL (28.8%)	14000 ng.hr/mL (30%)
C_{max}	43.9 ng/mL (27.5%)	114 ng/mL (35%)
t_{max} (hr) median (range)	71.9 (12 – 120)[a,b,c]	48 (24 – 72 hours)[a,b,d]

Intra-subject variability estimates for dulaglutide $AUC_{[0-168]}$ and C_{max} after a single 1.5 mg dose were 11.9% and 16.1%, respectively.

Abbreviations: $AUC_{(0-168)}$ = area under the plasma concentration versus time curve [AUC] from time zero to 168 hours; C_{max} = maximum observed drug concentration; t_{max} = time of maximum observed drug concentration.

[a] data from patients with T2DM only

[b] combined data from 0.75 mg and 1.5 mg

[c] number of observations = 57

[d] number of observations = 26

Source: Table APP.2.7.2.5.78., Table APP.2.7.2.5.81., Table APP.2.7.2.5.83., and Table APP.2.7.2.5.84.

Pharmacokinetics in target population

Potential differences in dulaglutide PK between healthy subjects and T2DM patients were mainly examined in the PK meta-analysis. Overall, after single dosing the extent of exposure to dulaglutide in patients with T2DM appears comparable to that of healthy volunteer. Dulaglutide PK after a single 1.5-mg dose was found generally similar between nondiabetic subjects and patients with T2DM with the exception of tmax, which occurred at approximately 72 hours (12 to 120 hours) in the diabetic population and approximately 48 hours (12 to 120 hours) in healthy subjects.

In the T2DM population alone, the combined data from single dose studies showed a geometric mean AUC(0-∞) after a 1.5 mg dose of 7410 ng.hr/mL, with an associated Cmax of 61 ng/mL. Half-life was approximately 4.5 hr days. Mean estimate for apparent clearance was approximately 0.125 L/hr and for apparent volume of distribution was 20 L. Combined data from multiple dose studies for the 1.5 mg dose in T2DM patients with data from Study H9X-MX-**GBCT** (elderly patients) and Study H9X-JE-**GBCL** (Japanese patients; see below) suggest an estimated geometric mean AUC(0-168) and AUC(0-∞) of 14000 and 23100 ng.hr/mL, respectively, with associated Cmax of 114 ng/mL. Median tmax was approximately 48 hours (range 24 to 72 hours). Half-life was approximately 4.7 days. Accumulation after multiple dose administration of a 1.5 mg dose was approximately 1.56-fold. Mean estimates for apparent clearance were approximately 0.10 L/hr and for apparent volume of distribution were 17.4 L.

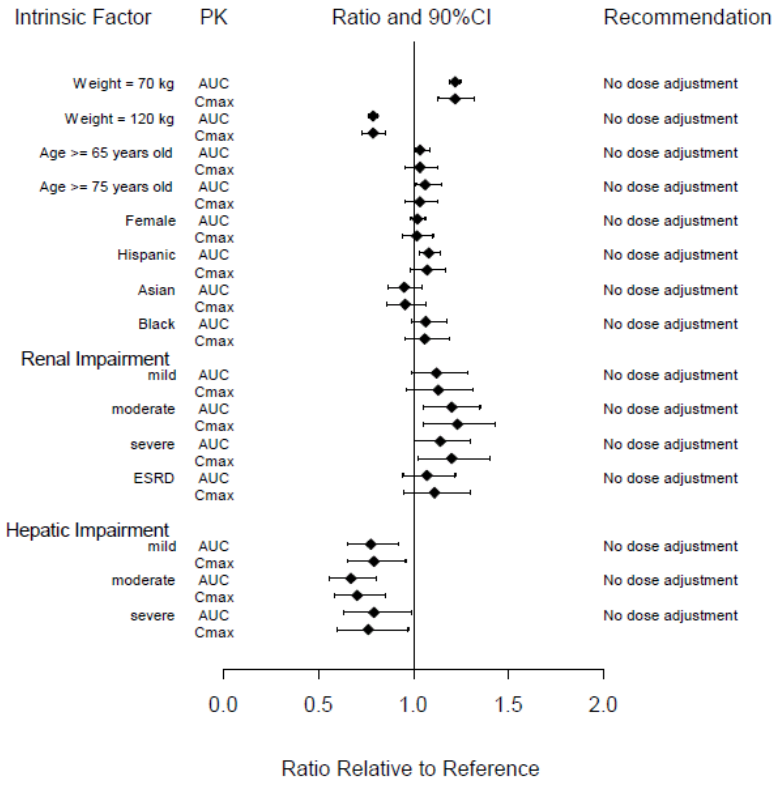
There are no multiple dose PK studies in healthy volunteers; therefore, a direct comparison of PK data at steady state between healthy subjects and T2DM patients is not possible. Moreover, multiple dose PK data come from studies in elderly and in Japanese T2DM patients so a question arises whether they are representative of the whole T2DM population although, as discussed below, there is no strong evidence of a significant effect of age and race on dulaglutide PK.

Special populations

Apart from specific studies in patients with renal and hepatic impairment, Japanese patients and elderly, the effect of most other intrinsic factors were tested in population PK analyses.

Based on the combined findings of individual studies and population PK data the Applicant provided the following summary graph showing the overall effect of the various examined intrinsic factors on the PK of dulaglutide together with relevant recommendations as to whether a dose adjustment may be required.

Figure 3 Effect of intrinsic factors on the pharmacokinetics of dulaglutide.



Note: Reference values for weight, age, gender, and race comparisons are 93 kg, 56 years old, male, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function from the respective clinical pharmacology studies.

Renal Impairment

Study H9X-MC-**GBCM** examined dulaglutide PK (after a single 1.5 mg SC dose) in 48 subjects (46 non-diabetic, 2 T2DM) with mildly impaired (estimated CrCL:50-80 mL/min; n=8), moderately impaired (estimated CrCL:30-50mL/min; n=8), severely impaired renal function (estimated CrCL:<30 mL/min; n=8) or end stage renal disease requiring dialysis (n=8) and a control group (n=16) with normal renal function. The primary PK analysis showed a limited and no consistent effect of impaired renal function on dulaglutide PK (Table 7). Based on a continuous statistical regression model examining CrCL and dulaglutide, no statistically significant linear relationship based on exposure [AUC(0-∞) and Cmax was found. No relationship was also observed between the PK parameters and renal function based on estimated eGFR.

Overall, the results suggest that kidneys play a less important role in the elimination of dulaglutide, which is not unexpected given the size of the protein. Consistent with Study GBCM, renal impairment was not found to significantly affect dulaglutide PK in the combined Phase 2 or Phase 3 population PK/PD analyses. Renal impairment is also discussed in the *Safety section* below.

Based on the overall evidence it is agreed that dose adjustment in patients with renal impairment is not necessary. The SmPC (section 4.2) therefore advises that no dose adjustment is needed in mild to moderate renal impairment but that it is not recommended in severe renal impairment (due to very limited experience in that group). This is further discussed in the *Safety section* below.

Table 7 Summary of Dulaglutide Noncompartmental Pharmacokinetic Parameters following Single Doses 1.5 mg Dulaglutide for Each Renal Function Group; Study H9X-MC-GBCM

	Geometric Mean (%CV)				
Parameter	Control	Mild Impairment	Moderate Impairment	Severe Impairment	ESRD
N	16	8	8	8	8
AUC(0-168) (ng·h/mL)	9460 (25)	10900 (11)	11400 (23)	10200 (19)	10400 (11)
AUC(0-∞) (ng·h/mL)	15900[c] (24)	19700 (18)	20500 (12)	17000[d] (15)	18300 (14)
C_{max} (ng/mL)	74.7 (29)	86.1 (15)	92.3 (26)	85.0 (20)	84.6 (13)
t_{max} [a] (h)	48.10 (12.02-96.05)	71.38 (47.37-94.47)	71.73 (47.88-97.02)	59.95 (47.60-97.47)	60.68 (46.70-72.33)
$t_{1/2}$ [b] (h)	108[c] (84.4-169)	119 (96.9-187)	137 (83.3-168)	103[d] (88.8-121)	123 (90.6-203)
CL/F (L/h)	0.0941[c] (24)	0.0763 (18)	0.0730 (12)	0.0881[d] (15)	0.0819 (14)
V_z/F (L)	14.6[c] (23)	13.1 (13)	14.4 (36)	13.1[d] (22)	14.6 (20)

Abbreviations: AUC(0-168) = area under the plasma concentration versus time curve (AUC) from time zero to 168 hours; AUC(0-∞) = AUC from time zero to infinity; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; ESRD = end-stage renal disease; N = number of subjects; $t_{1/2}$ = terminal half-life; t_{max} = time of C_{max}; V_z/F = apparent volume of distribution during the terminal phase after extra-vascular administration.

[a] Median (range).
[b] Geometric mean (range).
[c] N = 15.
[d] N = 7.

Impaired hepatic function

Study H9X-EW-**GBDO** compared dulaglutide PK (after a single 1.5 mg SC dose) between subjects with mild hepatic impairment (Child-Pugh A; 2 males and 4 females), moderate hepatic impairment (Child-Pugh B; 2 males and 4 females), severe hepatic impairment (Child-Pugh C, 2 males and 1 female), and a control group with normal hepatic function (5 males and 6 females). There were two T2DM subjects, both in the severe impairment group.

No increase in the dulaglutide exposure was seen in patients with hepatic impairment. In fact, statistically significant decreases in exposure were observed in all 3 hepatic impairment groups compared to healthy controls. The lowest mean values were observed in the moderate impairment group, with decreases in mean Cmax and AUC(0-∞) of approximately 30% and 33% respectively, compared to controls. Increases in median tmax of approximately 12 hours and 24 hours were observed in the moderate and severe impairment groups, respectively, compared to controls. Statistically significant increases compared to control in mean Vz/F and CL/F were also found for all 3 hepatic impairment groups. No notable trend in dulaglutide concentrations was observed between the mild, moderate, and severe hepatic impairment groups.

Overall, although the number of patients in the study was small, especially in the most severe hepatic impairment group there was no indication of a clinically relevant effect on the PK of dulaglutide. Therefore, it is agreed that a dose adjustment in patients with hepatic impairment is not necessary, which is also stated in the SmPC.

Gender

The effect of gender was not specifically examined in any PK study. However, in the population PK analyses gender was examined but was not identified as a significant covariate.

Race

The effect of ethnicities/races were tested in the population PK and PK/PD analyses with Caucasian representing the 52% of the examined population, African 7%, Asian 6%, Hispanic 23%, Native American 10% and other 2%. Race had no clinically relevant effect on dulaglutide PK or PD according to the combined Phase 3 population PK analysis. Hispanic ethnic origin was found to be a significant covariate for CL but the effect was relatively small and was not considered to be clinically relevant.

Two studies were carried out in Japanese patients only (H9X-JE-**GBCB** and H9X-JE-**GBCL**). Although a direct comparison is not possible, the main PK characteristics in the Japanese T2DM patients appear similar to their non-Japanese counterparts. PK parameters at steady state at a similar dose level in studies H9X-JE-GBCL and H9X-MC-GBCD (for example 1mg, a dose examined in both studies) showed similar results between Japanese and non-Japanese patients, although mean Cmax and AUC(0-168) were around 35% higher in the former group. Conclusions are difficult to draw when comparing results between studies with different methodologies and populations, but overall the data appear to support the absence of major ethnic differences likely to be of clinical relevance.

Weight

The effect of body size (body weight and BMI) on dulaglutide PK was prospectively investigated in the Phase 1 study H9X-MC-**GBCN** (that examined dulaglutide bioavailability at different injection sites). Dulaglutide overall exposure was found significantly lower in the high BMI group (30.0 to 45.0 kg/m^2, inclusive) compared to the low BMI (18.0 to 27.0 kg/m^2) group across 3 different administration sites (abdomen, arm, thigh). For AUC(0-∞), the geometric means for the high BMI group were 19% to 24% lower than the low BMI group for all administration sites, with the geometric means for Cmax being 23% to 29% lower than the low BMI group for all sites. There were no significant differences in median tmax (48 hours) or change in t1/2 between BMI groups. There were two subjects with detectable pre-dose dulaglutide levels before period 1. The GLP-1 active antibody used in the dulaglutide assay binds specifically to the N-terminus of active GLP- 1 and dulaglutide. The predose levels of dulaglutide concentrations detected before the administration of dulaglutide are likely due to elevated endogenous GLP-1 and/or glucagon levels in these subjects. However, the number of affected predose samples was minimal and the impact on the overall characterization of dulaglutide PK and subsequent conclusions was considered to be negligible.

Consistent with the Phase 1 data, both BMI and body weight were found to be significant covariates in the population PK analyses. Weight and BMI was not found to affect the dulaglutide PD effects (this is further discussed in *the Pharmacodynamic section* below). Overall, the Applicant suggests that the observed effect of weight is not clinically relevant and no relevant dose adjustment is needed. This conclusion is endorsed.

Elderly

The PK of dulaglutide in elderly patients (aged ≥65 years) with T2DM were examined in the placebo-controlled, multiple-dose study H9X-MC-**GBCT**, in which 39 patients (36 completed) received dulaglutide or placebo, as single subcutaneous doses of 0.5, 0.75, or 1.5 mg once a week for 6 weeks. Dulaglutide was absorbed slowly following once-weekly doses, with median tmax values of 48 to 72 hours across all doses on Days 1 and 36. A long elimination half-life, with mean values in week 6 of 117 to 131 hours was seen at all dose levels. AUC_T and Cmax, appeared to increase in a dose-proportional manner following once-weekly doses for 6 weeks, with the 90% CI for the exponent containing 1 and the 90% CI for the ratios of the dose normalized geometric means of the 1.5 mg dose level compared to the 0.5 and 0.75 mg dose levels also containing 1. There was an approximately 1.5-fold accumulation of dulaglutide in plasma compared to Day 1, with mean observed accumulation ratios of 1.45 to 1.51 across all dose levels. As in study GBCN, some subjects had detectable pre-dose dulaglutide levels before the administration of the first dose. Overall, PK parameters were consistent

with previous study results in both healthy subjects and younger patients with T2DM. In population PK analyses age was among the examined covariates but no significant effect was found.

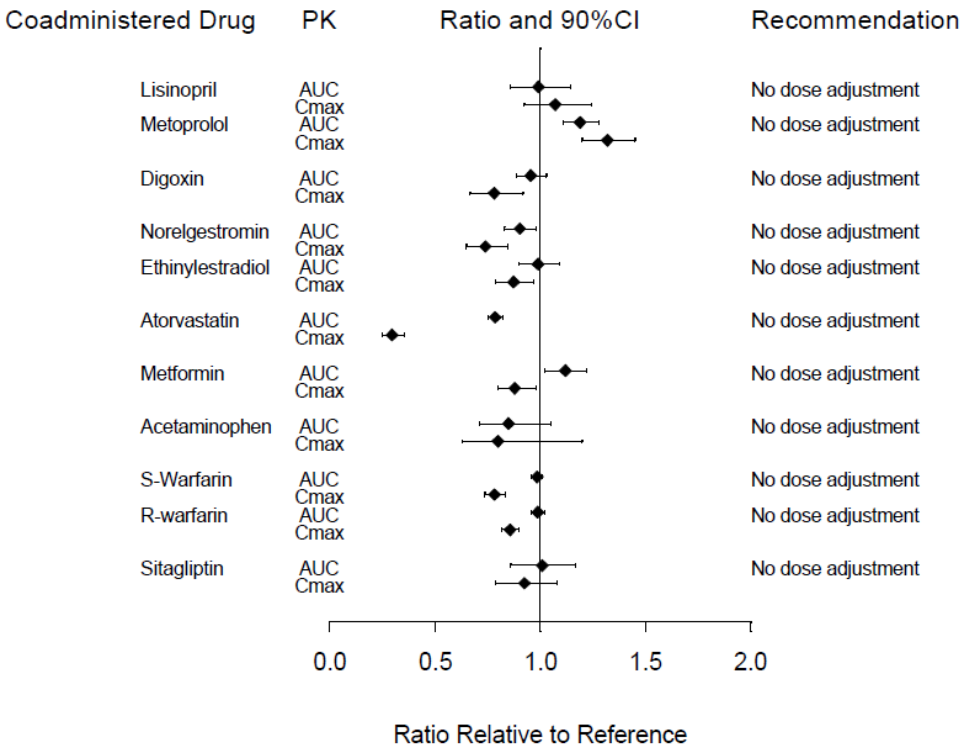
It needs to be noted that there were very few patients older than 75 years in the PK, PD studies. In the Phase 2 and 3 studies there were in total 115 (1.9%) patients ≥75yrs and only three >85yrs

Interactions

The elimination of dulaglutide is expected to be through proteolytic degradation into its amino acid components and is not anticipated to be eliminated intact in the urine or to be metabolized by the CYP enzymes. Therefore, PK interactions with drugs primarily renally eliminated or metabolized by CYP enzymes are unlikely. However, dulaglutide causes a delay in gastric emptying, a well known effect of the class, which may alter the PK of orally co-administered drugs. Consequently, the clinical pharmacology program included drug-drug interaction studies for a number of agents relevant to the T2DM population: acetaminophen, lisinopril, metoprolol, warfarin, metformin, digoxin, atorvastatin, oral contraceptives, and sitagliptin.

The following forest plot graph is showing the observed effect of dulaglutide on the various examined drugs together with the Applicant recommendations for possible need of relevant dose adjustments. The results of the individual studies are discussed in more detail below.

Figure 4 Potential for dulaglutide to influence the exposure (AUC or Cmax) of co-administered drugs



Note: Reference group is administration of coadministered medication alone

Study H9X-MC-**GBCH** evaluated the effect of dulaglutide (1mg or 3mg, at steady state) on gastric emptying using acetaminophen PK as a surrogate. For both 1 and 3 mg dulaglutide dose groups there was no statistically significant effect on acetaminophen AUC(0-24) when administered with dulaglutide compared to baseline. However, the rate of gastric emptying was slower following the first dose of 1 and 3 mg dulaglutide, with acetaminophen Cmax reduced by 36% and 50%, respectively, and the median tmax occurring statistically significantly later (3 and 4 hours, respectively). Overall, the greatest impact on the rate of gastric emptying was observed after the first dose of dulaglutide, while at steady state dulaglutide had no significant effect on the rate and extent of acetaminophen exposure. Based on these observations, it was concluded that no dose adjustment for acetaminophen is necessary when given together with 1.5 mg dulaglutide.

Lisinopril and metoprolol

Study H9X-MC-**GBCO** was a two-part (conducted in parallel) study that examined the effect of dulaglutide (weekly doses of 1.5 mg dulaglutide for 4 weeks) on the PK of lisinopril (Part 1) in hypertensive patients and also assessed the effect of dulaglutide on haemodynamics and PK of metoprolol (Part 2) in healthy volunteers. Part 1 found no significant effect of dulaglutide on lisinopril PK. Statistically significant delays in lisinopril tmax of approximately 1 hour observed on Days 3 and 24 consistent with dulaglutide-induced delay in gastric emptying were not considered clinically relevant. Ambulatory blood pressure monitoring (ABPM) in hypertensive subjects taking lisinopril revealed statistically significant increases in heart rate HR when co-administered with dulaglutide on Days 3 and 24 but no clinically significant effect on blood pressure.

There was a statistically significant increase in metoprolol exposure with dulaglutide (19% for AUC_T and 32% for Cmax). However, this increase in exposure was small compared to the much larger observed metoprolol PK variability (up to 69%). It is agreed that for metoprolol succinate with a wide therapeutic window an increase in exposure by about 20% and of Cmax by about 30% may not be clinically relevant. For prolonged release formulations of drugs with a small therapeutic window, the relevance remains to be individually determined. Dulaglutide delayed metoprolol tmax by 1 hour.

In general it was noted that an extended gastric residence time induced by dulaglutide may cause an increase in the release rate of a prolonged release formulation and thereby an increase in drug exposure. Albeit this depends on the type of extended release formulations there may be drugs with a smaller therapeutic window, where the effect may be relevant.

The ABPM data in this healthy subject population showed a significant increase from baseline in LS mean HR when dulaglutide was administered alone while administration of metoprolol alone lowered LS mean 24-hour HR from baseline by -7.74 bpm. An increase in HR was observed following co-administration of the two drugs, although to a lesser degree than following dulaglutide alone. Overall, no dose adjustments are proposed by the Applicant for either lisinopril or metoprolol when co-administered with dulaglutide. The PD data with metoprolol indicate that dulaglutide decreased the effect of metoprolol on diastolic blood pressure. The possible impact is not considered clinically relevant, since the increase in DBP was counterbalanced by a decrease in SBP leaving the mean BP largely unaffected.

Atorvastatin

Study H9X-MC-**GBCP** assessed the effect of dulaglutide (single 1.5 mg SC dose) on atorvastatin (single 40 mg dose) PK in healthy subjects. The absorption of atorvastatin was delayed when taken with dulaglutide with median tmax observed on average 2.5 hours later. The exposure of atorvastatin and o-hydroxyatorvastatin decreased, by up to 70% for Cmax and 21% for AUC(0-∞) respectively. Mean t1/2 of atorvastatin and o-hydroxyatorvastatin were 17% and 41% longer after dulaglutide administration respectively. The changes in atorvastatin PK and its active metabolite PK were not considered by the Applicant to be of clinical significance and no dose adjustment is recommended when given together with 1.5 mg dulaglutide.

Oral contraceptives

Study H9X-MC-**GBCQ** assessed the effect of dulaglutide (single 1.5 mg SC dose) on steady state PK of Ortho-Cyclen (OCY) a combination oral contraceptive (OC) of norgestimate (NGM) and ethinyl estradiol (EE) in 22 healthy female subjects. There was no significant effect of dulaglutide on the overall exposure (measured as AUC[0-τ] or AUC[0-∞]) to norelgestromin (NGMN), NGM's major metabolite, and EE with the 90% CIs of the ratio of geometric LS means falling within the 0.80 to 1.25 range for both. However, dulaglutide caused statistically significant reductions in the Cmax and increases in the tmax of both NGMN and EE. For NGMN an approximately 26% reduction in mean Cmax was observed, with the median tmax being increased by 2 hours. A smaller effect was observed for EE, with an approximately 13% reduction in mean Cmax and an increase in median tmax of 0.30 hours.

These observations were not considered clinically relevant considering the large inter-subject variability in the concentrations of OCs. Thus, based on PK, no dose adjustment for oral contraceptives is considered necessary when given together with 1.5 mg dulaglutide. The co-administration of dulaglutide and OCY was generally well tolerated; however, there was a higher incidence of vomiting and nausea following dulaglutide administration than for OCY alone.

Digoxin

Study H9X-MC-**GBCR** examined the effect of dulaglutide (single 1.5 mg SC dose) on digoxin PK at steady state in 24 healthy subjects (16 males and 8 females). PK parameters revealed no effect on digoxin steady-state AUCτ or tmax. Reductions of up to 22% and 17% in digoxin Cmax occurred following the first and second dulaglutide doses, respectively which was not considered clinically important. Dulaglutide was generally well tolerated. The AEs reported were mild in severity, and the most frequently observed were gastrooeosophageal reflux disease, nausea, first degree AV block, decreased appetite, and vomiting. Overall, dulaglutide administration did not affect digoxin PK in a clinically relevant way and no dose adjustment is considered necessary when given together. However, as with OCY, as mentioned above, serious GI adverse effects may affect digoxin absorption. Furthermore, there was a higher rate and number of patients with first degree heart block after co-administration of digoxin and dulaglutide. This is consistent with the finding of a PR prolongation in the thorough QT study GBCC (see below).

Warfarin

Study H9X-MC-**GBCS** examined the effect of dulaglutide (single 1.5 mg SC dose) on the PK of S- and R-warfarin (single warfarin 10 mg dose) in 28 healthy subjects (24 males and 4 females). Dulaglutide co-administration did not affect the AUC(0-∞) of S- and R-warfarin, or the Cmax for R-warfarin. The results for AUClast were consistent with the results for AUC(0-∞). However, an approximate 22% decrease in S-warfarin Cmax was observed. Dulaglutide also caused a significant increase in the tmax of S- and R-warfarin. The mean INR profiles for warfarin were similar whether warfarin was given alone, or in combination with dulaglutide. Dulaglutide treatment did cause a small increase in AUCINR (warfarin+dulaglutide vs warfarin: LS means 1.02, 90% CI [1.01 to 1.03]) that was not considered to be clinically relevant. Dulaglutide treatment had no significant effect on INRmax but there there was a delay in the time to INRmax of approximately 6 hours, consistent with the delays in tmax of approximately 4 and 6 hours for S- and R-warfarin respectively. The recalculation of the ratio of geometric LS means for INRAUC before and after co-administration of warfarin with dulaglutide by excluding the three subjects that were only available for the 10 mg warfarin treatment were consistent with a statistically significant, but clinically irrelevant increase in INR.

The most commonly reported treatment-related AEs overall were nausea, vomiting, and paraesthesia, with other less frequently reported AEs including decreased appetite, diarrhoea, headache and somnolence with higher incidence following dulaglutide administration. It was concluded that based on the overall PK, PD, safety,

and tolerability data in healthy subjects, dose adjustment for warfarin when given with dulaglutide is not necessary.

Sitagliptin

Study H9X-MC-**GBDW** assessed the effect of 1.5 mg dulaglutide on the PK of sitagliptin (100 mg sitagliptin for 18 days) and also the effect of sitagliptin on dulaglutide PK in 29 patients with T2DM (19 males and 10 females). Sitagliptin AUC(0-τ) was not affected after co-administration of a single dulaglutide dose. Sitagliptin AUC(0-τ) and Cmax decreased by approximately 7.4% and 23.1%, respectively, following co-administration of sitagliptin with 2 doses of dulaglutide compared to sitagliptin alone. There was a median increase of approximately 0.5 hours in sitagliptin tmax following co-administration with the first or second dose of dulaglutide compared to sitagliptin alone. These changes are not expected to be clinically significant.

Sitagliptin 100 mg at steady state increased dulaglutide exposure (AUC) approximately 38%, Cmax by approximately 27%, and median tmax by approximately 24 hours. These changes along with the observed delay in tmax with sitagliptin likely reflect the inhibition of DPP-4 activity by sitagliptin resulting in decreased dulaglutide hydrolysis. Generally, co-administration of the two drugs was well tolerated and there were no significant safety concerns. It was concluded that weekly injections of dulaglutide may be co-administered with sitagliptin without need for dose adjustment. Overall, the moderate PK interaction and the provided indirect external evidence do not support a dose reduction of dulaglutide or sitagliptin, when administered concomitantly. However, the SmPC (section 4.5) includes information about a potentially additive effect and that the increased exposure with sitagliptin may enhance the effects of dulaglutide on blood glucose levels.

Metformin

The placebo-controlled, multiple dose Study H9X-EW-**GBDM** evaluated the effect of dulaglutide on metformin PK at steady state as well as the effect of dulaglutide on gastric emptying using scintigraphy (see *Primary pharmacology* below) in 38 patients with T2DM (31 males and 7 females). Metformin exposure (AUCτ) appeared to be higher by approximately 15% following administration of dulaglutide but no statistically significant changes in metformin AUCτ or tmax compared to placebo occurred at any study time point. The changes were well within the observed PK variability of metformin (approximately 50%), similar to those seen after placebo, and therefore not considered to be clinically relevant. Dulaglutide did not affect metformin tmax. Only 1 patient taking extended release metformin was eligible for inclusion in the PK population; therefore, insufficient data were available to draw conclusions about the extended release formulation.

Multiple subcutaneous doses of 1.5 mg dulaglutide were moderately well-tolerated. A total of 156 AEs considered related to investigational product (dulaglutide or placebo) were reported by 22 (58%) patients during the study and all of these were resolved by the end of the study. The majority of these (136) were mild in severity and 4 events were severe. More than half of the related AEs were classified as GI disorders. Overall, it was concluded that weekly injections of dulaglutide may be co-administered with metformin without need for metformin dose adjustment.

The safety analysis addressing the co-administration of metformin and dulaglutide in phase 3 is reassuring (see Safety section below). Overall the rate of AEs was higher in study GBCF than in GBDC. Irrespectively of known cross-study variability related to design, treatment duration and patient characteristics this may reflect in part the accumulation of the AEs of both drugs. Of note, in the cross-study comparison the rate of hypoglycaemia was similar between dulaglutide 1.5 mg + metformin (12.8%, GBCF) and metformin alone (12.7%, GBDC) and in the PK/PD analysis metformin was not identified as a significant covariate for safety and efficacy. Therefore, overall no significant safety concerns were identified related to the co-administration in clinical studies.

2.4.3. Pharmacodynamics

Mechanism of action

Dulaglutide activates the GLP-1 receptor which is widely expressed in the pancreas and has been shown to be a valid therapeutic target in type 2 diabetes mellitus. The physiological GLP-1 receptor agonist, GLP-1, is a hormone (incretin) which is secreted from the L-cells of the gastrointestinal tract following ingestion of a meal. A number of studies have demonstrated the key pharmacodynamic effects of GLP-1 and its analogs indicating a significant role on the metabolism of nutrients, increase of intracellular cyclic adenosine monophosphate (AMP) in pancreatic beta cells leading to insulin release in the presence of high glucose levels, suppression of glucagon secretion, delaying of gastric emptying, and reducing body weight.

Primary and Secondary pharmacology

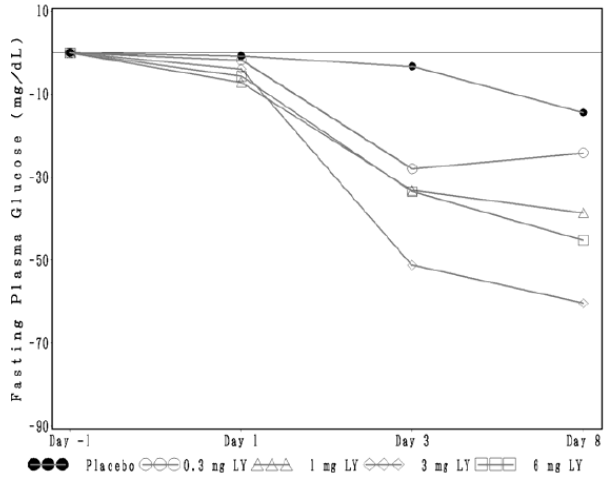
Primary pharmacology

Fasting and Postprandial Glucose

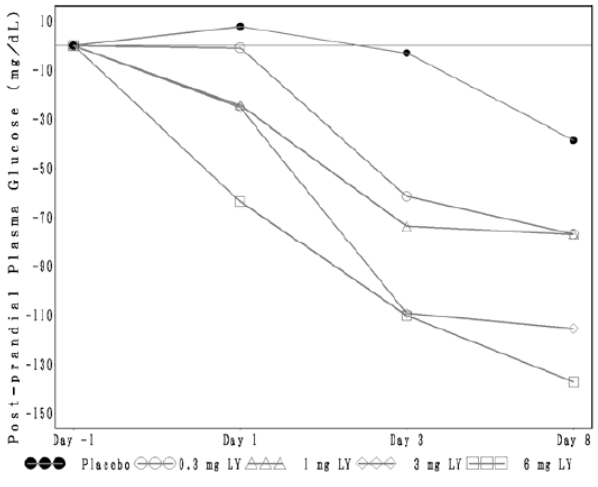
Dulaglutide improves glycaemic control by lowering fasting and postprandial glucose concentrations. In initial clinical pharmacology studies in patients with T2DM, statistically significant and clinically relevant reductions in fasting and postprandial glucose (LS mean differences of up to -38 mg/dL and -95 mg/dL, respectively) compared to placebo were observed for 7 days after single 1 to 6 mg dulaglutide doses (Study H9X-JE-**GBCB** in Japanese patients; Figures 5 a and b).

Figures 5 a and b. Mean changes in fasting plasma glucose (a) and post-prandial plasma glucose (b) from baseline; Study H9X-JE-GBCB

(a) Fasting blood glucose



(b) Post prandial plasma glucose



Similar effects were also seen in the multiple dose study H9X-MC-**GBCD** in patients with T2DM (see *Absorption* above) after once weekly dosing of 0.05 to 8 mg for 5 weeks. Glycaemic reductions (fasting and postprandial) were apparent from Day 3 (approximately 48 hours after the first dose) and were either sustained or showed further reduction for the duration of the study. After 5 weeks statistically significant and clinically meaningful

reductions compared to placebo occurred in fasting glucose with doses above 1mg (up to -74 mg/dL), PPG (up to -108 mg/dL), and gAUC (up to -411 mg·h/dL) (Table 8).

Table 8 Fasting and Postprandial and AUC of Glucose Relative to Placebo After 5 Weeks of Dulaglutide (LY2189265) Dosing; Study H9X-MC-GBCD

Fasting Plasma Glucose			Comparison to Placebo		
Treatment	n	Week 5	Diff.	90% C.I.	P-value
Placebo	22	169.57			
0.05 mg LY	4	140.38	-29.19	(-53.19, -5.20)	0.05
0.3 mg LY	12	154.02	-15.55	(-32.86, 1.75)	0.14
1 mg LY	10	125.10	-44.47	(-62.52, -26.43)	<.01
3 mg LY	4	115.67	-53.90	(-78.15, -29.65)	<.01
5 mg LY	16	123.56	-46.01	(-61.45, -30.57)	<.01
8 mg LY	8	95.64	-73.93	(-92.33, -55.54)	<.01
Postprandial Glucose at 2h			Comparison to Placebo		
Treatment	n	Week 5	Diff.	90% C.I.	P-value
Placebo	22	245.59			
0.05 mg LY	4	198.90	-46.68	(-90.24, -3.13)	0.08
0.3 mg LY	12	225.67	-19.91	(-50.58, 10.76)	0.28
1 mg LY	10	152.76	-92.83	(-124.7, -60.94)	<.01
3 mg LY	4	163.65	-81.94	(-126.1, -37.75)	<.01
5 mg LY	16	173.54	-72.05	(-99.94, -44.16)	<.01
8 mg LY	8	138.04	-107.5	(-140.5, -74.59)	<.01
Glucose AUC			Comparison to Placebo		
Treatment	n	Week 5	Diff.	90% C.I.	P-value
Placebo	22	880.45			
0.05 mg LY	4	729.89	-150.56	(-282.38, -18.74)	0.06
0.3 mg LY	12	782.46	-97.99	(-190.74, -5.24)	0.08
1 mg LY	10	575.04	-305.42	(-401.84, -208.99)	<.01
3 mg LY	4	594.14	-286.32	(-420.39, -152.24)	<.01
5 mg LY	16	612.39	-268.07	(-352.59, -183.54)	<.01
8 mg LY	8	469.05	-411.40	(-511.23, -311.58)	<.01
Model: Value = Baseline + Day + Dose + Day*Dose + (Subject) + (error)					

In Study H9X-MC-**GBCT** elderly patients with T2DM who received once weekly 1.5 mg doses for 6 weeks had fasting glucose concentrations, 2-hour PPG concentrations, and post-prandial serum gAUC significantly reduced compared to placebo (-25.6 mg/dL, -59.5 mg/dL, and -197 mg.h/dL, respectively). These effects were sustained throughout the entire 6-week period. Similarly, in patients with T2DM who received once weekly doses of 1.5 mg doses for 4 weeks (Study H9X-EW-**GBDM**), general glucose reductions were sustained throughout the 4- week period.

HbA1c

Decreases in HbA1c were observed in patients with T2DM in 3 multiple dose clinical pharmacology studies. Significant reductions in HbA1c of up to -1.38% (mean baseline HbA1c 5.6% to 10.2%) were seen after once weekly dulaglutide dosing for 5 weeks compared to placebo in Study H9X-MC-**GBCD** (0.05, 1, 3, 5, and 8 mg doses; see above) and Study H9X-JE-**GBCL** in Japanese patients (1.0, 1.5 mg doses). Similarly, significant reductions in HbA1c of up to -0.55% (mean baseline HbA1c 6.7% to 7.3%) compared to placebo were observed after once weekly 0.5, 0.75 and 1.5 mg dulaglutide dosing for 6 weeks in elderly patients in Study H9X-MC-**GBCT** (Table 9).

Table 9 Summary of the HbA1c (%) Following Subcutaneous Administration of Dulaglutide (LY2189265) or Placebo as Once-weekly Doses for 6 weeks; Study H9X-MC-GBCT

Treatment		**Arithmetic Mean (SD)**	

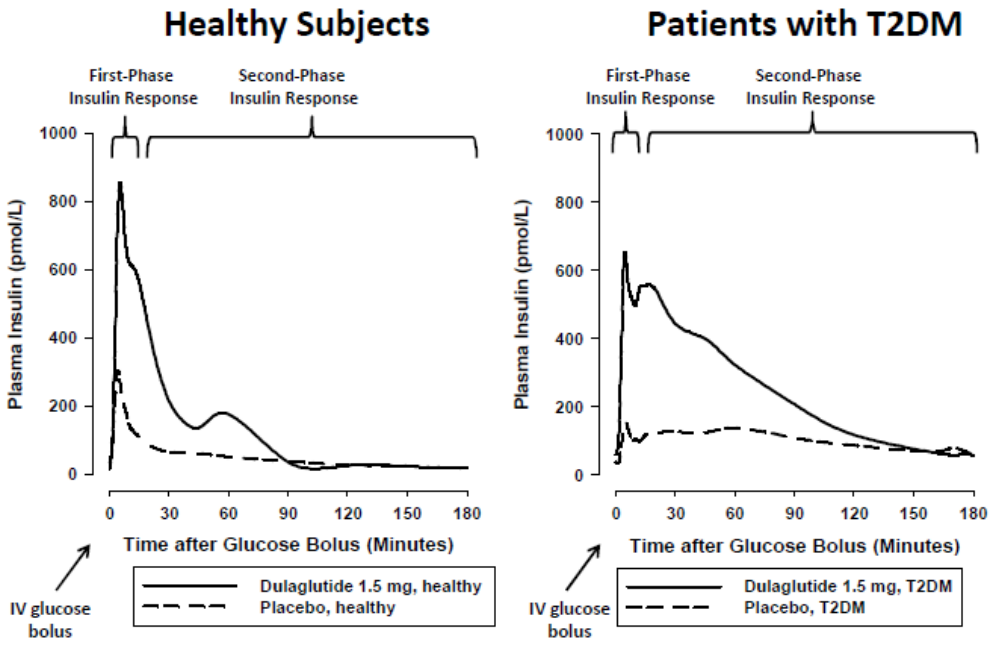
	Day -1	Day 36	Change from Baseline[a]
Placebo (N=8)	6.73 (0.43)	6.68 (0.38)	-0.05 (0.32)
0.5 mg dulaglutide (N=9)	7.26 (0.84)	6.64 (0.60)	-0.61 (0.31)
0.75 mg dulaglutide (N=11)	6.92 (0.40)	6.44 (0.47)	-0.48 (0.24)
1.5 mg dulaglutide (N=9)	6.83 (0.52)	6.14b (0.47)	-0.60b (0.37)
a Baseline is defined as Day -1; b N=8			

Insulin Secretion

Study H9X-MC-**GBCI** assessed the effect of dulaglutide on first and second phase insulin secretion in response to an IV glucose challenge, as well as the effect of dulaglutide on β-cell function in 22 patients with T2DM (15 males and 7 females) and 10 healthy controls (7 males and 3 females).

In both healthy subjects and subjects with T2DM, mean first- and second-phase insulin and C-peptide secretion in response to a 50% dextrose bolus appeared to be enhanced following SC administration of 1.5 mg dulaglutide, as compared with placebo. Also mean glucose levels following the dextrose bolus appeared to return to baseline more rapidly following administration of dulaglutide, as compared with placebo, in both groups.

Figure 6 Mean plasma insulin concentrations after dulaglutide or placebo administration to healthy subjects (left panel) and patients with type 2 diabetes; Study H9X-MC-GBCI



Patients received an IV infusion of insulin for 6 h, (discontinued 30 min before the glucose bolus), to normalize plasma glucose levels prior to an IV glucose bolus (0.3 g/Kg/2 min) at t=0 min.

Mean Homeostasis Model Assessment–β-Cell Function (HOMA-B) measured at baseline showed a trend towards being higher in healthy subjects than in T2DM patients. In the T2DM group, HOMA-B (ratio to Day 1; measured pre insulin infusion on Day 3) was statistically significantly different between treatments, with higher values

observed following administration of 1.5 mg dulaglutide compared to placebo. In healthy subjects, HOMA-B was not significantly different between treatments. HOMA-B was also not significantly different between subjects with T2DM and healthy subjects following administration of dulaglutide or placebo.

In the multiple-dose study H9X-MC-**GBCT** in elderly T2DM patients, testing 3 dose levels of dulaglutide (0.5, 0.75, or 1.5 mg) on Days 3 and 38, plasma insulin AUC, fasting concentrations, and 2 hour post-breakfast concentrations were higher than placebo following all dose levels of dulaglutide although there was no clear dose-related effect on plasma insulin concentrations on either day. On both Days 3 and 38, serum C-peptide AUC, fasting concentrations, and 2 hour post-breakfast concentrations were higher than placebo following all dulaglutide dose levels. Marked increases from baseline in mean plasma insulin levels of up to 60.63 pmol/L were also observed after once weekly 1.5 mg doses in patients with T2DM in Study H9X-EW-**GBDM**.

Glucagon Secretion

Dulaglutide can lower blood glucose by stimulating insulin secretion but also by decreasing glucagon secretion. In the Phase 3 Study H9X-MC-**GBDC** (see *Efficacy section* below), LS mean decreases from baseline in fasting glucagon of -2.05 pmol/L were observed at the 26-week time point after once weekly dulaglutide 1.5 mg dosing. In addition, decreases in postprandial glucagon AUC (0-3 hours post-meal) were observed following a standardized test meal in this study. After 26 and 52 weeks of treatment with dulaglutide 1.5 mg, LS mean decreases in Glucagon AUC from baseline were -5.91 pmol.h/L and - 8.04 pmol.h/L, respectively.

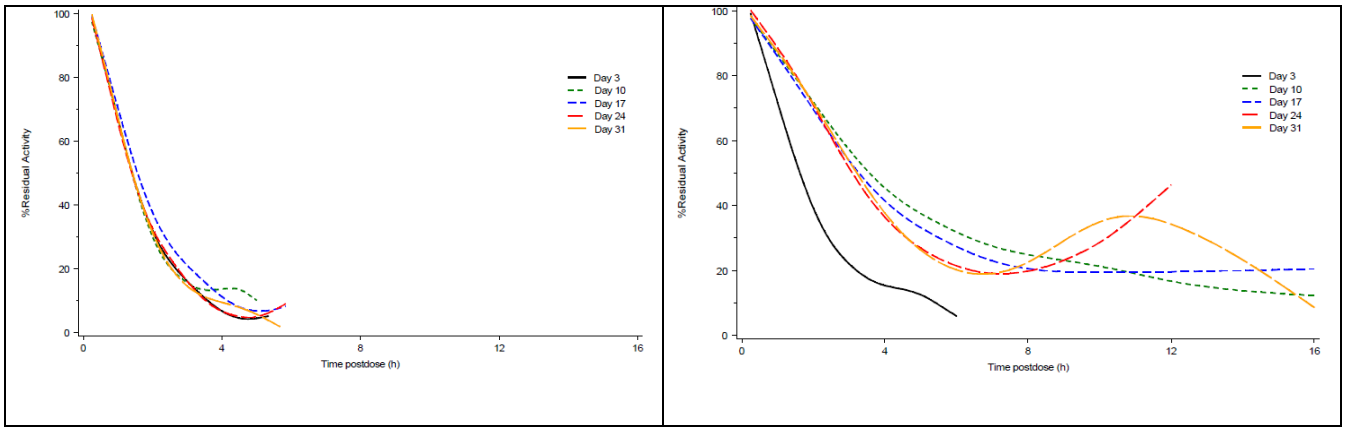
Gastric Emptying

Delaying gastric emptying is a known effect of this class and suggested as one of the factors contributing to glucose lowering but also to weight loss. The effect on gastric emptying of dulaglutide was examined in 3 clinical pharmacology studies (Studies H9X-MC-**GBCH**, H9X-MC-**GBCD**, and H9X-EW-**GBDM**). In Study H9X-MC-GBCH, as described in the *Interactions* section above, at steady state 1 and 3 mg dulaglutide had no clinically significant effect on the rate or extent of gastric emptying based on acetaminophen PK; however, the rate of gastric emptying was slower following the first dose of 1 and 3 mg dulaglutide, with reduced acetaminophen Cmax by 36% and 50%, respectively, and significantly delayed acetaminophen tmax by 3 and 4 hours, respectively. In Study H9X-MC-GBCD that also tested the effect of a range of dulaglutide doses 0.05 to 8 mg on gastric emptying oral acetaminophen in T2DM patients the changes to acetaminophen exposures in the absence and presence of dulaglutide suggested that gastric emptying was delayed by dulaglutide by up to 2.3 hours in average with the highest (8mg) dose.

Study H9X-EW-GBDM evaluated the effect of dulaglutide (1.5 mg SC for 4 weeks) on gastric emptying using scintigraphy. Repeat scintigraphy (following a radiolabeled breakfast) at the time of the expected dulaglutide tmax showed, statistically significant delays in gastric emptying rate following each of four 1.5 mg dulaglutide doses compared to baseline. The greatest delay was observed after the first dose, with a mean increase in the primary endpoint of time required for 50% of activity to empty from the stomach (t50) of approximately 2 hours from Day 3 to Day 10. The t50 values showed a trend to decrease from the second dose onwards, with mean t50 values following 2, 3, and 4 doses of 1.5 mg dulaglutide (Days 17, 24, and 31) being 88%, 87%, and 84%, respectively, of that after the first dose (Day 10).

Figure 7 Arithmetic mean % residual activity data by day [Placebo (1); dulaglutide (2)]; Study H9X-EW-GBDM

(1) Fasting blood glucose	(2) Post prandial plasma glucose



In addition to the above a visual analog scale (VAS) comprising 4 questions completed by patients every hour for 12 hours following each radiolabeled meal to assess satiety showed a good correlation with the scintigraphy data. Patients who received dulaglutide reported a statistically significant decrease in hunger on all days with dulaglutide compared to baseline, which was not observed in the placebo group.

Body Weight

Changes in body weight after administration of multiple doses of dulaglutide to patients with T2DM were evaluated as a secondary efficacy measure in 4 clinical pharmacology studies. In the first study, significant reductions of up to about 3 kg were noted after 5 weeks of once weekly 5 and 8 mg dulaglutide dosing compared to placebo in diabetic patients (H9X-MC-**GBCD**). In the second study (H9X-JE-**GBCL**; Japanese patients), body weight tended to be lower after 5 weeks of once weekly 1.0 and 1.5 mg dulaglutide dosing but no statistically significant differences were observed relative to placebo. In the third study H9X-MC-**GBCT** in elderly patients, a decrease from baseline of up to 3 kg in body weight occurred at all dulaglutide dose levels after once weekly 0.5, 1.0, and 1.5 mg dosing for 6 weeks, although the change was not statistically significantly different from placebo. The fourth study (H9X-EW-**GBDM**) showed no clinically significant changes in body weight for individual patients during 5 weeks of treatment with dulaglutide (despite some effects on satiety, as described above). The effects of dulaglutide on body weight are further considered in the *Efficacy section*.

Secondary pharmacology

QT interval

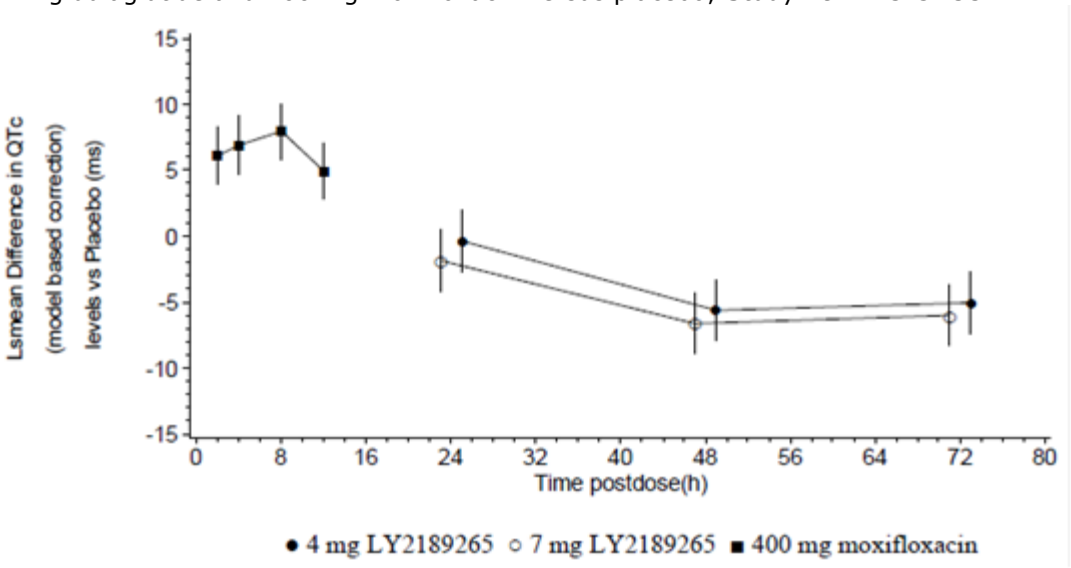
H9X-MC-**GBCC** was a thorough QT study in 147 healthy subjects (83 males and 64 females) to determine the effect of dulaglutide, at a supratherapeutic dose, on QT. Subjects were randomly assigned to 1 of 6 crossover treatment sequences and received single doses of SC dulaglutide, 400 mg moxifloxacin, and placebo on 3 separate occasions. The initial planned dose of dulaglutide was 7mg. However, this dose was poorly tolerated (high incidence of nausea, and 1 subject diagnosed with pancreatitis). Therefore, after 54 subjects had received the 7mg dose for the rest of the study the dose was reduced to 4mg which was also not well tolerated with a high incidence of nausea and vomiting and 3 subjects presenting with pancreatitis; therefore, dosing was temporarily suspended and the study was formally discontinued after 55 subjects had received the 4 mg dose. At the time that dosing was suspended, 147 healthy subjects had completed at least 1 of the dosing periods, 54 of whom received 7 mg dulaglutide, and 55 subjects of whom received 4 mg dulaglutide. Eighty subjects received all 3 treatments and completed the study.

To establish assay sensitivity for the study, moxifloxacin's effect on QTc interval was compared to that of placebo using data from subjects who received the 4 mg dulaglutide dose level. However, based on the lower limit of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo, was <5 msec at 2 and 4

hours postdose (time of highest moxifloxacin concentration) for each QT correction and therefore, assay sensitivity could not be established, according to the criteria outlined in the Statistical Analysis Plan (SAP). However, assay sensitivity could be established if data from subjects scheduled to receive 4 or 7 mg dulaglutide were included.

For the primary QT correction method, model based QTc interval, the upper limit of the 2-sided 90% CI for the mean difference between 4mg dulaglutide and placebo ranged from -0.7 to -6.2 ms. Similarly, for all other QT correction methods, QTcF, QTcI, and QTcP, the upper limit of the 2-sided 90% CI for the mean difference between 4 mg dulaglutide and placebo was below 10 ms (range: -0.9 to -8.4 ms). No individual subject had an absolute QTc interval >480 ms or a time-matched increase of >30 ms from baseline in QTc following single doses of 4 and 7 mg dulaglutide. No positive correlation was detected between placebo-corrected changes from baseline in QTc interval and dulaglutide plasma concentrations.

Figure 8 LS mean (90% CI) difference in change from baseline in QTc interval following administration of 4 and 7 mg dulaglutide and 400 mg moxifloxacin versus placebo; Study H9X-MC-GBCC



Statistically significant increases in mean PR interval from baseline were observed following both 4 mg and 7 mg dulaglutide administration compared to placebo. The mean QRS interval following dulaglutide administration (both 4 mg and 7 mg) tended to be shorter than following moxifloxacin or placebo.

In general, GBCC was a large study by the number of subjects included (n=147) with limited success. While the study overall did not find any evidence of QT prolongation there are a number of limitations including the intolerance seen with the higher doses that led to a large number of withdrawals (n=67) nearly 45% of the total subjects and the small effect noted with the moxifloxacin 400mg on QT and QTc. The effect size here was smaller than anticipated and smaller than the majority of other thorough QT studies; therefore, the study failed to provide adequate evidence of assay sensitivity. There could be several reasons for this, including study conduct and the population included but it is unclear if a specific reason could be ascribed.

Notwithstanding the above, the study did not show any evidence of prolongation of QT interval with dulaglutide. The correction formulae and model parameters appear adequate and appropriate. There is a consistency of effect (or lack of effect i.e., prolongation) across different correction methods and these have been described adequately. The interesting aspect of the study is the number of effects on different parameters of cardiac conduction that are noted in the study. There is the small change in heart rate (increase in HR) and a consistent

effect of shortening of QT, the magnitude varying with the correction method. Moreover, there is persistent PR prolongation of notable magnitude. While the increase in HR might be a potential mechanism for an apparent shortening of QT, the persistence after correction with different formulae remains unexplained and one wonders if there is an alternative mechanism for this observation. As Dulaglutide is a protein molecule, hERG related effect (see also Non-Clinical report) is unlikely and effect on other ion channels would need to be explored although the probability of such an ion channel mediated effect is fairly small. No other ion channels were studied during the development program.

Overall, the thorough QT study has a number of limitations and there is a slight increase in heart rate and effects on conduction system and cardiac repolarisation, including persistent PR prolongation and QT shortening. These are inconsistent for any one mechanism especially hERG mediated. Generally, the effects of dulaglutide on cardiac repolarisation and conduction system remain uncertain. However, the relevant findings from the clinical studies appear to be generally consistent with the rest of the class and the overall data so far do not raise any major safety concerns (see *Safety* section). Nevertheless, this is an issue that will need to remain under monitoring.

Heart rate and blood pressure

Study H9X-MC-**GBDN** was a multicenter, randomized, double-blind, parallel-arm, 26-week treatment, placebo-controlled study that evaluated the effects of 1.5- and 0.75-mg doses of dulaglutide on blood pressure (BP) and heart rate (HR), using ambulatory blood pressure monitoring (ABPM), in patients with T2DM receiving oral antihyperglycaemic medications (OAMs). The study included a 2-week screening and lead-in period, followed by a 26-week treatment period, and a 4-week safety follow-up period. 755 patients were randomized; 630 patients completed the treatment period (placebo: 206; dulaglutide 1.5 mg: 199; dulaglutide 0.75 mg: 225). A circadian rhythm model was developed for each ABPM variable (systolic BP, diastolic BP, and HR) using data from the placebo treated arm of the study.

Both doses of dulaglutide were found noninferior to placebo for mean 24-hour SBP at 16 weeks, using a noninferiority margin of 3 mmHg. The dulaglutide 1.5 mg dose was shown to significantly reduce mean 24-hour SBP compared to placebo at 16 weeks (-2.8 mmHg; p<.001) and at 26 weeks (-2.7 mmHg; p=.002). Both doses of dulaglutide were shown to be noninferior to placebo for mean 24-hour DBP at 16 and 26 weeks, using a noninferiority margin of 2.5 mmHg. Dulaglutide 0.75 mg was shown to be noninferior to placebo for mean 24-hour HR at 16 and 26 weeks, using a noninferiority margin of 3 bpm. Dulaglutide 1.5 mg compared with placebo did not satisfy the noninferiority criteria, and small increases in HR were observed at 16 weeks (2.84 bpm) and at 26 weeks (3.50 bpm).

None of the demographic factors tested: age, body weight, BMI, sex, ethnic origin, smoking status, hypertensive status, baseline ABPM value, anti-hypertensive medication use (ACE inhibitor, angiotensin receptor blocker, beta blocker, calcium channel blocker, or diuretic), and geographic region, were found to influence the relationship between dulaglutide concentration and ambulatory systolic BP response. No relationship was found between dulaglutide concentration and ambulatory diastolic BP. Ambulatory systolic BP was found to decrease with increasing dulaglutide concentration. These issues are further discussed in the *Safety section.*

Immunogenicity

All clinical pharmacology study subjects were tested for the presence and titer of anti-drug antibodies (ADA) for dulaglutide. Serum samples were collected prior to the first dulaglutide or placebo dose and at least 3 weeks after the last dose. The incidence of subjects with positive ADA for all clinical pharmacology studies was very low. The few subjects found with positive ADA titers had also positive titers prior to receiving dulaglutide as well

as at follow-up and, therefore, were not considered related to dulaglutide. No subject in the clinical pharmacology studies developed treatment emergent dulaglutide ADA, defined as a 4-fold increase compared with baseline.

In the population analyses performed using the Phase 2 and Phase 3 data, dulaglutide concentrations associated with positive antibody titers (defined as any titer with a positive result) were analyzed for patients in the 1.5 mg and 0.75 mg treatment arms. The percentage of concentrations with positive titers in both the Phase 2 and Phase 3 analyses relative to the overall concentration dataset was small (<4% in all cases). Overall, no association was found between dulaglutide concentrations and positive antibody titers.

Table 10 Percent of Dulaglutide Concentrations with Positive ADA Titers by Database and by Dose

Database	Dulaglutide Doses	% of concentration samples with positive ADA titers
Phase 2	0.75 mg	1.8
	1.5 mg	3.8
Phase 3	0.75 mg	2.6
	1.5 mg	2.5

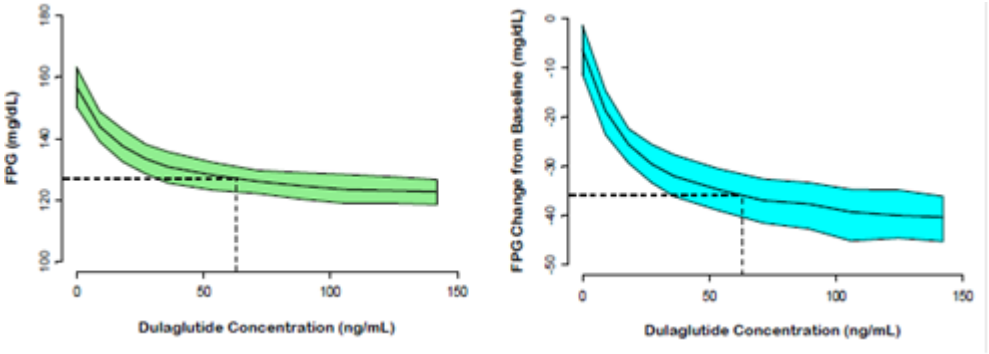
Relationship between plasma concentration and effect

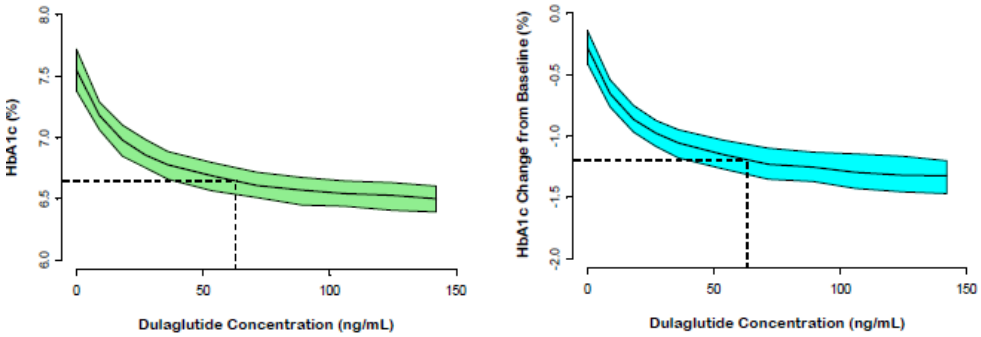
Fasting Plasma Glucose and HbA1c

A concentration-response model was developed to fit FPG and HbA1c data. The time course of FPG response over the course of two years was described using a disease progression model. The model estimated that dulaglutide may normalize HbA1c to goal, to a minimum value of approximately 6%. The concentration to achieve 50% of maximum HbA1c reduction (EC_{50}) was 22.0 ng/mL, with an inter-subject variability of 25.1% (%CV). The model described the observed data well. For both tested dose levels 0.75mg and 1.5mg, the time course of the response to dulaglutide for HbA1c and FPG showed that the decrease from baseline in both measures was sustained throughout the 104-week endpoint. Model-estimated reductions from baseline in FPG and HbA1c for the 1.5 mg dose of dulaglutide at 26, 52 and 104 weeks for the Phase 3 data were -2.2 mM (-40 mg/dL) and -1.2%, -1.9 mM (-35 mg/dL) and -1.1%, and -1.3 mM (-23 mg/dL) and -0.77%, respectively.

Exposure-response and dose-response relationships of both Phase 2 and Phase 3 data were consistent in demonstrating a decrease for both FPG and HbA1c with increasing dulaglutide concentrations and doses at both the 52-week (Figure 9) and 104-week endpoints. The dose-response relationship showed good agreement between the Phase 2 model prediction and the Phase 3 observed data, with an 18% and 31% greater glycaemic effect for the 1.5 mg dose relative to the 0.75 mg dose at the 52- and 104-week endpoints respectively.

Figure 9 Exposure-response relationships for fasting plasma glucose (top) and HbA1c (bottom) at 52 weeks; for absolute values (left) and change from baseline (right).





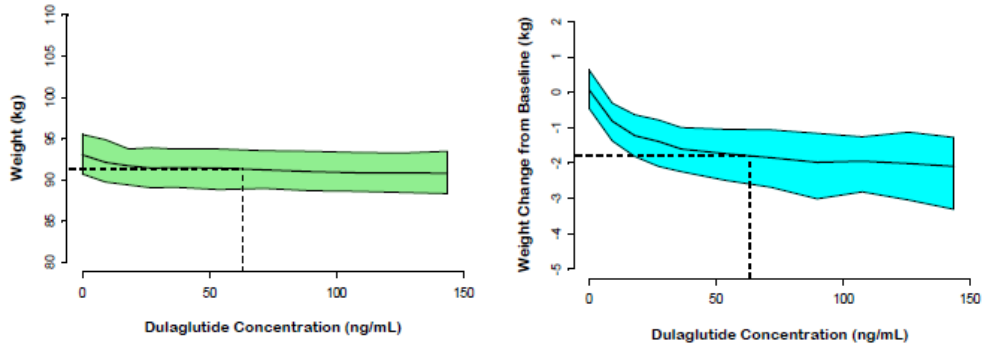
Solid lines represent the median model-estimated response for the Phase 2 population; colored polygons represent the 90% CI for the median, dashed lines represent the observed median concentration and magnitude of the effect for the 1.5 mg Phase 3 population. Baseline assumptions were 8.0 % for HbA1c and 93 kg for body weight.
Source: Phase 2 and Phase 3 poPK/PD analyses

Study- or patient-specific factors were evaluated for significance on parameters related to drug response due to their clinical relevance in patients with diabetes. Of all the covariates tested, those that influenced the effect of dulaglutide on glycaemic control were co-administration of TZDs and baseline FPG. Patients taking TZDs had a larger change at 12 months compared to the rest for both FPG and HbA1c.

Body Weight

The observed effect of dulaglutide on body weight was well described using an indirect response model. The phase exposure-response relationship demonstrated a decrease in body weight with increasing dulaglutide concentration with estimated changes from baseline in body weight at 52 weeks of -1.7 kg for the 1.5 mg dose of dulaglutide and -1.4 kg for the 0.75 mg dose. The dose-response relationship estimated a slightly greater weight loss for the 1.5 mg dose relative to the 0.75 mg dose and a good agreement between the Phase 3 and Phase 2 data for the 1.5 mg dose, while the magnitude of the 0.75 mg dose effect was lower for Phase 3 compared to the Phase 2 model.

Figure 10 Exposure-response relationships for absolute weight (left) and change from baseline on weight (right).

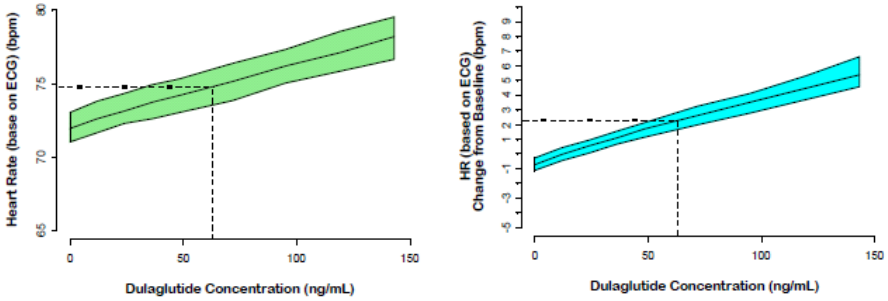


Solid lines represent the median model-estimated response for the Phase 2 population, colored polygons represent the 90%CI for the median, dashed lines represent the observed median concentration and effect size for the 1.5 mg Phase 3 population. Baseline assumption was 93 kg for body weight.
Source: Phase 2 and Phase 3 pop PK/PD analysis

Heart rate

Dose- and concentration-dependent increases in HR were reported following dulaglutide administration in healthy subjects and patients with T2DM. A model with data from Phase 3 trials and based on the findings of study H9X-MC-**GBDN** (see above) showed a small increase in the HR response with increasing dulaglutide concentrations at both the 52- and 104-week time points. Model-estimated increases in HR from the 72 bpm baseline for the 1.5 mg and 0.75 mg doses of dulaglutide were 2.6 bpm and 1.1 bpm, respectively, at the primary time point of 52 weeks. None of the examined covariates like age, baseline body weight, BMI, sex, HR baseline, use of concomitant medications race and ethnicity, alcohol intake, and smoking status influenced the HR response to dulaglutide in the final model.

Figure 11 Exposure-response relationships for absolute heart rate (left) and change from baseline on heart rate (right).



Solid lines represent the median model-estimated response for the Phase 2 population; colored polygons represent the 90%CI for the median, dashed lines represent the observed median concentration and effect size for the 1.5 mg Phase 3 population.
Source: Phase 2 and Phase 3 popPK/PD analyses

Blood Pressure

Increases in BP were reported following dulaglutide administration in patients with T2DM in Phase 1 studies but the results were inconsistent in later, as mentioned above, Phase 2 ABPM study H9X-MC-**GBDN** was conducted in order to fully characterize the effect of dulaglutide on BP and HR.

The Phase 2 exposure-response analyses, which included a wider range of doses, found small decreases in diastolic BP (-1.4 mmHg), and an effect of age on the systolic BP response to dulaglutide, with decreases of -7.7 mmHg and -4.8 mm Hg for 25 and 85 year old patients, respectively. The results from the Phase 2 exposure-response analysis were similar to the results from Study H9X-MC-GBDN, where 1.5 mg dulaglutide dosing demonstrated a statistically significant -2.8 mm Hg reduction in mean 24 hour systolic BP, and a neutral effect on mean 24 hour diastolic BP. No correlation between blood pressure and concentration was apparent; thus, PK/PD models were not developed for the BP measurements.

Amylase and Lipase

To assess any potential effects of dulaglutide on pancreas, amylase (pancreatic and total) and lipase values were monitored as potential biomarkers for pancreatitis. For pancreatic amylase, a small positive slope was observed for the absolute values; however, at the observed median dulaglutide concentration for the Phase 3 population at the 1.5 mg dose, the pancreatic amylase level was approximately 35 U/L, within the normal range of 13-53 U/L. No significant correlation was observed for change from baseline pancreatic amylase. Total amylase, comprised of amylase from different sources and therefore a less predictive biomarker for pancreatitis, showed a positive correlation in the overall concentration range studied. However, at the observed median dulaglutide concentration for the Phase 3 population at the 1.5 mg dose, the total amylase level was approximately 70 U/L, within the normal range of 20 to 112 U/L.

Consistent with the pancreatic amylase results, no significant correlation was observed for change of baseline total amylase. For lipase, no significant correlation with dulaglutide concentration for both absolute values and change from baseline was observed. In summary, the small changes in these measures at therapeutic dulaglutide doses remained largely in the normal range. For all of these parameters, no clear relationship between outliers and dulaglutide concentrations was detected, with outliers observed throughout the whole exposure range.

Calcitonin

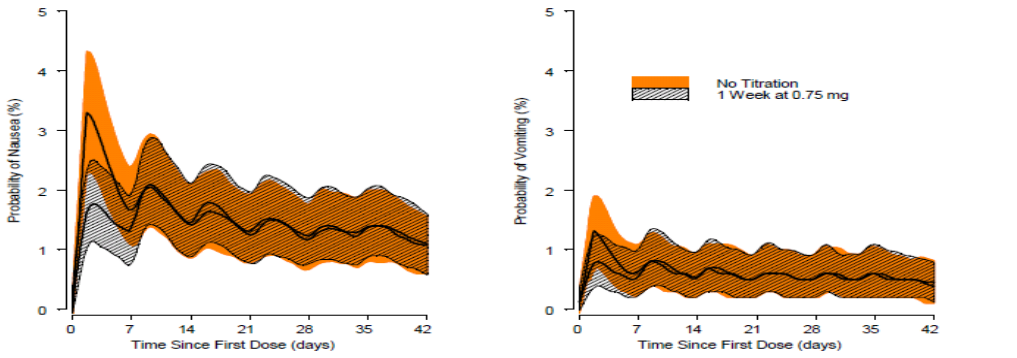
Serum calcitonin was measured in Phase 2 and 3 studies as a biomarker for thyroid C-cell abnormalities. For calcitonin, no significant correlation between dulaglutide concentrations and either absolute values or change from baseline was found.

Nausea and Vomiting

Gastrointestinal events are the most common TEAEs associated with dulaglutide with nausea and to a lesser extent vomiting amongst the most frequently reported. Combined safety data from clinical pharmacology studies indicated that nausea was reported during the first 2 to 3 days after the first dose and the incidence declined with subsequent doses. Exposure-response models for nausea and vomiting were developed to evaluate the effect of dose titration on incidence of these events using data from 4 clinical pharmacology studies in healthy subjects and patients with T2DM (Studies **GBCA**, **GBCB**, **GBCD**, and **GBCT**). These studies included PK and PD data in the 0.05 mg to 12 mg dose range. The model showed that higher dulaglutide concentrations were associated with increased probability of nausea and of moderate/severe nausea. Tolerance occurred with sustained exposure to dulaglutide. The probability of vomiting also increased with higher dulaglutide concentrations. As with nausea, tolerance occurred with sustained exposure.

The exposure-response relationships confirmed previous observations that nausea and vomiting are related to dulaglutide concentrations, with the highest incidence occurring at the time of dulaglutide Cmax (48 hours). There was a slightly higher probability of a patient experiencing nausea and vomiting for the 1.5 mg dose compared to the 0.75 mg dose (Figure 12). However, for both doses, the probabilities were very low. Even after a single dose, where the maximum effect was observed, the maximum median probabilities were <4% for nausea and <2% for vomiting per hour for both doses. At steady state, the median probability of nausea and vomiting was even lower per hour, <2% and <1% respectively.

Figure 12 Probability of nausea (left) and vomiting (right) over time for 1.5 mg dulaglutide with no titration and after titrating with 0.75 mg for 1 week



Solid lines represent median estimated probabilities, shaded or colored areas are 95% confidence intervals. Probabilities represent the likelihood of a patient experiencing an event at an hourly interval.

Further exposure-response analyses were conducted to determine if patients would benefit by using dose titration. There was no significant improvement in the model-estimated overall incidence of nausea and vomiting with different titration regimens that started with 0.75 mg doses for 1, 2, 3 or 4 weeks before dosing with 1.5 mg dulaglutide. Administration of dulaglutide 1.5 mg without titration resulted in an increased incidence of nausea (11%) and vomiting (7%) per week after the first dose only but tolerance developed that led to a marked decrease in the incidence of nausea and vomiting after the 2nd dose.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The Applicant has provided pharmacokinetic data from a number of studies and population PK analyses in healthy volunteers and patients with T2DM that are sufficient to determine the key PK characteristics of dulaglutide.

The statistical methods and the assays used in the studies to characterize PK of dulaglutide and other drugs, were validated. In some studies there were patients with detectable pre-dose dulaglutide levels. This is likely explained by elevated endogenous GLP-1 and/or glucagon levels in these individuals. However, the number of affected predose samples was minimal and the impact on the overall characterization of dulaglutide PK and subsequent conclusions was considered to be negligible. The biopharmaceutical development was appropriate to justify both, the single use syringe and the single use pen based on bioequivalence, safety assessment and human factor evaluation

Following subcutaneous administration dulaglutide is slowly absorbed reaching maximum concentrations between 48 and 72 hours, with a rate likely to be slower in diabetic patients than healthy volunteers (although the extent of absorption appears similar). Absolute bioavailability is relatively low 44-47% for the 1.5mg dose and appears to be dose dependent, with a higher bioavailability for the 0.75 mg dose (65%).

After repeated weekly dosing, steady state is suggested to be reached after two weeks. No significant differences in bioavailability and the extent of exposure to dulaglutide were found after injection at three different injection sites (arm, thigh and abdomen). However, patient BMI was found to be a significant factor, with an inverse relationship to bioavailability. From the population pharmacokinetic analysis, it was concluded that no dosage adjustment is necessary for patient weight. This conclusion is endorsed.

Mean apparent volumes of distribution (Vz/F) after single and multiple 1.5 mg SC dosing were 19.5 L and 17.4 L respectively. The volume of distribution after single IV dosing (0.1 mg) was 5.3 L indicating that dulaglutide distributes primarily in the blood volume. Dulaglutide is suggested to be degraded to amino acids by general protein catabolism pathways. Very limited data (pooled analysis of 2 subjects) were presented for a truncated GLP-Fc metabolite in vivo. Although the data showed that the metabolite concentrations accumulate more slowly than parent, given that the metabolite was shown to be 15,000 times less potent, the contribution of this metabolite to dulaglutide PD response is likely to be negligible. Apparent clearance (CL/F) in patients with T2DM after multiple 1.5 mg dosing was 0.107 L/hr. Mean t1/2 after multiple 1.5 mg dosing was approximately 4.7 days. Intra-subject variability appears to be low (less than 20% for both Cmax and AUC), while inter-subject variability was low to moderate (estimated between 18 and 35%).

Specific studies examined the dulaglutide PK in patients with renal and hepatic impairment, Japanese patients and elderly, without finding any clinically significant effects. The effect of other intrinsic factors such as gender

age, weight and BMI, was also tested but only the latter two were found to be consistently associated with reduced bioavailability and lower exposure, not however to an extent to be considered of major clinical relevance and requiring a dose adjustment.

Dulaglutide is not expected to be metabolized by the CYP enzymes and PK interactions through this route are unlikely. The potential for dulaglutide to affect oral drugs' absorption through its effect on gastric emptying was investigated in a number of studies. In general, the extent of interaction was low.

Pharmacodynamics

The mechanisms of action of GLP-1 receptor agonists are well known with three key elements that can be beneficial to T2DM patients i.e. increased insulin release in response to hyperglycaemia, decreased glucagon secretion and delayed gastric emptying possibly resulting in increased satiety and weight loss. The investigation of dulaglutide pharmacodynamics confirmed these effects without unexpected findings.

Dulaglutide was shown to restore both first- and second-phase insulin release in response to glucose challenge in T2DM patients and appears to increase maximal insulin secretion from the β-cells in response to glucagon under hyperglycaemic conditions. A glucagon suppressing effect was also observed in Study GBDC. The overall result is a decrease in fasting and post-prandial glucose and HbA1c which appears to be well correlated with dulaglutide concentrations and doses as the PK/PD models suggest. The delaying of gastric emptying, again an expected effect in this class, was confirmed by both scintigraphy and the impact on acetaminophen absorption. A positive long term effect on weight appears to be related to dose with a slightly greater weight loss with the 1.5 mg dose relative to lower doses estimated by the PK/PD modelling.

In terms of the investigation of off-target effects, the thorough QT study had a number of limitations and some of its findings needed further consideration. Although there was no clear evidence of QT prolongation, the study showed an increase in heart rate and effects on conduction system including persistent PR prolongation as well as QT shortening. These are inconsistent for any one mechanism especially hERG mediated and no other ion channels have been investigated. Generally, the effects of dulaglutide on cardiac repolarisation and conduction system remain uncertain. However, the relevant findings from the clinical studies appear to be generally consistent with the rest of the class and the overall data so far do not raise any major safety concerns (see *Safety* section). Nevertheless, this is an issue that will need to remain under monitoring. A large cardiovascular outcome study is ongoing and is expected to provide more robust evidence on the cardiac safety of dulaglutide.

From a different safety perspective, the very poor tolerability and the high rate of pancreatitis seen with high doses in this study is of concern and raises questions about the potential safety margins. The small increase in heart rate, which is likely to be dose related, was confirmed by other studies, whereas the findings on blood pressure are less consistent. These issues are discussed in detail in the *Safety* section. Some PD findings of the drug-drug interaction studies such as that dulaglutide could alter metoprolol's effect on diastolic BP and the observation that there was a higher rate and number of patients with first degree heart block after co-administration of digoxin do not appear to be clinically relevant.

The immunogenicity of dulaglutide was also examined in clinical studies with only a small percentage of patients detected with anti dulaglutide antibodies. The findings overall suggest little immunogenic potential. Immunogenicity is also further discussed in the *Safety* section.

Among the remaining examined safety parameters i.e. amylase, calcitonin and GI adverse effects, only nausea and vomiting showed a clear exposure-response relationship in the PK/PD models. Of interest, the findings suggest that the likelihood of experiencing nausea and vomiting is highest in the first couple of weeks but diminishes thereafter. Further analyses also found no major long term differences in terms of nausea and

vomiting between a stepwise titration regime (i.e. starting therapy with 0.75mg before moving to the 1.5mg dose) compared to the currently proposed no titration regime.

2.4.5. Conclusions on clinical pharmacology

Dulaglutide is a new GLP-1 agonist with general characteristics consistent with what is expected for products in this class but also some differences.

The pharmacokinetics of dulaglutide were in general thoroughly investigated and the methodology utilised for data analysis is generally endorsed. The only important covariate identified during the population pharmacokinetic analysis was patient weight. The Applicant concludes that no dosage adjustment is necessary. This conclusion is endorsed.

In terms of pharmacodynamics, the data confirm the key aspects of the mechanism of action of the class i.e increased insulin release in response to hyperglycaemia, decreased glucagon secretion and delayed gastric emptying. Similarly, dulaglutide is not immune to the known tolerability and safety issues of GLP-1 agonist class with GI adverse events shown to be related to dulaglutide concentrations. It is reassuring that GI tolerance appears to develop relatively quickly, and also that immunogenicity may not be a major issue. There are issues with the findings of the thorough QT study and certain haemodynamic effects, like a consistently observed increase in heart rate, but the overall findings do not raise any major concerns.

In conclusion, the overall PK and PD effects of dulaglutide have been sufficiently characterized. The data from the clinical pharmacology program support the pharmaceutical development, the once weekly dosing and posology.

2.5. Clinical efficacy

The primary efficacy data supporting this submission are based on 5 pivotal long-term controlled Phase 3 trials (52-104 weeks) which evaluated the efficacy, safety, and tolerability of once-weekly dulaglutide at doses of 1.5 mg and 0.75 mg versus placebo or and/or an active comparator used as monotherapy or in combination with OAMs or prandial insulin (with or without metformin). An overview of the 5 main studies is provided in Table 11 and Table 12 below. A sixth phase 3 study, considered supportive, was submitted during the procedure.

Table 11 Dulaglutide Pivotal Long-Term Phase 3 Studies and Treatment Duration

Study	Background Therapy	26 week Placebo-controlled period	Active Comparator (Dose)	Total Treatment Duration (Primary Time point)
GBDC	N/A		MET (1500-2000 mg QD)	52 (26) weeks
GBCF (AWARD-3)	MET	Yes	Sitagliptin (100 mg QD)	104 (52) weeks
GBDA (AWARD-1)	MET + TZD	Yes	Exenatide (10 µg BID)	52 (26) weeks
GBDB (AWARD-2)	MET + SU		Insulin Glargine [a]	78 (52) weeks
GBDD (AWARD-4)	Insulin Lispro ± MET		Insulin Glargine [a]	52 (26) weeks

Abbreviations: BID = twice daily injection; MET=metformin; SU= sulphonylurea; TZD = thiazolidinedione; N/A = not applicable; QD = once daily.
a Insulin glargine dose was adjusted based on treat-to-target algorithm to maintain fasting plasma glucose <100 mg/dL (<5.6 mmol/L).

Efficacy data were also obtained from four Phase 2 studies: Study H9X-MC-**GBCJ**, Study H9X-MC-**GBCK**, Study H9X-JE-**GBCZ**, and Study H9X-MC-**GBDN**. Three of the Phase 2 studies (Studies GBCJ, GBCK, and GBCZ) tested once weekly dulaglutide doses ranging from 0.1 to 3.0 mg for up to 16 weeks, and the fourth Phase 2 study

(GBDN) evaluated the effects of dulaglutide 1.5 mg and dulaglutide 0.75 mg on blood pressure and heart rate using ABPM for up to 26 weeks. There is also an ongoing program with an additional 10 studies (Table 2 above)

2.5.1. Dose response studies

The Initial clinical pharmacology studies assessed a dulaglutide dose range from 0.05 to 12 mg. Data from studies in healthy subjects and patients with T2DM, together with dose-concentration-response relationships of PD and safety parameters (see *Pharmacokinetics/Pharmacodynamics sections* above) provided information for the estimation of the minimum effective dose, the maximum tolerated dose, and the dulaglutide dose range for the dose-finding part of the Phase 2/3 Study H9X-MC-**GBCF**.

Study **GBCF**, was a 104-week, adaptive, inferentially seamless, Phase 2/3, placebo-controlled study comparing the efficacy and safety of once weekly dulaglutide to sitagliptin in patients with T2DM on metformin. The study's initial dose-finding part assessed seven doses of dulaglutide (0.25, 0.5, 0.75, 1, 1.5, 2, and 3 mg). An optimal or maximum utility dose (MUD) was to be selected from those, based on the use of a prospectively defined clinical utility index (CUI) for pre-specified measures of benefit (HbA1c and weight) and risk (diastolic BP and HR). If a dose met the maximum utility criteria and the pre-specified decision rules, a second, lower dose would be also selected for further assessment in Stage 2. This was based on the Food and Drug Administration's (FDA) recommendation to bring forward a second dose into Phase 3 development in case of an unexpected safety signal with the MUD. This second dose was required to have a CUI ≥0.6 and be ≤50% of the MUD.

In April 2009 randomization to the dulaglutide 3.0 mg dose was stopped prior to the 10th interim report based on the recommendation of the Data Monitoring Committee (DMC) following observations of increased heart rate and concerns related to pancreatic safety. After more than 200 patients had been enrolled, the 10th interim assessment was performed and the decision rules were applied. Non-validated data from 199 patients were included in the dose selection analysis. Table 13 presents a summary of the variables included in the CUI, as well as fasting glucose and systolic blood pressure (SBP), up to 6 months, excluding data after the Decision Point. The table shows that the 1.5 mg dose had the greatest effect on HbA1c and fasting glucose. The effects on body weight were similar to the adjacent doses. Regarding safety, the 1.5 mg dose also met the pre-specified requirements of change in DBP ≤2 mm Hg and change in pulse rate ≤5 bpm.

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

	Mean (Standard Deviation)[a] Change from Baseline								
Variable[b] (Units)	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)

Abbreviations: bpm = beats per minute; DBP = diastolic blood pressure; Dula = dulaglutide; HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; PL = placebo; SBP = systolic blood pressure; Sit = sitagliptin; N = number of patients randomized to a treatment group.

[a] Least squares means and confidence intervals could not be produced due to the lack of data at 6 months.

[b] HbA1c, body weight, pulse rate, and DBP were components of the clinical utility index used in the dose selection algorithm based on non-validated data collected up to Decision Point.

The 1.5 mg dose met the pre-specified criteria for dose selection as the MUD and the optimal dose for the dulaglutide program. The posterior probability that the CUI ≥0.6 was 0.982 and the posterior predictive probability that the 1.5 mg dose was noninferior to sitagliptin at 12 months, based on a total sample size of 263 in each arm, was >0.99.

Following the rules for selecting a second dose, the algorithm indicated the 0.75 mg dose met the pre-specified requirements. The DMC subsequently met and supported the continuation of the study **GBCF** with the selected dulaglutide doses. Patients enrolled during Stage 1 in the dulaglutide doses that were not selected for Stage 2, were discontinued from the study.

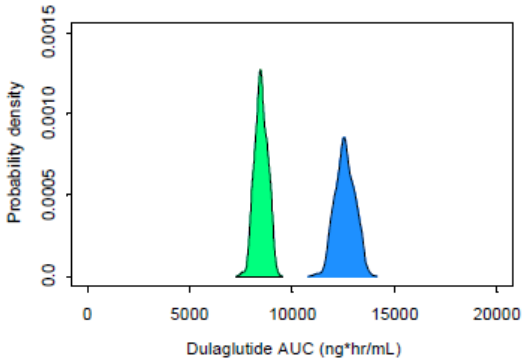
In summary, dulaglutide 1.5 mg was selected as the optimal dose, and 0.75 mg was chosen as the lower alternative dose for the confirmatory long-term safety and efficacy part of Study GBCF and subsequent Phase 3 Studies GBDC, GBDA, GBDB, and GBDD.

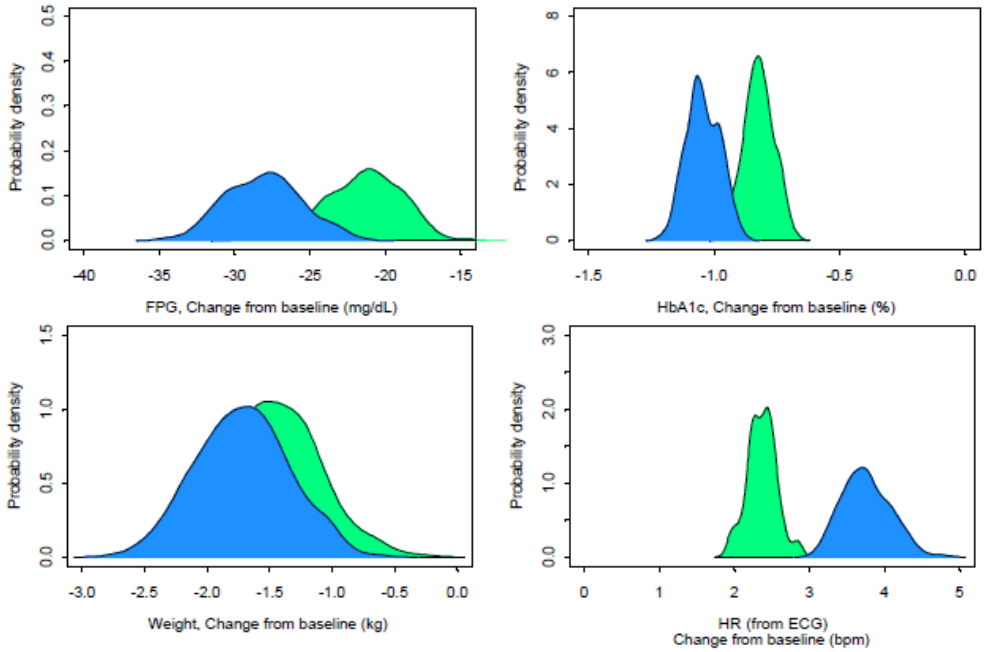
Selection of commercial doses

Although both doses (1.5 mg and 0.75 mg) were tested in the phase III studies only the 1.5 mg dose was initially intended to be marketed. The Applicant suggested that the totality of clinical safety and efficacy data, and the exposure-response model-based analyses support the once weekly administration of dulaglutide 1.5 mg as the most efficacious dose with an acceptable safety profile. The population exposure-response models estimated decreases from baseline of -35 mg/dL for FPG; -1.1% for HbA1c; and -1.7 kg for body weight at 1 year following the 1.5 mg dulaglutide dose in patients with T2DM. The model estimated an increase of 2.6 bpm in HR and no clinically relevant changes in BP, amylase (pancreatic and total), lipase, and calcitonin at the 1.5 mg dose level.

In order to determine the optimal commercial dose, efficacy and safety data from the individual and integrated Phase 3 studies were analysed to determine if there was a clear difference between the 0.75 mg and 1.5 mg doses. The probability of each dose of attaining a clearly distinguishable effect was also assessed using the population PK/PD models. The probability distributions of the effect for both doses for key PK, efficacy, and safety parameters demonstrated that the 1.5 mg dose separates from the 0.75 mg dose in terms of AUC, glycaemic control, and HR effects, while the weight effect has a higher degree of overlap between doses.

Figure 13 Model-estimated probability distributions of key pharmacokinetic, efficacy and safety parameters for the 1.5 mg and 0.75 mg doses.





The 1.5 mg dose is shown in blue, the 0.75 mg dose in green. Profiles represent simulations of 200 studies with 200 patients in each treatment arm. Simulations were run using covariate values representative of patients in phase 3 studies: mean weight 93 kg (SD 19), mean age 55 (SD 10). Abbreviations: AUC = area under the concentration-time curve; ECG = electrocardiogram; FPG = fasting plasma glucose; HbA1c = *glycosylated haemoglobin; HR = heart rate; SD = standard deviation.*

Individual study data and integrated efficacy and safety data from the 5 long-term, multinational Phase 3 studies confirmed the results of the dose-finding stage of Study GBCF and demonstrated that dulaglutide 1.5 mg is the most efficacious dose with an acceptable safety profile.

Dose titration

In order to assess the effect of dose titration, the company conducted Study H9X-MC-**GBCJ** that evaluated once-weekly injections of dulaglutide using two regimes involving dose titration (0.5 to 1.0mg and 1.0mg to 2.0mg) or a non-titration (1mg) compared to placebo on glycaemic control as measured by HbA1c change from baseline at 16 weeks and safety in overweight and obese BMI of 27 to 40 kg/m^2) T2DM patients who were taking any 2 OAMs. The study had a 2-week lead-in period during which placebo injections were administered, followed by a 16-week treatment period. Of the 262 randomized patients, 232 completed the study and 255 were analyzed for the primary efficacy measure.

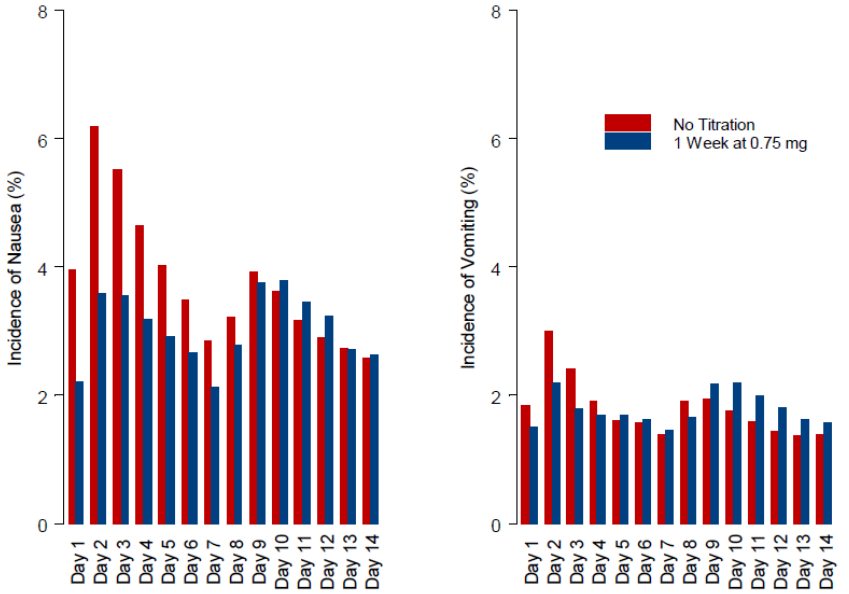
Statistically significantly greater decreases in HbA1c were observed in all dulaglutide treatment groups compared to placebo ($p<0.001$), with the largest numerical decrease in the dulaglutide 1.0/2.0mg treatment group. Overall dose titration over 4 weeks did not appear to have a significant effect on tolerability. Dulaglutide concentration increased as expected with dose titration, from 0.5 to 1 mg and from 1 to 2 mg. In the treatment group without titration, steady-state concentration was reached prior to the fourth dose. There was no statistically significant difference in the most frequent AEs (nausea vomiting, diarrhoea) for the 4 groups (overall $p>0.05$), and the percentage of patients reporting these events was lower than historically reported in clinical trials evaluating this class of drugs. Only 7 patients discontinued from the study due to GI AEs. The hypoglycaemia rate was low and was not statistically significantly different between groups.

In addition to study H9X-MC-GBCJ, as discussed above (see *Pharmacodynamics* section), exposure-response analyses were conducted to examine if patients would benefit by a dose titration regime. There was no significant improvement in the model-estimated overall incidence of nausea and vomiting with different titration

regimens that started with 0.75 mg doses for 1, 2, 3 or 4 weeks before dosing with 1.5 mg dulaglutide. The model estimated no benefit of different dose titration regimens or between different dose titration regimens beyond the first dose.

Figure 14 shows the model-estimated incidence of nausea and vomiting per day between administration of dulaglutide 1.5 mg with no titration and after titrating with 0.75 mg for 1 week for the first two weeks of dosing. Dulaglutide was administered on Day 1 and Day 8. Bars represent incidence of events per day. When starting with the 1.5 mg dose the incidence of nausea and vomiting is higher in the first week of dosing but rapidly declines due to tolerance development. Titrating, by starting with the lower 0.75 mg dose, was associated with a small rebound effect with increase in nausea and vomiting in the second week of dosing, due to a lack of tolerance development. Nausea increases from 7.9% on week 1 to 8.3% on week 2 and vomiting from 5.3% on week 1 to 6.0% on week 2. Conversely, the 1.5 mg dose has a higher incidence of nausea and vomiting per week after the first dose (11% and 7.0%), but the incidence is reduced to a level lower than that in in the titration regimen (7.9% and 5.9%), on the second week of dosing.

Figure 14 Model-estimated incidence of nausea (left) and vomiting (right) with no titration for 1.5 mg dulaglutide (red) and after titrating with 0.75 mg for 1 week (blue).



Dulaglutide was administered on Day 1 and Day 8. Bars represent incidence of events per day, colors are different titration methods.

In general, taking into account the totality of evidence from the dose response studies and the available PK/PD data, it is agreed that there is a dose dependent effect in terms of both efficacy and tolerability/safety, which was confirmed by the main dose-ranging study GBCF. Doses higher than 1.5 mg were shown to offer very little additional benefit while associated with poorer tolerability and a potentially higher risk of complications. Therefore, based on the overall evidence, the choice of the 1.5 mg as the highest dose appears well justified. The decision about the need or not of a lower dose was more debatable.

In addition to 1.5mg, the 0.75mg dose was also tested across the whole phase 3 program (based on FDA recommendations) as a back-up in case that serious tolerability/safety concerns arose with the higher dose. However, although both doses were examined only the 1.5 mg strength was initially submitted with this application and intended for commercial use. Indeed, as the Applicant argues, the 1.5mg appears more

efficacious than the 0.75mg dose but is also associated with a slightly poorer tolerability and higher incidence of certain events (as discussed in more detail in the *Safety* section below). Nevertheless, the overall evidence appears to support the choice of once weekly 1.5mg as the dose with the most favourable benefit:risk profile for most patients**.** Nonetheless, a question was raised whether a lower strength would be useful for dose up-titration, aiming at improved tolerability at the beginning of therapy, or for down titration for patients who for various reasons may not be able to tolerate the higher dose.

To address the first point, the Applicant carried out study GBCJ that showed no clear benefit of regimes involving dose titration compared to starting and continuing therapy with the same dose, although it should be noted that the currently recommended posology (0.75mg to 1.5mg) was not tested. A model estimating the effect of a dose-titrating regime on nausea and vomiting suggested that starting with a lower dose may be temporarily better tolerated but can delay the development of tolerance. Although the arguments appear reasonable, the data were generally limited. There were also concerns about the potential usefulness of a lower strength in case that a patient cannot receive the higher dose or when down titration may be required. In the latter case a patient would need to discontinue therapy and seek alternative options.

Introduction of the 0.75mg formulation

The issues about the usefulness of a lower 0.75mg formulation, particularly in a monotherapy setting (please see *Efficacy* and *Safety* sections below) were extensively discussed during the procedure. At Day 180, following the CHMP request, the Applicant included the 0.75 mg strength in this application and updated the related documentation and the Product Information, accordingly.

Once weekly dosing and missed doses

Pharmacokinetic data support a once weekly administration of dulaglutide. Following SC administration, maximum concentrations of dulaglutide are reached at approximately 48 hours and the half-life is approximately 4.7 days; apparent CL is 0.107 L/hr. Steady state is reached between the 2nd and 4th dose. Consistent with its PK profile, dulaglutide has a glycaemic profile suitable for once weekly administration. Reductions in HbA1c, fasting, and postprandial glucose, as well as corresponding increases in insulin and C-peptide, were observed after the first dose and were sustained throughout the once weekly dosing interval, with maximum effects observed by 2 weeks. Simulations of the effect of missed doses on the PK of dulaglutide were also carried out to provide administration instructions in such cases.

2.5.2. Main studies

As mentioned above in support of this application the Applicant at time of submission of the application the results of 5 Phase 3 trials which assessed the efficacy and safety of once-weekly dulaglutide at doses of 1.5 mg and 0.75 mg versus placebo or active comparators taken alone, or in combination with OAMs or prandial insulin (with or without metformin).

Table 12 Overview of Dulaglutide Phase 3 Studies

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Durationa
Phase 3 Studies -Comparative Efficacy						

H9X-MC-**GBCF**	Stage 1: Identify up to 2 doses of DUL (referred to as high and low dose) for confirmatory studies. Stage 1 and Stage 2: Demonstrate DUL was noninferior (0.25% margin) to sitagliptin on HbA1c change from baseline at 52 weeks.	Phase 2/3, adaptive, inferentially seamless, multicenter, randomized, Placebo-controlled, double-blind, parallel-arm study	Stage 1: DUL: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0 mg; SC, once weekly PLAC: SC, once weekly Sitagliptin: 100 mg, PO, once daily PLAC: PO, once daily Stage 2: DUL: 1.5, 0.75 mg; SC, once weekly PLAC: PO, once daily; SC, once weekly up to 26 weeks Sitagliptin: 100 mg, PO, once daily Patients added assigned therapy to MET ≥1500 mg once daily.	Stage 1: ITT = 230 (DUL = 150; PLACb = 38; comparator = 42) Stage 1 and 2, primary treatment groups: ITT = 1098 (DUL 1.5 mg = 304; DUL 0.75 mg = 302; PLAC = 177; sitagliptin = 315)	T2DM suboptimally controlled with MET, 1 other OAM, MET + 1 other OAM, or antihyperglycaemic medication-naïve (screening HbA1c ≥7.0% to ≤9.5%).	104 wks (primary time point = 52 wks, final time point = 104 wks) Note: PLAC-controlled = 26 wksb
H9X-MC-**GBDC** (**AWARD-3**)	Demonstrate DUL 1.5 mg was noninferior (0.4% margin) to MET on HbA1c change from baseline at 26 weeks.	Phase 3, randomized, parallel-arm, active comparator, double-blind, double-dummy, noninferiority study	DUL: 0.75, 1.5 mg; SC, once weekly PLAC: PO, twice daily; SC, once weekly MET: 1000 mg, PO, twice daily (total dose of 2000 mg/day or 1500 mg/day as tolerated by the patient)	ITT = 807 (DUL 1.5 mg = 269; DUL 0.75 mg = 270; MET = 268)	T2DM for ≥3 months and ≤5 years, suboptimally controlled with 1 OAM or treatment-naïve (screening HbA1c ≥6.5% to ≤9.5%).	52 wks (primary time point = 26 wks; final time point = 52 wks)
H9X-MC-**GBDA** (**AWARD-1**)	Demonstrate DUL 1.5 mg was superior to PLAC on HbA1c change from baseline at 26 weeks.	Phase 3, multicenter, parallel-arm, double blind PLAC-controlled, open-label to comparator, randomized, study	DUL: 0.75, 1.5 mg; SC, once weekly PLAC: SC, once weekly for 26 weeks Exenatide: 5 mcg, twice daily for 4 weeks followed by 10 mcg twice daily thereafter Patients added assigned therapy to MET up to 2550 mg/day or the highest tolerable local label dose, and pioglitazone up to 45 mg/day or the highest tolerable local label dose.	ITT = 976 (DUL 1.5 mg = 279; DUL 0.75 mg = 280; PLAC = 141; exenatide = 276)	T2DM suboptimally controlled with up to 3 OAM(s) (screening HbA1c ≥7.0% and ≤11.0% if on 1 OAM and ≥7.0% and ≤10.0% if on >1 OAM).	52 wks (primary time point = 26 wks; final time point = 52 wks)
H9X-MC-**GBDB** (**AWARD-2**)	Demonstrate DUL 1.5 mg was noninferior (0.4% margin) to insulin glargine on HbA1c change from baseline at 52 weeks.	Phase 3, open-label to comparator, double-blind to DUL dose, multicenter, parallel-arm, randomized study	DUL: 0.75, 1.5 mg; SC, once weekly Insulin glargine: starting dose 10 IU, SC; thereafter, adjusted based on treat-to-target algorithm of self-monitored FPG target <100 mg/dL Patients added assigned therapy to maximally tolerated doses of MET ≥1500 mg/day and glimepiride ≥4 mg/day.	ITT = 807 (DUL 1.5 mg = 273; DUL 0.75 mg = 272; insulin glargine = 262)	T2DM suboptimally controlled with up to 3 OAM(s), at least 1 of which must have been MET or SU (screening HbA1c ≥7.0% and ≤11.0% if on 1 OAM and ≥7.0% and ≤10.0% if on >1 OAM).	78 wks (primary time point = 52 wks; final time point = 78 wks)
H9X-MC-**GBDD** (**AWARD-4**)	Demonstrate DUL 1.5 mg was noninferior (0.4% margin) to insulin glargine on HbA1c change from baseline at 26 weeks.	Phase 3, parallel-arm, open-label, active comparator study	DUL: 0.75, 1.5 mg; SC, once weekly Insulin glargine: starting dose 50% of pre-randomization total daily dose, SC, at bedtime; thereafter, adjusted based on treat-to-target algorithm of self-monitored FPG target >70 to <100 mg/dL All patients added assigned therapy to prandial insulin lispro (starting dose 50% of pre-randomization total daily dose; thereafter adjusted to pre-specified pre-meal FPG targets) ± MET.	ITT = 884 (DUL 1.5 mg = 295; DUL 0.75 mg = 293; insulin glargine = 296)	T2DM suboptimally controlled with ≥3 months of a conventional insulin regimen (≤2 doses of insulin per day), alone or in combination with OAMs (screening HbA1c ≥7.0% and ≤11.0%).	52 wks (primary time point = 26 wks; final time point = 52 wks)

Abbreviations: ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DPP-4 = dipeptidyl peptidase-IV; DUL= Dulaglutide; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin A1c; HTN = hypertension; ITT = intent-to-treat; IU = International Unit; MET = metformin; mmHg = millimeters of mercury; N = number of patients; OAM = oral antidiabetic medication; PLAC= Placebo; PO = orally; SC = subcutaneous; SU = sulphonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones.
a An additional 4-week safety follow-up period was included in all studies with the exception of Study GBCJ; the follow-up period is not included in the treatment duration.
b Total duration of placebo-controlled period was 26 weeks; after 26 weeks, patients originally randomized to placebo were converted to active therapy (GBCF: sitagliptin; GBDA: dulaglutide 1.5 mg or dulaglutide 0.75 mg) in an effort to maintain study blind and collect long-term, controlled safety data across the treatment groups.

Methods

The Phase 3 studies were designed to assess safety and efficacy in patients across different stages of the T2DM management from monotherapy, combination with 1 or 2 OAMs, and combination with insulin; more specifically, to establish the superiority of dulaglutide to placebo and/or noninferiority/superiority of dulaglutide to active comparator (metformin, sitagliptin, exenatide twice daily [hereafter referred to as exenatide], or insulin glargine).

All trials were conducted as randomized, parallel-arm trials. Placebo-controlled trials were double-blinded. All studies had active-comparator control arms through the final treatment time point. Three of the 5 trials had a 52-week treatment period, 1 trial had a 78-week treatment period, and 1 trial had a 104-week treatment period. The primary outcome measure in all 5 studies was glycosylated haemoglobin A1c (HbA1c) change from baseline to the primary time point (26 or 52 weeks); various secondary safety and efficacy measures were also evaluated, including effects on body weight, fasting serum glucose (FSG), 8-point SMPG profile, proportion of patients achieving target HbA1c <7% and ≤6.5%, indices of insulin sensitivity and beta cell function. Long-term, comparator-controlled safety and efficacy data were collected through the final time points (52, 78, or 104 weeks).

The initial Phase 3 study was Study H9X-MC-**GBCF** (as mentioned in the *Dose Response* section above), an adaptive, dose-finding and confirmatory inferentially seamless Phase 2/3 study. As discussed, the purpose of the dose-finding portion of GBCF was to identify an optimal dose, utilizing prespecified measures of safety and efficacy. Dulaglutide 1.5 mg was selected as the optimal dose and dulaglutide 0.75 mg was selected as the alternative lower dose to mitigate the potential risk if a safety signal were to be subsequently observed with the optimal dose. These doses were used in the subsequent Phase 3 program.

Two of the Phase 3 studies had a 26-week placebo-controlled period, after which patients in the placebo arm were switched to the active comparator sitagliptin (Study **GBCF**) or dulaglutide 1.5 mg or dulaglutide 0.75 mg (Study **GBDA**) for the remainder of the study duration (≥52 weeks). The insulin-comparator studies (Studies **GBDB** and **GBDD**) were conducted as open-label comparator studies due to the complexity of blinding insulin, given the need to titrate insulin doses. The 2 doses of dulaglutide were double-blinded. The exenatide twice daily comparator study (Study **GBDA** was also open-label with respect to the active comparator due to the complexity of blinding the exenatide BID pen device. The 2 doses of dulaglutide and placebo were double-blinded in that study.

Rescue therapy was not used in Study GBCF; patients who met pre-specified thresholds for hyperglycaemia were required to be discontinued from the study. In the subsequent Phase 3 studies (GBDC, GBDA, GBDB, and GBDD), rescue therapy (additional or alternative antihyperglycaemic medication) could have been initiated for: i. meeting pre-specified thresholds for severe, persistent hyperglycaemia; ii. following study drug discontinuation. If rescue therapy was initiated, the specific antihyperglycaemic medication was determined by

the investigator based on standards of care. Glucagon-like peptide-1 receptor agonists were not permitted as rescue therapy.

The key inclusion criterion was a diagnosis of T2DM based on WHO disease criteria for over 6 month duration at study entry. Both male and female patients were eligible for enrolment. The age range was ≥18 in most phase 3 studies. Inadequate glycaemic control was defined differently in the phase 3 studies (please refer to specific inclusion criteria); in most phase 3 studies patients had to have a stable weight (±5%) for at least 3 months prior to screening and a BMI between 23 and 45 kg/m2.

Exclusion criteria common to the phase 3 studies were T1DM, uncontrolled T2DM (>2 episodes of ketoacidosis or hyperosmolar state requiring hospitalisation), treatment with a GLP-1 agonist within 6 months prior to study entry, known clinically meaningful gastric emptying abnormality, gastric bypass surgery, or chronic use of drugs that directly reduce gastrointestinal motility, intake of a nervous system stimulant or prescription or over the counter medication to promote weight loss at study entry, a clinically relevant CV event within 2 month of study entry or between study entry or randomisation, poorly controlled hypertension at study entry, increased serum calcitonin (20 pg/mL) and significant liver or kidney disease or a significant active uncontrolled endocrine or autoimmune abnormality.

In general, the five phase 3 trials (together with the supportive studies) meet the main requirements for confirmatory studies in the investigation of medicinal products in the treatment of diabetes mellitus, according to the relevant European Guideline (CPMP/EWP/1080/00 Rev. 1), testing the superiority of dulaglutide over placebo, alone or when added to an appropriate background therapy, as well as the non-inferiority to an established active comparator.

Indeed dulaglutide was compared to placebo in two phase 3 studies (GBCF and GBDA) and to active comparators in all five of them (GBCF, GBDC, DBDA, GBDB and GBDD). It was also tested as monotherapy (study GBDC) or in combination with other treatments as double (with metformin, insulin lispro) or triple therapy (with metformin+sulphonylurea [SU], metformin+thiazolidinedione [TZD] or metformin+insulin lispro), and data available for up to 104 weeks. Background treatments were continued or their levels were stabilised at maximum tolerated doses for the duration of the studies. It should be noted that although a monotherapy study vs metformin was carried out, a monotherapy indication was not initially sought. However, as part of their responses to the Day 120 LoQ, the Applicant requested an amendment of the indications to also include a monotherapy indication which was considered acceptable, based on the submitted data.

There are, however, some gaps in the available evidence with regard to some treatment combinations that may be encountered in clinical practice; for example, there are no data on double therapy with dulaglutide in combination with SU or TZD, or triple combination with SU+TZD. Also in a non-traditional approach dulaglutide was tested as add-on therapy to prandial instead of basal insulin. With regard to the lack of a study on a combination with SU, the Applicant indicated that because of the declining use of SU at the time of initial Phase 3 program planning such a study was not considered to be of high priority.

Currently ongoing studies appear to address some of these points, like study GBDG that compares dulaglutide with placebo in T2DM patients on background SU therapy. Various other combinations and different comparators are also under investigation in other studies.

NOTE: The studies are presented below not in chronological order but in an order representing the stages of the T2DM treatment continuum from monotherapy, combination with one or more OAMs, and combination with insulin: Studies **GBDC, GBCF, GBDA, GBDB**, and **GBDD**.

Study H9X-MC-GBDC

The Impact of LY2189265 versus Metformin on Glycemic Control in Early Type 2 Diabetes Mellitus (AWARD-3: Assessment of Weekly AdministRation of LY2189265 in Diabetes-3)

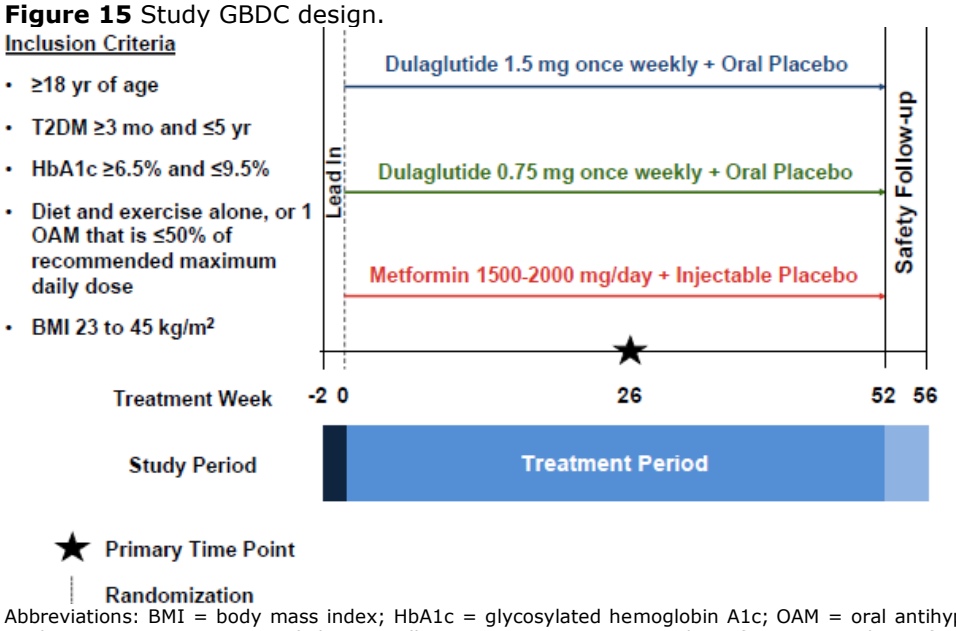
Study **GBDC** was a 52-week, randomized, parallel-arm, active comparator, double-blind, double-dummy, noninferiority monotherapy study comparing dulaglutide (1.5 mg or 0.75 mg once-weekly) with metformin in patients with early T2DM. This is the pivotal study for the monotherapy indication.

The study consisted of 3 periods: a lead-in period of approximately 2 weeks, a 52-week treatment period, and a 4-week safety follow-up period. The primary objective of this study was to show noninferiority of dulaglutide 1.5 mg to metformin at 26 weeks of treatment based on HbA1c change from baseline in patients with T2DM (noninferiority margin 0.4%).

The study enrolled male and nonpregnant female patients ≥18 years who had had T2DM for ≥3 months and ≤5 years; been not optimally controlled with diet and exercise and either treatment-naïve or on 1 OAM (≤50% of the recommended maximum daily dose [per the local label]), excluding TZDs (the Applicant clarified that because TZDs are recognized to have a prolonged waning of glycaemic effect following discontinuation compared to other OAMs, recent use of TZDs was excluded to limit the potential for a confounding effect on baseline glycaemia), for at least 3 months; had an HbA1c ≥6.5% and ≤9.5% (Visit 1); had stable weight (±5%) ≥3 months prior to screening (Visit 1) and a BMI between 23 and 45 kg/m^2, inclusive. It is noted that patients with moderate and severe renal failure were excluded and this, as discussed also below, is the case in most phase 3 trials. Similarly patients with heart failure NYHA III/VI, recent MI, stroke or hepatic disease were not included in the study (as is also the case for most pivotal trials).

All patients in the study received both an injectable and an oral study agent to maintain treatment blinding. Dulaglutide (SC injection 1.5 mg or 0.75 mg) was administered once-weekly, with metformin given as two 500 mg tablets 2 times daily by mouth (total daily dose [TDD] of 2000 mg/day) or three 500 mg tablets (TDD 1500 mg/day) as tolerated by the patient.. During the 2-week lead-in period, all patients self-injected placebo injection solution for training purposes.

Figure 15 Study GBDC design.



Abbreviations: BMI = body mass index; HbA1c = glycosylated hemoglobin A1c; OAM = oral antihyperglycemic medication; T2DM = type 2 diabetes mellitus. Note: Patients initiated metformin at a dose of 500 mg and uptitrated weekly to a total dose of 2000 mg or at least 1500 mg based on ability to tolerate medication

Study H9X-MC-GBCF

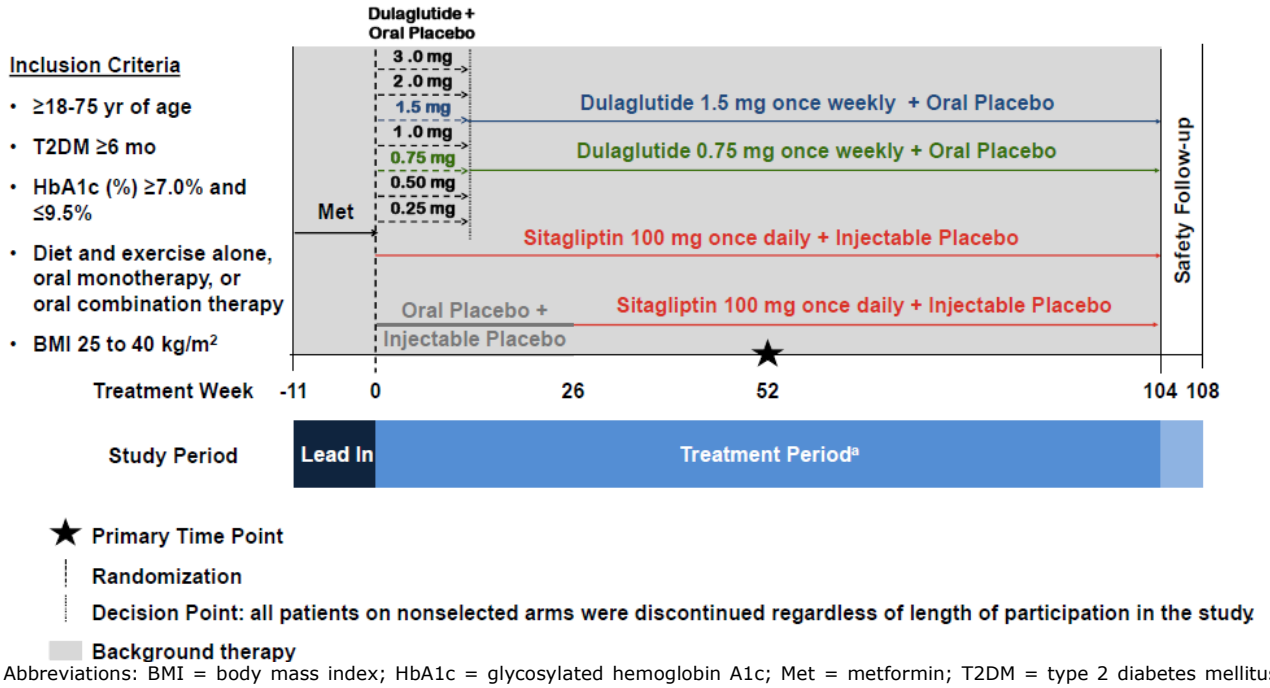
A Phase 2/3, Placebo-Controlled, Efficacy and Safety Study of Once-Weekly, Subcutaneous LY2189265 Compared to Sitagliptin in Patients with Type 2 Diabetes Mellitus on Metformin

Study **GBCF** was an adaptive, inferentially seamless, confirmatory, multicenter, randomized, double-blind, double-dummy, parallel group clinical trial comparing once-weekly dulaglutide to once-daily sitagliptin (100 mg) and placebo in patients with type 2 diabetes mellitus (T2DM) treated with metformin. As discussed in *Dose response* section above in the initial dose-finding part (Stage 1) of the study, 7 doses of dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, and 3.0 mg), sitagliptin, and placebo were assessed. At the completion of the dose-finding part, the dulaglutide 1.5 mg and 0.75 mg doses were selected for the second stage (Stage 2). Patients assigned to the non-selected dulaglutide doses in Stage 1 were discontinued. The final analyses were based on pooled data (across both stages) from the primary treatment arms (dulaglutide 1.5 mg and dulaglutide 0.75 mg, placebo, and sitagliptin) in patients enrolled before and after dose selection (that is, inferentially seamless).

The use of this inferentially seamless design is controversial. By the nature of the design patients on certain doses are being chosen to carry on in the study because they have a good response to treatment, and therefore the phase III part of the study analysis is not an independent confirmation of the efficacy of the selected doses. However in this case Stage 2 was also sufficiently powered to enable these data to be assessed in a stand-alone manner. The applicant has also justified the validity of combining both stages by using simulations that demonstrate the type I error is well controlled, as well as discussing the similarity in patients characteristics for both stages and the consistency of results when both stages are analysed together versus including only Stage 2 subjects.

The primary objective was to show noninferiority of the higher dulaglutide dose (if 2 doses were selected) to sitagliptin with respect to change in HbA1c at 12 months (52 weeks). The final endpoint was 24 months (104 weeks). Placebo comparisons were planned at 6 months (before switching patients from placebo to sitagliptin in a blinded manner). The noninferiority margin was 0.25%. The primary analysis consisted of data from all patients assigned to the primary treatment arms throughout both stages of the study. However, Stage 2 was also sufficiently powered to enable these data to be assessed in a stand-alone manner.

Figure 16 Study GBCF design, dulaglutide versus placebo or sitagliptin, in combination with metformin.



Abbreviations: BMI = body mass index; HbA1c = glycosylated hemoglobin A1c; Met = metformin; T2DM = type 2 diabetes mellitus. a All treatments were added to metformin ≥1500 mg/day.

If patients were receiving OAMs at screening, other than metformin, they were to discontinue those. Patients were required to continue a stable dose metformin (≥1500 mg/day) throughout the treatment period, except in certain clinical situations.

The study enrolled male and female patients 18 to 75 years of age (inclusive) with T2DM for ≥6 months; had been treated with diet and exercise alone, or taking metformin or another OAM as monotherapy, or taking metformin in combination with another OAM at screening; must have been able to tolerate metformin at a dose ≥1500 mg daily for 6 weeks or more prior to randomization; had an HbA1c ≥7.0% to ≤9.5% as determined at screening, except patients on diet and exercise therapy, who must have had HbA1c values >8.0% to ≤9.5% at that visit; had a body mass index (BMI) between 25 and 40 kg/m^2, inclusive, and stable weight during the 3 months prior to screening. Again, patients with significant kidney or liver disease as well as those with recent cardiovascular events were excluded.

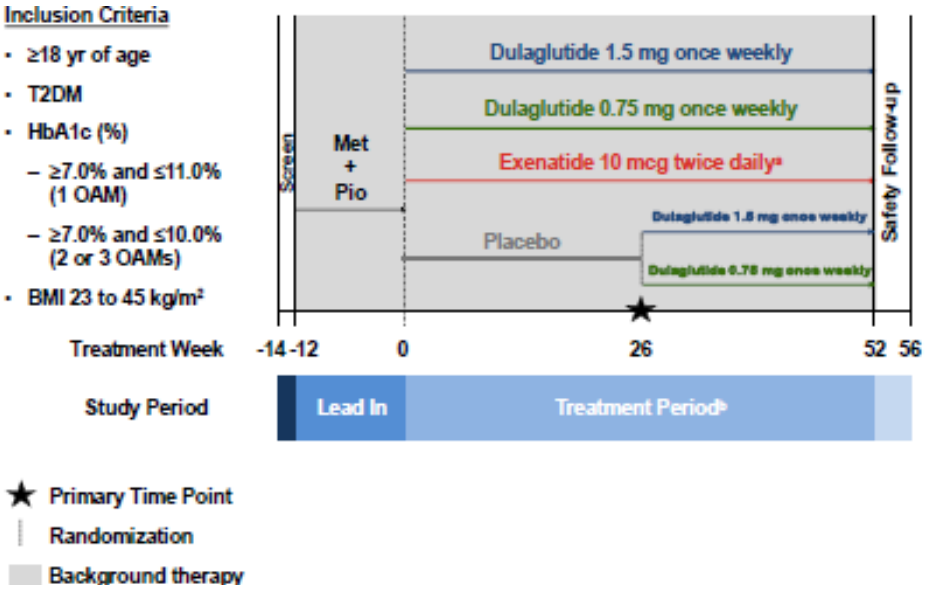
All patients were assigned to both an injectable and an oral study agent to maintain treatment blinding. If patients were receiving OAMs at screening, other than metformin, they were to discontinue those. Patients were required to continue a stable dose metformin (≥1500 mg/day) throughout the treatment period, except in certain clinical situations. Dulaglutide was administered SC (left or right abdominal wall), once weekly. Patients in the sitagliptin group received a 100 mg dose administered orally as a single, once daily tablet. They also administered placebo injection once weekly to match dulaglutide administration.

Study H9X-MC-GBDA

A Randomized, Placebo-Controlled Comparison of the Effects of Two Doses of LY2189265 or Exenatide on Glycemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Pioglitazone (AWARD-1: Assessment of Weekly AdministRation of LY2189265 in Diabetes-1)

Study **GBDA** was a 12-month, parallel-arm, placebo-controlled, active comparator study comparing 2 doses of dulaglutide with open label exenatide, or placebo, in T2DM patients treated with maximally tolerated concomitant OAMs, metformin and pioglitazone. The primary objective was to demonstrate the superiority of once-weekly SC dulaglutide 1.5 mg versus placebo on HbA1c at 26 weeks (change from baseline) in patients with T2DM who were taking maximally tolerated doses of metformin and pioglitazone. Among the secondary objectives was to demonstrate that dulaglutide 1.5 mg is noninferior to exenatide at 26 weeks. Figure 17 below shows the study design.

Figure 17 Study GBDA design, dulaglutide versus placebo or exenatide, in combination with metformin + TZD.



Abbreviations: BMI = body mass index; HbA1c = glycosylated hemoglobin A1c; Met = metformin; OAM= oral antihyperglycemic medication(s); Pio = pioglitazone, T2DM = type 2 diabetes mellitus. a Exenatide dose was 5 mcg twice daily for first 4 weeks and 10 mcg twice daily thereafter. b All treatments were added to maximally tolerated doses of metformin and pioglitazone.

Patients included were male and non-pregnant female T2DM ≥18 years of age. Qualifying HbA1c values at Visit 1 were ≥7% and ≤11% if on stable doses of OAM monotherapy for 3 months before screening (on minimal therapeutic dose or higher at Visit 1 [metformin 1500 mg; pioglitazone 15 mg; rosiglitazone 2 mg]); or ≥7% and ≤10% if on 2 or 3 OAMs at screening. Patients were required to be able to tolerate a minimum dosage of metformin of 1500 mg/day or the highest tolerable local label dose, and pioglitazone up to 30 mg/day, or the highest tolerable local label dose.

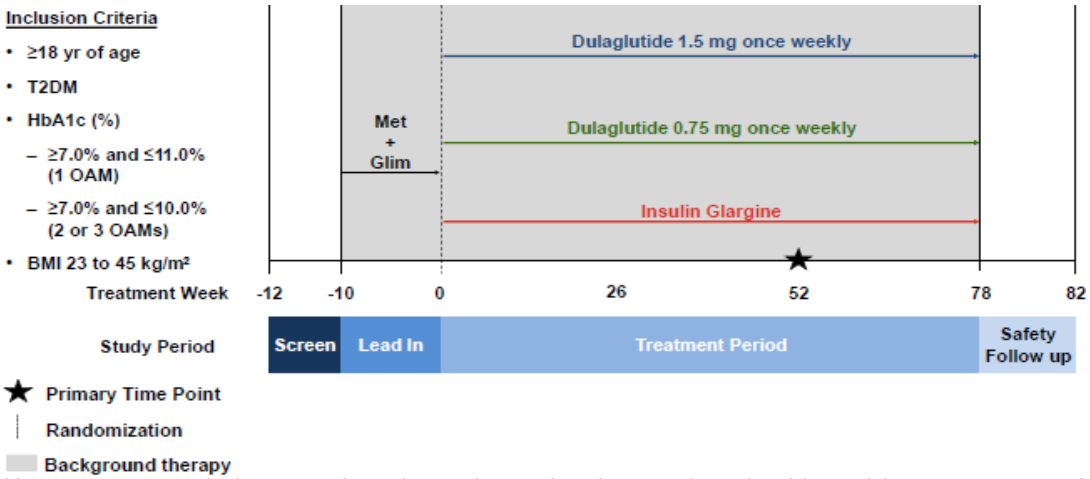
Patients who satisfied the eligibility criteria (at screening, Visit 1) continued in lead-in period (12 weeks; Visits 2 through 5). At Visit 5 eligible patients were randomized in a 2:2:2:1 ratio to the following 4 treatment arms: dulaglutide 1.5 mg/week; dulaglutide 0.75 mg/week; exenatide 5 mcg twice-daily for 4 weeks followed by 10 mcg twice daily; placebo injection once weekly for 26 weeks, followed by a switch (1:1 ratio) to active dulaglutide 1.5 mg/week or 0.75 mg/week. In each arm, patients were also to take metformin (up to 2550 mg/day or the highest tolerable local label dose) and pioglitazone (up to 45 mg/day or the highest tolerable local label dose) after up-titration during the lead-in period, and continuing throughout the treatment period (unless dose modifications were required). The main phase of the trial was the open-label to comparator and double-blind to dulaglutide dose assignment and placebo initial treatment period (26 weeks; Visits 5 through 10) followed by a safety treatment period (26 weeks; Visits 10 through 12).

Study H9X-MC-GBDB

A Randomized, Open-Label, Parallel-Arm, Noninferiority Comparison of the Effects of 2 Doses of LY2189265 and Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Glimepiride (AWARD-2: Assessment of Weekly AdministRation of LY2189265 in Diabetes-2)

Study **GBDB** was an open-label comparator (double-blind with respect to dulaglutide dose assignment), parallel-arm, randomized, 78-week treatment study with 4 study periods: a lead-in period of approximately 10 weeks, a treatment period of 52 weeks, an extended treatment period of 26 weeks, and a safety follow-up period of 4 weeks (Figure 16). The primary objective was to show noninferiority (noninferiority margin 0.4%) of dulaglutide 1.5 mg relative to insulin glargine (titrated-to-target) for HbA1c at 52 weeks (change from baseline) in patients with T2DM who were taking metformin and glimepiride.

Figure 16 Study GBDB design, dulaglutide versus insulin glargine, in combination with metformin +SU.



Abbreviations: BMI = body mass index; Glim = glimepiride; HbA1c = glycosylated hemoglobin A1c; Met = metformin; OAM= oral antihyperglycemic medication; SU = sulphonylurea; T2DM = type 2 diabetes mellitus. a All treatments were added to maximally tolerated doses of metformin and glimepiride.

The study included male and nonpregnant female patients aged ≥18 years with T2DM not optimally controlled with 1, 2, or 3 OAMs (at least 1 of which must have been metformin or a sulphonylurea). At Visit 1 HbA1c was to be (a) ≥7% and ≤11% if on OAM monotherapy for 3 months before screening AND on the minimal monotherapy required dose or higher at Visit 1 (metformin 1500 mg; glimepiride 4 mg; for other sulphonylureas, the minimal required dose must have been at least 50% of the recommended maximum daily dose) OR (b) ≥7 and ≤10% if on 2 or 3 OAMs for 3 months before screening; other allowed OAMs were DPP-IV inhibitors, thiazolidinediones, glinides and alpha-glucosidase inhibitors.

After the lead in phase all patients who continued to meet the eligibility criteria were randomly assigned to 1 of 3 arms (1:1:1): dulaglutide 1.5 mg/week, dulaglutide 0.75 mg/week, or once-daily insulin glargine. In each of the 3 treatment arms, patients also took concomitantly metformin (at least 1500 mg/day or the maximum approved dose in the local label in participating countries) and glimepiride (at least 4 mg/day, or maximum approved dose in the local label in participating countries) starting at Visit 2 and until the last on-treatment visit (unless dose modifications were required). During the initial 4 to 8 weeks of the treatment period (Visits 7 to 8), patients in the insulin glargine arm were expected to achieve optimal glycaemic control; they were required to adjust their insulin dose as needed in order to decrease their fasting plasma glucose (FPG) to the target level (<5.6 mmol/L).

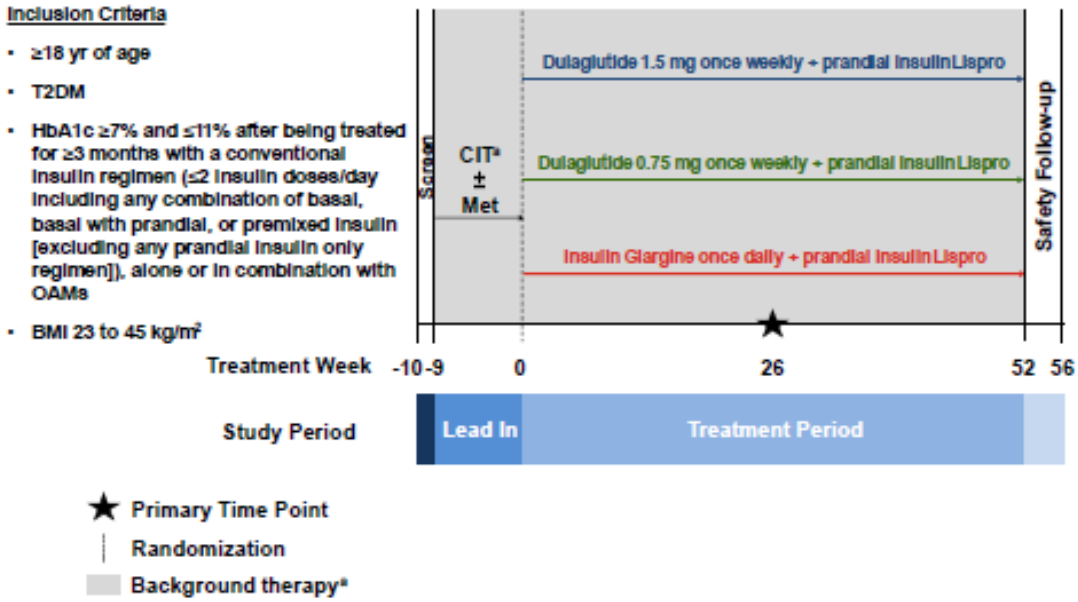
All randomized patients who completed the treatment period, or an early termination visit after starting treatment, were required to complete Visit 17 (LV30), a safety follow-up visit approximately 4 weeks after their last visit.

Study H9X-MC-GBDD

The Impact of LY2189265 versus Insulin Glargine Both in Combination with Insulin Lispro for the Treatment to Target of Type 2 Diabetes Mellitus (AWARD-4: Assessment of Weekly AdministRation of LY2189265 in Diabetes-4)

Study **GBDD** was a parallel-arm, open-label, double-blind (with respect to dulaglutide dose), active comparator study. The study consisted of 3 study periods: a screening and lead-in period of approximately 10 weeks, a 52-week treatment period, and a 4-week safety follow-up period (LV30) for 30 days after the last treatment period visit (Figure 18). The primary objective was to show noninferiority (noninferiority margin 0.4%) of once-weekly SC 1.5-mg dulaglutide to insulin glargine (treated-to-target) on HbA1c at 26 weeks (change from baseline) in patients with T2DM who were treated in combination with prandial insulin lispro with or without metformin.

Figure 18 Study GBDD design, dulaglutide versus insulin glargine, in combination with insulin lispro ± metformin.



Abbreviations: BMI = body mass index; CIT = conventional insulin therapy; HbA1c = glycosylated hemoglobin A1c; Met = metformin; OAM= oral antihyperglycemic medication; T2DM = type 2 diabetes mellitus. a During lead-in and treatment period, metformin was allowed but not mandated. Conventional insulin therapy was continued through the lead-in period, and at randomization patients were switched to one of the three treatment arms.

The study population included male and nonpregnant/non-breastfeeding female T2DM patients age ≥18 years and a screening HbA1c ≥7% and ≤11% after treated for ≥3 months with a conventional insulin regimen (≤2 insulin doses/day including any combination of basal, basal with prandial, or premixed insulin [excluding any prandial insulin only regimen]), alone or in combination with OAMs. Eligible patients must have been on stable doses of insulin (to confirm that increase of therapy was needed). Investigators should use the following criteria to assess whether the most appropriate (or optimized) insulin dose had been administered during a 3 month period: (a) FPG target as suggested in the American Diabetes Association (ADA) and European Association for

the Study of Diabetes (EASD) consensus statement on treatment of T2DM (70–130mg/dL [3.9–7.2mmol/L]); and (b) hypoglycaemia risk associated with insulin dose titration. Patients treated with a multiple daily insulin (MDI) injection regimen (defined as the need to administer ≥3 insulin doses daily, at different timepoints) were considered as ineligible.

After screening at Visit 2 eligible patients were instructed to discontinue all OAMs with the exception of metformin. For patients already on metformin but on a dose <1500 mg/day it was required that the dose be adjusted to reach the final dose (≥1500 mg/day). At Visit 4 (Week 0) patients who had achieved optimal PG control could be considered for discontinuation before randomization. Eligible patients discontinued their current insulin therapy and were randomized (1:1:1) to 1 of 3 treatment groups: prandial insulin lispro in combination with 1.5mg or 0.75mg dulaglutide, or insulin glargine. For patients on metformin, the dose of metformin was to remain unchanged throughout the treatment period, except when allowed by the protocol.

In general, Study GBDD, as a trial aiming at investigating the efficacy and safety of the combination of a new antidiabetic agent with insulin, is unusual as it departs from the most common scenario with the new drug expected to be administered with basal insulin (with or without another OAM like metformin) in non-adequately controlled patients. Instead, dulaglutide was administered as add-on to prandial insulin.

The Applicant suggested that Study GBDD adopted a unique strategy investigating a direct comparison between insulin glargine and dulaglutide as basal treatment for glucose control. This is an interesting concept and the findings of the study are valuable; however, this is an approach not fully in line with current treatment principles and the sequential insulin strategies suggested by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) recommending basal insulin alone as the optimal initial insulin regimen (possibly in conjunction with one to two noninsulin agents), with the addition of shorter-acting insulins when better control is required. Study GBDD does not provide any information about the efficacy and especially the safety of dulaglutide in combination with basal insulin and the current lack of such data in the dulaglutide clinical program is an issue that requires further consideration. The Applicant indicated that, a Phase 3b, randomised, double-blind, placebo-controlled trial (Study GBDI) is currently ongoing, evaluating the glycaemic effects (change in HbA1c) of dulaglutide 1.5 mg once weekly versus placebo in combination with insulin glargine over 28 weeks.

Statistical methods

The primary analysis model was ANCOVA for the change from baseline to endpoint in the ITT population. Missing endpoints were imputed with the last observation carried forward (LOCF). If there was no data after the date of randomization, the endpoint was considered missing and baseline data were not used as an endpoint. This imputation could overestimate the treatment effect in those patients that withdraw due to reasons other than lack of efficacy, such as adverse events, as it will carry forward a good treatment effect even when they can no longer tolerate treatment. The overestimation may be even larger for those subjects that withdraw early in the studies with the primary endpoint at 52 weeks, as it can be seen from the results that the treatments seem to have a greater effect at 26 weeks than at 52.

Sensitivity analyses using MMRM were provided, but these also suffer from the same problem of assuming that patients that withdraw from the study keep benefiting from treatment, therefore the applicant was asked to discuss the pattern of missing data on each treatment and to provide more conservative sensitivity analyses including baseline observation carried forward and multiple imputation. The missing data pattern was similar between treatments and did not raise concerns. The sensitivity analyses provided were also satisfactory and supported the conclusions of the primary analyses, therefore no concerns remain over the handling of missing data.

A tree gatekeeping strategy was used in all studies to control the family-wise Type I error rate across comparisons of dulaglutide versus placebo, dulaglutide versus active comparator and testing for superiority after non-inferiority.

Confidence intervals (CI) were calculated at nominal 95%, 2-sided. These confidence intervals should be interpreted with care as their simultaneous coverage probability is smaller than 95%.

For the additional continuous secondary efficacy measures, the MMRM model was applied; body weight was also analysed using the ANCOVA (LOCF). The analyses of binary outcomes were performed using a logistic regression model (LOCF, also GEE model for repeated outcomes).

Study GBCF was an adaptive inferential seamless phase 2/3 trial. There are 3 main features which make this design "adaptive". First, the probability of a new patient being assigned to a given dulaglutide dose was adapted based on accumulating data in stage 1. Second, dose selection for stage 2 was determined in stage 1 based on accumulating data, third, the sample sizes in stage 1 and stage 2 were determined adaptively. The seamless design permitted a single trial to combine objectives traditionally addressed in separate trials. It allowed the final analysis to use data from patients enrolled before and after the adaptation (that is, inferentially seamless). The seamless component of the design was expected to enable a more robust safety and efficacy assessment of the chosen dulaglutide doses by allowing inclusion of all randomized patients (from both randomization stages) in the planned analyses. In addition, this design would provide longer-term safety data earlier in the clinical development program. Although it seems questionable whether it was meaningful to use this trial design, it appears that no particular concern on the validity of the efficacy conclusions from the trial arises due to the adaptive seamless design, especially since the conclusions still hold when only data from the second stage is analysed. Nevertheless thinking of the results that might eventually populate the SPC, a justification that the two stages of the trial can be combined was requested. The applicant has justified the validity of combining both stages by using simulations that demonstrate the type I error is well controlled, as well as discussing the similarity in patients characteristics for both stages and the consistency of results when both stages are analysed together versus including only Stage 2 subjects. Measures were also put in place to minimise the operational and statistical bias that may be introduced by interim analyses.

Results

NOTE: As in the Methods section the studies are presented not in chronological order but in an order representing the stages of the T2DM treatment continuum from monotherapy, combination with one or more OAMs, and combination with insulin: Studies **GBDC, GBCF, GBDA, GBDB**, and **GBDD**.

Study populations – Baseline data

The T2DM population was generally well represented by the patients participating across the 5 Phase 3 studies with approximately 51.0% males and a mean baseline age of 56.2 years (Table 14). The majority of the patients were white (69.1%) and approximately one-third of the patient population was of Hispanic/Latino ethnicity. Trials were conducted world-wide in a total of 27 countries. Approximately 41.4%, 23.4%, 10.0%, and 25.3% of the patients were enrolled from countries in United States and Canada, Europe, Asia, and other regions, respectively. Across the 5 studies at baseline mean body mass index (BMI) ranged from 31.2 kg/m^2 to 33.3 kg/m^2. 18.5% of patients were at least 65 years of age or older, while 1.9% of patients were at least 75 years of age or older.

Table 14 Summary of Patient Demographics in the Five Long-Term Dulaglutide Phase 3 Studies, ITT

	GBDC (Mono)	GBCF (MET)	GBDA (MET+TZD)	GBDB (MET+SU)	GBDD (Lispro±MET)	Total

ITT, N	807	1098	976	807	884	4572
Sex, n (%)						
Male	353 (43.7)	521 (47.4)	570 (58.4)	414 (51.3)	473 (53.5)	2331 (51.0)
Female	454 (56.3)	577 (52.6)	406 (41.6)	393 (48.7)	411 (46.5)	2241 (49.0)
Age (years)						
Mean (SD)	55.6 (10.4)	54.1 (9.9)	55.6 (9.8)	56.7 (9.5)	59.4 (9.2)	56.2 (9.9)
Median Min;	55.6	54.7	56.1	57.3	59.7	56.7
Max	25.3; 83.6	19.8; 76.3	19.9; 85.7	27.0; 86.5	27.8; 83.8	19.8; 86.5
Age Group, n (%)						
<65 years	664 (82.3)	954 (86.9)	820 (84.0)	646 (80.0)	641 (72.5)	3725 (81.5)
≥65 years	143 (17.7)	144 (13.1)	156 (16.0)	161 (20.0)	243 (27.5)	847 (18.5)
<75 years	786 (97.4)	1096 (99.8)	958 (98.2)	793 (98.3)	853 (96.5)	4486 (98.1)
≥75 years	21 (2.6)	2 (0.2)	18 (1.8)	14 (1.7)	31 (3.5)	86 (1.9)
Ethnicity, n (%)a						
Hispanic/Latino	272 (33.7)	210 (19.1)	331 (33.9)	291 (36.1)	303 (34.3)	1407 (30.8)
Not ispanic/Latino	535 (66.3)	887 (80.8)	644 (66.0)	516 (63.9)	581 (65.7)	3163 (69.2)
Unknown	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.0)
Race, n (%)						
American Indian/Alaskan	85 (10.5)	1 (0.1)	135 (13.8)	89 (11.0)	46 (5.2)	356 (7.8)
Asian	61 (7.6)	273 (24.9)	24 (2.5)	137 (17.0)	35 (4.0)	530 (11.6)
Black/African American	53 (6.6)	44 (4.0)	76 (7.8)	4 (0.5)	85 (9.6)	262 (5.7)
Multiple/Unknown a	7 (0.9)	211 (19.2)	12 (1.2)	7 (0.9)	20 (2.3)	257 (5.6)
Hawaiian/Pacific	1 (0.1)	1 (0.1)	3 (0.3)	0 (0.0)	1 (0.1)	6 (0.1)
White	600 (74.3)	568 (51.7)	726 (74.4)	570 (70.6)	697 (78.8)	3161 (69.1)
Weight at Baseline (kg)						
Mean (SD)	92.3 (18.9)	86.4 (17.3)	96.0 (19.6)	86.3 (18.6)	91.1 (18.4)	90.4 (18.9)
Median	90.2	84.2	94.8	84.8	89.9	88.6
Min; Max	47.0; 173.0	49.5; 156.2	46.0; 157.3	46.6; 152.5	51.0; 154.0	46.0; 173.0
Weight Group at Baseline, n (%)						
<90 kg	396 (49.1)	666 (60.7)	396 (40.6)	488 (60.5)	445 (50.3)	2391 (52.3)
≥90 kg	411 (50.9)	432 (39.3)	580 (59.4)	319 (39.5)	439 (49.7)	2181 (47.7)
BMI at Baseline (kg/m^2)						
Mean (SD)	33.3 (5.5)	31.2 (4.4)	33.2 (5.4)	31.5 (5.5)	32.5 (5.2)	32.3 (5.2)
Median	32.6	30.8	32.8	31.2	31.9	31.8
Min; Max	22.4; 54.3	22.9; 51.2	21.3; 48.0	21.0; 45.7	19.8; 46.8	19.8; 54.3
BMI Group at Baseline, n (%)						
<25 kg/m^2	35 (4.3)	50 (4.6)	57 (5.8)	93 (11.5)	45 (5.1)	280 (6.1)
≥25 and <30 kg/m^2	210 (26.0)	437 (39.8)	242 (24.8)	247 (30.6)	260 (29.4)	1396 (30.5)
≥30 and <35 kg/m^2	273 (33.8)	358 (32.6)	321 (32.9)	269 (33.3)	316 (35.7)	1537 (33.6)
≥35 kg/m^2	289 (35.8)	253 (23.0)	356 (36.5)	198 (24.5)	263 (29.8)	1359 (29.7)

Abbreviations: BMI = body mass index; eCRF = electronic case report form; ITT = intent-to-treat; Lispro = insulin lispro; Max = maximum; MET = metformin; Min = minimum; n = number of patients in category; N = number of patients; SD = standard deviation; SU = sulphonylurea; TZD = thiazolidinedione. a Ethnicity was not collected in Study GBCF. However, Hispanic was listed as a choice in the eCRF for race; therefore, those patients who selected Hispanic have been noted as such for ethnicity analyses and have their race noted as unknown.

Duration of diabetes ranged from 2.6 [Study GBDC] to 12.7 years [Study GBDD] and previous antidiabetic treatments reflected the prespecified inclusion criteria in each study. Mean baseline HbA1c ranged from 7.6% (Study GBDC) to 8.5% (Study GBDD), mean FBG at baseline ranged from 153.9 mg/dL (8.5 mmol/L; Study GBDD) to 174.5 mg/dL (9.7 mmol/L; Study GBCF), and mean PPG at baseline ranged from 190.2 mg/dL (10.56 mmol/L; Study GBDB) to 203.0 mg/dL (11.27 mmol/L; Study GBDD).

Table 15 Summary of Diabetes Disease Characteristics in the Five Long-Term Dulaglutide Phase 3 Studies, ITT

	GBDC (Mono)	GBCF (MET)	GBDA (MET+TZD)	GBDB (MET+SU)	GBDD (Lispro ±MET)	Total
ITT, N	807	1098	976	807	884	4572
Duration of Diabetes (yrs)						
Mean (SD)	2.6 (1.8)	7.1 (5.2)	8.8 (5.6)	9.1 (6.0)	12.7 (7.0)	8.1 (6.3)
Median	2.5	6.0	8.0	8.0	11.8	7.0

Min; Max	0.1; 25.0	1.0; 34.0	0.3; 42.0	0.3; 38.0	0.4; 53.0	0.1; 53.0
Duration of Diabetes Group, n (%)						
<10 years	803 (99.5)	815 (74.2)	582 (59.6)	484 (60.0)	300 (33.9)	2984 (65.3)
≥10 years	4 (0.5)	283 (25.8)	394 (40.4)	323 (40.0)	584 (66.1)	1588 (34.7)
Antidiabetic Treatment at Screening, n (%)						
No OAMa	201 (24.9)b	63 (5.7)	11 (1.1)	0 (0.0)	0 (0.0)	275 (6.0)
1 OAMa	606 (75.1)b	728 (66.3)	241 (24.7)	128 (15.9)	0 (0.0)	1703 (37.2)
>1 OAMa	0 (0.0)	307 (28.0)	724 (74.2)	679 (84.1)	0 (0.0)	1710 (37.4)
Insulin±OAM(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	884 (100)	884 (19.3)
Unknown	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
HbA1c (%) at Baseline						
Mean (SD)	7.6 (0.9)	8.1 (1.1)	8.1 (1.3)	8.1 (1.0)	8.5 (1.0)	8.1 (1.1)
Median	7.4	7.9	7.7	8.0	8.3	7.9
Min; Max	6.0; 11.3	4.9; 13.9	6.2; 13.8	6.6; 13.3	6.0; 13.0	4.9; 13.9
HbA1c (%) Group at Baseline, n (%)						
<8.5%	658 (81.5)	745 (67.9)	667 (68.3)	523 (64.8)	470 (53.2)	3063 (67.0)
≥8.5%	149 (18.5)	351 (32.0) 2	309 (31.7)	284 (35.2)	405 (45.8)	1498 (32.8)
Unknown	0 (0.0)	(0.2)	0 (0.0)	0 (0.0)	9 (1.0)	11 (0.2)
FBG (mg/dL) at Baselinec, d						
Mean (SD)	162.1 (47.0)	174.5 (54.5)	162.0 (53.5)	163.2 (48.5)	153.9 (53.2)	163.7 (52.2)
Median	151.2	162.3	149.4	156.6	147.6	153.0
Min; Max	72.0; 419.4	48.6; 403.2	59.4; 415.8	43.2; 343.8	41.4; 437.4	41.4; 437.4
Mean PPG (mg/dL) at Baselinec, d						
Mean (SD)	193.5 (49.6)	NA	201.9 (56.3)	190.2 (47.5)	203.0 (48.1)	197.5 (51.0)
Median	184.1	NA	189.8	182.1	197.2	188.7
Min; Max	95.8; 439.8	NA	107.8; 465.7	82.7; 428.5	104.0; 384.9	82.7; 465.7

Abbreviations: FBG = fasting blood glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; IVRS = interactive voice response system; Lispro = insulin lispro; Max = maximum; MET = metformin; Min = minimum; n = number of patients in category; N = number of patients; NA = not applicable; OAM = oral antihyperglycaemic medication; PPG = postprandial glucose (self-onitored); SU = sulphonylurea; TZD = thiazolidinedione.

Within each study, treatment groups were well balanced with regard to baseline demographics and diabetes characteristics.

In general, the main studies included a wide range of patients with T2DM that, to a large extent, appear to represent well the intended target population. Depending on the specific requirements of the each study, patients with less to more advanced disease were examined, as indicated by the range of the duration of diabetes and the glycaemic parameters. This also ensures a decent representation of common coexisting conditions and risk factors. However, there are some limitations.

In all five Phase 3 studies, 18.5% of patients were 65 years or older, but there were only 86 patients (1.9%) above 75 years, a small number that may not be sufficient to permit clear conclusions about the benefit:risk of dulaglutide in this age group. In addition, as also discussed in the Methods section above, patients with certain conditions (mostly reflecting contraindications of the comparators or background therapy, particularly metformin) including moderate and severe renal failure, advanced heart failure or hepatic abnormalities were mostly excluded from the trials. Further justification will be required for the use dulaglutide in all the above patient groups that have not been sufficiently examined.

It is noted that approximately 23% of patients were from Europe (from 23.4% in study GBDD to 37.3% in study GBDB; study GBDA was carried out in US and Latin America), which is sufficient to ensure a good representation of European clinical standards.

Summary of main studies

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).

Title: GBDC - the impact of dulaglutide versus metformin on glycemic control in early type 2 diabetes mellitus (AWARD-3: Assessment of weekly administration of Dulaglutide in diabetes-3)		
Study design	52-week, multicentre, randomised, parallel-arm, active comparator, double-blind, double-dummy, non-inferiority monotherapy study to compare glycemic control achieved with 2 doses of dulaglutide (1.5 mg or 0.75 mg once-weekly) or metformin in patients with early T2DM. The study consisted of 3 periods: a lead-in period of approximately 2 weeks, a 52-week treatment period, and a 4 week safety follow-up period. An optional test meal addendum was also part of the study	
Primary objectives	To demonstrate the effect of once-weekly dulaglutide 1.5 mg injected subcutaneously compared to metformin on HbA_{1c} change from baseline at 26 weeks in patients with early T2DM.	
Hypothesis	Non-inferiority	
Treatments groups	Dulaglutide 1.5 mg/week + oral placebo Dulaglutide 0.75 mg/week + oral placebo Metformin 1500 mg/day or 2000 mg/day + injectable placebo	Number of subjects treated by treatment group: <u>Main Study:</u> dulaglutide 1.5 mg/week + oral placebo N=269, dulaglutide 0.75 mg/week + oral placebo N=270 metformin 1500 mg/day or 2000 mg/day + injectable placebo N=268 <u>Test Meal Addendum:</u> dulaglutide 1.5 mg/week, N=133; dulaglutide 0.75 mg/week, N=136; metformin N=140
Duration of Run-in Period	2-week lead-in period	
Duration of treatment	52 weeks double-blind treatment period, 4 week safety follow-up period	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline at week 26
	Secondary	Change from baseline at week 26 in: Fasting serum glucose (FSG) Patients at target HbA_{1c} <7.0% or ≤6.5% Body weight
Database lock date	30 August 2012	
Primary analysis description	Analysis of covariance (ANCOVA) model for the change from baseline to endpoint, with treatment, country, and prior medication group (not on OAM versus on OAM) as fixed effects and HbA_{1c} baseline value as a covariate. Missing endpoints were imputed with LOCF (post-baseline values only). A tree gate-keeping strategy to control the family-wise Type 1 error was used for a superiority comparison of dulaglutide 1.5 mg/week vs. metformin and non-inferiority and superiority comparisons of dulaglutide 0.75 mg/week vs. metformin.	
Analysis population	Number of subjects in ITT population (Main Study): dulaglutide 1.5 mg/week N=269, dulaglutide 0.75 mg/week N=270, metformin N=268; completed 26 weeks dulaglutide 1.5 mg/week N=233, dulaglutide 0.75 mg/week N=242, Metformin N=226	
Primary efficacy results (Main Study)	Baseline	Week 26
	HbA_{1c} Mean (SD): Dulaglutide 1.5 mg/week 7.63 (0.92) Dulaglutide 0.75 mg/week 7.58 (0.87) Metformin 7.60 (0.82)	Change in HbA_{1c} , LS mean difference (SE): Dulaglutide 1.5 mg/week -0.78 (0.06) Dulaglutide 0.75 mg/week -0.71 (0.06) Metformin -0.56 (0.06) LS Mean Difference (95% CI) vs. metformin: Dulaglutide 1.5 mg/week -0.22 (-0.36, -0.08) Dulaglutide 0.75 mg/week -0.15 (-0.29, -0.01)
	P value (multiplicity adjusted, 1-sided):	Dulaglutide 1.5 mg/week vs. metformin <0.001 for non-inferiority, 0.002 for superiority Dulaglutide 0.75 mg/week vs. metformin <0.001 for non-inferiority, 0.02 for superiority
Secondary Results (Main Study)	FSG (mmol/l), change from baseline at week 26, MMRM, LS mean (SE): Dulaglutide 1.5 mg/week -1.61 (0.13) Dulaglutide 0.75 mg/week -1.46 (0.13) Metformin -1.34 (0.13)	
	Patients at target HbA_{1c} <7.0% or ≤6.5% at week 26, logistic regression (LOCF): Dulaglutide 1.5 mg/week 61.5%, 46% Dulaglutide 0.75 mg/week 62.6%, 40%	

	Metformin 53.6%, 29.8%
	Body Weight (kg), change from baseline at Week 26, ANCOVA, LOCF, LS Mean (SE): Dulaglutide 1.5 mg/week -2.29 (0.24) Dulaglutide 0.75 mg/week -1.36 (0.24) Metformin -2.22 (0.24)

Title: GBCF - a phase 2/3, placebo controlled, efficacy and safety study of once- weekly, subcutaneous dulaglutide compared to sitagliptin in patients with T2DM on metformin		
Study design	Study GBCF was an adaptive, inferentially seamless, Phase 2/3, outpatient multicenter, randomized, placebo-controlled, 24-month, double-blind, parallel clinical trial comparing once-weekly dulaglutide to once-daily sitagliptin (100 mg) and to placebo in patients with T2DM on metformin. The treatment period for Study GBCF was 24 months, with database locks at 12 and 24 months. The placebo period lasted up to 6 months	
Primary objectives	To demonstrate that the glycemic control of the high dose of dulaglutide selected at the decision point is noninferior to that of sitagliptin at 52 weeks, as measured by HbA_{1c} change from baseline in patients with T2DM on metformin. The noninferiority margin was 0.25%. The trial design also incorporated an initial dose-finding stage to enable selection of 1 or 2 doses of dulaglutide (from the 0.25 to 3.0 mg range) to be assessed in the confirmatory part of thestudy and the remainder of the phase 3 program	
Hypothesis	Non-inferiority	
Treatments groups	Background metformin therapy in all treatment groups (oral daily dose ≥1500 mg/day) Stage 1: Dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, and 3.0 mg) injected SC once weekly+ oral placebo Stage 2: Dulaglutide 0.75, and 1.5 mg/week + oral placebo Sitagliptin 100 mg/day+ injectable placebo Placebo:oral placebo+ injectable placebo (switched blinded after 6 months to Sitagliptin 100 mg/day+ injectable placebo)	Number of subjects treated by treatment group: Dose-finding (phase 1 adaptive randomization): N=230; 38 placebo/sitagliptin; 42 sitagliptin; 24 dulaglutide 0.25 mg; 25 dulaglutide 0.5 mg; 21 dulaglutide 0.75 mg; 10 dulaglutide 1.0 mg; 25 dulaglutide 1.5 mg; 30 dulaglutide 2.0 mg, 15 dulaglutide 3.0 mg. Primary treatment arms (stage 1 and stage 2 adaptive and fixed-allocation randomization): N=1098; 177 placebo/sitagliptin; 315 sitagliptin; 302 dulaglutide 0.75 mg; 304 dulaglutide 1.5 mg Primary treatment arms (stage 2 fixed randomization only): N=972; 139 placebo/sitagliptin; 273 sitagliptin; 281 dulaglutide 0.75 mg; 279 dulaglutide 1.5 mg
Duration of Run-in Period	4 to 11 week lead-in period	
Duration of treatment	104 weeks double-blind treatment period including 26 weeks placebo treatment (blinded switch to sitagliptin), 4 week safety follow-up period	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline at week 52
	Secondary	Change from baseline at week 52 in: Fasting serum glucose (FSG) Patients at target HbA_{1c} <7.0% or ≤6.5% Body weight
Database lock date	27 August 2012	
Primary analysis description	Analysis of covariance (ANCOVA) with fixed effects for treatment, country, and baseline HbA_{1c} as a covariate. Missing endpoints were imputed with LOCF. Key secondary efficacy measures included change in HbA1c from baseline at 6 and 12 months. The analyses for the primary and key secondary objectives comprised 6 ordered hypotheses for non-inferiority and superiority using a tree-gatekeeping testing strategy to control the family-wise Type 1 error rate. All analyses were conducted using patients randomized to the primary treatment arms throughout the study. An adjusted, nominal family-wise 1-sided alpha of .02 was used for the analysis of the primary objective and key secondary objectives to account for potential selection bias (alpha level of .025, 1-sided). Selected analyses were repeated for patients randomized using the fixed-allocation strategy (Stage 2 randomization) alone. These were conducted without adjustment to the	

	nominal-alpha level (no potential for selection bias).	
Analysis population	Results presented for: ITT Primary treatment arms, adaptive and fixed-allocation randomization: N=1098; 177 placebo/sitagliptin; 315 sitagliptin; 302 dulaglutide 0.75 mg; 304 dulaglutide 1.5 mg	
Primary efficacy results	Baseline	Week 52 (week 26 vs. placebo)
	HbA_{1c} Mean (SD): Dulaglutide 1.5 mg/week 8.12 (1.05) Dulaglutide 0.75 mg/week 8.19 (1.11) Sitagliptin 8.09 (1.09) Placebo/ Sitagliptin 8.10 (1.14)	Change in HbA_{1c} , LS mean difference (SE): Dulaglutide 1.5 mg/week -1.10 (0.06) Dulaglutide 0.75 mg/week -0.87 (0.06) Sitagliptin -0.39 (0.06) Placebo 0.03 (0.07) at week 26 LS Mean Difference (nominal 95% CI) vs. sitagliptin: Dulaglutide 1.5 mg/week -0.71 (-0.87, -0.55) Dulaglutide 0.75 mg/week -0.47 (-0.63, -0.31) LS Mean Difference (nominal 95% CI) vs. placebo/sit: Dulaglutide 1.5 mg/week -1.26 (-1.42, -1.09) Dulaglutide 0.75 mg/week -1.05 (-1.21, -0.88)
	P value (multiplicity adjusted, 1-sided):	Dulaglutide 1.5 mg/week vs. sitagliptin <0.001 for non-inferiority, <0.001 for superiority Dulaglutide 0.75 mg/week vs. sitagliptin <0.001 for non-inferiority, <0.001 for superiority Dulaglutide 1.5 mg/week vs. placebo/sit <0.001 for superiority Dulaglutide 0.75 mg/week vs. placebo/sit <0.001 for superiority
Secondary Results	FPG (mmol/l), change from baseline at week 52, MMRM, LS mean (SE): Dulaglutide 1.5 mg/week -2.38 (0.13) Dulaglutide 0.75 mg/week -1.63 (0.13) Sitagliptin -0.90 (0.13) Placebo/ sit -0.92 (0.18)	
	Patients at target HbA_{1c} <7.0% or ≤6.5% at week 52, logistic regression (LOCF): Dulaglutide 1.5 mg/week 57.6%, 41.7% Dulaglutide 0.75 mg/week 48.8%, 29.0% Sitagliptin 33.0%, 19.2% Placebo/sit 34.7%, 24.4%	
	Body Weight (kg), change from baseline at Week 52, ANCOVA, LOCF, LS Mean (SE): Dulaglutide 1.5 mg/week -3.03 (0.22) Dulaglutide 0.75 mg/week -2.60 (0.23) Sitagliptin -1.53 (0.22) Placebo/sit -1.61 (0.29)	

Title: GBDA: a randomized, placebo-controlled comparison of the effects of two doses of dulaglutide or exenatide on glycemic control in patients with type 2 diabetes on stable doses of metformin and pioglitazone (AWARD-1: Assessment of weekly administration of LY2189265 in diabetes-1)		
Study design	Study GBDA was a 12-month, Phase 3, outpatient, parallel-arm, placebo-controlled, active comparator study comparing the safety and glycemic control achieved with 2 doses of dulaglutide, open-label exenatide, or placebo, in patients with type 2 diabetes mellitus treated with maximally tolerated concomitant oral metformin and pioglitazone. The study consisted of 4 periods: a 12-week lead-in period during which all patients were required to take metformin and pioglitazone in maximally tolerated doses. A 26-week initial (dulaglutide vs. placebo) treatment period followed by a 26-week safety treatment period and a 4-week safety follow-up period	
Primary objectives	The primary objective of this study was to demonstrate the superiority of once-weekly dulaglutide 1.5 mg injected subcutaneously versus placebo on change from baseline in HbA_{1c} at 26 weeks in patients with T2DM who were taking maximally tolerated doses of metformin and pioglitazone.	
Hypothesis	Superiority	
Treatments groups	Dulaglutide 0.75 mg/week Dulaglutide 1.5 mg/week	Number of subjects treated by treatment group: Randomized N=978 dulaglutide 1.5 mg/week N=279

	Exenatide 10 mcg twice daily Placebo + <u>in each of the 4 treatment arms</u> metformin (up to 2550 mg/day or the highest tolerable local label dose) and pioglitazone (up to 45 mg/day or the highest tolerable local label dose)	dulaglutide 0.75 mg/week N=280 exenatide N=278 placebo N=141
Duration of Run-in Period	12 week lead-in period	
Duration of treatment	52 weeks double-blind treatment period including 26 weeks placebo treatment (switch to dulaglutide 0.75 or 1.5 mg/week), 4 week safety follow-up period	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline at week 26
	Secondary	Change from baseline at week 26 in: Fasting serum glucose (FSG) Patients at target HbA_{1c} <7.0% or ≤6.5% Body weight
Database lock date	10 July 2012, re-opening and re-lock for optimization of dulaglutide ADA	
Primary analysis description	Analysis of covariance (ANCOVA) with fixed effects for treatment, country and baseline HbA_{1c} as a covariate. Missing endpoints were imputed with LOCF. The analyses for the primary and key secondary objectives comprised ordered hypotheses using a tree-gatekeeping testing strategy to control the family-wise type 1 error rate. Key secondary objectives compared HbA_{1c} for dulaglutide (1.5 mg and 0.75 mg) and exenatide as well as placebo for non-inferiority and superiority at 26 weeks. A non-inferiority margin of 0.4% was defined.	
Analysis population	ITT population dulaglutide 1.5 mg/week N=279 dulaglutide 0.75 mg/week N=280 exenatide N=278 placebo N=141	
Primary efficacy results	Baseline	Week 26
	HbA_{1c} Mean (SD): Dulaglutide 1.5 mg/week 8.10 (1.34) Dulaglutide 0.75 mg/week 8.05 (1.24) Exenatide 8.07 (1.34) Placebo 8.06 (1.31)	Change in HbA_{1c} , LS mean difference (SE): Dulaglutide 1.5 mg/week -1.51 (0.06) Dulaglutide 0.75 mg/week -1.30 (0.06) Exenatide -0.99 (0.06) Placebo -0.46 (0.08) LS Mean Difference (<u>nominal</u> 95% CI) vs. placebo: Dulaglutide 1.5 mg/week -1.05 (-1.22, -0.88) Dulaglutide 0.75 mg/week -0.84 (-1.01, -0.67) LS Mean Difference (nominal 95% CI) vs. exenatide: Dulaglutide 1.5 mg/week -0.52 (-0.66, -0.39) Dulaglutide 0.75 mg/week -0.31 (-0.44, -0.18)
	P value (multiplicity adjusted, 1-sided):	Dulaglutide 1.5 mg/week vs. placebo <0.001 Dulaglutide 0.75 mg/week vs. placebo <0.001 Dulaglutide 1.5 mg/week vs. exenatide <0.001 for non-inferiority, <0.001 for superiority <0.001 Dulaglutide 0.75 mg/week vs. exenatide <0.001 for non-inferiority, <0.001 for superiority
Secondary Results	FPG (mmol/l), change from baseline at week 26, MMRM, LS mean (SE): Dulaglutide 1.5 mg/week -2.36 (0.12) Dulaglutide 0.75 mg/week -1.90 (0.12) Exenatide -1.35 (0.12) Placebo-0.26 (0.17)	
	Patients at target HbA_{1c} <7.0% or ≤6.5% at week 26, logistic regression (LOCF): Dulaglutide 1.5 mg/week 78.2%, 62.7% Dulaglutide 0.75 mg/week 65.8%, 53.2% Exenatide 52.3%, 38.0% Placebo 42.9%, 24.4%	

	Body Weight (kg), change from baseline at Week 26, ANCOVA, LOCF, LS Mean (SE): Dulaglutide 1.5 mg/week -1.30 (0.29) Dulaglutide 0.75 mg/week 0.20 (0.29) Exenatide -1.07 (0.29) Placebo 1.24 (0.37)

Title: GBDB - a randomized, open-label, parallel-arm, non-inferiority comparison of the effects of 2 doses of LY2189265 and Insulin Glargine on glycemic control in patients with type 2 diabetes on stable doses of metformin and glimepiride (AWARD-2: Assessment of weekly administration of LY2189265 in Diabetes)		
Study design	Open-label comparator (double blind with respect to dulaglutide dose assignment), parallel arm, randomized, multicenter, 78-week treatment study with 4 study periods: a 10-week lead-in period, a 52-week treatment period, a 26-week extended treatment period, and a 4-week safety follow-up period. All patients who continued to meet eligibility criteria (a. o. ,who remained hyperglycemic despite therapy with a combination of metformin and glimepiride at maximal and stable doses) were randomly assigned to 1 of 3 arms (1:1:1): dulaglutide 1.5 mg/week, dulaglutide 0.75 mg/week, or once-daily insulin glargine	
Primary objectives	The primary objective of this study was to compare the effect of once-weekly dulaglutide 1.5 mg to that of insulin glargine (titrated to target) on change in HbA_{1c} from baseline at 52 weeks in patients with T2DM who were taking metformin and glimepiride. Non-inferiority relative to insulin glargine was assessed using a non-inferiority margin of 0.4%.	
Hypothesis	Non-inferiority	
Treatments groups	Dulaglutide 1.5 mg/week Dulaglutide 0.75 mg/week Insulin glargine titrated to target + in each of the 3 treatment arms metformin and glimepiride in doses established during the lead-in period	Number of subjects treated by treatment group: Randomized N=810, ITT=807 dulaglutide 1.5 mg/week N=273 dulaglutide 0.75 mg/week N=272 Insulin glargine N=262
Duration of Run-in Period	10 week lead-in period	
Duration of treatment	52 weeks open-label (double –blind with respect to dulaglutide dose), 4 week safety follow-up period	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline at week 52
	Secondary	Change from baseline at week 52 in: Fasting serum glucose (FSG) Patients at target HbA_{1c} <7.0% or ≤6.5% Body weight
Database lock date	18 June 2012, re-opening and re-lock for optimization of dulaglutide ADA	
Primary analysis description	Analysis of covariance (ANCOVA) with fixed effects for treatment, country and baseline HbA_{1c} as a covariate for assessment of non-inferiority of dulaglutide 1.5 mg/week compared to insulin glargine. Missing endpoints were imputed with LOCF. The analyses for the primary and key secondary objectives comprised ordered hypotheses using a gate-keeping strategy to control the family-wise type 1 error rate. Key secondary objectives compared HbA_{1c} for dulaglutide (1.5 mg and 0.75 mg) and insulin glargine for non-inferiority and superiority at 52 weeks	
Analysis population	ITT population N=807, dulaglutide 1.5 mg/week N=273, dulaglutide 0.75 mg/week N=272,insulin glargine N=262	
Primary efficacy results	Baseline	Week 52
	HbA_{1c} Mean (SD): Dulaglutide 1.5 mg/week 8.18	Change in HbA_{1c} , LS mean difference (SE): Dulaglutide 1.5 mg/week -1.08 (0.06)

	(1.03) Dulaglutide 0.75 mg/week 8.13 (0.98) Insulin glargine 8.10 (0.95)	Dulaglutide 0.75 mg/week -0.76 (0.06) Insulin glargine -0.63 (0.06) LS Mean Difference (nominal 95% CI) vs. insulin glargine: Dulaglutide 1.5 mg/week -0.45 (-0.60, -0.29) Dulaglutide 0.75 mg/week -0.13 (-0.29, 0.02)
	P value (multiplicity adjusted, 1-sided):	Dulaglutide 1.5 mg/week vs. insulin glargine <0.001 for non-inferiority, <0.001 for superiority Dulaglutide 0.75 mg/week vs. insulin glargine <0.001 for non-inferiority, 0.05 for superiority
Secondary Results	FPG (mmol/l), change from baseline at week 52, MMRM, LS mean (SE): Dulaglutide 1.5 mg/week -1.50(0.14) Dulaglutide 0.75 mg/week -0.87 (0.14) Insulin glargine -1.76 (0.14)	
	Patients at target HbA_{1c} <7.0% or ≤6.5% at week 52, logistic regression (LOCF): Dulaglutide 1.5 mg/week 53.2%, 27.0% Dulaglutide 0.75 mg/week 37.1%, 22.5% Insulin glargine 30.9%, 13.5%	
	Body Weight (kg), change from baseline at Week 52, ANCOVA, LOCF, LS Mean (SE): Dulaglutide 1.5 mg/week -1.87 (0.24) Dulaglutide 0.75 mg/week -1.33 (0.24) Insulin glargine 1.44 (0.24)	

Title: GBDD - the Impact of LY2189265 versus Insulin Glargine Both in Combination with Insulin Lispro for the Treatment to Target of Type 2 Diabetes Mellitus (AWARD-4: Assessment of Weekly AdministRation of LY2189265 in Diabetes – 4)		
Study design	A 52-week, phase 3, open-label comparator (double blind with respect to dulaglutide dose assignment), parallel, active comparator, outpatient trial to assess the safety and efficacy of dulaglutide compared with insulin glargine both in combination with prandial insulin lispro (with or without metformin). Random treatment assignment was to 1 of 3 arms (1:1:1): dulaglutide 1.5 mg/week, dulaglutide 0.75 mg/week, or once-daily insulin glargine.	
Primary objectives	The primary objective was to compare effects of of once-weekly dulaglutide 1.5 mg to that of insulin glargine (treated to target) on change in HbA_{1c} from baseline at 52 weeks in patients with T2DM, both in combination with prandial insulin lispro. Non-inferiority relative to insulin glargine was assessed using a non-inferiority margin of 0.4%.	
Hypothesis	Non-inferiority	
Treatments groups	Dulaglutide 1.5 mg/week Dulaglutide 0.75 mg/week Insulin glargine titrated to target + in each of the 3 treatment arms with prandial insulin lispro (with or without metformin)	Number of subjects treated by treatment group: Randomized N=884, ITT=884 dulaglutide 1.5 mg/week N=295 dulaglutide 0.75 mg/week N=293 Insulin glargine N=296
Duration of Run-in Period	9 week lead-in period	
Duration of treatment	52 weeks open-label (double –blind with respect to dulaglutide dose), 4 week safety follow-up period	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline at week 26
	Secondary	Change from baseline at week 26 in: Fasting serum glucose (FSG) Patients at target HbA_{1c} <7.0% or ≤6.5% Body weight
Database lock date	19 November 2012, re-opening and re-lock for optimization of dulaglutide ADA	
Primary analysis description	Analysis of covariance (ANCOVA) with fixed effects for treatment, country and baseline HbA_{1c} as a covariate for assessment of non-inferiority of dulaglutide 1.5 mg/week compared to insulin glargine. Missing endpoints were imputed with LOCF.	

	The analyses for the primary and key secondary objectives comprised ordered hypotheses using a gate-keeping strategy to control the family-wise type 1 error rate. Key secondary objectives compared HbA_{1c} for dulaglutide (1.5 mg and 0.75 mg) and insulin glargine for non-inferiority and superiority at 26 weeks	
Analysis population	ITT population N=884, dulaglutide 1.5 mg/week N=295, dulaglutide 0.75 mg/week N=293,insulin glargine N=296	
Primary efficacy results	Baseline	Week 26
	HbA_{1c} Mean (SD): Dulaglutide 1.5 mg/week 8.46 (1.08) Dulaglutide 0.75 mg/week 8.40 (1.03) Insulin glargine 8.53 (1.03)	Change in HbA_{1c} , LS mean difference (SE): Dulaglutide 1.5 mg/week -1.64 (0.07) Dulaglutide 0.75 mg/week -1.59 (0.07) Insulin glargine -1.41 (0.07) LS Mean Difference (nominal 95% CI) vs. insulin glargine: Dulaglutide 1.5 mg/week -0.22 (-0.38, -0.07) Dulaglutide 0.75 mg/week -0.17 (-0.33, -0.02)
	P value (multiplicity adjusted, 1-sided):	Dulaglutide 1.5 mg/week vs. insulin glargine <0.001 for non-inferiority, 0.005 for superiority Dulaglutide 0.75 mg/week vs. insulin glargine <0.001 for non-inferiority, 0.015 for superiority
Secondary Results	FPG (mmol/l), change from baseline at week 26, MMRM, LS mean (SE): Dulaglutide 1.5 mg/week -0.27 (0.20) Dulaglutide 0.75 mg/week 0.22 (0.20) Insulin glargine -1.58 (0.20)	
	Patients at target HbA_{1c} <7.0% or ≤6.5% at week 26, logistic regression (LOCF): Dulaglutide 1.5 mg/week 67.6%, 48.0% Dulaglutide 0.75 mg/week 69.0%, 43.0% Insulin glargine 56.8%, 37.5% Patients at target HbA1c <7% at week 26 without documented symptomatic hypoglycemia. Dulaglutide 1.5mg/week 20.7% Dulaglutide 0.75 mg/week 20.9% Insulin glargine 12.9% Patients at target HbA1c <7% at week 26 without nocturnal or severe hypoglycemia: Dulaglutide 1.5 mg: 53.8% Dulaglutide 0.75 mg: 54.5% Insulin glargine: 28.2%	
	Body Weight (kg), change from baseline at Week 26, ANCOVA, LOCF, LS Mean (SE): Dulaglutide 1.5 mg/week -0.87 (0.27) Dulaglutide 0.75 mg/week 0.18 (0.27) Insulin glargine 2.33 (0.27)	

In addition to the above, as part of their Day 121 responses the Applicant also submitted the findings of the recently completed of Study H9X-MC-**GBDE** (A Randomized, Open-Label, Parallel-Arm Study Comparing the Effect of Once-Weekly Dulaglutide with Once-Daily Liraglutide in Patients with Type 2 Diabetes). This was a Phase 3b, multicenter, randomised, outpatient, open-label, parallel-arm, 32-week, active comparator noninferiority trial in adult T2DM with HbA1c ≥7.0% to ≤10% not optimally controlled with diet and exercise and a dose of metformin that was at least 1500 mg/day. The main aspects are shown below**.**

Title: GBDE - A Randomized, Open-Label, Parallel-Arm Study Comparing the Effect of Once-Weekly Dulaglutide with Once-Daily Liraglutide in Patients with Type 2 Diabetes (AWARD-6: Assessment of Weekly AdministRation of LY2189265 in Diabetes-6)	
Study design	A Phase 3b, multicenter, randomised, outpatient, open-label, parallel-arm, 32 week, active comparator noninferiority trial with 3 study periods: a screening period lasting 2 weeks; a treatment period lasting 26 weeks; and a safety follow-up period lasting 4 weeks.
Primary objectives	The primary objective of this study was to demonstrate that once weekly dulaglutide 1.5 mg was noninferior to once-daily liraglutide 1.8 mg as measured by change from baseline in HbA1c at 26 weeks in patients with T2DM who were taking concomitant metformin. The noninferiority margin was 0.4%.

Hypothesis	Non-inferiority	
Treatments groups	Background metformin therapy in all treatment groups (oral daily dose ≥1500 mg/day) Dulaglutide 1.5 mg, given once weekly as a subcutaneous injection. Liraglutide once daily as an injection, 0.6 mg for the first week, 1.2 mg for the second week, and 1.8 mg for Weeks 3 through 26.	Patients were male or nonpregnant females ⩾18 years of age who had type 2 diabetes, with HbA1c ⩾7.0% to ⩽ 10% (as performed at the central laboratory at Visit 1) and body mass index (BMI) ⩽45 kg/m^2, not optimally controlled with diet and exercise and a dose of metformin that was at least 1500 mg/day and stable for at least 3 months prior to Visit 1 Number of Patients: Planned: 296 dulaglutide, 296 liraglutide Randomised: 299 dulaglutide, 300 liraglutide Treated (at least 1 dose): 299 dulaglutide, 300 liraglutide Completed: 277 dulaglutide, 282 liraglutide
Duration of Run-in Period	2 week lead-in period	
Duration of treatment	26 weeks open-label tretament period, 4 week safety follow-up period	
Endpoints and definitions	Primary	Change in HbA_{1c} from baseline at week 26
	Secondary	Change from baseline at week 26 in: Fasting serum glucose (FSG) Patients at target HbA_{1c} <7.0% or ≤6.5% Body weight Beta cell function
Primary analysis description	Analysis of covariance (ANCOVA) with fixed effects for treatment, country and baseline HbA1c as a covariate for assessment of non-inferiority of dulaglutide 1.5 mg/week compared to liraglutide. Missing endpoints were imputed with MMRM.	
Analysis population	ITT population N=599, dulaglutide 1.5 mg/week N=299, liraglutide 1.8mg/day N=300	
Primary efficacy results	Baseline	Week 26 (ITT, LOCF)
	HbA_{1c} Mean (SD): Dulaglutide 1.5 mg/week 8.06 (0.81) Liraglutide 1.8mg/day 8.05 (1.03)	Change in HbA_{1c} , LS mean difference (SE): Dulaglutide 1.5 mg/week -1.47 (0.05) Liraglutide 1.8mg/day -1.40 (0.05) LS Mean Difference (nominal 95% CI) vs. Liraglutide: Dulaglutide 1.5 mg/week -0.06 (-0.19, +0.07)
	P value (raw, no multiplicity adjusted, 1-sided):	Dulaglutide 1.5 mg/week vs. Liraglutide 1.8mg/day <0.001 for non-inferiority, 0.17 for superiority
Secondary Results	Patients at target HbA_{1c} <7.0% or ≤6.5% at week 26: Dulaglutide 1.5 mg/week 68.3%, 54.6% Liraglutide 1.8mg/day 67.9%, 50.9%	

Study H9X-MC-GBDC

GBDC was the monotherapy study comparing the two dose of dulaglutide with metformin in treatment naïve (24.9%) and patients previously on an OAM (75.1%). The mean duration of diabetes was short, mean 2.6 years, which is expected for this population and with mean baseline HbA1c 7.6%.

Patient disposition related to efficacy for the primary (26 weeks) and final (52 weeks) time points is shown in Table 16. A total of 807 patients were randomized and included in the ITT population. A relatively small percentage of patients discontinued from the study by the time of primary analysis at 26 weeks or needed rescue therapy, with similar numbers between groups. This was also the case for the rest of the trial up to 52 weeks.

Table 16 Patient Disposition (Related to Ineffective Therapy versus Other Reasons), Dulaglutide versus Metformin, ITT, Study GBDC, as Monotherapy

Patient Disposition	Dula 1.5 N=269 n (%)	Dula 0.75 N=270 n (%)	Metformin N=268 n (%)
Primary Time Point (26 weeks)[a]			
Completed	233 (86.6)	242 (89.6)	226 (84.3)
Rescued[b,c]	6 (2.2)	6 (2.2)	7 (2.6)
Discontinued from Study Drug[c]	8 (3.0)	7 (2.6)	5 (1.9)
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	1 (0.4)
Other[e]	8 (3.0)	7 (2.6)	4 (1.5)
Discontinued from Study[c]	36 (13.4)	28 (10.4)	42 (15.7)
Ineffective Therapy[d]	2 (0.7)	3 (1.1)	6 (2.2)
Other[e]	34 (12.6)	25 (9.3)	36 (13.4)
Final Time Point (52 weeks)[f]			
Completed	220 (81.8)	218 (80.7)	213 (79.5)
Rescued[b,c]	12 (4.5)	8 (3.0)	14 (5.2)
Discontinued from Study Drug[c,g]	19 (7.1)	16 (5.9)	14 (5.2)
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	1 (0.4)
Other[e]	19 (7.1)	16 (5.9)	13 (4.9)
Discontinued from Study[c]	49 (18.2)	52 (19.3)	55 (20.5)
Ineffective Therapy[d]	3 (1.1)	4 (1.5)	6 (2.2)
Other[e,g]	46 (17.1)	48 (17.8)	49 (18.3)

Abbreviations: CRF = case report form; ITT = intent-to-treat; n = number of patients in specified category; N = number of patients. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. **a** From randomization to primary time point. **b** Patients required additional antihyperglycaemic intervention for severe, persistent hyperglycemia. **c** Patients may appear in more than 1 category: rescued, discontinued from study drug and/or study. **d** Patients who discontinued the study drug or study for reasons suggestive of ineffective therapy: lack of efficacy, hyperglycemia, diabetes mellitus inadequate control, glycosylated hemoglobin increased, or blood glucose increased. **e** Patients who discontinued the study drug or study for reasons not suggestive of ineffective therapy. **f** From randomization to final time point. **g** One patient in the dulaglutide 0.75-mg group and 1 patient in the metformin group are incorrectly indicated as discontinued from study drug (sponsor decision) due to inadvertent completion of the study drug discontinuation CRF; they simultaneously discontinued the study and study drug and are also included in the discontinued from study (other) group.

The majority of patients assigned to metformin received a 2000-mg dose (191/225 [84.9%] patients and 178/212 [84.0%] patients at 26 and 52 weeks, respectively). At 26 weeks, the mean (SD) dose of metformin was 1902 (286) mg. Approximately 13% of patients received a metformin dose of 1500 mg and approximately 2% of patients received a metformin dose <1500 mg at 26 and 52 weeks.

From baseline to 26 weeks, significant LS mean (SE) reductions in HbA1c were observed in all treatment groups. Dulaglutide 1.5 mg was superior to metformin (LS mean difference, -0.22 % [adjusted p=.002]). Dulaglutide 0.75 mg was also superior to metformin (LS mean difference, -0.15 % [adjusted p=.020]). (Table 17).

Table 17 Summary of Efficacy Measures at the Primary Time Point (26 Weeks), Dulaglutide versus Metformin, ITT, Study GBDC, as Monotherapy; Study GBDC

Outcome Measure[a]	Dula 1.5 N=269	Dula 0.75 N=270	Metformin N=268
HbA1c (%)			
Baseline HbA1c, mean (SD)	7.63 (0.92)	7.58 (0.87)	7.60 (0.82)
HbA1c at 26 wks, LS Mean (SE)	6.81 (0.06)††	6.88 (0.06)††	7.03 (0.06)
ΔHbA1c, LS Mean (SE)	-0.78 (0.06)††	-0.71 (0.06)††	-0.56 (0.06)
LS Mean Difference (95% CI)			
vs. metformin	-0.22 (-0.36, -0.08)††	-0.15 (-0.29, -0.01)††	NA
vs. dula_0.75	-0.07 (-0.21, 0.07)	NA	NA
HbA1c <7.0%, n (%)[b]	163 (61.5)#	166 (62.6)#	142 (53.6)
HbA1c ≤6.5%, n (%)[b]	122 (46.0)##	106 (40.0)#	79 (29.8)
Fasting Serum Glucose (mg/dL)[c]			
Baseline FSG, mean (SD)	164.16 (50.22)	160.74 (47.34)	161.28 (43.20)
ΔFSG, LS Mean (SE)	-28.98 (2.34)	-26.28 (2.34)	-24.12 (2.34)
LS Mean Difference (95% CI)			
vs. metformin	-4.86 (-10.62, 0.54)	-2.16 (-7.74, 3.42)	NA
vs. dula_0.75	-2.70 (-8.46, 2.70)	NA	NA
Mean Postprandial Glucose (mg/dL)[c]			
Baseline PPG, mean (SD)	196.20 (49.86)	191.70 (52.20)	192.24 (46.26)
ΔPPG, LS Mean (SE)	-43.38 (2.52)	-41.40 (2.34)	-38.88 (2.52)
LS Mean Difference (95% CI)			
vs. metformin	-4.50 (-10.62, 1.62)	-2.52 (-8.46, 3.42)	NA
vs. dula_0.75	-1.98 (-8.10, 4.14)	NA	NA
Weight (kg)			
Baseline Weight, mean (SD)	92.7 (18.8)	91.8 (18.7)	92.4 (19.2)
ΔWeight, LS Mean (SE)	-2.29 (0.24)+	-1.36 (0.24)#	-2.22 (0.24)
LS Mean Difference (95% CI)			
vs. metformin	-0.07 (-0.63, 0.49)	0.86 (0.30, 1.43)#	NA
vs. dula_0.75	-0.93 (-1.50, -0.37)+	NA	NA
Homeostasis Model Assessment			
Baseline HOMA2-%B, mean (SD)	70.8 (45.2)	71.0 (43.4)	70.1 (43.1)
ΔHOMA2-%B, LS Mean (SE)	36.6 (3.4)##	29.0 (3.4)##	14.1 (3.4)

Abbreviations: Δ = change from baseline; CI = confidence interval; FSG = fasting serum glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; HOMA2-%B = Homeostasis Model Assessment 2 of betacell function; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; n = number of patients meeting criterion; N = number of patients; NA = not applicable; PPG = postprandial glucose (selfmonitored). Note: Dula_x.x refers to dulaglutide x.x mg once weekly. b Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator for percent to target analyses of HbA1c.
†multiplicity adjusted 1-sided p-value <.025, for noninferiority,
††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to metformin, assessed only for HbA1c.
#p<.05,
##p<.001 dulaglutide treatment group compared to metformin.
+p<.05 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.

The results showed a significant reduction in HbA1c with both dulaglutide doses compared to baseline (-0.78% and -0.71% respectively). These findings appear to be closer to the lower end of the range reported for the class and what was observed with dulaglutide in the remaining trials. The Applicant suggests that this could be due to two factors: the relatively low, at 7.6%, baseline HbA1c and that most patients were previously treated with an OAM. The short lead-in period of only 2 weeks might not have been long enough to ensure washout from prior OAM therapy which may have attenuated the treatment effect in all groups. Nevertheless, the results are still significant and clinically relevant, and not far from those previously reported with other agents in the class.

The 25% of patients who were OAM naïve achieved substantially larger mean HbA1c reductions from baseline in all treatment groups compared to the 75% of patients previously treated with an OAM. This was the case despite lower baseline HbA1c values in the treatment naïve patients and can be explained by HbA1c values not having stabilized at the time of randomisation after discontinuation of previous OAMs in the pre-treated group. Overall, this finding is unlikely to have an impact on study results.

With regard to the secondary endpoints, at 26 weeks (ITT, LOCF), a significantly greater percentage of patients had HbA1c decreased to <7.0% and ≤6.5% with dulaglutide 1.5 mg compared to metformin. The difference in changes from baseline in mean body weight for dulaglutide 1.5 mg compared to metformin was not significant. Least-square mean changes from baseline in mean body weight indicated a significantly greater decrease with metformin compared to dulaglutide 0.75 mg (p=0.003). Dulaglutide 1.5 mg also increased pancreatic ß-cell function (assessed by HOMA2-B%-model) to a greater extent than metformin. As indicated by the results of the patients reported outcome measures patients appeared to be satisfied with treatment in all treatment groups.

At 52 weeks, the mean (SD) dose of metformin was 1889 (320) mg. At 52 weeks, significant LS mean (SE) reductions from baseline in HbA1c were again observed in all treatment groups. Dulaglutide 1.5 mg was superior to metformin (LS mean difference, -0.19% [adjusted p=.024]) and dulaglutide 0.75 mg was noninferior to metformin based on the prespecified margin of 0.4% (LS mean difference, -0.04% [adjusted p<.001]).

A secondary analysis of the primary and key secondary objectives in the ITT population using an MMRM model showed again that dulaglutide 1.5 mg was superior to metformin similar to the primary ANCOVA (LOCF). Reductions in HbA1c as well as LS mean differences in HbA1c reductions with dulaglutide compared to metformin in the PP (without post-rescue visits and without rescued patients) and completer (without post-rescue visits and without rescued patients) populations demonstrated a consistent direction of between-group changes in HbA1c compared to the ITT population at 26 and 52 weeks.

Study H9X-MC-GBCF

Study GBCF included T2DM patients with longer duration of diabetes 7.1 (5.2) and mean baseline HbA1c 8.1%(1.1) and compared the effect of dulaglutide as add-on to metformin with sitagliptin at 12 months (as well as placebo in 6 months).

Patient disposition related to efficacy for the 26-week placebo-controlled period, the primary time point (52 weeks), and the final time point (104 weeks) is presented in Table 18. A total of 1098 patients were randomized and included in the ITT population: dulaglutide 1.5 mg, 304; dulaglutide 0.75 mg, 302; placebo, 177; and sitagliptin, 315. The overall discontinuation rate of approximately 40% for the whole duration of the study was high, but not unexpected for a 2 year study and comparable with that seen in similar previous trials of such duration in this class. The proportion of discontinued patients in the placebo/sitagliptin arm (46.3%) at end of the study was higher compared to other treatments (dulaglutide 1.5mg: 36.8%; dulaglutide 0.75 mg: 39.1%; sitagliptin: 41.0%) due, for the most part, to a higher rate or hyperglycaemia in the control groups, which was even more evident in the placebo arm during the first 26 weeks. At the time of the primary analysis, at 12 months, the discontinuation rate was similar between groups (although lower for the dulaglutide 0.75mg) and still not unreasonably high (at <25%) so that to raise concerns about the conduct and validity of the study.

Table 18 Patient Disposition (Related to Ineffective Therapy versus Other Reasons), Dulaglutide versus Placebo or Sitagliptin, ITT, Study GBCF, in Combination with Metformin

Patient Disposition	Dula_1.5 N=304 n (%)	Dula_0.75 N=302 n (%)	Sitagliptin N=315 n (%)	Placebo N=177 n (%)
Placebo-Controlled Period (26 weeks)				
Completed	258 (84.9)	268 (88.7)	270 (85.7)	124 (70.1)
Rescued[a]	NA	NA	NA	NA
Discontinued from Study Drug[b]	NA	NA	NA	NA
Discontinued from the Study	46 (15.1)	34 (11.3)	45 (14.3)	53 (29.9)
Ineffective Therapy[c]	6 (2.0)	2 (0.7)	8 (2.5)	24 (13.6)
Other[d]	40 (13.2)	32 (10.6)	37 (11.7)	29 (16.4)
Primary Time Point (52 weeks)[e]				
Completed	238 (78.3)	243 (80.5)	238 (75.6)	NA
Rescued[a]	NA	NA	NA	NA
Discontinued from Study Drug[b]	NA	NA	NA	NA
Discontinued from the Study	66 (21.7)	59 (19.5)	77 (24.4)	NA
Ineffective Therapy[c]	10 (3.3)	11 (3.6)	20 (6.3)	NA
Other[d]	56 (18.4)	48 (15.9)	57 (18.1)	NA
Final Time Point (104 weeks)[f]				
Completed	192 (63.2)	184 (60.9)	186 (59.0)	NA
Rescued[a]	NA	NA	NA	NA
Discontinued from Study Drug[b]	NA	NA	NA	NA
Discontinued from the Study	112 (36.8)	118 (39.1)	129 (41.0)	NA
Ineffective Therapy[c]	34 (11.2)	41 (13.6)	51 (16.2)	NA
Other[d]	78 (25.7)	77 (25.5)	78 (24.8)	NA

Abbreviations: ITT = intent-to-treat; n = number of patients in specified category; N = number of patients; NA = not applicable. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a Patients who experienced ineffective therapy were not allowed to receive rescue therapy and were discontinued from the study. b Patients were not allowed to discontinue study drug and remain in the study. c Patients who discontinued the study for reasons suggestive of ineffective therapy: lack of efficacy, hyperglycaemia, diabetes mellitus inadequate control, glycosylated haemoglobin increased, or blood glucose increased. d Patients who discontinued the study for reasons not suggestive of ineffective therapy. e From randomization to primary time point. f From randomization to final time point

Concomitant medication use was similar among the treatment groups up to 6, 12, and 24 months and was generally compliant with the protocol. At screening, 94.2% of patients were treated with at least one antidiabetic, mostly monotherapy (65.9%). The most common was metformin (87%), followed by sulphonylureas (29%). At baseline, all randomized patients were taking metformin for the treatment of type 2 diabetes mellitus (T2DM). For most patients (98%), this was the only hyperglycaemic drug being used. The median dose of background metformin at 12 months was sufficiently high at 2000mg/day (mean 1941mg) and similar between treatment groups. For all treatment arms at 6, 12, and 24 months, the mean of injectable and oral treatment compliance was approximately 97% and was balanced across treatment groups.

At the primary endpoint (52 weeks), significant LS mean (SE) reductions from baseline in HbA1c were observed in all treatment groups. Both dulaglutide 1.5 mg and 0.75 mg were superior to sitagliptin (LS mean difference, -0.71% and -0.47% respectively [adjusted p<.001]). Dulaglutide was also superior to sitagliptin (LS mean difference, [adjusted p<.001]) (Table 19).

Table 19 Summary of Efficacy Measures at the Primary Time Point (52 Weeks), Dulaglutide versus Sitagliptin, ITT, Study GBCF, in Combination with Metformin

Outcome Measure[a]	Dula_1.5 N=304	Dula_0.75 N=302	Sitagliptin N=315
HbA1c (%)			
Baseline HbA1c, mean (SD)	8.12 (1.05)	8.19 (1.11)	8.09 (1.09)
HbA1c at 52 wks, LS Mean (SE)	7.02 (0.06)††,+	7.26 (0.06)††	7.73 (0.06)
ΔHbA1c, LS Mean (SE)	-1.10 (0.06)††,+	-0.87 (0.06)††	-0.39 (0.06)
LS Mean Difference (95% CI)			
vs. sitagliptin	-0.71 (-0.87, -0.55)††	-0.47 (-0.63, -0.31)††	NA
vs. dula_0.75	-0.24 (-0.40, -0.08)+	NA	NA
HbA1c <7.0%, n (%)[b]	174 (57.6)##,+	145 (48.8)##	103 (33.0)
HbA1c ≤6.5%, n (%)[b]	126 (41.7)##,++	86 (29.0)##	60 (19.2)
Fasting Plasma Glucose (mg/dL)[c]			
Baseline FPG, mean (SD)	175.50 (58.86)	174.24 (52.92)	172.08 (50.40)
ΔFPG, LS Mean (SE)	-42.84 (2.34)##, ++	-29.34 (2.34)##	-16.20 (2.34)
LS Mean Difference (95% CI)			
vs. sitagliptin	-26.46 (-32.76, -20.34)##	-13.14 (-19.26, -7.02)##	NA
vs. dula_0.75	-13.50 (-19.62, -7.20)++	NA	NA
Mean Postprandial Glucose[d]	NA	NA	NA
Weight (kg)			
Baseline Weight, mean (SD)	86.7 (17.5)	86.2 (18.0)	86.0 (16.9)
ΔWeight, LS Mean (SE)	-3.03 (0.22)##	-2.60 (0.23)##	-1.53 (0.22)
LS Mean Difference (95% CI)			
vs. sitagliptin	-1.50 (-2.08, -0.92)##	-1.07 (-1.65, -0.48)##	NA
vs. dula_0.75	-0.43 (-1.02, 0.15)	NA	NA
Homeostasis Model Assessment			
Baseline HOMA2-%B, mean (SD)	55.0 (36.6)	53.1 (37.3)	54.3 (36.6)
ΔHOMA2-%B, LS Mean (SE)	33.6 (2.5)##,++	22.3 (2.5)##	6.66 (2.53)

Abbreviations: Δ = change from baseline; CI = confidence interval; FPG = fasting plasma glucose (central); HbA1c = glycosylated hemoglobin A1c; HOMA2-%B = Homeostasis Model Assessment 2 of beta-cell function; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; n = number of patients meeting criterion; N = number of patients; NA = not applicable. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. b Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator for percent to target analyses of HbA1c. d Self-monitoring blood glucose profiles, including postprandial glucose, were not assessed in Study GBCF

††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to sitagliptin, assessed only for HbA1c.

##p<.001 dulaglutide treatment group compared to sitagliptin.

+p<.05,

++p<.001 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.

For the secondary endpoints, at 52 weeks, 57.6% of dulaglutide 1.5 mg, 48.8% of dulaglutide 0.75 mg, and 33.0% of sitagliptin-treated patients achieved the HbA1c target of <7.0%. The percentage of patients who achieved HbA1c <7.0% or ≤ 6.5% was significantly greater in both dulaglutide groups compared to sitagliptin (p<.001; both). Treatment with dulaglutide 1.5 mg or 0.75 mg resulted in significantly greater reductions from baseline in FPG compared to sitagliptin. For body weight a significant difference was seen for both dulaglutide doses compared to sitagliptin (p<.001; both). Least-squares mean HOMA2-%B was significantly increased from baseline in the dulaglutide 1.5-mg and 0.75-mg groups compared to sitagliptin (p<.001; both).

At 104 weeks, significant LS mean (SE) reductions from baseline in HbA1c were observed in all treatment groups. Again both dulaglutide 1.5 mg and 0.75 mg were superior to sitagliptin (LS mean difference, -0.67% and -0.39% respectively [adjusted p<.001; both]).

The secondary analyses using MMRM and in the PP population showed a similar magnitude of HbA1c reduction within and between treatments. In addition, due to previous concerns about the design of the study and the integration of the two stages of the trial a sensitivity analysis was carried out including only patients randomised

at Stage 2. This analysis which includes only patients randomised in stage 2 is the best confirmation of efficacy, as it is independent of the stage 1 dose selection. The results of this analysis were consistent with those of the primary analysis, demonstrating that the results are robust regardless of whether stage 1 patients are included or not.

Study H9X-MC-GBDA

Study GBDA assessed the effect of dulaglutide in a triple therapy regime, on top of metformin and pioglitazone, in T2DM patients not adequately controlled despite double OAM treatment, in comparison to placebo and exenatide BID. The study patients were representative of a T2DM population with a long duration of diabetes (8.8 [5.6] years) and several co-morbidities. Patient disposition related to efficacy for the primary (26 weeks) and final (52 weeks) time points is shown in Table 20. A total of 978 patients were randomized, and 976 were included in the ITT population: 279 to dulaglutide 1.5 mg, 280 to dulaglutide 0.75 mg, 141 to placebo, and 276 to exenatide. The overall discontinuation rate was generally low during the trial; higher, as expected, for placebo but not to a rate that would raise concerns about the relevance of the results. Similarly, the number of rescued patients was small, especially among the dulaglutide 1.5mg treated patients.

Table 20 Patient Disposition (Related to Ineffective Therapy versus Other Reasons), Dulaglutide versus Placebo or Exenatide, ITT, Study GBDA, in Combination with Metformin + TZD

Patient Disposition	Dula_1.5 N=279 n (%)	Dula_0.75 N=280 n (%)	Exenatide N=276 n (%)	Placebo N=141 n (%)
Primary Time Point (26 weeks)[a]				
Completed	260 (93.2)	263 (93.9)	252 (91.3)	124 (87.9)
Rescued[b,c]	4 (1.4)	12 (4.3)	11 (4.0)	22 (15.6)
Discontinued from Study Drug[c]	11 (3.9)	13 (4.6)	20 (7.2)	7 (5.0)
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[e]	11 (3.9)	13 (4.6)	20 (7.2)	7 (5.0)
Discontinued from the Study[c]	19 (6.8)	17 (6.1)	24 (8.7)	17 (12.1)
Ineffective Therapy[d]	1 (0.4)	0 (0.0)	1 (0.4)	3 (2.1)
Other[e]	18 (6.5)	17 (6.1)	23 (8.3)	14 (9.9)
Final Time Point (52 weeks)[f]				
Completed	245 (87.8)	254 (90.7)	237 (85.9)	NA
Rescued[b,c]	9 (3.2)	25 (8.9)	24 (8.7)	NA
Discontinued from Study Drug[c]	20 (7.2)	17 (6.1)	33 (12.0)	NA
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	0 (0.0)	NA
Other[e]	20 (7.2)	17 (6.1)	33 (12.0)	NA
Discontinued from the Study[c]	34 (12.2)	26 (9.3)	39 (14.1)	NA
Ineffective Therapy[d]	1 (0.4)	0 (0.0)	2 (0.7)	NA
Other[e]	33 (11.8)	26 (9.3)	37 (13.4)	NA

Abbreviations: ITT = intent-to-treat; n = number of patients in specified category; N = number of patients; NA = not applicable; TZD = thiazolidinedione. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a From randomization to primary time point. b These patients required additional antihyperglycaemic intervention for severe persistent hyperglycemia. c Patients may appear in more than 1 category: rescued, discontinued from study drug and/or study. d Patients who discontinued the study drug or study for reasons suggestive of ineffective therapy: lack of efficacy, hyperglycemia, diabetes mellitus inadequate control, glycosylated hemoglobin increased, or blood glucose increased. e Patients who discontinue the study drug or study for reasons not suggestive of ineffective therapy. f From randomization to final time point.

The treatment groups were similar with respect to demographic characteristics at baseline, with no statistically significant differences observed for any characteristic. Demographic and baseline characteristics in the PP population were similar to the ITT population.

The vast majority of patients were on high background doses of pioglitazone and metformin which is reassuring for the assessment of dulaglutide incremental effects (as well as the safety of the triple combination at the

higher end of the posology range). At baseline and Week 52, the majority of patients were receiving pioglitazone 45 mg (baseline, 95.9%; Week 52, 92.4%) and metformin ≥2500 mg (baseline, 88.7%; Week 52, 85.5%; Table GBDA.14.39). 86.2% of patients at baseline and 82.9% of patients at Week 52 were receiving both pioglitazone 45 mg and metformin ≥2500 mg.

Compliance to study treatments remained generally high for the duration of the study (but numerically higher at both visits in patients in each of the 2 dulaglutide treatment arms) suggesting appropriate levels for the active comparator. Actual exenatide dose levels were not recorded during the study but there were clear instructions for up-titration to the maximum dose and both efficacy and tolerability data were similar to the findings of previous studies. Also the effect of exenatide on glycaemic parameters appears consistent with what is reported in its SmPC, suggesting appropriate therapeutic levels.

At 26 weeks, significant LS mean (SE) reductions from baseline in HbA1c were observed in all treatment groups. Dulaglutide 1.5 mg and 0.75 were both superior to placebo (LS mean difference, -1.05% and -0.84% respectively [adjusted p<.001; both]) and to exenatide (LS mean difference, -0.52% and -0.31% respectively [adjusted p<.001; both]) (Table 21).

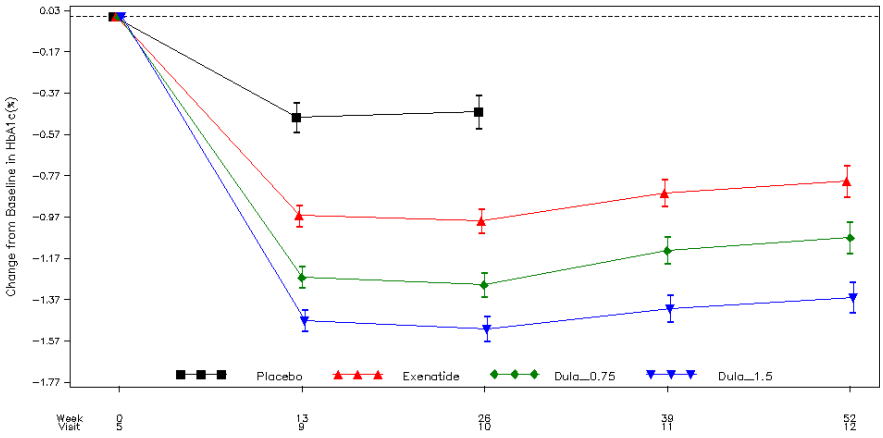
Table 21 Summary of Efficacy Measures at the Primary Time Point (26 Weeks), Dulaglutide versus Placebo or Exenatide, ITT, Study GBDA, in Combination with Metformin + TZD

Outcome Measure[a]	Dula 1.5 N=279	Dula 0.75 N=280	Exenatide N=276	Placebo N=141
HbA1c (%)				
Baseline HbA1c, mean (SD)	8.10 (1.34)	8.05 (1.24)	8.07 (1.34)	8.06 (1.31)
HbA1c at 26 wks, LS Mean (SE)	6.55 (0.89)‡‡,††,+	6.73 (0.96)‡‡,††	7.05 (1.03)**	7.44 (1.16)
ΔHbA1c, LS Mean (SE)	-1.51 (0.06) ‡‡,††,+	-1.30 (0.06)‡‡,††	-0.99 (0.06)**	-0.46 (0.08)
LS Mean Difference (95% CI)				
vs. placebo	-1.05 (-1.22, -0.88)‡‡	-0.84 (-1.01, -0.67)‡‡	-0.53 (-0.70, -0.36)**	NA
vs. exenatide	-0.52 (-0.66, -0.39)††	-0.31 (-0.44, -0.18)††	NA	NA
vs. dula_0.75	-0.21 (-0.35, -0.08)+	NA	NA	NA
HbA1c <7.0%, n (%)[b]	212 (78.2)**,##,++	177 (65.8)**,##	139 (52.3)*	51 (42.9)
HbA1c ≤6.5%, n (%)[b]	170 (62.7)**,##,+	143 (53.2)**,##	101 (38.0)**	29 (24.4)
Fasting Serum Glucose (mg/dL)[c]				
Baseline FSG, mean (SD)	162.00 (55.62)	159.12 (49.68)	163.98 (54.72)	165.96 (54.18)
ΔFSG, LS Mean (SE)	-42.48 (2.16)**, ##,+	-34.20 (2.16)**, ##	-24.30 (2.16)**	-4.68 (3.06)
LS Mean Difference (95% CI)				
vs. placebo	-37.98 (-44.64, -31.14)**	-29.52 (-36.36, -22.68)**	-19.62 (-26.46, -12.78)**	NA
vs. exenatide	-18.36 (-23.58, -12.96)##	-9.90 (-15.30, -4.50)##	NA	NA
vs. dula_0.75	-8.28 (-13.68, -3.06)+	NA	NA	NA
Mean Postprandial Glucose (mg/dL)[c]				
Baseline PPG, mean (SD)	201.49 (54.31)	196.45 (50.79)	206.79 (61.16)	204.20 (60.43)
ΔPPG, LS Mean (SE)	-52.06 (2.13)**, #,+	-45.89 (2.12)**	-46.86 (2.13)**	-18.93 (3.09)
LS Mean Difference (95% CI)				
vs. placebo	-33.13 (-39.91, -26.35)**	-26.96 (-33.74, -20.18)**	-27.93 (-34.75, -21.11)**	NA
vs. exenatide	-5.20 (-10.35, -0.06)#	0.97 (-4.20, 6.14)	NA	NA
vs. dula_0.75	-6.17 (-11.29, -1.06)+	NA	NA	NA
Weight (kg)				
Baseline Weight, mean (SD)	96.2 (19.6)	95.5 (20.6)	97.4 (18.9)	94.1 (19.3)
ΔWeight, LS Mean (SE)	-1.30 (0.29)**, ++	0.20 (0.29)*, ##	-1.07 (0.29)**	1.24 (0.37)
LS Mean Difference (95% CI)				
vs. placebo	-2.54 (-3.33, -1.76)**	-1.04 (-1.82, -0.25)*	-2.31 (-3.09, -1.52)**	NA
vs. exenatide	-0.24 (-0.88, 0.41)	1.27 (0.63, 1.92)##	NA	NA
vs. dula_0.75	-1.51 (-2.15, -0.87)++	NA	NA	NA
Homeostasis Model Assessment				
Baseline HOMA2-%B, mean (SD)	50.8 (35.7)	52.1 (38.5)	53.4 (44.3)	47.9 (30.8)
ΔHOMA2-%B, LS Mean (SE)	36.1 (2.6)**,##,++	23.6 (2.7)**,#	15.0 (2.6)**	0.93 (3.7)

Abbreviations: Δ = change from baseline; CI = confidence interval; FSG = fasting serum glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; HOMA2-%B = Homeostasis Model Assessment 2 of beta-cell function; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; n = number of patients meeting criterion; N = number of patients; NA = not applicable; PPG = postprandial glucose (self-monitored); TZD = thiazolidinedione. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. b Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator for percent to target analyses of HbA1c.

††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to exenatide, assessed only for HbA1c.
‡‡multiplicity adjusted 1-sided p-value <.001 for superiority of dulaglutide compared to placebo, assessed only for HbA1c.
*p<.05, **p<.001 dulaglutide or exenatide treatment group compared to placebo.
#p<.05, ##p<.001 dulaglutide treatment group compared to exenatide.
+p<.05, ++p<.001 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.

Figure 19 Plot of HbA1C (%) change from Baseline to 52 weeks without post rescue Visits; ANCOVA (LOCF) LS Mean +/- SE by Treatment Group. ITT Population; Study GBDA



With regard to the secondary endpoints, at 26 weeks the percentages of patients who achieved HbA1c <7.0% and ≤6.5% were significantly greater in both dulaglutide groups compared to placebo and exenatide (p<.001; all). Treatment with either dulaglutide 1.5 mg or dulaglutide 0.75 mg also resulted in significantly greater reductions from baseline in FSG compared to placebo and exenatide (p<.001; all). Dulaglutide 1.5 mg significantly reduced PPG from baseline compared to placebo (p<.001) and exenatide (p<.05)

At 26 weeks, LS mean changes in body weight were: dulaglutide 1.5 mg, -1.30 kg; dulaglutide 0.75 mg, 0.20 kg; placebo, 1.24 kg, and exenatide, -1.07 kg. Significant reductions from baseline in body weight were observed with dulaglutide 1.5 mg and exenatide compared to placebo (p<.001; both). There was no significant difference in body weight change between dulaglutide 1.5 mg and exenatide. Least-square mean HOMA2-%B was significantly increased from baseline with dulaglutide 1.5 mg and dulaglutide 0.75 mg compared to placebo (p<.001; both) and exenatide (dulaglutide 1.5 mg, p<.001; dulaglutide 0.75 mg, p<.05).

At 52 weeks, significant LS mean (SE) reductions from baseline in HbA1c were observed in all treatment groups: dulaglutide 1.5 mg, -1.36% (0.08); dulaglutide 0.75 mg, -1.07% (0.08); and exenatide -0.80% (0.08) (p<.001; all). Dulaglutide 1.5 mg and 0.75 mg were still superior to exenatide (LS mean difference, -0.56% and -0.27% respectively [adjusted p<.001; both]).

The sensitivity analyses using MMRM and the analysis in the PP population revealed a similar magnitude of HbA1c, supporting the primary results.

Study H9X-MC-GBDB

Study GBDB assessed the incremental effects of dulaglutide when added to metformin and a sulphonylurea, in T2DM patients not adequately on the double OAM treatment, in comparison to basal insulin. The T2DM study population had a long history of diabetes (9.1 [6.0] years) and the majority of them had already been treated with more than one OAM.

Patient disposition related to efficacy for the primary (52 weeks) and final (78 weeks) time points is summarized in Table 22. A total of 810 patients were randomized, and 807 were included in the ITT population. The overall discontinuation rate during the whole trial was generally low, with few patients needing rescue. However, the number of study drug discontinuations was higher in the dulaglutide groups (up to 6.6% at 52 weeks and 8.8% at 78 weeks with dulaglutide 1.5%, compared to none in the insulin group), mostly due to adverse reactions.

Table 22 Patient Disposition (Related to Ineffective Therapy versus Other Reasons), Dulaglutide versus Insulin Glargine, ITT, Study GBDB, in Combination with Metformin + SU

Patient Disposition	Dula_1.5 N=273 n (%)	Dula_0.75 N=272 n (%)	Glargine N=262 n (%)
Primary Time Point (52 weeks)[a]			
Completed	248 (90.8)	252 (92.6)	240 (91.6)
Rescued[b,c]	11 (4.0)	20 (7.4)	8 (3.1)
Discontinued from Study Drug[c]	18 (6.6)	15 (5.5)	0 (0.0)
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	0 (0.0)
Other[e]	18 (6.6)	15 (5.5)	0 (0.0)
Discontinued from Study[b]	25 (9.2)	20 (7.4)	22 (8.4)
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	0 (0.0)
Other[e]	25 (9.2)	20 (7.4)	22 (8.4)
Final Time Point (78 weeks)[f]			
Completed	242 (88.6)	243 (89.3)	238 (90.8)
Rescued[b,c]	24 (8.8)	34 (12.5)	16 (6.1)
Discontinued from Study Drug[c]	24 (8.8)	17 (6.3)	0 (0.0)
Ineffective Therapy[d]	0 (0.0)	0 (0.0)	0 (0.0)
Other[e]	24 (8.8)	17 (6.3)	0 (0.0)
Discontinued from Study[b]	31 (11.4)	29 (10.7)	24 (9.2)
Ineffective Therapy[d]	1 (0.4)	1 (0.4)	0 (0.0)
Other[e]	30 (11.0)	28 (10.3)	24 (9.2)

Abbreviations: ITT = intent-to-treat; n = number of patients in specified category; N = number of patients; SU = sulphonylurea. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a From randomization to primary time point. b These patients required additional antihyperglycaemic intervention for severe persistent hyperglycemia. c Patients may appear in more than 1 category: rescued, discontinued from study drug, and/or study. d Patients who discontinued the study drug or study for reasons suggestive of ineffective therapy: lack of efficacy, hyperglycemia, diabetes mellitus inadequate control, glycosylated hemoglobin increased, or blood glucose increased. e Patients who discontinued the study drug or study for reasons not suggestive of ineffective therapy. f From randomization to final time point.

Overall demographic and baseline characteristics in the ITT population were comparable between arms. At Screening, as per protocol, all 810 randomized patients were receiving at least 1 OAM; 130 patients (16.0%) were taking 1 OAM, 539 patients (66.5%) were taking 2 OAMs, and 141 patients (17.4%) were taking >2 OAMs; these were similar across the 3 arms.

The vast majority of patients remained on high background doses of metformin and glimepiride for the whole study, with relatively small and similarly distributed dose adjustments across groups. For glimepiride, at baseline the median dose for all arms was 6 mg/day and 1.5% or fewer in each arm were taking less than 4 mg at baseline. Post-baseline, on average, patients progressively adjusted doses downward; however, the median dose remained 6 mg at all timepoints in each of the 3 arms. For metformin, at baseline, the median dose was 2550 mg for each arm, and 1.5% or fewer in each arm were taking less than 1500 mg at baseline. Post-baseline, few patients had dose adjustments; the means exhibited little fluctuation across the time points, and the median remained at 2550 mg at all timepoints in each of the 3 arms.

Per the study protocol, patients randomized to insulin glargine were to start therapy with a single subcutaneous injection of 10 units per day; subsequent doses were to be adjusted according to a titration algorithm targeting a FPG of <5.6 mmol/L. Insulin glargine doses increased progressively throughout the study from up to Week 78. At Week 26, the mean (SD) daily dose (LOCF) of insulin glargine was 26.21 units (23.88) or 0.29 units/kg

(0.21). At Week 52, the mean (SD) daily dose (LOCF) of insulin glargine was 29.40 units (25.85) or 0.33 units/kg (0.24). At Week 78, the mean (SD) daily dose (LOCF) of insulin glargine was 31.44 units (24.94) or 0.35 units/kg (0.24).

In the insulin glargine arm, at each time point, 21.7% to 27.0% met the <5.6 mmol/L target while 57% to 61.5% of patients met the <6.7 mmol/L target. The proportion of patients meeting the fasting glucose targets (SMPG) within each arm was similar for all 3 time points (Weeks 26, 52, and 78), with a higher proportion in the insulin glargine arm than in the dulaglutide arms. Through Week 52 and Week 78, mean (SD) total overall compliance with study medication was 97.72% (10.95) and 97.69% (10.92), respectively. At both Week 52 and Week 78 compliance in the insulin glargine arm was higher but the differences were clinically negligible.

In the primary analysis at 52 weeks, significant LS mean (SE) reductions from baseline in HbA1c were observed in all treatment groups (Table 23). Dulaglutide 1.5 mg was superior to insulin glargine (LS mean difference, -0.45% [adjusted p<.001]). Dulaglutide 0.75 mg was noninferior to insulin glargine at the prespecified noninferiority margin of 0.4% (LS mean difference, -0.13% [adjusted p<.001]).

Table 23 Summary of Efficacy Measures at the Primary Time Point (52 Weeks), Dulaglutide versus Insulin Glargine, ITT, Study GBDB, in Combination with Metformin + SU

Outcome Measure[a]	Dula_1.5 N=273	Dula_0.75 N=272	Glargine N=262
HbA1c (%)			
Baseline HbA1c, mean (SD)	8.18 (1.03)	8.13 (0.98)	8.10 (0.95)
HbA1c at 52 wks, LS Mean (SE)	7.05 (0.06)††,++	7.37 (0.06)†	7.50 (0.06)
ΔHbA1c, LS Mean (SE)	-1.08 (0.06)††,++	-0.76 (0.06)†	-0.63 (0.06)
LS Mean Difference (95% CI)			
vs. glargine	-0.45 (-0.60, -0.29)††	-0.13 (-0.29, 0.02)†	NA
vs. dula_0.75	-0.32 (-0.47, -0.16)++	NA	NA
HbA1c <7%, n (%)[b]	140 (53.2)##,++	99 (37.1)	80 (30.9)
HbA1c ≤6.5%, n (%)[b]	71 (27.0)##	60 (22.5)#	35 (13.5)
Fasting Serum Glucose (mg/dL)[c]			
Baseline FSG, mean (SD)	164.88 (49.14)	161.28 (48.60)	163.44 (47.88)
ΔFSG, LS Mean (SE)	-27.00 (2.52)+	-15.66 (2.52)##	-31.68 (2.52)
LS Mean Difference (95% CI)			
vs. glargine	4.68 (-1.98, 11.52)	16.02 (9.18, 22.86)##	NA
vs. dula_0.75	-11.34 (-18.18, -4.50)+	NA	NA
Mean Postprandial Glucose (mg/dL)[c]			
Baseline PPG, mean (SD)	192.24 (49.32)	189.72 (48.06)	188.10 (45.00)
ΔPPG, LS Mean (SE)	-35.10 (2.34)	-29.52 (2.34)	-28.80 (2.34)
LS Mean Difference (95% CI)			
vs. glargine	-6.30 (-12.42, -0.36)#	-0.72 (-6.84, 5.22)	NA
vs. dula_0.75	-5.58 (-11.52, 0.36)	NA	NA
Weight (kg)			
Baseline Weight, mean (SD)	85.2 (17.8)	86.4 (18.0)	87.6 (19.7)
ΔWeight, LS Mean (SE)	-1.87 (0.24)##	-1.33 (0.24)##	1.44 (0.24)
LS Mean Difference (95% CI)			
vs. glargine	-3.31 (-3.90, -2.71)##	-2.77 (-3.36, -2.17)##	NA
vs. dula_0.75	-0.54 (-1.13, 0.05)	NA	NA
Homeostasis Model Assessment			
Baseline HOMA2-%B, mean (SD)	61.2 (56.4)	62.4 (47.6)	NA
ΔHOMA2-%B, LS Mean (SE)	28.8 (4.0)	23.1 (3.9)	NA

Abbreviations: Δ = change from baseline; CI = confidence interval; FSG = fasting serum glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; HOMA2-%B = Homeostasis Model Assessment 2 of betacell function; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; n = number of patients meeting criterion; N = number of patients; NA = not applicable; PPG = postprandial glucose (selfmonitored); SU = sulphonylurea. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator

for percent to target analyses of HbA1c. c FSG and PPG values in mmol/ .
†multiplicity adjusted 1-sided p-value <.025, for noninferiority, ††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to glargine, assessed only for HbA1c.
#p<.05, ##p<.001 dulaglutide treatment group compared to glargine.
+p<.05, ++p<.001 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.

For the secondary endpoints, at 52 weeks fasting glucose showed a greater decrease with insulin glargine than with either dose of dulaglutide, not an unexpected finding as insulin dosing was based on glucose targets and was gradually up titrated throughout the treatment period. However, dulaglutide 1.5 mg significantly reduced PPG compared to insulin glargine. Also significantly greater percentages of dulaglutide treated patients achieved HbA1c ≤6.5% compared to insulin glargine-treated patients. Patients in the insulin glargine arm showed an increase in mean body weight; in contrast, significant reductions in body weight from baseline were seen with both dulaglutide doses. Both dulaglutide 1.5 mg and dulaglutide 0.75 mg significantly reduced body weight from baseline compared to insulin glargine (p<.001)

At 78 weeks, significant LS mean (SE) reductions from baseline in HbA1c were observed again in all treatment groups (p<.001; all). Dulaglutide 1.5 mg was superior to insulin glargine (LS mean difference, -0.31% [adjusted p<.001]). Dulaglutide 0.75 mg was noninferior to insulin glargine based on the prespecified margin of 0.4%.

The MMRM and PP sensitivity analyses were consistent with the primary analysis findings.

Study H9X-MC-GBDD

Study GBDD examined the effect of dulaglutide when added to prandial insulin against a combination of basal and prandial insulin in T2DM who required intensive therapy due to poor glycaemic control; most patients were also treated with background metformin. The T2DM patients in this study had the longest history of diabetes and most advanced disease in the Phase 3 program, and had already been treated with insulin (the majority with basal insulin alone) with or without concomitant OAM.

Patient disposition related to efficacy for the primary (26 weeks) and final (52 weeks) time points is shown in Table 24. A total of 884 patients were randomized and included in the ITT population. The rate of discontinuation was relatively low and similar between groups, while very few patients required rescue.

Table 24 Patient Disposition (Related to Ineffective Therapy versus Other Reasons), Dulaglutide versus Insulin Glargine, ITT, Study GBDD, in Combination with Insulin Lispro ± Metformin

Patient Disposition	Dula_1.5 N=295 n (%)	Dula_0.75 N=293 n (%)	Glargine N=296 n (%)
Primary Time Point (26 weeks)[a]			
Completed	248 (84.1)	255 (87.0)	256 (86.5)
Rescued[b,c]	0 (0.0)	2 (0.7)	1 (0.3)
Discontinued from Study Drug[c]	60 (20.3)	50 (17.1)	48 (16.2)
Ineffective Therapy[d]	2 (0.7)	4 (1.4)	1 (0.3)
Other[e]	58 (19.7)	46 (15.7)	47 (15.9)
Discontinued from Study[c]	47 (15.9)	38 (13.0)	40 (13.5)
Ineffective Therapy[d]	2 (0.7)	0 (0.0)	0 (0.0)
Other[e]	45 (15.3)	38 (13.0)	40 (13.5)

Final Time Point (52 weeks)[f]			
Completed	237 (80.3)	238 (81.2)	244 (82.4)
Rescued[b,c]	1 (0.3)	4 (1.4)	2 (0.7)
Discontinued from Study Drug[c]	73 (24.7)	69 (23.5)	60 (20.3)
Ineffective Therapy[d]	3 (1.0)	7 (2.4)	2 (0.7)
Other[e]	70 (23.7)	62 (21.2)	58 (19.6)
Discontinued from Study[c]	58 (19.7)	55 (18.8)	52 (17.6)
Ineffective Therapy[d]	2 (0.7)	0 (0.0)	0 (0.0)
Other[e]	56 (19.0)	55 (18.8)	52 (17.6)

Abbreviations: ITT = intent-to-treat; n = number of patients in specified category; N = number of patients. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a From randomization to primary time point. b These patients required additional antihyperglycaemic intervention for severe persistent hyperglycemia. c Patients may appear in more than 1 category: rescued, discontinued from study drug and/or study. d Patients who discontinued the study drug or study for reasons suggestive of ineffective therapy: inadequate response, hyperglycemia, diabetes mellitus inadequate control, glycosylated hemoglobin increased, or blood glucose increased. e Patients who discontinue the study drug or study for reasons not suggestive of ineffective therapy. f From randomization to final time point.

The 3 treatment groups were generally similar with respect to demographic and other patient characteristics at baseline, except for BMI which was higher in the dulaglutide 0.75mg group. The mean daily insulin dose at baseline was 56 units. The use of OAMs was similar in the 3 treatment groups during this period. The majority of patients (75% to 77%) were using biguanides, in compliance with the study protocol; 17 (1.9%) patients (dulaglutide 1.5 mg: 5; dulaglutide 0.75 mg: 6; insulin glargine: 6) reported using other medications, such as sulphonylureas, which was a protocol violation.

During the treatment period, before censoring for primary analysis, 77% of patients used concomitant medications (biguanides 76.7%; short-term insulin use 2.5%). The use of these agents was balanced across treatment groups. The 3 treatment groups were also similar with respect to metformin dose adjustment or metformin discontinuation during the lead-in and treatment periods.

In the insulin glargine group, at 26 weeks, the mean (SD) total daily insulin (TDI) dose was 132 ± 79 U, with 64 ± 40 U (49.8% of TDI) as insulin glargine and 68 ± 45 U as insulin lispro. In the dulaglutide 1.5-mg group, the mean (SD) insulin lispro dose was 93 ± 78 U; in the dulaglutide 0.75-mg group, the mean (SD) insulin lispro dose was 97 ± 62 U.

The mean overall compliance rate was 95.2% at 26 weeks (dulaglutide 1.5 mg: 93.5%; dulaglutide 0.75 mg: 97.2%; insulin glargine: 94.8%) and 94.6% at 52 weeks (dulaglutide 1.5 mg: 92.9%; dulaglutide 0.75 mg: 96.7%; insulin glargine: 94.1%). There was a significant difference among the treatment groups at both timepoints, due to higher compliance rate seen in the dulaglutide 0.75 mg group at 26 and 52 weeks.

From baseline to 26 weeks, significant LS mean (SE) reductions in HbA1c were observed in all treatment groups (p<.001; all). Both dulaglutide 1.5 mg and 0.75 mg were superior to insulin glargine (LS mean difference, -0.22% [adjusted p=.005] and -0.17% [adjusted p=.015] respectively) (Table 25, Figure 20).

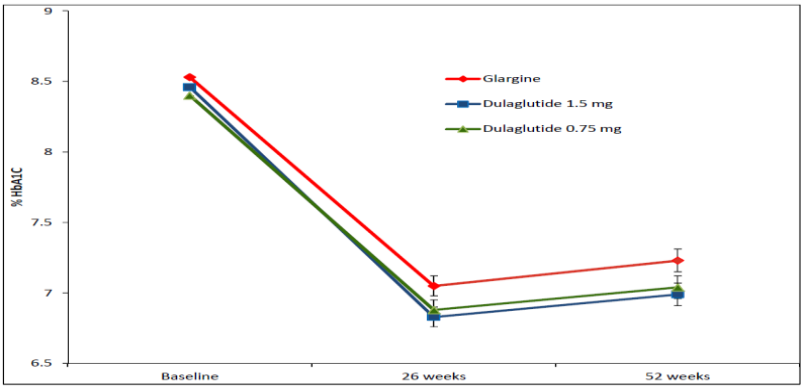
Table 25 Summary of Efficacy Measures at the Primary Time Point (26 Weeks), Dulaglutide versus Insulin Glargine, ITT, Study GBDD, in Combination with Insulin Lispro ± Metformin

Outcome Measure[a]	Dula_1.5 N=295	Dula_0.75 N=293	Glargine N=296
HbA1c (%)			
Baseline HbA1c, mean (SD)	8.46 (1.08)	8.40 (1.03)	8.53 (1.03)
HbA1c at 26 wks, LS Mean (SE)	6.83 (0.07)††	6.88 (0.07)††	7.05 (0.07)
ΔHbA1c, LS Mean (SE)	-1.64 (0.07)††	-1.59 (0.07)††	-1.41 (0.07)
LS Mean Difference (95% CI)			
vs. glargine	-0.22 (-0.38, -0.07)††	-0.17 (-0.33, -0.02)††	NA
vs. dula_0.75	-0.05 (-0.21, 0.11)	NA	NA
HbA1c <7%, n (%)[b]	186 (67.6)#	191 (69.0)#	159 (56.8)
HbA1c ≤6.5%, n (%)[b]	132 (48.0)#	119 (43.0)	105 (37.5)

Fasting Serum Glucose (mg/dL)[c]			
Baseline FSG, mean (SD)	157.14 (53.82)	150.12 (49.86)	154.08 (55.80)
ΔFSG, LS Mean (SE)	-4.86 (3.60)##,+	3.96 (3.60)##	-28.44 (3.60)
LS Mean Difference (95% CI)			
vs. glargine	23.58 (14.94, 32.22)##	32.40 (23.76, 41.04)##	NA
vs. dula_0.75	-8.82 (-17.46, -0.18)+	NA	NA
Mean Postprandial Glucose (mg/dL)[c]			
Baseline PPG, mean (SD)	201.96 (48.60)	201.24 (45.54)	205.20 (50.04)
ΔPPG, LS Mean (SE)	-76.14 (2.52)#	-74.16 (2.52)	-69.66 (2.34)
LS Mean Difference (95% CI)			
vs. glargine	-6.48 (-12.42, -0.54)#	-4.50 (-10.44, 1.44)	NA
vs. dula_0.75	-1.98 (-8.10, 3.96)	NA	NA
Weight (kg)			
Baseline Weight, mean (SD)	91.0 (18.2)	91.7 (18.0)	90.8 (18.9)
ΔWeight, LS Mean (SE)	-0.87 (0.27)##,++	0.18 (0.27)##	2.33 (0.27)
LS Mean Difference (95% CI)			
vs. glargine	-3.20 (-3.81, -2.59)##	-2.15 (-2.76, -1.54)##	NA
vs. dula_0.75	-1.05 (-1.67, -0.43)++	NA	NA
Homeostasis Model Assessment	NA	NA	NA

Abbreviations: Δ = change from baseline; CI = confidence interval; FSG = fasting serum glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; N = number of patients; NA = not applicable; PPG = postprandial glucose (selfmonitored). Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a Analysis methods are provided. b Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator for percent to target analyses of HbA1c. c FSG and PPG values in mmol/L provided.
††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to glargine, assessed only for HbA1c.
#p<.05, ##p<.001 dulaglutide treatment group compared to glargine.
+p<.05 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.

Figure 20 LS mean (SE) HbA1c values at baseline, 26 weeks, and 52 weeks in the 3 treatment groups.



With regard to the secondary endpoints, at 26 weeks, significantly greater percentages of patients achieved HbA1c <7.0% with both dulaglutide doses compared to insulin glargine (p<.05; both). Also significantly greater percentages of patients achieved HbA1c ≤6.5% with dulaglutide 1.5 mg compared to insulin glargine (p<.05). However, insulin glargine significantly reduced FSG from baseline compared to dulaglutide. Dulaglutide had a clear advantage in relation to body weight, although the effect was not as great as in the previous trials. Still, a small weight loss or even preventing further weight gain in such a population may be important.

At 52 weeks, significant LS mean (SE) reductions from baseline in HbA1c were observed in all treatment groups (p<.001; all). Both dulaglutide 1.5 mg and 0.75 mg were superior to insulin glargine. In the insulin glargine group, at 52 weeks, the mean (SD) TDI was 133 ± 81 U, with 64 ± 39 U (50.0% of TDI) as insulin glargine and

69 ± 49 U as insulin lispro. In the dulaglutide 1.5-mg group, the mean (SD) insulin lispro dose was 88 ± 63 U; in the dulaglutide 0.75-mg group, the mean (SD) insulin lispro dose was 95 ± 68 U.

Results from sensitivity analyses (including ITT population using the MMRM model) were consistent with the primary analysis.

Clinical studies in special populations

No specific efficacy studies were carried out in special populations.

As discussed below, supportive studies H9X-MC-GBCJ and H9X-JE-GBCZ provided efficacy data in overweight patients and in a Japanese population respectively.

A patient group of special interest are patients with renal failure but, as noted above, patients with significant disease were excluded from the main efficacy studies (this is further discussed in the *Safety* section below). A study in T2DM patients with moderate or severe chronic kidney disease is currently ongoing with the results likely to become available by 2016.

Supportive studies

Efficacy data were also obtained from four Phase 2, randomized, double-blind, placebo-controlled studies Study H9X-MC-**GBCJ**, Study H9X-MC-**GBCK**, Study H9X-JE-**GBCZ**, and Study H9X-MC-**GBDN**. Three of the Phase 2 studies (Studies GBCJ, GBCK, and GBCZ) tested once weekly dulaglutide doses ranging from 0.1 to 3.0 mg for up to 16 weeks, and the fourth Phase 2 study (GBDN) evaluated the effects of dulaglutide 1.5 mg and dulaglutide 0.75 mg on blood pressure and heart rate using ABPM for up to 26.

Study H9X-MC-GBCJ

Study **GBCJ** (see also *Dose response studies* above) was a multicenter, multiple titrated- and nontitrated-dose, placebo-controlled, parallel-group, double-blind study conducted in overweight and obese patients with T2DM, aged 18 years and older, who were taking any 2 OAMs. The study comprised a 2-week lead-in period, followed by a 16-week treatment period. Patients were randomized to 1 of 4 treatment groups: (1) dulaglutide 1.0 mg for 4 weeks, then 2.0 mg for an additional 12 weeks (dulaglutide 1.0/2.0 mg) (2) dulaglutide 1.0 mg for 16 weeks (dulaglutide 1.0/1.0 mg) (3) dulaglutide 0.5 mg for 4 weeks, then 1.0 mg for an additional 12 weeks (dulaglutide 0.5/1.0 mg) (4) placebo. In addition to study drug, patients continued prestudy OAMs throughout the study. The main purpose was to assess the response to dose titration. The primary efficacy measure was HbA1c change from baseline to 16 weeks.

Significant reductions from baseline were observed in HbA1c (p<.001), FPG (p<.001), and body weight (p<.001) in each dulaglutide treatment group compared to placebo after 16 weeks (Table 26). Treatment with dulaglutide resulted in significant dose-dependent effect on glycaemic control. As noted in section 3.3 above, a dulaglutide dose titration regime over 4 weeks did not reduce the incidence of treatment-emergent adverse events or result in an improvement in overall gastrointestinal tolerability.

Table 26 Summary of Efficacy Measures, Change from Baseline to 16 Weeks, Dulaglutide versus Placebo, ITT, Study GBCJ, in Combination with 2 OAMs

	LS Mean (SE) Change from Baseline[a]			
Outcome Measure[b] (units)	Dula 1.0/2.0 N=65	Dula 1.0/1.0 N=65	Dula 0.5/1.0 N=66	Placebo N=66
ΔHbA1c (%)	-1.52 (0.12)**	-1.29 (0.12)**	-1.28 (0.12)**	-0.27 (0.12)
ΔFPG (mg/dL)[c]	-47.52 (5.94)**	-36.72 (6.12)**	-37.62 (6.12)**	-8.82 (5.76)
ΔWeight (kg)	-2.51 (0.38)**	-1.40 (0.38)**	-1.58 (0.37)**	-0.07 (0.38)

Abbreviations: Δ = change from baseline; Dula = dulaglutide; FPG = fasting plasma glucose (central laboratory); HbA1c = glycosylated hemoglobin

A1c; ITT = intent-to-treat; LS = least square; N = number of patients treated; OAM = oral antihyperglycaemic medication; SE = standard error. a Patients on dulaglutide were administered either 1 mg for 16 weeks (1.0/1.0-mg group), or 1 of 2 titrated doses of dulaglutide (0.5 mg for 4 weeks then 1 mg for 12 weeks [0.5/1.0-mg group], or 1 mg for 4 weeks then 2 mg for 12 weeks [1.0/2.0-mg group]). b Analysis methods are provided in FPG values in mmol/L are provided p<.001 dulaglutide treatment group compared to placebo.

Study H9X-MC-GBCK

Study **GBCK** was designed and implemented based on FDA guidance for Lilly to conduct a 12-week, Phase 2, monotherapy trial to confirm that the doses chosen in Study **GBCF** were the optimal doses to carry forward in other Phase 3 studies. It was a multicenter, parallel-arm, randomized, 12-week treatment period, double-blind, placebo-controlled study that evaluated the dose-dependent safety and efficacy of dulaglutide administered as monotherapy in 167 patients with T2DM who were OAM-naïve or had discontinued metformin monotherapy.

The study had 4 periods: a 2-week screening period, an 8-week lead-in period (with washout if previously on metformin), a 12-week treatment period, and a 4-week safety follow-up period. The primary objective was to demonstrate a dose-dependent effect of once weekly dulaglutide (1.5, 1.0, 0.5, and 0.1 mg), injected subcutaneously, on glycaemic control as measured by HbA1c at 12 weeks (change from baseline). The study GBCK was originally designed to evaluate 3.0-, 1.0-, 0.5-, and 0.1-mg doses of dulaglutide. However, the dulaglutide 3.0-mg dose was discontinued and replaced with a dulaglutide 1.5-mg dose in a protocol amendment (following a recommendation from the DMC).

The mean duration of diabetes (3.9±3.7 years) and clinical characteristics (including 7.2±0.6% HbA1c, 32.1±4.8 kg/m2 BMI) were similar across treatment groups. At entry, 81.1% of patients were on metformin therapy and 18.9% of patients were treated with diet and exercise alone. There were no statistically significant differences between the dulaglutide and placebo treatment groups with respect to key characteristics.

At the 12-week time point, significant dose-dependent reductions in HbA1c were observed across dulaglutide 1.5 mg, 1.0 mg, and 0.5 mg doses (p<.001) (Table 27). Significant reductions in FPG from baseline were also demonstrated for the 1.5-, 1.0-, and 0.5-mg doses compared to placebo (p<.001; all). There was no significant difference in change from baseline to the 12-week final time point in body weight in any dulaglutide treatment group compared to placebo. This was mainly due to the large placebo response, demonstrated primarily by 2 patients.

Table 27 Summary of Efficacy Measures, Change from Baseline to 12 Weeks, Dulaglutide versus Placebo, ITT, Study GBCK, as Monotherapy

	LS Mean (SE) Change from Baseline				
Outcome Measure[a] (units)	Dula_1.5 N=29	Dula_1.0 N=34	Dula_0.5 N=34	Dula_0.1 N=35	Placebo N=32
ΔHbA1c (%)	-1.04 (0.13)**	-1.03 (0.11)**	-0.89 (0.12)**	-0.37 (0.11)	0.01 (0.13)
ΔFPG (mg/dL)[b]	-37.49 (4.78)**	-33.73 (4.18)**	-30.31 (4.26)**	-11.59 (4.09)	-3.78 (4.44)
ΔWeight (kg)	-1.49 (0.48)	-1.11 (0.42)	-0.34 (0.43)	-0.19 (0.42)	-1.38 (0.45)

Abbreviations: Δ = change from baseline; FPG = fasting plasma glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LS = least squares; N = number of patients treated; SE = standard error. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a Analysis methods are provided FPG values in mmol/L provided p<.001 dulaglutide treatment group compared to placebo.

It was concluded that Study GBCK confirmed the dose-dependent effect of dulaglutide on HbA1c and daily blood glucose across the examined range and support the outcome of the dose-finding stage of Study GBCF.

Study H9X-JE-GBCZ

Study **GBCZ** was a Phase 2, multicenter, placebo-controlled, randomized, double-blind, parallel arm study assessing the safety and efficacy of dulaglutide as monotherapy in Japanese patients with T2DM who were OAM-naïve or had discontinued OAM monotherapy. A total of 145 patients were randomly assigned to 1 of 3

dulaglutide treatment groups (0.75, 0.5, or 0.25 mg) or placebo. The study consisted of 4 periods: a screening period, a lead-in period (including a washout period if needed based on previous treatment status), a 12-week treatment period, and a safety follow-up period. The primary efficacy measure was change in HbA1c from baseline at 12 weeks.

Two hundred and nineteen patients (219) entered the study; of these, 145 were randomized to treatment, and 138 completed the 12-week treatment period. The mean±SD duration of diabetes was 4.62±4.10 years, mean HbA1c was 8.00%±0.64%. At entry, 27.6% of patients were on ≥1 antihyperglycaemic medication.

The primary efficacy measure was change in HbA1c from baseline to the 12-week endpoint using MMRM for the full analysis set (FAS), excluding post rescue visits. A statistically significant reduction in LS means of change from baseline in HbA1c was demonstrated at the 12-week visit (Visit 7) for all doses as compared to placebo ($p<0.001$ in all groups) (Table 28). Similar results were seen in the analysis using MMRM for the per protocol set (PPS), and ANCOVA for the FAS based on the LOCF approach. Significant reductions from baseline in FPG were also demonstrated for the dulaglutide 0.75, 0.5-, and 0.25-mg doses compared to placebo ($p<.05$; all). At Week 12, no significant changes in body weight were observed with dulaglutide 0.75 mg or 0.5 mg compared to placebo.

Table 28 Summary of Efficacy Measures, Change from Baseline to 12 Weeks, Dulaglutide versus Placebo, ITT, Study GBCZ, as Monotherapy

	LS Mean (SE) Change from Baseline			
Outcome Measure[a] (units)	Dula 0.75 N=35	Dula 0.50 N=37	Dula 0.25 N=36	Placebo N=37
ΔHbA1c (%)	-1.35 (0.09)**	-1.15 (0.08)**	-0.90 (0.09)**	-0.18 (0.09)
ΔFPG (mg/dL)[b]	-37.48 (4.81)**	-28.55 (4.62)*	-29.21 (4.67)*	-9.00 (4.75)
ΔWeight (kg)	-0.58 (0.32)	-0.40 (0.31)	0.41 (0.31)*	-0.84 (0.31)

Abbreviations: Δ = change from baseline; FPG = fasting plasma glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LS = least square; N = number of patients; SE = standard error. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a Analysis methods are provided in FPG values in mmol/L provided in *p<.05, **p<.001 dulaglutide treatment group compared to placebo

Study H9X-MC-GBDN

Study GBDN (see also *Secondary pharmacology* above and *Safety section* below) was a multicenter, randomized, double-blind, parallel-arm, 26-week treatment period, placebo-controlled study that evaluated the effects of dulaglutide 1.5 mg and dulaglutide 0.75 mg on blood pressure and heart rate using ABPM in a total of 755 patients with T2DM on at least 1 OAM. The study included a 2-week screening and lead-in period, followed by a 26-week treatment period, and a 4-week safety follow-up period. In addition to study drug, patients continued their prestudy OAM regimen throughout the course of the study. The primary objective was to evaluate the effects of dulaglutide on systolic blood pressure. HbA1c, fasting serum glucose (FSG), and weight were examined as secondary parameters.

A total of 755 were randomized (1:1:1) to 1 of the 3 treatment arms and received at least 1 dose of protocol-specified treatment; 630 (83.4%) patients completed the treatment period (26 weeks) and 125 (16.6%) discontinued. The 3 treatment groups were generally similar with respect to demographic characteristics at baseline. The mean age of the patients was 56.5 years, 52% were male, 80.5% were white. The mean HbA1c was 7.9%, and the mean duration of diabetes was 8.3 years (median 7.0 years). The duration of diabetes was significantly different among the treatment groups (shorter duration in the dulaglutide 1.5 mg patients; p=.029).

Dulaglutide 0.75 mg and 1.5 mg significantly reduced mean HbA1c levels at 16 (-1.02% and -1.18%, respectively) and 26 (-0.88% and -1.02%, respectively) weeks compared with placebo (-0.03% at 16 weeks and -0.01% at 26 weeks) (Table 29). The differences between dulaglutide doses were not significant. Both doses of dulaglutide also significantly reduced FSG as early as Week 4 (steady state) and this reduction persisted throughout the trial. Significant reductions from baseline in weight were observed for dulaglutide 1.5 mg and dulaglutide 0.75 mg compared to placebo (p<.001 and p<.05, respectively).

Table 29 Summary of Secondary Measures, Change from Baseline to 26 Weeks, Dulaglutide versus Placebo, ITT, Study GBDN, in Combination with ≥1 OAM

	LS Mean (SE) Change from Baseline		
Outcome Measure[a] (units)	Dula_1.5 N=251	Dula_0.75 N=254	Placebo N=250
ΔHbA1c (%)	-1.01 (0.07)**	-0.89 (0.06)**	-0.02 (0.06)
ΔFSG (mg/dL)[b]	-30.06 (2.70)**	-29.88 (2.70)**	0.00 (2.70)
ΔWeight (kg)	-1.85 (0.23)**	-0.86 (0.22)*	-0.08 (0.22)

Abbreviations: Δ = change from baseline; FSG = fasting serum glucose (central laboratory); HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LS = least squares; N = number of patients; OAM = oral antihyperglycaemic medication; SE = standard error. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. a Analysis methods are provided in FSG values in mmol/L provided *p<.05, **p<.001 dulaglutide treatment group compared to placebo

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

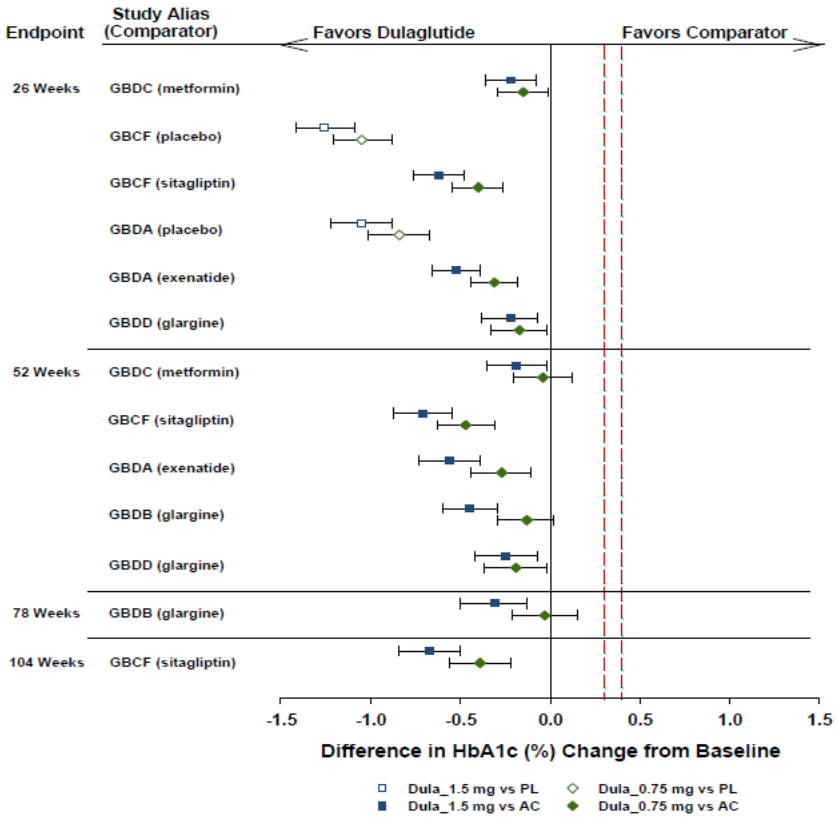
The Applicant provided also analyses of results across the Phase 3 studies conducted on the ITT population for the same efficacy measures reported for the individual studies: changes from baseline in HbA1c (ANCOVA [LOCF]); percentages of patients achieving HbA1c targets (logistic regression [LOCF]); changes from baseline in FBG, PPG, and beta-cell function (MMRM); and changes from baseline in weight (ANCOVA [LOCF]).

Haemoglobin A1c

Figure 21a shows the differences in changes from baseline in HbA1c for dulaglutide treatment relative to placebo or active comparator in the 5 Phase 3 studies at the 26-, 52-, 78, and 104-week time points.

Table 30 presents the differences in changes from baseline in HbA1c with dulaglutide 1.5 mg and dulaglutide 0.75 mg versus placebo and active comparators and percentage of patient achieving HbA1c targets in all 5 Phase 3 studies. Across the 5 Phase 3 studies both dulaglutide doses led to a consistent improvement in HbA1c from 26 to 104 weeks.

Figure 21a Differences in HbA1c LS mean change from baseline (%) relative to active comparator or placebo (± 95% CI) at 26-, 52-, 78-, and 104- week time points, ITT, Studies GBDC, GBCF, GBDA, GBDB, and GBDD.



Abbreviations: AC = active comparator; BID = twice daily; CI = confidence interval; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LS = leastsquare; PL = placebo; QD = once daily. Note: Dula_x.x refers to dulaglutide x.x mg once weekly. Note: Reference lines – dashed red reference lines are at 0.3% and 0.4%. Note: Active comparator doses: metformin, 1500 to 2000 mg QD, sitagliptin, 100 mg QD; exenatide, 10 mcg BID, insulin glargine, adjusted based on treat-to-target algorithm to maintain FPG <100 mg/dL (<5.6 mmol/L).

Table 30 Mean HbA1c and Percent of Patients Achieving Target HbA1c for the ITT Population (LOCF), H9X-MCGBDC, GBCF, GBDA, GBDB, and GBDD

TRT (Week)	n	HbA1c (%) LS Mean (SE)	LS Mean (SE) Change from Baseline in HbA1c (%)	LS Mean Difference vs. Placebo	LS Mean Difference vs. AC	HbA1c <7.0% n (%)	HbA1c ≤6.5% n (%)
GBDC							
Dula_1.5 (26)	265	6.81 (0.06)	-0.78 (0.06)#	NA	-0.22	163 (61.5)#	122 (46.0)##
Dula_1.5 (52)	265	6.89 (0.07)	-0.70 (0.07)#	NA	-0.19	159 (60.0)#	112 (42.3)##
Dula_0.75 (26)	265	6.88 (0.06)	-0.71 (0.06)#	NA	-0.15	166 (62.6)#	106 (40.0)#
Dula_0.75 (52)	265	7.03 (0.07)	-0.55 (0.07)	NA	-0.04	141 (53.2)	92 (34.7)
Metformin (26)	265	7.03 (0.06)	-0.56 (0.06)	NA	NA	142 (53.6)	79 (29.8)
Metformin (52)	265	7.08 (0.07)	-0.51 (0.07)	NA	NA	128 (48.3)	75 (28.3)
GBCF							
Dula_1.5 (26)	302	6.90 (0.05)	-0.22(0.05)**,##	-1.26	-0.62	184 (60.9)**,##	141 (46.7)**,##
Dula_1.5 (52)	302	7.02 (0.06)	-1.10 (0.06)##	NA	-0.71	174 (57.6)##	126 (41.7)##
Dula_1.5 (104)	302	7.13 (0.06)	-0.99 (0.06)##	NA	-0.67	164 (54.3)##	118 (39.1)##
Dula_0.75 (26)	297	7.11 (0.06)	-1.01(.06)**,##	-1.05	-0.40	164 (55.2)**,##	92 (31.0)**,##
Dula_0.75 (52)	297	7.26 (0.06)	-0.87 (0.06)##	NA	-0.47	145 (48.8)##	86 (29.0)##
Dula_0.75(104)	297	7.41 (0.07)	-0.71 (0.07)##	NA	-0.39	133 (44.8)##	72 (24.2)##
Sitagliptin (26)	312	7.52 (0.05)	-0.61 (0.05)**	–0.64	NA	118 (37.8)**	68 (21.8)*
Sitagliptin (52)	312	7.73 (0.06)	-0.39 (0.06)	NA	NA	103 (33.0)	60 (19.2)
Sitagliptin (104)	312	7.80 (0.06)	-0.32 (0.06)	NA	NA	97 (31.1)	44 (14.1)
Placebo (26)	176	8.16 (0.07)	0.03 (0.07)	NA	NA	37 (21.0)	22 (12.5)
GBDA							
Dula_1.5 (26)	271	6.47 (0.06)	-1.51(0.06)**,##	-1.05	-0.52	212 (78.2)**,##	170 (62.7)**,##
Dula_1.5 (52)	271	6.66 (0.08)	-1.36 (0.08)##	NA	-0.56	192 (70.9)##	155 (57.2)##

Dula_0.75 (26)	269	6.69 (0.06)	-1.30(0.06)**,##	-0.84	-0.31	177 (65.8)**,##	143 (53.2)**,##
Dula_0.75 (52)	269	6.95 (0.08)	-1.07 (0.08)#	NA	-0.27	159 (59.1)#	130 (48.3)##
Exenatide (26)	266	7.00 (0.06)	-0.99 (0.06)**	-0.53	NA	139 (52.3)*	101 (38.0)**
Exenatide (52)	266	7.23 (0.08)	-0.80 (0.08)	NA	NA	131 (49.3)	92 (34.6)
Placebo (26)	119	7.53 (0.08)	-0.46 (0.08)	NA	NA	51 (42.9)	29 (24.4)
GBDB							
Dula_1.5 (26)	263	6.97 (0.06)	-1.16 (0.06)##	NA	-0.51	153 (58.2)##	97 (36.9)##
Dula_1.5 (52)	263	7.05 (0.06)	-1.08 (0.06)##	NA	-0.45	140 (53.2)##	71 (27.0)##
Dula_1.5 (78)	263	7.23 (0.07)	-0.90 (0.07)##	NA	-0.31	129 (49.1)##	74 (28.1)##
Dula_0.75 (26)	266	7.24 (0.05)	-0.89 (0.05)##	NA	-0.24	122 (45.9)##	74 (27.82)##
Dula_0.75 (52)	267	7.37 (0.06)	-0.76 (0.06)	NA	-0.13	99 (37.1)	60 (22.5)#
Dula_0.75 (78)	267	7.51 (0.07)	-0.62 (0.07)	NA	-0.03	91 (34.1)	59 (22.1)
Glargine (26)	258	7.48 (0.06)	-0.65 (0.06)	NA	NA	84 (32.6)	40 (15.5)
Glargine (52)	259	7.50 (0.06)	-0.63 (0.06)	NA	NA	80 (30.9)	35 (13.5)
Glargine (78)	259	7.54 (0.07)	-0.59 (0.07)	NA	NA	79 (30.5)	43 (16.6)
GBDD							
Dula_1.5 (26)	275	6.83 (0.07)	-1.64 (0.07)#	NA	-0.22	186 (67.6)#	132 (48.0)#
Dula_1.5 (52)	275	6.99 (0.08)	-1.48 (0.08)#	NA	-0.25	161 (58.6)#	101 (36.7)
Dula_0.75 (26)	277	6.88 (0.07)	-1.59 (0.07)#	NA	-0.17	191 (69.0)#	119 (43.0)
Dula_0.75 (52)	277	7.04 (0.08)	-1.42 (0.08)#	NA	-0.19	156 (56.3)	96 (34.7)
Glargine (26)	280	7.05 (0.07)	-1.41 (0.07)	NA	NA	159 (56.8)	105 (37.5)
Glargine (52)	280	7.23 (0.08)	-1.23 (0.08)	NA	NA	138 (49.3)	85 (30.4)

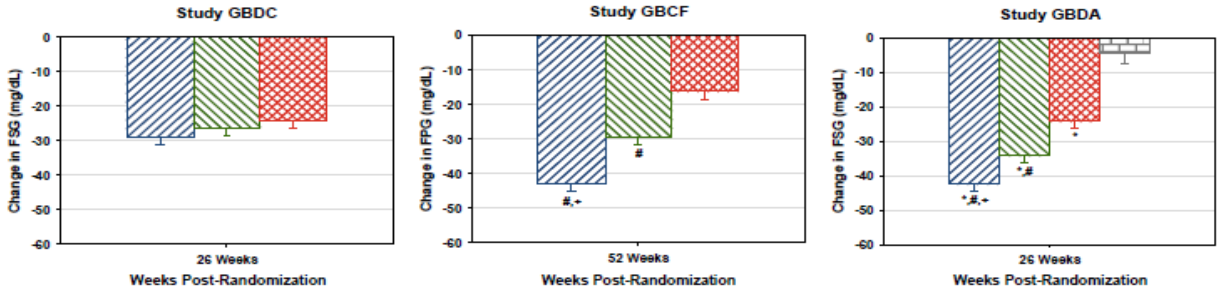
Abbreviations: AC = active comparator; HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; n = number of patients with at least one post-baseline measurement prior to rescue; NA = not applicable; SE = standard error; TRT = treatment. Note: Dula_x.x refers to dulaglutide x.x mg once weekly.
***p<.05, **p<.001 dulaglutide or active comparator treatment group compared to placebo. #p<.05, ##p<.001 dulaglutide treatment group compared to active comparator**.

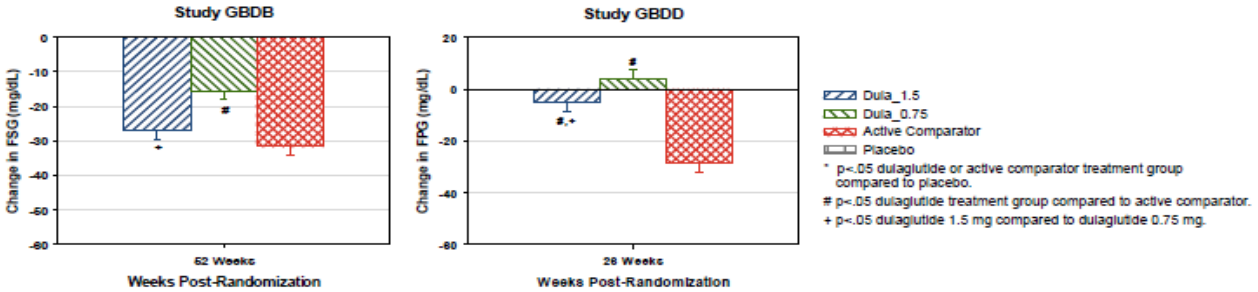
At the primary time point, treatment with dulaglutide 1.5 mg also resulted in significantly greater percentages of patients who achieved HbA1c <7.0% or ≤6.5% compared to placebo, as applicable, and/or active comparator in all 5 Phase 3 studies. Treatment with dulaglutide 0.75 mg also resulted in significantly greater percentages of patients who achieved HbA1c <7.0% compared to placebo and/or active comparator in 4 of the 5 Phase 3 studies.

Fasting and Postprandial Blood Glucose

At the primary time point for each of the 5 Phase 3 studies, treatment with dulaglutide 1.5 mg alone or in combination with OAMs or prandial insulin resulted in significant reductions from baseline in FBG, as measured by the central laboratory (Figure 22). In 4 of the Phase 3 studies, treatment with dulaglutide 0.75 mg also resulted in significant reductions in FBG from baseline to the primary time point. The improvement in FBG concentrations from baseline was observed through the final time point (52 to 104 weeks) for 4 of the 5 studies.

Figure 22 Fasting blood glucose LS mean (SE) changes from baseline (mg/dL) at the primary time point (26 or 52 weeks), ITT, Studies GBDC, GBCF, GBDA, GBDB, and GBDD.





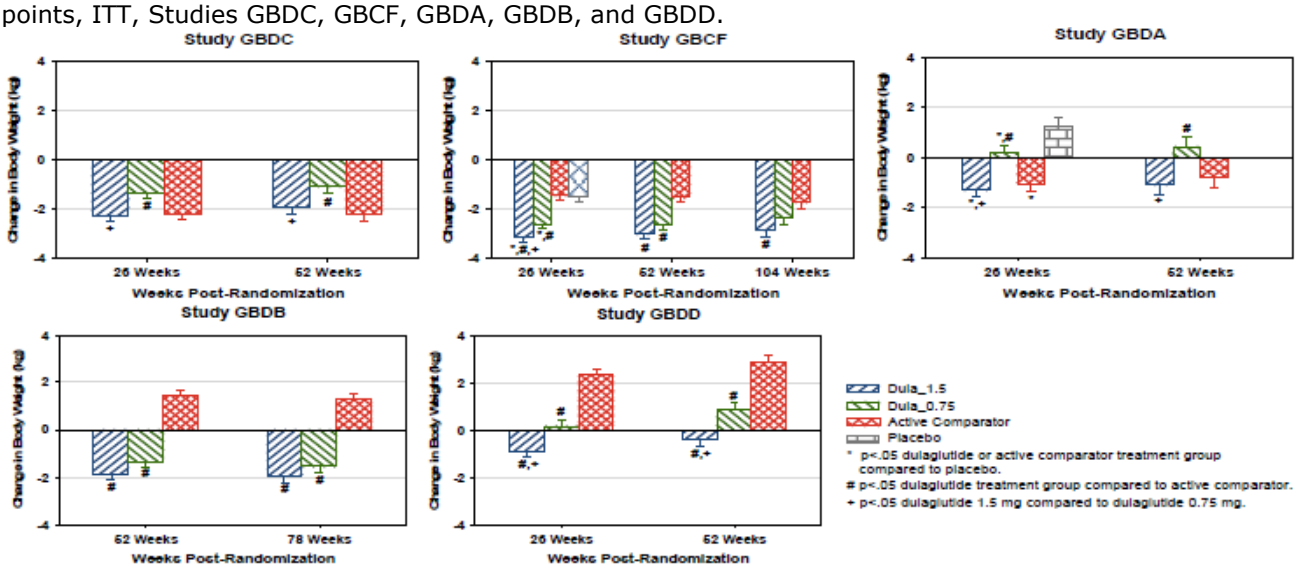
Note: Active comparator doses: GBDC metformin, 1500 to 2000 mg QD; GBCF sitagliptin, 100 mg QD; GBDA exenatide, 10 mcg BID, GBDB/GBDD insulin glargine, adjusted based on treat-to-target algorithm to maintain FPG <100 mg/dL (<5.6 mmol/L).

At the primary time points for Studies GBDC, GBDA, GBDB, and GBDD, treatment with dulaglutide alone or in combination with OAMs or prandial insulin reduced self-monitored mean PPG from baseline. Least-square mean changes from baseline ranged from -35.10 mg/dL (Study GBDB) to -76.14 mg/dL (Study GBDD) (-1.95 mmol/L to -4.23 mmol/L) for dulaglutide 1.5 mg and -29.52 mg/dL (Study GBDB) to -74.16 mg/dL (Study GBDD) (-1.64 to -4.12 mmol/L) for dulaglutide 0.75 mg. Self-monitored PPG was not collected in Study GBCF. Reductions from baseline in PPG at the primary time point were significant for dulaglutide 1.5 mg and dulaglutide 0.75 mg compared to placebo (Study GBDA), as well as for dulaglutide 1.5 mg versus exenatide (Study GBDA) and versus insulin glargine (Studies GBDB and GBDD).

Body Weight

In the 5 Phase 3 studies, dulaglutide 1.5 mg was associated with a sustained weight reduction from baseline over the duration of the studies, including the longest study, GBCF (104-week final time point). In 3 of the 5 Phase 3 studies, dulaglutide 0.75 mg also showed weight reduction from baseline over the duration of the studies. Due to concomitant antihyperglycaemic therapies, TZD and prandial insulin in particular, the range of weight changes varied between individual studies (Figure 23). The LS mean changes in body weight from baseline to primary time point with dulaglutide 1.5-mg treatment ranged from -0.87 kg (Study GBDD, 26 weeks) to -3.03 kg (Study GBCF, 52 weeks). The LS mean changes from baseline to final time point with dulaglutide 1.5-mg treatment ranged from -0.35 kg (Study GBDD, 52 weeks) to -2.88 kg (Study GBCF, 104 weeks).

Figure 23 Least-square mean (SE) changes from baseline in body weight (kg) at the primary and final time points, ITT, Studies GBDC, GBCF, GBDA, GBDB, and GBDD.



Note: Study GBCF data are included at 26 weeks since the placebo comparison at this time point was a primary objective of the study. Note: Active comparator doses: GBDC metformin, 1500 to 2000 mg QD; GBCF sitagliptin, 100 mg QD; GBDA exenatide, 10 mcg BID; GBDB/GBDD insulin glargine, adjusted based on treat-to-target algorithm to maintain fasting plasma glucose <100 mg/dL (<5.6 mmol/L).

The Applicant also examined the association between body weight change and the incidence of nausea and vomiting. At the primary time point of each Phase 3 study, mean reduction in body weight was seen in patients treated with dulaglutide 1.5 mg irrespective of the occurrence of nausea, although the reduction was numerically larger in the group with nausea (mean changes from baseline -1.0 to -3.9 kg with nausea, versus -0.2 to -2.9 kg without nausea). Similar results were observed with vomiting, and with nausea and/or vomiting.

Subgroups

Subgroup analyses were prespecified and performed on the ITT population with respect to change in HbA1c from baseline at the primary time point for each of the 5 Phase 3 studies. 2-way treatment-by-subgroup interactions were examined for the following baseline measurements: sex, age, ethnicity, race (white and non-white), body weight, body mass index, duration of diabetes, baseline HbA1c, renal status (estimated glomerular filtration rate [eGFR] calculated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] <60 and ≥60 mL/min/1.73 m^2 and Urinary Albumin Creatinine Ratio [UACR] >300 and ≤300 mg/g) and dulaglutide anti-drug antibody (ADA). For subgroup analyses, a treatment-by-subgroup interaction p-value <0.1 was considered significant.

No significant treatment-by-subgroup interaction was found for sex, age (across the 5 main studies, 18.5% of patients were ≥65 years and 1.9% were ≥75 years), ethnicity, BMI (6.1% of patients had BMI <25 kg/m^2, 30.5% had BMI ≥25 and <30 kg/m^2, 33.6% had BMI ≥30 and <35 kg/m^2, and 29.7% had BMI ≥35 kg/m^2) or duration of diabetes (across the other 4 Phase 3 studies, 65.3% of patients had duration of diabetes <10 years and 34.7% had duration of diabetes ≥10 years. The distribution of patients with a duration of diabetes <10 years and ≥10 years within each treatment group was similar in each study. Inclusion criteria for Study GBDC specified a duration of diabetes >3 months and ≤ 5 years and was not included in this analysis). Significant subgroup effects were found for race, weight, baseline HbA1c and renal status.

Race. Analysis of the Phase 3 studies showed a significant treatment-by race interaction effect on the change from baseline in HbA1c in 2 of the 5 studies. In Studies GBDA and GBDD, reduction in HbA1c with dulaglutide was relatively consistent but varied somewhat more for placebo and exenatide groups (Study GBDA) and insulin glargine (Study GBDD) between white and non-white patients. The between-group differences were directionally consistent with the overall population and therefore are considered that they do not affect the interpretation of the overall study results.

Weight. Across the 5 Phase 3 studies, 52.3% of patients weighed <90 kg and 47.7% weighed ≥90 kg. The distribution of patients within each treatment group was similar in each study. Analysis of individual study data showed a significant treatment-by-weight interaction effect on change in HbA1c in 3 studies. In Studies GBDA and GBDB, mean reduction from baseline in HbA1c with dulaglutide was relatively consistent but varied somewhat more for patients in the comparator groups who were <90 kg versus ≥90 kg. In Study GBDD, for patients <90 kg, dulaglutide 0.75 mg resulted in a numerically greater mean reduction in HbA1c compared to dulaglutide 1.5 mg, whereas the reverse was observed in patients who weighed ≥90 kg; the differences were modest and not significant. Also in Study GBDD, insulin glargine resulted in numerically greater mean reductions in patients ≥90 kg.

Baseline HbA1c. The primary analysis model in each of the Phase 3 studies adjusted for baseline HbA1c. Across the 5 Phase 3 studies, 67.0% of patients had baseline HbA1c <8.5%, and 32.8% of patients had baseline HbA1c ≥8.5% with similar distribution within each treatment group in each study. The magnitude of treatment effects with dulaglutide 1.5 mg and dulaglutide 0.75 mg were greater for the subgroup with a higher baseline HbA1c value (≥8.5%) compared to the rest. Clinically meaningful reductions in HbA1c were observed with dulaglutide

regardless of baseline HbA1c. In Studies GBCF and GBDA a significant treatment-by-baseline HbA1c interaction effect on change in HbA1c was observed, based on a nominal alpha level of 0.1 (p<.001 and p=.016, respectively). In Study GBCF (in which randomization was stratified by baseline HbA1c), the significant treatment-by-baseline HbA1c interaction effect appeared to be driven by the sitagliptin group. In Study GBDA (in which randomization was again stratified by baseline HbA1c), the interaction effect appeared to be largely driven by the placebo group.

Renal Status. Mean baseline eGFR (CKD-EPI) (<60 and ≥60 mL/min/1.73 m^2) and albuminuria (UACR ≤300 and >300 mg/g) were fairly well balanced across treatment groups in the individual Phase 3 studies. There was no significant treatment-by-eGFR (CKD-EPI) interaction effect on the change in HbA1c from baseline in any of the 5 studies. Analysis of individual study data from 4 of the 5 Phase 3 studies (Studies GBDC, GBCF, GBDB, and GBDD) did not show a significant treatment-by-renal status interaction (as measured by albuminuria) effect on the change in HbA1c from baseline. In Study GBDA, a significant treatment-by-renal status interaction effect as measured by albuminuria on change in HbA1c from baseline was observed (p=.039). However, there were very few patients with macroalbuminuria (UACR >300 mg/g; n=27 overall across all 4 treatment groups), which makes drawing conclusions difficult.

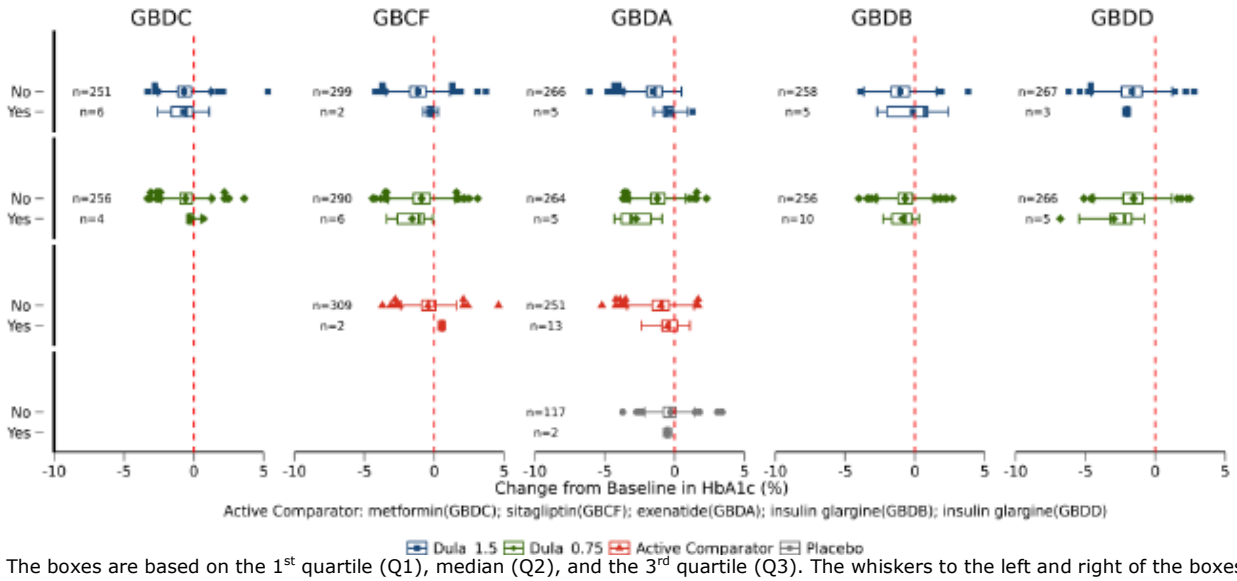
In general, the subgroup analyses in the phase 3 trials did not identify any particular factor having a major impact on the efficacy of dulaglutide. Of note, parameters such as BMI or weight found in PK studies to be inversely associated with dulaglutide bioavailability do not appear to have a significant impact on efficacy.

Not unexpectedly, patients with higher baseline HbA1c values benefited more from dulaglutide treatment although the real extent of this effect is difficult to determine, as the results are somewhat biased due to the inclusion of the monotherapy study GBDC which had some methodological limitations (short lead-in period) as discussed above. The subgroup observations in renal patients should be interpreted with caution as only few patients with eGFR<60 mL/min/1.73 m^2 and/or UACR ≤300 mg/g) were included in the studies.

Immunogenicity

Across the 5 Phase 3 studies, 21/1388 (1.5%) of patients randomized to dulaglutide 1.5 mg and 31/1385 (2.2%) of patients randomized to dulaglutide 0.75 mg had treatment-emergent (TE) dulaglutide ADA. At Week 26, the median (interquartile range [IQR]) changes from baseline in HbA1c were -0.6% (-1.8%, 0%; n=21) and -1.2% (-1.9%, -0.6%; n=1341) in patients with and without TE dulaglutide ADA, respectively, in the dulaglutide 1.5-mg group. Figure 24 presents by-study box plots of changes from baseline in HbA1c for patients with or without TE dulaglutide ADA at the primary time point.

Figure 24 Box-and-whisker plots of change from baseline in HbA1c (%) by treatment-emergent ADA status at primary time points (using LOCF), ITT, without post-rescue visits, H9X-MCGBDC, GBCF, GBDA, GBDB, and GBDD.



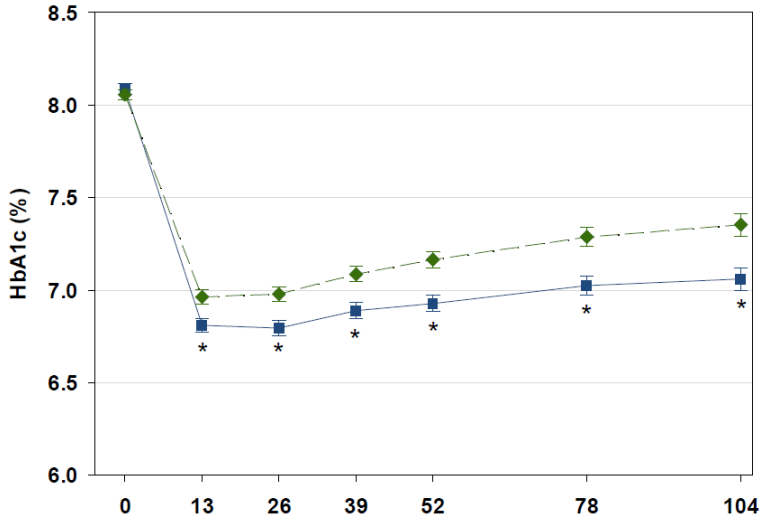
The boxes are based on the 1st quartile (Q1), median (Q2), and the 3rd quartile (Q3). The whiskers to the left and right of the boxes extend to the smallest and largest data points ≤1.5 x interquartile range (Q3-Q1) from Q1 and Q3, respectively. Individual points beyond the whiskers are plotted. Primary time point is 26 weeks for Studies GBDA, GBDC, and GBDD and 52 weeks for Studies GBDB and GBCF

Overall, the number of patients with treatment emergent dulaglutide ADA was very low. No obvious pattern was detected in the relationship between the presence of dulaglutide ADA and HbA1c change. In some cases the effect of dulaglutide on HbA1c was smaller in ADA positive patients but the findings are inconsistent and conclusions are difficult to draw. Nevertheless, the overall data do not raise any particular concerns. Immunogenicity is further discussed in the *Safety* section below

Integrated efficacy analyses Dulaglutide 1.5 mg vs dulaglutide 0.75 mg

Integrated analyses of the Phase 3 studies were also performed to compare the dulaglutide 1.5 mg and dulaglutide 0.75 mg doses. Figure 25 presents MMRM analyses through 104 weeks of the change from baseline in HbA1c over time in the integrated dulaglutide 1.5 mg and dulaglutide 0.75 mg treatment groups (ITT). Dulaglutide 1.5 mg significantly reduced HbA1c from baseline compared to dulaglutide 0.75 mg at all time points (p<.001). The LS mean differences (dulaglutide 1.5 mg minus dulaglutide 0.75 mg) at 26, 52, and 104 weeks (only GBCF had actual data at this time point) were -0.19%, -0.24%, and -0.30%, respectively. Similarly, in the PP without rescued patients population (supportive analysis) across all 5 Phase 3 studies, dulaglutide 1.5 mg significantly reduced HbA1c from baseline compared to dulaglutide 0.75 mg at all time points (p<.001)

Figure 25 Least-square mean HbA1c (%) (± SE) over time, MMRM by treatment group and week, ITT, integrated (Studies GBDC, GBCF, GBDA, GBDB, and GBDD).



N							
dula_1.5	1417	1321	1274	714	1154	438	195
dula_0.75	1415	1334	1276	723	1152	425	191

Note: Dula_x.x refers to dulaglutide x.x mg once weekly. Note: Not all studies included in the integrated analysis had data at Week 39. *p<.001 between treatment p-value.

Significantly greater percentages of ITT patients treated with dulaglutide 1.5 mg also achieved HbA1c <7.0% at all time points (p≤.006; all) or ≤6.5% across all studies beginning at 13 weeks (p<.001; all) compared to dulaglutide 0.75 mg. The integrated analysis also showed that dulaglutide 1.5 mg resulted in significantly greater LS mean reductions in body weight from baseline compared to 0.75 mg at all time points (p≤.004). The LS mean differences (dulaglutide 1.5 mg minus dulaglutide 0.75 mg) were -0.92 kg, -0.97 kg, and -0.93 kg at Weeks 26, 52, and 104 (only Study GBCF had actual data at this time point), respectively. Similar results were observed in the PP without rescued patients' population.

Monotherapy indication

As previously noted, as part of their responses to the Day 120 LoQ, the Applicant requested an amendment of the initially proposed indications to include a monotherapy indication based mainly on the results of the monotherapy Study H9X-MC-GBDC [GBDC].

Study H9X-MC-GBDC (The Impact of LY2189265 versus Metformin on Glycemic Control in Early Type 2 Diabetes Mellitus [AWARD-3: Assessment of Weekly AdministRation of LY2189265 in Diabetes-3]) compared the two doses of dulaglutide (0.75mg and 1.5mg once weekly) with metformin in patients with early stage type 2 diabetes either treatment naïve (24.9%) or previously on an OAM (75.1%). At 26 weeks the results showed a significant reduction in HbA1c with both dulaglutide doses compared to baseline (-0.71% and -0.78% for 0.75mg and 1.5mg respectively).

In addition, the primary objective of the study was achieved showing that both dulaglutide doses were not only non-inferior (the primary objective) but also superior to metformin although by only a small margin. The results of all other secondary parameters were generally in the same direction, further supporting the primary analysis. A significant weight loss (mean -2.29kg with dulaglutide 1.5mg) was also observed. Dulaglutide effects were also to a large extent maintained throughout the extended period up to 52 weeks. A relatively small percentage of patients discontinued from the study by the time of the primary analysis at 26 weeks or needed rescue therapy, with similar numbers between groups. This was also the case for the rest of the trial up to 52 weeks.

The vast majority of patients also remained on a sufficiently high dose of metformin during the trial (at 26 weeks, the mean dose of metformin was 1902 mg, and at 52 weeks, the mean dose was 1889 mg).

The above results provide clear evidence that both dulaglutide doses 1.5mg and 0.75mg could perform at least as well as metformin in a monotherapy setting. Therefore, from an efficacy point of view the monotherapy indication for patients who cannot receive metformin is considered well supported and acceptable.

The safety aspects are further discussed in the *Safety* section below.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of this application and on the basis of PK and PD data from the clinical pharmacology studies, the applicant designed and implemented a clinical program to assess the efficacy and safety of dulaglutide in a wide-ranging T2DM population. The initial step involved identification of a dose range suitable for further development. Study GBCF (Stage 1), the principal dose-range finding study, identified, based on pre-specified efficacy/safety criteria, the 1.5mg dose as the optimal one, which together with a lower (0.75mg) dose were tested in the main trials. Four Phase 2, randomized, double-blind, placebo-controlled studies provided supporting data, including a dose titration study, a monotherapy dose-response study, a study of dulaglutide in Japanese patients, and an ambulatory blood pressure monitoring study.

The primary efficacy data come from the five pivotal long-term controlled Phase 3 trials which meet the main requirements for confirmatory studies in the investigation of medicinal products in the treatment of diabetes mellitus, according to the relevant European Guidelines, as they were designed to test the superiority of dulaglutide over placebo, alone or when added to an appropriate background therapy, as well as the non-inferiority to established active comparators. The studies were of sufficient duration to evaluate efficacy, and most included a substantial percentage of patients from Europe. The phase 3 program is generally in line with the previous CHMP Scientific Advice.

All trials were conducted as randomized, parallel-arm trials with four periods: a screening period, a lead-in period, a treatment period, and a safety follow-up period. Dulaglutide was compared to placebo in two double-blinded trials (GBCF and GBDA) and a range of active comparators (metformin, sitagliptin, exenatide and insulin glargine) in all five of them (GBCF, GBDC, DBDA, GBDB and GBDD). The insulin comparator studies (GBDB, GBDD) and the exenatide study (GBDA) were conducted as open label studies due to the complexity of blinding to insulin/exenatide pen device. The provided justification is accepted. Three of the 5 trials had a 52-week treatment period, one had a 78-week treatment period, and another trial had a 104-week treatment period. Long-term safety and efficacy data were collected through the final time points (52, 78, or up to 104 weeks). Dulaglutide was also tested, in a sequential approach, as monotherapy (study GBDC) or in combination with other treatments as double (with MET; study GBCF) or triple therapy (with MET+SU, study GBDB; MET+TZD; study GBDA or MET+insulin lispro; study GBDD).

In general, most trials were similar with previous ones with other products in this field and there are no major concerns about their design or conduct. The inclusion criteria were generally appropriate for each study, reflecting the expected characteristics and stage of diabetes of the target population who would be likely to receive the relevant study therapy. Similarly, the exclusion criteria were as expected, to a large degree reflecting the contraindications of the study treatments such as metformin which was included in all trials either as background therapy or as comparator. This, however, resulted in exclusion of certain special groups such as patients with significant kidney disease or patients with advanced heart failure, which raised some concerns

about the extrapolation of the findings in these groups. These limitations are reflected in the product information.

In order to assess the incremental benefits of dulaglutide in all trials appropriate measures were taken to ensure that the included patients were those not adequately controlled on previous treatment(s). In the add-on studies, baseline therapy was sufficiently up-titrated before randomizing patients and maintained at a constant dose throughout the study in line with the guideline recommendations. With the exception of the monotherapy study GBDC, patients' background therapy was optimized with maximally tolerated/effective doses and then remained stable during a 9 to 12 week lead-in period (with a dose stabilization period of 6 to 8 weeks prior to baseline HbA1c measurement) which in most cases was also sufficient to ensure wash out of previous therapies. The recommended doses of background OAM therapy (metformin, glimepiride, pioglitazone) and active comparators (metformin, sitagliptin, exenatide) were appropriate and in line with European licenses.

The active comparators are generally considered meaningful, although, in study GBCF a SU instead of sitagliptin may have been preferable. In the active controlled studies, almost all patients were treated with the target doses of the active comparators, sufficient to elicit their full glucose-lowering potential, thus allowing valid conclusions regarding non-inferiority or superiority. Although, in study GBDB the antihyperglycaemic effect of insulin glargine may have been increased due to a more aggressive up-titration regimen (mean doses were 26.5, 29.8 and 32.1 Units at 26, 52, and 78 weeks, respectively) the risk of hypoglycaemia must always be adequately taken into account. In fact, titration of insulin glargine was performed according to a standard dosing algorithm (e.g. assessed in: Diabetes Care January 2006 vol. 29 no. 1, 1-8) targeting an FPG <5.6 mmol/L (100 mg/dL), which reflects clinical practice and is, from an efficacy assessment point of view, acceptable. In addition, insulin doses were up-titrated throughout the study and were comparable to those achieved in other studies investigating GLP-1-receptor agonists.

The primary outcome measure in all 5 studies was HbA1c change from baseline (at 26 or 52 weeks) which together with a range of secondary parameters provided a comprehensive assessment of the dulaglutide effects on glycaemic control. From an efficacy perspective the duration of the trials of up to 2 years was also sufficient to evaluate the longer term effects of the drug. It is noted that with the exception of Study GBCF, which used a noninferiority margin of 0.25% for HbA1c change from baseline, 0.4% was used in the remaining 4 trials that was not entirely in line with the CHMP guideline on diabetes (0.3% is recommended). Although this might have had an impact on sample size calculations, since superiority against the comparators was shown for dulaglutide 1.5 mg in all studies, this point is of little relevance at this stage.

Further to the evaluation of dulaglutide on glycaemic endpoints, its effect on BMI and body weight was also investigated. Pharmacodynamic endpoints were also examined in selected phase 3 studies to characterise the mechanism of action including beta-cell function and insulin secretion PD parameters. The patients' perspective was also evaluated through the administration of seven patient-reported outcome questionnaires as secondary objectives in the protocols. The most clinically relevant questionnaire was treatment satisfaction measured in Studies GBDA and GBDC using the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) and change (DTSQc). This focused on patients' rating of salient aspects of a treatment experience, including ease of use, side effects and efficacy. Inclusion of PRO measures is in line with the CHMP reflection paper on Health related Quality of Life (2005) and is generally supported.

Four Phase 2, randomized, double-blind, placebo-controlled studies provided supporting data, including a dose titration study, a monotherapy dose-response study, a study of dulaglutide in Japanese patients, and an ambulatory blood pressure monitoring (ABPM) study.

There are, however, as noted above some gaps in the available evidence with regard to certain treatment

combinations that are possibly to be encountered in clinical practice; for example, there are no data on double therapy with dulaglutide in combination with SU or TZD as well as with DPP-4 inhibitors or SGLT2 inhibitors, and triple combination with SU+TZD or SU+insulin. Also in a non-traditional approach dulaglutide was tested as add-on therapy to prandial instead of basal insulin. This is discussed further below.

Efficacy data and additional analyses

In terms of the dulaglutide dose selection, the overall evidence, from PK/PD analyses and data from the dose ranging part of Study GBCF indicated a dose dependent effect in terms of both efficacy and tolerability/safety and the 1.5mg was identified as the optimal one for clinical use. Doses higher than 1.5 mg were shown to offer very little additional benefit while associated with poorer tolerability and a potentially higher risk of complications. In addition to 1.5mg, the 0.75mg dose was also tested across the whole phase 3 program mainly as a back-up in case that serious tolerability/safety concerns arose with the higher dose.

The five main studies included patients across the whole range of T2DM population with characteristics that appear to represent well the intended target population. The mean duration of diabetes ranged from 2.6 years to 12.7 years, mean baseline HbA1c ranged from 7.6% to 8.5% (from treatment naïve patients to those treated with combination with 1 or 2 OAMs, or insulin) and mean BMI from 31.2 kg/m2 to 33.3 kg/m^2. There was also an approximately equal percentage of men and women and the mean baseline age was 56.2 years with 18.5% of patients at least 65 years or older. However, in the whole Phase 3 program, there were only 84 (1.8%) patients 75 years or older. In the phase 2 studies only two age groups were differentiated: <65 versus ≥65 years of age. Overall, in the Phase 2 and 3 studies there were in total 115 (1.9%) patients ≥75yrs and only three >85yrs. The range of the study populations across the spectrum of T2DM ensured that patients with common co-morbidities such as dyslipidaemia and hypertension were included, but as noted before, certain groups were excluded, including patients with significant renal or hepatic disease or advanced heart failure.

In the four of the Phase 3 Studies (GBDC, GBDA, GBDB, and GBDD) between 80% and 90% of the randomized patients completed the studies through the final 52 to 78 week time points; the percentage of patients who discontinuation the study drug at the time of the primary analyses did not exceed 16% in any of these studies. The number of patients needing rescue therapy was generally small, with less that 4% among those treated with dulaglutide 1.5mg. This may also be due to the fact that in most cases patients remained on high doses of background OAMs during the trials. In the longest study (GBCF) through the 104-week final time point 63.2%, 60.9%, and 59.0% of patients treated with dulaglutide 1.5 mg, dulaglutide 0.75 mg, and sitagliptin respectively completed the study. Most discontinuations in the studies were related to adverse effects rather than lack of efficacy.

Generally although the rates of discontinuations were similar between the arms and therefore not expected that the use of LOCF in the primary analyses may have benefited one treatment more than another, more conservative sensitivity analyses were requested for all studies to provide reassurance that the handling of missing data does not affect the conclusions**.** Sensitivity analyses which included BOCF and multiple imputation were provided and these confirmed the robustness of the results.

At the time of the primary analysis in all five main trials, both dulaglutide doses showed a significant and clinically relevant mean reduction in HbA1c from baseline. For dulaglutide 1.5mg the mean changes ranged from -0.78% (Study GBDC, 26 weeks) to -1.64% (Study GBDD, 26 weeks). For dulaglutide 0.75mg treatment the mean changes from baseline ranged from -0.71% (Study GBDC, 26 weeks) to -1.59% (Study GBDD, 26 weeks). Both dulaglutide doses were superior to placebo. Furthermore, although all active controlled trials were designed as non-inferiority studies, at the time of the primary analysis in all five dulaglutide 1.5mg was shown to be superior to the active comparator at a statistically significant level although only by a small margin in some

cases. The differences were maintained to a large extent, throughout the extended treatment periods up to the final time points of the studies. Dulaglutide 0.75 mg was superior to the active comparators in four of the five phase 3 studies and non-inferior to insulin glargine in one study.

In the monotherapy study GBDC the dulaglutide effect on HbA1c was generally modest and dulaglutide 1.5mg was superior to metformin in HbA1c change from baseline by only a small margin (mean difference -0.22%, 95% CI [-0.36%, -0.08%]) which was attributed to the relatively low HbA1c, at 7.6%, at baseline and the short lead-in period that might not be sufficient to ensure complete washout from previous OAMs. Nevertheless, dulaglutide efficacy was much greater in the remaining studies. In study GBCF dulaglutide 1.5mg (as add-on to metformin) was better in reducing HbA1c from baseline than sitagliptin at 12 months by -0.71% [-0.87%, -0.55%], and in study GBDA it was again shown (as add-on to metformin plus pioglitazone) superior to exenatide twice daily by -0.52% [-0.66%, -0.39%]. In the GBDB trial dulaglutide 1.5mg in combination with metformin and glimepiride was superior to insulin glargine by -0.45% [-0.60%, -0.29%] as was also in study GBDD in combination with insulin lispro (with or without metformin) against the insulin glargine+inslulin lispro regimen by -0.22% [-0.38%, -0.07%].

In all main studies dulaglutide 1.5mg also resulted in significantly greater percentages of patients reaching HbA1c <7.0% or ≤6.5% than the comparators. In study GBDD, the target threshold of <7% was attained with fewer patients experiencing episodes of (severe) hypoglycaemia and/or weight gain in both dulaglutide dose treated patients (GBDD). This is an important finding since hypoglycaemia is often prohibitive for tight glycaemic control with insulin.

Patients treated with dulaglutide 1.5 mg alone or in combination with OAMs or prandial insulin also had, significant in most cases, reductions in fasting blood glucose with mean changes from -4.86 mg/dL (Study GBDD) to -42.84 mg/dL (Study GBCF), as well as in self-monitored mean postprandial glucose, from -35.10mg/dL (Study GBDB) to -76.14 mg/dL (Study GBDD) (-1.95 mmol/L to -4.23 mmol/L). In addition, a significant effect on body weight was also observed in most trials with mean changes from baseline to primary time point ranging from -0.87kg (Study GBDD, 26 weeks) to -3.03 kg (Study GBCF, 52 weeks). The clinical relevance of the observed effect size with the 1.5 mg dose is uncertain but weight loss was generally consistent with that observed with marketed GLP-1 receptor agonists (e. g. mean weight change from baseline exenatide -1.5 to -2.9 kg, liraglutide -0.23 kg to -3.5 kg). There was no indication that weight loss might be associated with nausea or vomiting. Of importance, most the observed effects were shown to persist until the final points of the trials. Also, reassuringly, the sensitivity analyses confirmed the findings of the primary analysis.

Consistent improvements in treatment satisfaction (as assessed with Patient-reported outcome questionnaire [PRO]) from studies GBDA and GBDC indicate a positive effect of dulaglutide treatment. Where subjects were able to distinguish between treatments (GBDA, open-label compared to exenatide BID), dulaglutide improved treatment satisfaction to a greater extent than exenatide BID. Results from PRO measures suggest that patients on average considered the improvements in clinical parameters of greater significance than the inconvenience of an injection. The high treatment compliance throughout the studies may also be due to patient satisfaction.

In general, the subgroup analyses in the phase 3 trials did not identify any particular factor having a major impact on the efficacy of dulaglutide. Parameters such as BMI or weight found in PK studies to be inversely associated with dulaglutide bioavailability were not seen to have a significant impact on efficacy. Treatment emergent dulaglutide ADA were detected in only a small number of patients. In some cases the effect of dulaglutide on HbA1c was smaller in ADA positive patients but the findings are inconsistent and conclusions are difficult to draw, but generally the data do not raise any particular concerns.

Overall, dulaglutide showed a consistent and significant effect on the primary and secondary parameters across

all main clinical trials, further supported by the findings of the Phase 2 studies. However, there are some issues that require further consideration.

Although dulaglutide, as discussed above, was studied under various conditions, there are some gaps in the available evidence with regard to certain treatment combinations that can be encountered in clinical practice; for example, there are no data on double therapy in combination with a sulphonylurea or a thiazolidinedione alone or triple combination with sulphonylurea plus thiazolidinedione or insulin. Although these may not be first line combinations, they may be relevant to certain patients. Nevertheless, based on the available efficacy data and the consistency of the effects seen across the whole program, there is no reason to believe that dulaglutide in combination with a sulphonylurea or a thiazolidinedione alone or both, or in any similar combination will be less efficacious than in the regimens tested in the clinical trials. It should be noted that a study examining the dulaglutide+sulphonylurea combination is ongoing. There are also no data for other combinations such as with DPP-4 inhibitors or SGLT2 inhibitors.

A more challenging issue is the lack of efficacy data in combination with basal insulin. As previously noted, in a non-traditional approach study GBDD examined dulaglutide together with prandial insulin (with or without metformin) against a basal+prandial insulin regimen, investigating the place of dulaglutide as basal treatment for glucose control. Again, taking into account the totality of available efficacy data and the fact that, from a clinical perspective, dulaglutide does not appear to be considerably different or less efficacious than other GLP-1 agonists so far, there is no reason to believe that dulaglutide would not perform equally well when given together with insulin glargine. In fact the Applicant has indicated that a Phase 3b trial evaluating the glycaemic effects (change in HbA1c) of dulaglutide 1.5 mg once weekly versus placebo used in combination with insulin glargine over 28 weeks, is planned. Safety aspects i.e. if there are issues when dulaglutide is administered with sulphonylureas or insulin are discussed in the *Safety* section below.

With regard to the relative efficacy of the two doses it is agreed, as the Applicant suggests, that 1.5mg was shown to be slightly more efficacious than the lower dose. However, 0.75 mg also achieved clinically relevant reductions in HbA1c from -0.71% to -1.59% with consistent results on the secondary glycaemic endpoints. Although the difference in body weight reduction between the two doses was about 1 kg, the overall effect on weight was modest, even with the 1.5 mg dose and is of uncertain clinical relevance. Conversely, 0.75mg seems to have a slightly better tolerability and safety profile.

Study GBCJ showed no clear benefit of regimes involving dose titration compared to starting and continuing therapy with the same dose and a model estimating the effect of a dose-titrating regime on nausea and vomiting suggested that starting with a lower dose may be temporarily better tolerated but can delay the development of tolerance. The argument against the use of step-wise titration appears reasonable although the data are limited.

The CHMP requested from the applicant to make the 0.75 mg strength available to be used as follows: The 0.75mg is now suggested as the recommended posology for the monotherapy indication. Moreover, for dulaglutide as add-on therapy the recommended dose is 1.5mg/week with the 0.75mg suggested as starting dose for potentially vulnerable group of patients.

2.5.4. Conclusions on the clinical efficacy

The efficacy of dulaglutide was evaluated in five Phase 3 studies of 52 to 104 weeksboth as monotherapy and in combination with different oral glucose lowering agents and insulin lispro in a wide-ranging population with type 2 diabetes. A sixth phase 3 study, considered supportive, was submitted during the procedure. Dulaglutide both

0.75mg and 1.5mg had a consistent and significant effect on the primary endpoint of HbA1c change from baseline and the secondary parameters, and showed superior efficacy to placebo and active comparators in the trials. Although there are some methodological limitations, the studies have provided sufficient data to support the efficacy of dulaglutide under the conditions that it was examined.

Remaining uncertainties and gaps in the available evidence, including the lack of robust data in patients older than 75 years and in certain special groups, are generally reflected in the product information. Furthermore, the absence of data on specific oral combinations and with basal insulin raised some concerns about the generalizability of the findings to support the proposed broad indication. Nevertheless, CHMP concluded that the totality of evidence does not give reasons to suspect a reduced efficacy of dulaglutide as part of such regimens.

2.6. Clinical safety

The safety review includes data from the whole dulaglutide clinical program with 30 completed clinical studies (21 clinical pharmacology and 9 Phase 2 and 3 clinical studies) and up to 104 weeks of patient exposure to treatment (Table 1 above). A total of 6005 patients with T2DM, of whom 4006 received at least 1 dose of dulaglutide, comprise the principal safety population from the Phase 2 and 3 clinical studies. Clinical pharmacology studies contributed also 680 dulaglutide-treated healthy subjects, patients with T2DM, and subjects in special populations (such as renally or hepatically impaired patients) to safety analyses.

All Phase 3 studies and the Phase 2 studies, except one study (GBCJ), included a 30-day safety follow-up period after the last week of scheduled dosing (or early discontinuation visit during the dosing period) in the study protocol. These assessments permitted evaluation of patients after the last visit of the treatment period. An important protocol element in one of the completed Phase 2 studies (GBCJ) is that patients who were inadvertently enrolled were required to stop study drug but were permitted to remain in the study. In addition, in four of the completed Phase 3 studies (GBDA, GBDB, GBDC, and GBDD), patients may have continued in the study following the initiation of an additional or alternative antihyperglycaemic medication. The other Phase 2 and 3 studies, including Study GBCF, did not have this element in the study design.

Safety data are primarily reported for the Safety Population: all patients who were randomly assigned to study treatment and received at least 1 dose of assigned study treatment. For some special topics, all patients who entered a clinical study (whether or not they were later randomized to receive study treatment) were included in analyses that describe the population prior to treatment. Across the Phase 2 and 3 studies, several sites were terminated due to GCP noncompliance. In most instances, data for all patients were included in safety analyses for the individual studies. For two sites (Site 504 in Study GBDB and Site 100 in Study GBDD), there were significant data integrity issues and thus patients enrolled at these sites were excluded from summaries and listings presented in this document.

Dulaglutide Safety Analyses

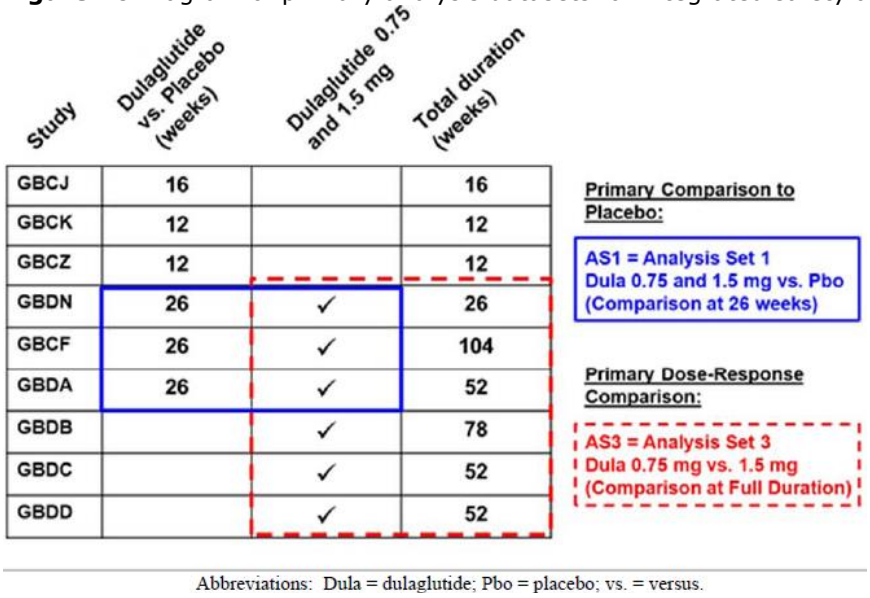
The primary purpose of the safety analyses is to characterize the safety of dulaglutide by identifying drug and dose effects with two specific data sets. The primary safety analyses assessed the drug effects using Analysis Set 1 and dose effects using Analysis Set 3 (Figure 26).

Analysis Set 1 (AS1): Integrated comparisons of both dulaglutide 0.75 mg and 1.5 mg doses (combined) versus placebo for all studies that had a treatment duration ≥26 weeks. Two subsets of AS1 provide comparisons of each dulaglutide dose versus placebo:

- Analysis Set 1a (AS1a): integrated comparison of dulaglutide 1.5 mg versus placebo.
- Analysis Set 1b (AS1b): integrated comparison of dulaglutide 0.75 mg versus placebo.

Analysis Set 3 (AS3): Integrated comparisons of dose effects for dulaglutide 0.75 mg versus 1.5 mg for all clinical studies (placebo- or comparator-controlled) that included both doses and had a treatment duration ≥26 weeks, covering the full treatment period (26 to 104 weeks). This analysis set provides long-term exposure data for dulaglutide for the 0.75 mg and 1.5 mg doses individually and combined (all dulaglutide).

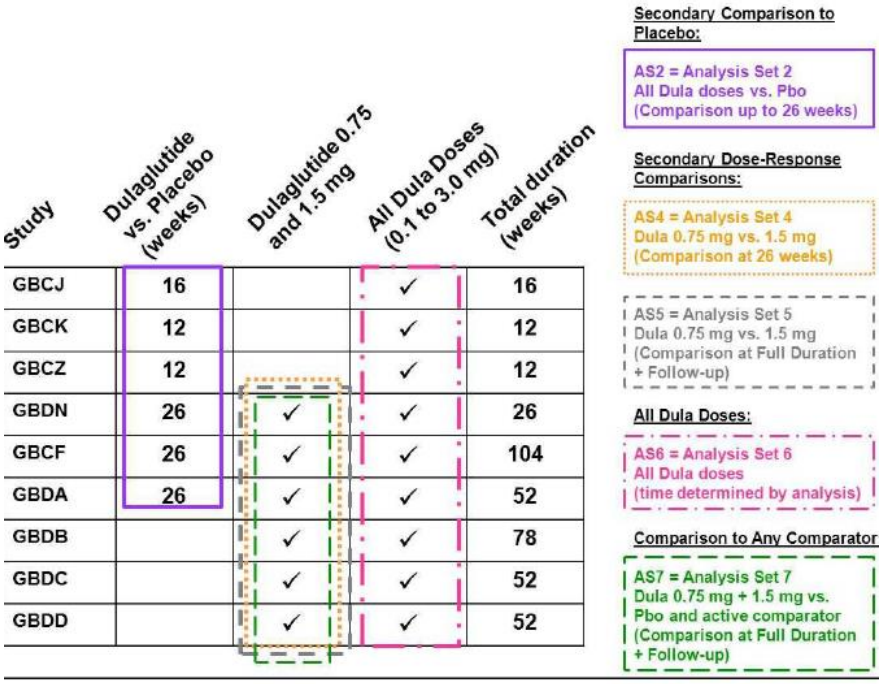
Figure 26 Diagram of primary analysis datasets for integrated safety analyses of completed studies



Abbreviations: Dula = dulaglutide; Pbo = placebo; vs. = versus.

Six additional supporting analysis sets (AS2, AS4, AS5, AS6, including subgroups of AS1 [AS1a and AS1b]) were carried out to compare dulaglutide with placebo, compare dulaglutide 0.75 mg and 1.5 mg doses, and characterize all dulaglutide doses in Phase 2 and 3 studies (0.1 to 3.0 mg) using data integrated at distinct time points (Figure 27). An additional analysis set (AS7) provides limited comparisons of dulaglutide and all comparators (placebo and active comparators)

Figure 27 Diagram of secondary analysis datasets for integrated safety analyses of completed studies.



Abbreviations: Dula = dulaglutide; Pbo = placebo; vs. = versus.

Generally, the way that data pools were constructed and the selection of the pools for the main safety evaluation have some limitations. It is agreed that the placebo-controlled studies (AS1) provide a good picture of the (short-term) safety profile of dulaglutide. On the other hand, for antidiabetic drugs rare but potentially serious long-term effects may be even more relevant. These effects may only be identified if a suitable control is present. Hence, data set AS3 using dulaglutide 0.75 mg as the control for dulaglutide 1.5 mg is considered rather inappropriate since, depending on the position and slope of the dose-effect curve, the difference between doses is expected to be much smaller in many cases than the possible difference between dulaglutide 1.5 mg and another comparator. Hence, the sensitivity of detection of dulaglutide specific AEs is markedly diminished with this approach.

Patient exposure

A total of 6005 unique individuals received study drug in the 9 completed Phase 2 and 3 studies. Of those, 4006 received dulaglutide for 3531 patient-years, 703 received placebo for 284 patient-years, and 1541 received active comparator for 1722 patient-years. Two studies (GBCF and GBDA) included a treatment arm that started patients on placebo and after 26 weeks switched them to sitagliptin or dulaglutide.

Table 31 Summary of Exposure to Dulaglutide and Comparators in Completed Phase 2 and 3 Studies (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

	Exposure to Study Drug *a		Time on Observation	
	N	Patients-Years	N	Patients-Years
Safety Population	6005	5536.6	6005	6194.0
Dulaglutide	4006	3531.2	4006	3983.7
Dula<0.75	191	42.9	191	60.3
Dula_0.75	1765	1724.2	1765	1932.8
Dula_0.75 only	1706	1695.1	1706	1898.1
Dula_0.75 after Placebo *b,c	59	29.1	59	34.6
Dula~1.0	175	47.2	175	55.2
Dula_1.5	1762	1689.1	1762	1900.6

Dula_1.5 only	1700	1661.0	1700	1865.3
Dula_1.5 after Placebo *b,c	62	28.1	62	35.3
Dula>1.5	113	27.7	113	34.9
Placebo *d	703	283.9	703	324.3
Active Comparator				
Metformin	268	226.7	268	254.8
Sitagliptin	439	637.3	439	680.6
Sitagliptin only	315	475.5	315	507.2
Sitagliptin after Placebo *c	124	161.8	124	173.5
Exenatide	276	236.3	276	274.8
Insuline Glargine	558	621.2	558	675.7

*a - For some studies (GBDA, GBDB, GBDC, GBDD), if a patient ceased study drug during the study, the patient was requested to remain in the study. "Treatment exposure" does not include any time after cessation of study drug.
*b - This group excludes patients in GBDA Placebo/Dula who discontinued study treatment while on Placebo, yet continued in study into the Dula portion of the study (n=3 Dula_0.75, n=0 Dula_1.5).
*c - This group includes patients who received Placebo prior to receiving Dulaglutide or Sitagliptin.
*d - This group includes patients who received Placebo only, and those who subsequently received Dulaglutide or Sitagliptin.

A total of 3045 patients received dulaglutide for at least 24 weeks in Phase 2 and 3 studies, with 2279 patients continuing treatment through at least 50 weeks (Table 32). 369 patients were treated with dulaglutide for approximately 2 years. The duration that patients were exposed to comparators in Phase 2 and 3 studies differed depending on the individual study designs.

Table 32 Summary of Patient Exposure to Study Treatment by Duration in Completed Phase 2 and 3 Studies (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

Variable	**All_Dula (N=4006) m M (%)**
Exposure duration thresholds in weeks; n (%)	
< 1 week	83 4006 (2.1)
>= 1 week	3923 4006 (97.9)
>= 2 weeks	3877 4006 (96.8)
>= 4 weeks	3802 4006 (94.9)
>= 8 weeks	3708 4006 (92.6)
>= 13 weeks	3405 3784 (90.0)
>= 24 weeks	3045 3567 (85.4)
>= 26 weeks	2821 3567 (79.1)
>= 50 weeks	2279 2941 (77.5)
>= 52 weeks	1595 2941 (54.2)
>= 78 weeks	642 1255 (51.2)
>= 100 weeks	369 710 (52.0)
>= 104 weeks	157 710 (22.1)
Exposure duration in weeks	
Mean	45.8
Minimum	0.0
Q1	25.0
Median	51.0
Q3	53.0
Maximum	119.0

Abbreviations: m = number of patients remaining in study for the specified time period; M = number of patients allocated to remain in study for the specified time period; N = total number of patients in specified treatment arm; Q1 = first quartile; Q3 = third quartile.
Note: All patients are included in M for at least the number of weeks expected to complete the study, according to protocol. If the actual duration of treatment exposure is greater than the protocol-specified planned treatment period duration, the patient is included in m and M through the actual number of weeks of treatment exposure. Exposure to study drug may be shorter than time in study, since patients who discontinue study drug were requested to remain in study, for studies GBDA, GBDB, GBDC, GBDD. All_Dula refers to all dulaglutide treatment groups combined.

In addition, 787 healthy subjects, patients with T2DM, and subjects in special populations (for example, renally or hepatically impaired) participated in the clinical pharmacology studies; 680 of them received a dose of dulaglutide (Table 33).

Table 33 Exposure to Dulaglutide in All Clinical Pharmacology Studies

Dulaglutide dose (mg)	Healthy Subjects (N=492)	T2DM (N=181)	Renally impaired (N=32)	Hepatically** impaired (N=15)	Hypertensives*** (N=23)	Overall (N=680)
<0.5	34 [34]	17 [53]				51 [87]
0.5		9 [54]				9 [54]
0.75	8 [16]	11 [66]				19 [82]
1	28 [91]	20 [64]				48 [155]
1.5	258 [425]	90 [274]	32 [32]	15 [15]	23 [84]	418[830]
3	12 [30]	11 [20]				23 [50]
>3	121 [121]	23 [76]				144[197]

N = Number of subjects who received at least one dose of Dulaglutide Subjects dosed multiple times at a specific dose level will be counted only once Subjects dosed with various dose levels will be counted at each dose level Values in parentheses [] show the number of exposures; **Subjects who were classified as hepatically impaired in study GBDO only Any renally/hepatically impaired subjects who were also T2DM are counted in the renal/hepatic groups only for Studies GBCM and GBDO; ***Hypertensive subjects from Part 1 of Study GBCO Single dose studies: GBCC, GBCN, GBDO, GBCP, GBCI, GBDR, GBCS, GBCA, GBCQ, GBDT, GBCM, GBCO (Part 2 only), GBDW (Treatment 1), GBCB Multiple dose studies: GBCH, GBCR, GBCL, GBCT, GBDM, GBDW(Treatment 2), GBCD, GBCO (Part 1 only)

The overall exposure to dulaglutide, in terms of number of patients included in the clinical program, is considered sufficient to provide a reasonable picture of its safety profile. However, it should be noted that of the total number of patients who received the drug in the Phase 2 and 3 studies (n=4006) less than half received the proposed to be licensed dose of 1.5mg or more (n=1762). In addition, a relatively small number of patients were exposed to the drug for more than a 1.5-2 years and this is a limitation in view of its intended long term use.

Characteristics of Study Population

The patient characteristics in data set AS1 appear to represent well European diabetics and are sufficiently balanced across treatment groups.

Generally, patients' baseline characteristics were balanced across studies with a few notable differences. Patients in Study GBDD (insulin glargine comparator; concomitant insulin lispro with or without metformin) had a mean age of approximately 59 years which was approximately 3 to 5 years older than in the other studies; this study recruited patients in later stages of diabetes, already treated with insulin. Likewise, diabetes duration varied across studies with a mean 2.6-year duration in patients who were treated primarily with diet and exercise or a single OAM prior to enrollment (Study GBDC) to mean a 12.7-year duration in patients who were using prior insulin therapy (Study GBDD).

More than 90% of patients within each analysis set reported at least one preexisting medical condition. The most frequently reported were in the MedDRA SOCs vascular disorders (incidence across treatment groups in AS1 and AS3: 68% to 70%), metabolism and nutrition disorders (63% to 70%), musculoskeletal and connective tissue disorders (29% to 34%), nervous system disorders (24% to 30%), and GI disorders (23% to 26%). The most frequently reported MedDRA Preferred Terms (PTs) were hypertension (65% to 67%) and hyperlipidaemia (21% to 26%). Aside from an imbalance in the reporting of obesity between placebo (20.6%) and all dulaglutide (16.1%) within AS1, preexisting conditions were generally comparable both within and between treatment groups in AS1 and AS3.

Nearly all patients (approximately 99%) in AS1 and approximately 85% of patients in AS3 were receiving an antihyperglycaemic agent at baseline. In both AS1 and AS3, the majority of patients (approximately 99% and 81%, respectively) were taking an OAM at baseline with half of these patients taking OAMs from 2 different medication classes. There were no notable differences at baseline in the proportion of patients within or between

AS1 and AS3 who were taking antihypertensives, lipid-lowering agents, anticoagulants, anti-inflammatory agents, or other cardiac therapy.

In general, it is positive, as discussed also in the *Efficacy* section above, that the study population comprised a wide range of diabetic patients both in terms of demographic and disease characteristics as well as common comorbidities and background medications, which is reassuring for the relevance of the findings to the dulaglutide target population. However, as previously noted, there are areas and groups with little or missing information including the lack of data about concomitant use of dulaglutide with SU alone or with basal insulin, as well as in special groups such as patients with moderate and severe renal insufficiency, patients with hepatic disease or advanced heart failure

Adverse events

- **Common adverse events**

The profiles of TEAEs that occurred in ≥5% of patients during the planned treatment period (e.g. the entire time in study even if study drug had been discontinued) compared with those that occurred while patients were receiving study drug are presented below for patients in AS1 and AS3 (Table 34 and Table 35, respectively). The percentage of patients reporting ≥1 TEAE was similar for placebo and all dulaglutide groups up to 26 weeks of the planned treatment period (66.7% and 69.8%, respectively) and while patients were receiving study drug (66.0% and 68.5%) in AS1.

Likewise, the percentage of patients reporting ≥1 TEAE was similar for dulaglutide 0.75 mg and 1.5 mg throughout the planned treatment period (74.2% and 75.4%) and while patients were receiving study drug (72.4% and 73.4%) in AS3. With the exception of 2 PTs in AS1 (hyperglycaemia, back pain), and 1 PT (urinary tract infection) and 2 SOCs (renal and urinary disorders, vascular disorders) in AS3, the same event terms were reported in ≥5% of patients whether events occurred during the planned treatment period or while patients were receiving study drug.

Table 34 Summary and Analysis of Treatment-Emergent Adverse Events Occurring in at least 5% of Patients during the Planned Treatment Period or While Patients Received Study Drug, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

	Number (%) of Patients							
	Through 26 Weeks of Planned Treatment Period[a]				Through 26 Weeks While Receiving Study Drug[a]			
System Organ Class Preferred Term	Pbo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)	Pbo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)
Patients with ≥1 TEAE	**379 (66.7)**	**569 (68.1)**	**597 (71.6)**	**1166 (69.8)**	**375 (66.0)**	**561 (67.1)**	**583 (69.9)**	**1144 (68.5)**
Gastrointestinal disorders	121 (21.3)	264 (31.6)	342 (41.0)	606 (36.3)	119 (21.0)	258 (30.9)	334 (40.0)	592 (35.4)
Nausea	30 (5.3)	104 (12.4)	176 (21.1)	280 (16.8)	30 (5.3)	102 (12.2)	167 (20.0)	269 (16.1)
Diarrhoea	38 (6.7)	74 (8.9)	105 (12.6)	179 (10.7)	37 (6.5)	69 (8.3)	101 (12.1)	170 (10.2)
Vomiting	13 (2.3)	50 (6.0)	105 (12.6)	155 (9.3)	13 (2.3)	43 (5.1)	100 (12.0)	143 (8.6)
Dyspepsia	13 (2.3)	34 (4.1)	48 (5.8)	82 (4.9)	12 (2.1)	34 (4.1)	48 (5.8)	82 (4.9)
General disorders and administrative site conditions	67 (11.8)	108 (12.9)	107 (12.8)	215 (12.9)	65 (11.4)	104 (12.4)	100 (12.0)	204 (12.2)
Infections and infestations	143 (25.2)	212 (25.4)	229 (27.5)	441 (26.4)	143 (25.2)	205 (24.5)	224 (26.9)	429 (25.7)
Nasopharyngitis	42 (7.4)	65 (7.8)	65 (7.8)	130 (7.8)	42 (7.4)	63 (7.5)	64 (7.7)	127 (7.6)
Injury, poisoning and procedural complications	25 (4.4)	50 (6.0)	56 (6.7)	106 (6.3)	23 (4.0)	50 (6.0)	54 (6.5)	104 (6.2)
Investigations	43 (7.6)	74 (8.9)	78 (9.4)	152 (9.1)	37 (6.5)	68 (8.1)	72 (8.6)	140 (8.4)
Metabolism and nutrition disorders	65 (11.4)	80 (9.6)	114 (13.7)	194 (11.6)	61 (10.7)	78 (9.3)	111 (13.3)	189 (11.3)
Decreased appetite	9 (1.6)	41 (4.9)	72 (8.6)	113 (6.8)	9 (1.6)	40 (4.8)	71 (8.5)	111 (6.6)
Hyperglycemia	30 (5.3)	5 (0.6)	5 (0.6)	10 (0.6)	26 (4.6)	5 (0.6)	4 (0.5)	9 (0.5)

Musculoskeletal and connective tissue disorders	89 (15.7)	113 (13.5)	99 (11.9)	212 (12.7)	87 (15.3)	113 (13.5)	98 (11.8)	211 (12.6)
Back pain	29 (5.1)	33 (3.9)	32 (3.8)	65 (3.9)	28 (4.9)	33 (3.9)	32 (3.8)	65 (3.9)
Nervous system disorders	68 (12.0)	113 (13.5)	135 (16.2)	248 (14.9)	64 (11.3)	108 (12.9)	131 (15.7)	239 (14.3)
Headache	40 (7.0)	50 (6.0)	67 (8.0)	117 (7.0)	38 (6.7)	47 (5.6)	65 (7.8)	112 (6.7)
Respiratory, thoracic and mediastinal disorders	49 (8.6)	48 (5.7)	62 (7.4)	110 (6.6)	47 (8.3)	46 (5.5)	62 (7.4)	108 (6.5)
Skin and subcutaneous tissue disorders	23 (4.0)	50 (6.0)	43 (5.2)	93 (5.6)	23 (4.0)	49 (5.9)	42 (5.0)	91 (5.4)

Abbreviations: Dula = dulaglutide; N = total number of patients in specified treatment group; Pbo = placebo; TEAE = treatment-emergent adverse event. a Events reported during the planned treatment period are events that occurred while the patient was enrolled whether or not that patient was receiving study drug. Events reported while on study drug occurred only during study drug exposure.

Table 35 Summary and Analysis of Treatment-Emergent Adverse Events Occurring in at least 5% of Patients during the Planned Treatment Period or While Patients Received Study Drug, All Observations During the Planned Treatment Period – Phase 2 and 3 Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS3)

	Number (%) of Patients			
	During All of Planned Treatment Period[a]		While on Study Drug in Planned Treatment Period[a]	
System Organ Class Preferred Term	Dula_0.75 (N=1671)	Dula_1.5 (N=1671)	Dula_0.75 (N=1671)	Dula_1.5 (N=1671)
Patients with ≥1 TEAE	**1240 (74.2)**	**1260 (75.4)**	**1210 (72.4)**	**1227 (73.4)**
Gastrointestinal disorders	576 (34.5)	734 (43.9)	562 (33.6)	714 (42.7)
Nausea	216 (12.9)	355 (21.2)	211 (12.6)	339 (20.3)
Diarrhoea	179 (10.7)	229 (13.7)	170 (10.2)	219 (13.1)
Vomiting	114 (6.8)	192 (11.5)	102 (6.1)	180 (10.8)
Dyspepsia	68 (4.1)	115 (6.9)	67 (4.0)	112 (6.7)
General disorders and administrative site conditions	234 (14.0)	217 (13.0)	221 (13.2)	205 (12.3)
Infections and infestations	568 (34.0)	572 (34.2)	540 (32.3)	548 (32.8)
Nasopharyngitis	143 (8.6)	140 (8.4)	137 (8.2)	136 (8.1)
Upper respiratory tract infection	89 (5.3)	85 (5.1)	86 (5.1)	83 (5.0)
Urinary tract infection	85 (5.1)	80 (4.8)	77 (4.6)	73 (4.4)
Injury, poisoning and procedural complications	144 (8.6)	134 (8.0)	139 (8.3)	126 (7.5)
Investigations	178 (10.7)	178 (10.7)	154 (9.2)	156 (9.3)
Metabolism and nutrition disorders	247 (14.8)	278 (16.6)	232 (13.9)	257 (15.4)
Decreased appetite	85 (5.1)	129 (7.7)	81 (4.8)	126 (7.5)
Musculoskeletal and connective tissue disorders	304 (18.2)	275 (16.5)	296 (17.7)	268 (16.0)
Nervous system disorders	269 (16.1)	286 (17.1)	256 (15.3)	281 (16.8)
Headache	111 (6.6)	133 (8.0)	105 (6.3)	130 (7.8)
Renal and urinary disorders	69 (4.1)	83 (5.0)	64 (3.8)	77 (4.6)
Respiratory, thoracic and mediastinal disorders	131 (7.8)	140 (8.4)	127 (7.6)	136 (8.1)
Skin and subcutaneous disorders	115 (6.9)	97 (5.8)	111 (6.6)	92 (5.5)
Vascular disorders	82 (4.9)	83 (5.0)	74 (4.4)	78 (4.7)

Abbreviations: Dula = dulaglutide; N = total number of patients in specified treatment group; TEAE = treatment-emergent adverse event. a Events reported during the planned treatment period are events that occurred while the patient was enrolled whether or not that patient was receiving study drug. Events reported while on study drug occurred only during study drug exposure.

- **Treatment emergent adverse events comparisons**

Dulaglutide vs Placebo (AS1)

The most frequently reported TEAEs were within the GI disorders SOC with more patients in the all dulaglutide than placebo (36.3% and 21.3%, respectively) group reporting these events. The all dulaglutide group had a higher incidence than placebo for nausea (16.8% and 5.3%), diarrhoea (10.7% and 6.7%), vomiting (9.3% and 2.3%), dyspepsia (4.9% and 2.3%), constipation (3.7% and 0.7%), abdominal distension (2.6% and 0.7%), gastroesophageal reflux disease (GERD) (1.9% and 0.5%), and eructation (1.1% and 0.2%).

Within metabolism and nutrition disorders, more all dulaglutide- than placebo-treated patients (6.8% and 1.6%) reported decreased appetite. In contrast, more patients in the placebo than all dulaglutide (5.3% and 0.6%) group reported hyperglycaemia as a TEAE. Within hepatobiliary disorders, the incidence of cholelithiasis

was higher for all dulaglutide than placebo-treated patients (0.7% and 0%). No other notable differences were observed between dulaglutide and placebo patients in AS1.

Dulaglutide 1.5 mg had a higher incidence than placebo of fatigue (3.5% and 1.8%), upper abdominal pain (3.4% and 1.6%), and flatulence (34.4% and 1.4%). The remaining results of TEAE assessments for dulaglutide 0.75 mg versus placebo and dulaglutide 1.5 mg versus placebo are consistent with those above for all dulaglutide versus placebo.

Dulaglutide 1.5mg vs 0.75mg (AS3)

The most frequently reported TEAEs overall in AS3 were GI disorders (dulaglutide 1.5 mg: 43.9%; dulaglutide 0.75 mg: 34.5%). Dulaglutide 1.5 mg had a higher incidence than dulaglutide 0.75 mg of the following GI events: nausea (21.2% and 12.9%), diarrhoea (13.7% and 10.7%), vomiting (11.5% and 6.8%), dyspepsia (6.9% and 4.1%), constipation (4.9% and 3.4%), abdominal pain (4.0% and 2.5%), abdominal discomfort (2.5% and 1.5%), and flatulence (2.6% and 1.4%). For metabolism and nutrition disorders and investigations, more patients receiving dulaglutide 1.5 mg reported decreased appetite (7.7% and 5.1%) and weight decreased (1.3% and 0.3%). No other notable differences were observed between the dulaglutide 0.75 and 1.5 mg doses in AS3.

Dulaglutide Doses by Concomitant Antihyperglycaemic Therapy

In the Phase 3 trials where dulaglutide was administered together with other antidiabetics treatments the overall adverse event profile was consistent across the studies with the GI events and infections and infestations reported most commonly. Nausea was the most common GI event followed by diarrhoea and vomiting. These events were reported consistently at a higher incidence for dulaglutide 1.5 mg compared with dulaglutide 0.75 mg. The incidence of nausea with dulaglutide 1.5 mg ranged from 15.4% (study GBDB, concomitant metformin plus glimepiride) to 29.0% (study GBDA, concomitant metformin plus TZD). The most commonly reported infection was nasopharyngitis which was reported at a similar rate for dulaglutide 0.75 mg and 1.5 mg within each study.

Hyperglycaemia was among the TEAEs reported in ≥5% of patients only in Study GBCF (placebo/sitagliptin: 15.8%; sitagliptin: 15.9%; dulaglutide 0.75 mg: 12.6%; dulaglutide 1.5 mg: 9.9%).

Overall, the data indicate a wide range of TEAEs and incidences across studies the differences between the studies do not appear to be related to the type of concomitant antihyperglycaemic medications used, with the exception of hypoglycaemia which is discussed separately below.

Dulaglutide vs All Comparators (AS7)

To address regulatory requests, an analysis was performed for TEAEs in all dulaglutide groups combined versus all comparators combined. The analysis included all studies of dulaglutide versus any comparator (placebo as well as active agents) that had a planned treatment duration of at least 26 weeks (the placebo/sitagliptin treatment sequence from Study GBCF was also included). To avoid including patients in both the all dulaglutide and the all comparator groups, patients in the Study GBDA placebo/dulaglutide treatment sequences are excluded from this analysis. Overall this analysis includes data from a wide spectrum of T2DM disease stages, management strategies and background regimens as well as various comparators.

Table 36a presents a summary of dulaglutide (all doses) versus all comparators analysis for TEAEs occurring in ≥5% of patients. Events with higher incidence with dulaglutide were nausea, diarrhoea, vomiting, decreased appetite, and dyspepsia. The primary events where all dulaglutide separated from all comparators (either direction) tend also to be characterized by significant study-to-study heterogeneity.

Table 36a All Dulaglutide versus All Comparator Analysis of TEAEs in ≥5% of Dulaglutide Patients, By Descending Frequency of Preferred Term, Full Duration of Phase 2 and 3 Studies of at Least 26 Weeks in Length (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS7).

Preferred Term	All Comparator (N=1844) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Patients with >=1 TEAE	1359 (73.7)	2540 (76.0)	1.13	.099	.014
Nausea	182 (9.9)	574 (17.2)	1.89	<.001	<.001
Diarrhoea	148 (8.0)	419 (12.5)	1.64	<.001	<.001
Vomiting	81 (4.4)	307 (9.2)	2.20	<.001	<.001
Nasopharyngitis	197 (10.7)	294 (8.8)	0.81	.003	.127
Headache	142 (7.7)	245 (7.3)	0.95	.425	.748
Decreased appetite	40 (2.2)	214 (6.4)	3.09	.001	<.001
Dyspepsia	63 (3.4)	183 (5.5)	1.64	<.001	<.001
Upper respiratory tract infection	96 (5.2)	182 (5.4)	1.05	.201	.576
Urinary tract infection	92 (5.0)	177 (5.3)	1.06	.865	.443

Abbreviations: CMH = Cochran-Mantel-Haenszel; Dula = dulaglutide; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment-emergent adverse event; TEAE = treatment-emergent adverse event. Note: All_Dula refers to 0.75 milligrams dulaglutide once weekly and 1.5 milligrams dulaglutide once weekly treatment groups combined. All Comparator = metformin for Study GBDC, placebo/sitagliptin or sitagliptin for Study GBCF, exenatide for Study GBDA, insulin glargine for Studies GBDB and GBDD, placebo for study GBDN. Patients randomized to the Placebo/Dulaglutide switch arms of Study GBDA are excluded from this analysis. *a - Mantel-Haenszel Odds Ratio. All_Dula is numerator, All Comparator is denominator. *b - Heterogeneity of odds ratios across studies was assessed using the Breslow-Day test. *c - p-values are from Cochran-Mantel-Haenszel (CMH) test comparing All_Dula to All Comparator stratified by study.

In order to detect less frequent but potentially relevant AEs, the broad, long-term data set AS7 was further analysed and the results are compiled in the table below. The most salient findings are marked in **bold**.

Table 36b. All Dulaglutide versus All Comparator Analysis of Treatment-Emergent Adverse Events, By Descending Frequency of Preferred Term - Full Duration of Phase 2 and 3 Studies of at Least 26 Weeks in Length (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS7) combined with Table APP.2.7.4.52 (shortened). Summary and Analysis of TEAEs Occurring During the Planned Treatment Period, By Descending Frequency of Preferred Term, All Observations During the Planned Treatment Period – Phase 2 and 3 Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS3)

	All Comparator (N=1844) n (%)	Dula 0.75 (N=1671) n (%)	Dula 1.5 (N=1671) n (%)	All Dula (N=3342) n (%)	Odds Ratio All Dula vs. All Comp.	CMH p-value*c
Patients with >=1 TEAE	1359 (73.7)	1240 (74.2)	1260 (75.4)	2540 (76.0)	1.13	.014
Nausea	182 (9.9)	216 (12.9)	355 (21.2)	574 (17.2)	1.89	<.001
Diarrhoea	148 (8.0)	179 (10.7)	229 (13.7)	419 (12.5)	1.64	<.001
Vomiting	81 (4.4)	114 (6.8)	192 (11.5)	307 (9.2)	2.20	<.001
Decreased appetite	40 (2.2)	85 (5.1)	129 (7.7)	214 (6.4)	3.09	<.001
Dyspepsia	63 (3.4)	68 (4.1)	115 (6.9)	183 (5.5)	1.64	<.001
Constipation	23 (1.2)	56 (3.4)	82 (4.9)	138 (4.1)	3.41	<.001
Abdominal pain upper	42 (2.3)	52 (3.1)	70(4.2)	126 (3.8)	1.68	.002
Abdominal distension	24 (1.3)	49 (2.9)	42 (2.5)	91 (2.7)	2.12	<.001
Flatulence	18 (1.0)	23 (1.4)	43 (2.6)	67 (2.0)	2.08	.006
Pancreatic enzymes increased	12 (0.7)	18 (1.1)	30 (1.8)	50 (1.5)	2.32	.007
Eructation	7 (0.4)	16 (1.4)	23 (1.4)	39 (1.2)	3.10	.006
Hyperchlorhydria	4 (0.2)	9 (0.5)	17 (1.4)	26 (0.8)	3.61	.005
Weight decreased	5 (0.3)	5 (0.3)	21 (8.3)	26 (0.8)	2.88	.019
Tachycardia	**6 (0.3)**	**11(0.7)**	**12 (0.7)**	**24 (0.7)**	**2.22**	**.056**
Abdominal pain lower	4 (0.2)	10 (0.6)	10 (0.6)	20 (0.6)	2.77	.052
Arthritis	**3 (0.2)**	**7 (0.4)**	**12 (0.7)**	**19 (0.6)**	**3.51**	**.029**
Rhinitis	**5 (0.3)**	**11 (0.7)**	**6 (1.4)**	**19 (0.6)**	**2.10**	**.120**
Localised infection	**4 (0.2)**	**4 (0.2)**	**9 (0.5)**	**16 (0.5)**	**2.21**	**.176**
Syncope	**4 (0.2)**	**9 (0.5)**	**6 (0.4)**	**15 (0.4)**	**2.07**	**.182**
Cataract	*21 (1.1)*	*8 (0.5)*	*6 (0.4)*	*14 (0.4)*	*0.37*	*.005*
Hypotension	**3 (0.2)**	**8 (0.5)**	**4 (0.2)**	**14 (0.4)**	**2.58**	**.101**
Laryngitis	**2 (0.1)**	**7 (0.4)**	**6 (0.4)**	**14 (0.4)**	**3.87**	**.042**
Benign prostatic hyperplasia	2 (0.1)	6 (0.4)	6 (0.4)	12 (0.4)	3.32	.094

Colitis	**2 (0.1)**	**4 (0.2)**	**8 (0.5)**	**12 (0.4)**	**3.32**	**.092**
Erectile dysfunction	2 (0.1)	5 (0.3)	7 (0.4)	12 (0.4)	3.32	.049
Injection site pain	3 (0.2)	6 (0.4)	6 (0.4)	12 (0.4)	2.21	.251
Proteinuria	2 (0.1)	5 (0.3)	7 (0.4)	12 (0.4)	3.32	.073
Tinea pedis	**2 (0.1)**	**7 (0.4)**	**5 (0.3)**	**12 (0.4)**	**3.32**	**.065**
Dermatitis	**3 (0.2)**	**4 (0.2)**	**6 (0.4)**	**11 (0.3)**	**2.03**	**.268**
Meniscus lesion	1 (<0.1)	6 (0.4)	4 (0.2)	10 (0.3)	5.53	.069
Muscular weakness	2 (0.1)	5 (0.3)	4 (0.2)	10 (0.3)	2.76	.199
Musculoskeletal stiffness	2 (0.1)	5 (0.3)	3 (0.2)	9 (0.3)	2.49	.164
Rhinorrhoea	*15 (0.8)*	*1 (<0.1)*	*8 (0.5)*	*9 (0.3)*	*0.33*	*.017*
Sleep apnoea syndrome	*11 (0.6)*	*4 (0.2)*	*4 (0.2)*	*9 (0.3)*	*0.45*	*.076*
Subcutaneous abscess	**0 (0.0)**	**5 (0.3)**	**3 (0.2)**	**9 (0.3)**	**NA**	**.029**

*a - Mantel-Haenszel Odds Ratio. All_Dula is numerator, All Comparator is denominator.
*c -p-values are from Cochran-Mantel-Haenszel (CMH) test comparing All_Dula to All Comparator stratified by study.

Like in data set AS1, GI symptoms were most noticeable. However, there are also two other clusters of potentially related AEs, namely effects regarding heart function and infections. Tachycardia, syncope and hypotension were at least doubled in incidence in the all dulaglutide group as compared to the all comparator group. This observation is in line with the finding of decreased mean systolic blood pressure and increased mean heart rate (see below). Therefore, dulaglutide appears to affect circulation by, to date, unknown mechanisms. Other GLP-1 mimetics had similar effects so that this could be regarded as a class effect.

In respect to infections, there is an imbalance between all dulaglutide and all comparator for several infectious disorders, e.g. "localised infection", "dermatitis" and "subcutaneous abscess". The accumulation of terms related to infection among the AEs that were biased towards dulaglutide is noted. The incidence of the events was low, and in most cases these were no serious conditions. Among the serious events (see respective section below) there were a few cases of pneumonia and urinary tract infection with a numerical imbalance between dulaglutide and all comparators. Taken together, it cannot be clearly derived from the existing data whether dulaglutide might be associated with an increased incidence of infections and – if so - whether this is of clinical relevance.

In conclusion, as expected for this class, the most frequent adverse events were GI disorders, with nausea, diarrhoea and vomiting being the most common and rates generally higher with dulaglutide 1.5mg than the 0.75mg dose. Small differences in the other most common AEs are noted between dulaglutide and placebo and between dulaglutide doses (although there is a trend toward a higher rate with the dulaglutide 1.5mg dose in most cases). In general, the types of common events seen with dulaglutide were consistent with those reported with other GLP-1 agonists, particularly GI and injection site disorders. A high rate of infections and infestations was also observed although there were no notable differences between the key groups.

In terms of the impact of concomitant treatments, the incidence of nausea and vomiting with dulaglutide 1.5mg was at its highest (29.0% and 16.8% respectively) in study GBDA when dulaglutide was given together with metformin plus pioglitazone but otherwise the variations were inconsistent. The most significant difference in relation to concomitant background diabetic therapy was noted for hypoglycaemia which is discussed in detail below.

Serious adverse event/deaths/other significant events

- ***Deaths***

There was one death in a clinical pharmacology study. The investigator considered the death unrelated to dulaglutide. The subject had severe hepatic impairment and was enrolled in Study GBDO (see *Hepatic Safety* below). Based on the patient's history and course of disease, it is unlikely that the death is related to dulaglutide.

There were fifteen (15) deaths during Phase 2 and 3 studies after patients received at least 1 dose of study treatment and are included in the clinical trial database (Table 37): sitagliptin 3 (0.68%); insulin glargine 5 (0.90%); dulaglutide 0.75 mg 3 (0.17%); dulaglutide 1.5 mg 4 (0.23%). As would be expected in patients with T2DM, CV events, including events of sudden death, cardio-respiratory arrest, MI, cerebrovascular accident, cardiogenic shock, cardiac failure, ventricular fibrillation, were the most commonly reported reasons for death. There was no significant difference between the all dulaglutide group compared with the all comparators group for risk of adjudicated death from CV causes (3[0.08%]; 5[0.24%]). None of the deaths were judged by the respective investigators to be related to dulaglutide or protocol procedures.

Table 37 Deaths in Dulaglutide Phase 2 and 3 Studies; All Postbaseline Observations, Including Follow-up Period; Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of Death	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBCF	46	2373	Placebo/Sitagliptin*	72	M	Cardio-respiratory arrest /cardiopulmonary arrest	14DEC2011	400	400	ongoing
	401	5003	Dula 1.5	65	M	Cerebrovascular accident /Stroke	18APR2010	176	182	6
	504	6157	Sitagliptin	61	M	Sudden death /sudden death	07SEP2009	210	210	ongoing
	924	9700	Sitagliptin	58	F	Uterine cancer /uterine cancer	15OCT2010	196	213	17
GBDA	12	555	Dula 1.5	56	F	Pancreatic carcinoma /Pancreatic cancer	22SEP2011	162	166	4
	64	3151	Dula 1.5	61	M	Myocardial infarction /Myocardial Infarction	30NOV2010	56	90	34
	75	3716	Dula 0.75	63	M	Death /Death- Natural Causes	17JAN2011	89	102	13
GBDB	302	3106	Dula 0.75	53	M	Cardiac failure /Heart failure	01MAY2012	456	504	48
	501	5052	Insulin Glargine	44	F	Respiratory failure /Respiratory Failure	02OCT2011	309	356	47
	856	8628	Insulin Glargine	74	F	Sudden death /suddent death	28FEB2012	318	352	34
GBDD	7	408	Dula 0.75	61	M	Pneumonia /pneumonia	16SEP2011	78	81	3
GBDD	251	4045	Dula 1.5	66	M	Staphylococcal sepsis /Septicemia Staphylococcus aureus	01DEC2011	190	213	23
	455	5392	Insulin Glargine	63	F	Cardiogenic shock /Cardiogen shock	24MAR2012	291	292	1
	552	6104	Insulin Glargine	62	M	Death /Death	18DEC2011	244	245	1
	602	6451	Insulin Glargine	51	M	Ventricular fibrillation /Ventricular fibrilation	19MAY2012	189	312	123

Abbreviations: AE = adverse event; F = female; Inv = investigator identification number; M = male; Pat = patient identification number. Notes: Dula_x.x refers to x.x milligrams dulaglutide once weekly. For patients who can switch treatment, the most-recently received study medication is marked with '*'. All 'Days' variables are computed as at the Date of AE. Days on Therapy and Days Since First Dose are computed from initiation of most-recently received study medication. Days Since First Dose can be greater than Days on Therapy, for patients who ceased study drug but remained in study. Days Since Final Dose is indicated as 'ongoing' when the patient was still receiving study drug at the Date of AE.

In addition to the above, one patient (in study GBCZ, on dulaglutide 0.75 mg) died of a pancreatic carcinoma after the study. The patient had received only 1 dose of study drug. Also two patients (one in study GBDD and one in study GBDD [infected skin ulcer] died following screening but before randomization. Another patient died while participating in a clinical pharmacology study.

In total 17 deaths occurred after patients received study drug in completed clinical pharmacology, Phase 2, and Phase 3 studies in the dulaglutide program; 9 of the deaths were in patients who received dulaglutide.

In general, the number of deaths in the dulaglutide program was relatively small; there is no indication of a higher rate in the dulaglutide groups.

- ***Other Serious Adverse Events (SAE)***

Dulaglutide vs Placebo (AS1)

Table 38 presents a summary of SAEs by PT occurring in 2 or more dulaglutide treated patients in AS1. Patients in the placebo (4.4%) and all dulaglutide (4.2%) groups reported a similar incidence of SAEs in these studies. The most frequently reported SAEs for placebo and all dulaglutide were appendicitis (0% and 0.3%, respectively), cholelithiasis (0% and 0.2%), atrial fibrillation (0.4% and 0.2%), and coronary artery disease (0.4% and 0.1%).

Serious GI events were reported for 7 (0.4%) of all dulaglutide-treated patients. No placebo-treated patient reported serious GI events. Gastritis was reported as a serious event for 2 patients while lower abdominal pain, Barrett's oesophagus, obstructive femoral hernia, GERD, and gastric ulcer were each reported by 1 patient. Overall, no important differences were observed between patients in the placebo and dulaglutide group with respect to SAEs.

Table 38 Serious Adverse Events by Preferred Term, Occurring in Two or More Dulaglutide-Treated Patients, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

	Number (%) of SAEs[a]			
Preferred Term	Placebo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)
Patients with ≥1 SAE	25 (4.4)	33 (3.9)	37 (4.4)	70 (4.2)
Appendicitis	0	3 (0.4)	2 (0.2)	5 (0.3)
Cholelithiasis	0	1 (0.1)	3 (0.4)	4 (0.2)
Atrial fibrillation	2 (0.4)	1 (0.1)	2 (0.2)	3 (0.2)
Blood calcitonin increased	0	3 (0.4)	0	3 (0.2)
Nephrolithiasis	0	1 (0.1)	2 (0.2)	3 (0.2)
Non-cardiac chest pain	0	0	3 (0.4)	3 (0.2)
Pneumonia	1 (0.2)	3 (0.4)	0	3 (0.2)
Urinary tract infection	0	2 (0.2)	1 (0.1)	3 (0.2)
Calculus ureteric	0	1 (0.1)	1 (0.1)	2 (0.1)
Cerebrovascular accident	0	0	2 (0.2)	2 (0.1)
Coronary artery disease	2 (0.4)	1 (0.1)	1 (0.1)	2 (0.1)
Gastritis	0	0	2 (0.2)	2 (0.1)
Gastroenteritis	0	0	2 (0.2)	2 (0.1)
Myocardial infarction	0	0	2 (0.2)	2 (0.1)
Neck pain	0	1 (0.1)	1 (0.1)	2 (0.1)
Prostatic adenoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Subdural haematoma	0	1 (0.1)	1 (0.1)	2 (0.1)

Abbreviations: Dula = dulaglutide; N = total number of patients in specified treatment arm; SAE = serious adverse event. Note: Dula_x.x refers to x.x mg dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined. a This table reports incidence of SAEs occurring in 2 or more dulaglutide-treated patients. All other SAEs were reported by 1 dulaglutide- and/or placebo-treated patient.

Dulaglutide 1.5mg vs 0.75mg (AS3)

The incidence of SAEs was similar between dulaglutide 0.75 mg and 1.5 mg (8.7% and 8.0%, respectively) in this analysis set. The most frequently reported SAEs for dulaglutide 0.75 mg and 1.5 mg were hypoglycaemia (0.5% and 0.7%, respectively; events of severe hypoglycaemia were to be reported as SAEs), pneumonia (0.5% and 0.1%), appendicitis (0.2% and 0.2%), and cholelithiasis (0.1% and 0.4%). No other individual PT was reported as serious by more than 0.3% in either dose group. Importantly, events of severe hypoglycaemia were to be reported as SAEs.

The SOC with the highest incidence of SAEs was infections and infestations (dulaglutide 0.75 mg: 1.9%; dulaglutide 1.5 mg: 1.8%), which includes appendicitis and pneumonia. Serious GI events were reported for 16

(1%) dulaglutide 0.75 mg and 13 (0.8%) 1.5 mg-treated patients. Gastritis was reported as serious for 1 patient treated with dulaglutide 0.75 mg and for 2 patients treated with 1.5 mg. Serious colitis, GI haemorrhage, GERD, and lower GI haemorrhage were each reported by 2 patients. Overall, no important differences were observed between the dulaglutide 0.75 mg- and 1.5 mg treated patients with respect to SAEs.

Dulaglutide vs All Comparators (AS7)

Overall the incidence of SAEs was similar in the all dulaglutide and all comparator groups (8.5% and 10.1%, respectively). There were no significant differences between all dulaglutide and all comparator groups. The most common individual preferred term for both groups was hypoglycaemia (all comparator: 1.0%; all dulaglutide: 0.6%). Aside from hypoglycaemia, no events occurred at greater than 0.3% in the all dulaglutide group; the only events exceeding this threshold in the all comparator group were coronary artery disease (0.4%), angina pectoris (0.4%), and MI (0.4%).

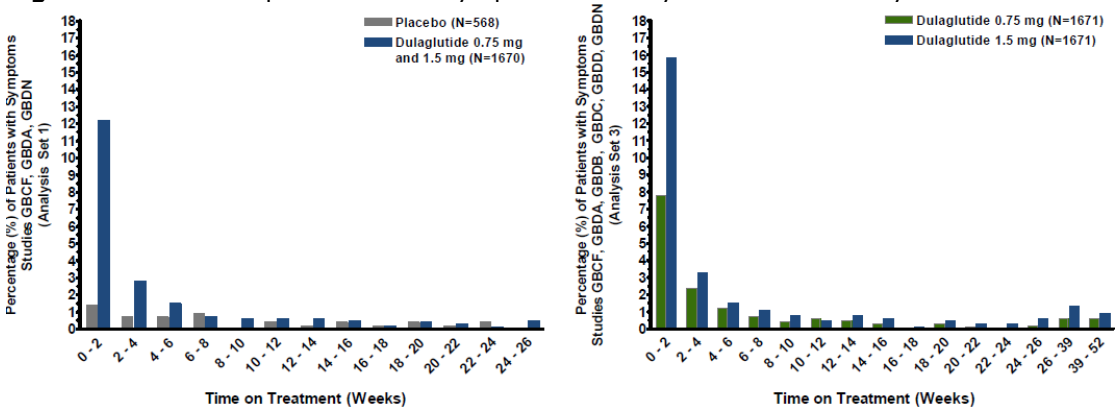
- ***Adverse events of special interest***

Gastrointestinal Tolerability

As discussed above, the most common adverse events with dulaglutide in Phase 2 and 3 studies were generally GI in nature with a higher incidence with dulaglutide than placebo group, and with dulaglutide 1.5 mg than 0.75 mg. GI adverse events were also associated with the highest incidences of early discontinuation from study drug or study during the full planned treatment duration (dulaglutide 0.75 mg: 2.5%; dulaglutide 1.5 mg: 4.8%).

In Phase 2 and 3 studies, the onset of nausea was dose dependent, peaked during the first 2 weeks of treatment, and then rapidly declined (Figure 28). By 4 to 6 weeks of dosing, new nausea events with dulaglutide was <2%, similar to placebo, and remained so or lower throughout the observation period. The time course of vomiting or diarrhoea followed a similar pattern.

Figure 28 Onset of specific nausea symptoms in Analysis Set 1 and Analysis Set 3.



Specific nausea symptom preferred terms: nausea, procedural nausea. Note: Patients within each interval represent those who reported their first event of specific nausea during the discrete interval or who reported a subsequent event of specific nausea when all previous events had resolved within a previous interval.

As previously discussed, the company examined the possible effect of dose titration on GI events (see *Dose response study* above). Overall, it was concluded that although initiating dulaglutide treatment with 0.75 mg is associated with lower rates of initial GI symptoms compared to initiating dulaglutide at 1.5 mg, implementing a dose titration strategy would be expected to decrease symptoms only for the first dose but ultimately would delay development of tolerance. However, the overall data are limited.

The Applicant also compared the incidence of GI events with exenatide BID and metformin. In study GBDA there was no significant difference in the incidence of reported GI TEAEs for dulaglutide 1.5 mg compared with titrated exenatide BID, with the exception of constipation, which was more common with dulaglutide 1.5 mg than exenatide. In study GBDC the incidence of most GI events was not significantly different between either dulaglutide dose or metformin, though dulaglutide 0.75 mg had a lower rate of nausea and diarrhoea. Both dulaglutide doses had a significantly higher incidence of constipation than metformin.

The SmPC includes information about GI events and a warning that dulaglutide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients. This is appropriate. Additional information about the observed incidence of the most common GI events has also been included in section 4.8 of the SmPC.

Other Potentially Clinically Important GI Events

Early in clinical development, Lilly observed a potential imbalance in the reporting of cholelithiasis in Study GBDN among dulaglutide and other comparator groups. In addition, a cluster of acute appendicitis cases (initially reported only in Study GBDA) prompted review of such cases. Lilly also became aware of a regulatory interest in the occurrence of GI stenosis and obstruction in patients with diabetes being treated with GLP-1 receptor agonists. A review of the above events in the dulaglutide clinical program was performed.

Thirty-eight patients (38) reported cholelithiasis across the Phase 2 and 3 studies. The exposure-adjusted rate of cholelithiasis (Table 39) was similar for dulaglutide 0.75 mg and 1.5 mg. Based on the available data it was concluded that there is no increased risk of cholelithiasis in patients treated with dulaglutide.

Table 39 Summary of Cholelithiasis Events by Treatment in Phase 2 and 3 Studies

Study Treatment	N	n	%	Patient-Years	n/1000 patient-years
Placebo	703	1	0.1	283.9	3.52
Metformin	268	2	0.7	226.7	8.82
Sitagliptin	439	5	1.1	637.3	7.84
Exenatide BID	276	0	0	236.3	0
Insulin glargine	558	4	0.7	621.2	6.44
Dula_0.75	1765	15	0.8	1724.2	8.70
Dula_1.5	1762	13	0.7	1689.1	7.70

Ten cases of appendicitis were reported for patients treated with either exenatide BID (n=1, 0.4%), insulin glargine (n=1, 0.2%), or dulaglutide 1.5 mg (n=4, 0.2%) and 0.75 mg (n=4, 0.2%) during Phase 2 and 3. Five of the events were reported in Study GBDA. There were no reports of appendicitis with placebo, metformin, or sitagliptin. The exposure-adjusted rate of appendicitis was similar for dulaglutide 0.75 mg (2.32 events/1000 patient-years) and 1.5 mg (2.37 events/1000 patient-years).

Fifteen (15) patients reported events of Gastrointestinal Stenosis and Obstruction during the planned treatment periods in Phase 2 and 3 studies. A total of 8 patients reported GI obstruction alone in these studies (metformin: 1 [0.4%]; insulin glargine: 2 [0.6%]; exenatide BID: 1 [0.4%]; dulaglutide 0.75 mg: 2 [0.6%]; dulaglutide 1.5 mg: 2 [0.6%]). The incidence of GI obstruction events was similarly distributed across the active comparators and dulaglutide 0.75 mg and 1.5 mg groups, with no suggestion of a dose relationship.

Pancreas

The pancreatic safety assessment plan for the overall dulaglutide program was guided by key interactions with regulatory agencies. The applicant implemented measures to minimize potential risks of pancreatitis and address other concerns raised by regulatory authorities:

- Patients with a history of acute or chronic pancreatitis were excluded from dulaglutide clinical studies. Patients

diagnosed with pancreatitis were permanently discontinued from study drug, and no rechallenge was allowed.
- Measures were implemented to identify actual and potential cases of pancreatitis based on clinical signs, symptoms, laboratory assessments, and expert evaluations.

Pancreatitis

Events were identified and reported using a Pancreatic Follow-up Assessment Form (PFUA) case report form for investigator-reported cases of pancreatitis; cases of severe and/or serious abdominal pain of unknown origin; confirmed elevations (>3x ULN) in lipase, pancreatic amylase, or total amylase, irrespective of symptoms and imaging results.

Across Phase 2 and 3 studies, 171 patients had 226 PFUA forms. A total of 151 patients received adjudication outcomes. Nineteen patients (comparators: 7; dulaglutide: 12) had investigator-reported pancreatitis (acute or chronic). Of the 151 patients with events that had an adjudication outcome:

- nine (9) patients had events determined to be pancreatitis (placebo: 1 and sitagliptin: 3 [all acute pancreatitis]; dulaglutide: 5 patients [acute pancreatitis: 2; chronic pancreatitis: 2; type unknown: 1]).
- Four (4) patients had cases that were deemed as "unknown if pancreatitis" (insulin glargine: 1; dulaglutide: 3).

From the 9 patients determined to have pancreatitis 6 had acute pancreatitis, 2 chronic pancreatitis, and 1 type unknown. Exposure-adjusted incidence rates (patients/1000 patient-years) were as follows: placebo 3.523, sitagliptin 4.707, and dulaglutide 1.416. There were no events for exenatide BID (Study GBDA), metformin (Study GBDC), or insulin glargine (Study GBDB and Study GBDD). Acute pancreatitis exposure–adjusted incidence rates (patients/1000 patient-years) were for placebo 3.523, sitagliptin 4.707, and dulaglutide 0.566. Two dulaglutide-treated patients had cases of chronic pancreatitis (0.566 patients/1000 patient-years). A total of 4 cases (insulin glargine: 1; dulaglutide: 3) were adjudicated as "unknown if pancreatitis."

For patients with pancreatitis, there was no clear clinical pattern with respect to baseline characteristics, clinical presentation and course, presence of major risk factors and exposure duration (1 day to 65 weeks) before the occurrence of the event.

In the clinical pharmacology studies, pancreatitis was not observed in the single-dose safety study in healthy subjects (Study GBCA) at single doses up to 12 mg or in the multiple-dose safety study in patients with T2DM (Study GBCD) at once weekly doses up to 8 mg for 5 weeks. In the TQT study, Study GBCC, following single supratherapeutic doses of 4 or 7 mg dulaglutide, 4/109 healthy subjects had a diagnosis of pancreatitis after showing notable elevations in pancreatic enzymes; 3 of the subjects received 4 mg and 1 subject received 7 mg of dulaglutide. Adjudication of these 4 events was requested and 2 of the 4 of the cases were determined as acute pancreatitis while 2 were determined as no pancreatitis.

Pancreatic enzymes

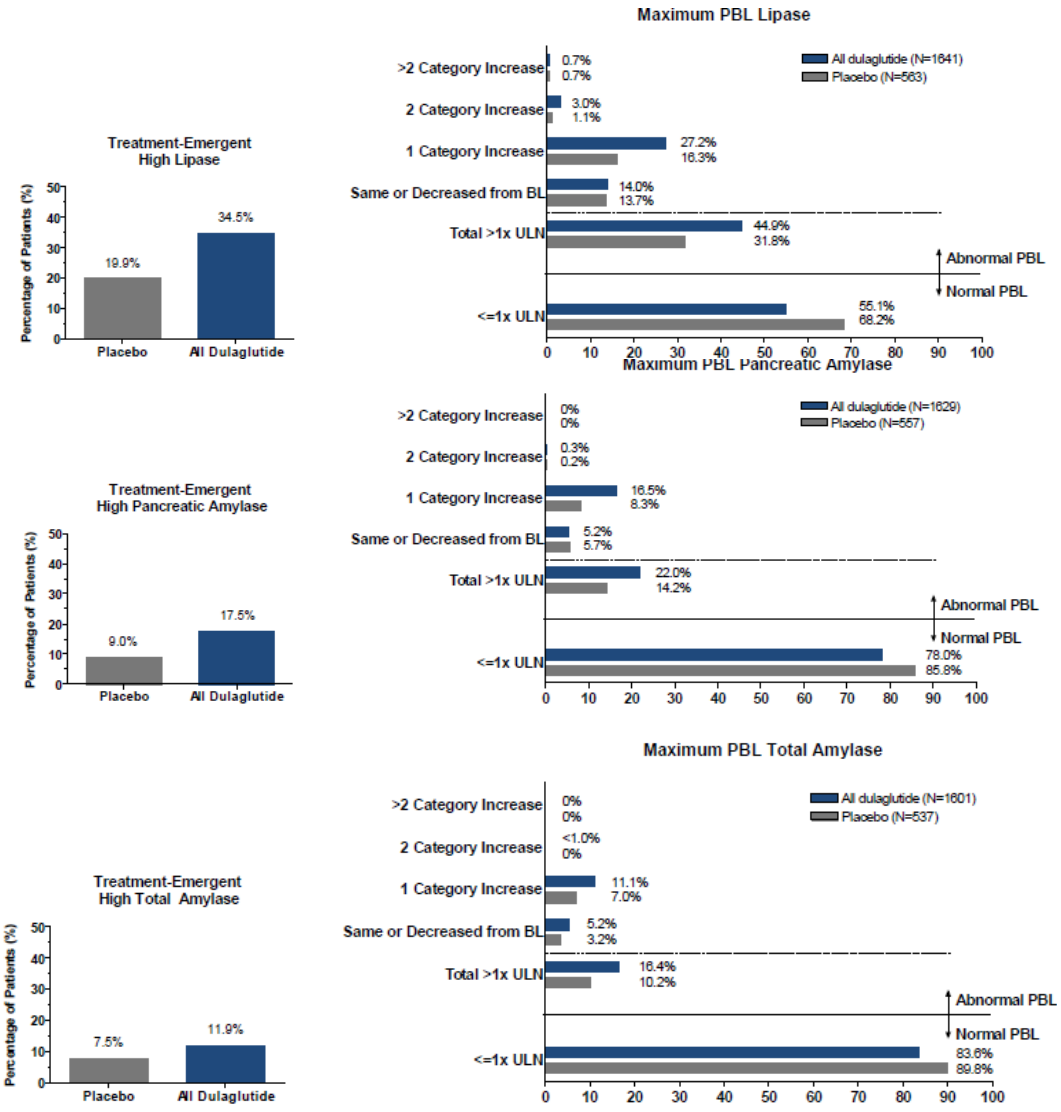
Baseline pancreatic enzyme measurements indicated that a proportion of patients with T2DM have elevated exocrine pancreatic enzymes, particularly lipase, before initiating study treatment. The mean values of pancreatic enzymes at randomization were similar across the Phase 2 and 3 clinical trials.

In AS1, after randomization lipase increased from baseline, approximately 14% to 20% over time. The LS mean increase for pancreatic amylase ranged from approximately 17% to 20% whereas the increase for total amylase ranged from approximately 9% to 12%. For each analyte, patients treated with placebo had small changes (≤3% of the baseline mean value). The difference between dulaglutide and placebo was significant at all time points for each analyte.

Dulaglutide-treated patients had a numerically higher incidence of treatment-emergent high lipase, pancreatic amylase, and total amylase values (>1x ULN) compared to placebo but most patients in both the placebo and all

dulaglutide groups had pancreatic enzymes within the normal range (Figure 29). The incidence of patients with postbaseline values ≥3 to <5x ULN was higher for all dulaglutide than placebo (4.6% and 2.5%, respectively) whereas the incidence of patients with values ≥5x ULN was similar for all dulaglutide and placebo (1.8% and 1.6%).

Figure 29 Plot of treatment-emergent high pancreatic enzymes and maximum postbaseline pancreatic enzymes by category –observations through 26 weeks - placebo-controlled studies with 0.75 mg and 1.5 mg dulaglutide (Studies GBCF, GBDA, and GBDN) (AS1).



In safety set AS3 the analyses showed that the increase in pancreatic enzymes was generally larger for dulaglutide 1.5 mg than 0.75 mg.

No interaction between dulaglutide and various concomitant therapies was observed for pancreatic enzymes measured across Phase 3 trials. Similar changes in pancreatic enzymes were seen for dulaglutide compared with exenatide BID, sitagliptin, and metformin. Changes in pancreatic enzymes with insulin glargine were inconsistent across studies (no change or small increases).

Warnings about pancreatitis are included in section 4.4 of the proposed SmPC.Section 4.8 includes information

about the reported cases of acute pancreatitis and the observed increases in pancreatic enzymes.

Thyroid

Based on advice regulatory authorties and external thyroid experts, the applicant implemented measures to assess and minimize potential thyroid safety risks during Phase 2 and 3 studies with ≥12 weeks of treatment, except Studies GBCJ and GBCK that were ongoing at the time of implementation:

- Exclusion criteria: Patients with self or family history of increased risk for MTC or multiple endocrine neoplasia syndrome type 2 (MEN2), and patients with a screening/baseline serum calcitonin ≥20 pg/mL were excluded (the 20 pg/mL cutoff was chosen to allow enrolment of patients with a low risk of preexisting thyroid C-cell disease and facilitate characterizing the effect of dulaglutide on these cells)
- Serial monitoring of calcitonin: Patients who met specified calcitonin values (>35 pg/mL) were to be discontinued from the study and an endocrinology consultation was to be obtained.

Calcitonin

Mean calcitonin values at randomization were near the lower limit of the reference range across studies and generally was lower for females than males. When compared to placebo (AS1), mean baseline calcitonin values were similar for the placebo and all dulaglutide group. Through 16 and 26 weeks postbaseline, mean calcitonin changed little within treatments resulting in similar mean calcitonin values between placebo and all dulaglutide at 26 weeks. Using last postbaseline observation, the LS mean difference (95% CI) in calcitonin was not notably different for all dulaglutide compared with placebo (0.17 [-0.03, 0.36]). In safety set AS3, mean baseline calcitonin values were found similar for dulaglutide 0.75 mg and 1.5 mg. For postbaseline anchor points up to 104 weeks, mean calcitonin changed little within treatments resulting in similar mean calcitonin between dulaglutide doses. Using last postbaseline observation, the LS mean difference (95% CI) in calcitonin was not notably different for dulaglutide 1.5 mg compared with 0.75 mg (-0.02 [-0.16, 0.11]). A numerically higher proportion of patients who received dulaglutide (1.0%) than placebo (0.4%) had maximum postbaseline values ≥20 pg/mL. In AS3, similar proportions of patients who received dulaglutide 0.75 mg and 1.5 mg (1.0% and 1.0%, respectively) had maximum postbaseline values ≥20 pg/mL.

Compared to all active comparators in the Phase 2 and 3 studies, similar proportions of patients across treatment groups had potentially clinically important postbaseline calcitonin values (placebo: 0.3%; insulin glargine: 0.7%; sitagliptin: 0.7%; exenatide BID: 0.4%; dulaglutide 0.75 mg: 0.6%; dulaglutide 1.5 mg: 0.8%; dulaglutide >1.5 mg: 2.2%). The exposure-adjusted incidence rates of potentially clinically important calcitonin values were similar for dulaglutide 0.75 mg (6.38 events/1000 patient-years) and dulaglutide 1.5 mg (7.72 events/1000 patient-years). The event rates per 1000 patient-years for comparators in the Phase 2 and 3 studies were: placebo (7.75), insulin glargine (6.44), sitagliptin (4.71), and exenatide BID (4.23). No metformin-treated patients had potentially clinically important postbaseline calcitonin values.

Thyroid Neoplasia, Including Malignancies

Searches in the safety database revealed: i. 15 patients with the PT goiter (placebo: 2; insulin glargine: 1; sitagliptin: 1; exenatide BID: 2; dulaglutide 0.75 mg: 4; dulaglutide 1.5 mg: 5) and ii. 15 patients reporting 17 events in the thyroid neoplasm HLT (insulin glargine: 3; sitagliptin: 1; exenatide BID: 1; dulaglutide 0.75 mg: 5; dulaglutide 1.5 mg: 4; dulaglutide >1.5 mg: 1).

Among the 15 patients with thyroid neoplasm, 3 patients reported thyroid cancer. One event was an MTC determined by Lilly to be preexisting (Patient GBCF-013-0701, dulaglutide 2.0 mg). The other 2 events were papillary thyroid cancers (Patient GBCF-608-6653, dulaglutide 1.5 mg; Patient GBDB-202-2102, dulaglutide 1.5 mg). Neither of these patients had any abnormal measurements of serum calcitonin.

As with other very rare events, especially neoplasias, considering the relatively short exposure with only a limited number of patients treated for more than 18-24 months, it is very difficult to evaluate the potential risks associated with the long-term use of dulaglutide. This is reflected in the pharmacovigilance plan.

Hypoglycaemia

During clinical development the assessment of hypoglycaemia risk was based on the consensus statement developed by the American Diabetes Association Hypoglycaemia Working Group in 2005 and later adopted by the FDA and the EMA. Analyses of hypoglycaemia risk include categories defined by 2 plasma glucose cutoffs. The principal set of analyses was based on the ≤70 mg/dL (3.9 mmol/L) cutoff, as recommended by the ADA and adopted by the FDA and the EMEA. Another set is based on <54 mg/dL (3 mmol/L) cutoff based on criteria similar to those used in development and evaluation of other recent marketing applications for antihyperglycaemic agents (such as Bydureon) and the literature [results available but not shown in this report]. Severe hypoglycaemia was defined as a hypoglycaemic event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, as judged by investigators.

Table 40 summarizes the incidence and estimated event rate per patient per year (event/patient/year) for total, documented symptomatic, and severe hypoglycaemia (plasma glucose ≤70 mg/dL, excluding post-rescue) in each Phase 3 study. Relevant data when the <54 mg/dL (3 mmol/L) cutoff was used have been submitted but are not shown here.

Table 40 By-Study Summary of Total, Documented, and Severe Hypoglycaemia (Plasma Glucose Less than or Equal to 70 mg/dL, Excluding Post-Rescue Visits) – Dulaglutide and Comparator-Treated Patients in Phase 3 Studies (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD)

	Percentage of Patients [Estimated Event Rate/Patient/Year]		
Monotherapy (52 weeks; Study GBDC)	**MET (N=268)**	**Dulaglutide 0.75 mg (N=270)**	**Dulaglutide 1.5 mg (N=269)**
Total	12.7 [0.28]	11.1 [0.47]	12.3 [0.89]
Documented symptomatic	4.9 [0.09]	5.9 [0.15]	6.3 [0.62]
Severe	0 [0.0]	0 [0.0]	0 [0.0]
In Combination with MET (26-week placebo-controlled period; Study GBCF)	**Placebo (N=177)**	**Dulaglutide 0.75 mg (N=302)**	**Dulaglutide 1.5 mg (N=304)**
Total	1.1 [0.08]	4.0 [0.18]	7.9 [0.39]
Documented symptomatic	1.1 [0.08]	2.6 [0.13]	5.6 [0.26]
Severe	0 [0.0]	0 [0.0]	0 [0.0]
In Combination with MET (104 weeks; Study GBCF)	**Sitagliptin (N=315)**	**Dulaglutide 0.75 mg (N=302)**	**Dulaglutide 1.5 mg (N=304)**
Total	8.6 [0.20]	8.6 [0.21]	12.8 [0.26]
Documented symptomatic	5.7 [0.17]	6.3 [0.18]	10.9 [0.19]
Severe	0 [0.0]	0 [0.0]	0 [0.0]
In Combination with MET+PIO (26-week placebo-controlled period; Study GBDA)	**Placebo (N=141)**	**Dulaglutide 0.75 mg (N=280)**	**Dulaglutide 1.5 mg (N=279)**
Total	3.5 [0.35]	10.7 [1.09]	10.4 [0.44]
Documented symptomatic	1.4 [0.06]	4.6 [0.18]	5.0 [0.22]
Severe	0 [0.0]	0 [0.0]	0 [0.0]
In Combination with MET+PIO (52 weeks; Study GBDA)	**Exenatide BID (N=276)**	**Dulaglutide 0.75 mg (N=280)**	**Dulaglutide 1.5 mg (N=279)**
Total	18.5 [1.13]	15.4 [0.90]	12.5 [0.40]
Documented symptomatic	13.4 [0.75] 0.7	6.1 [0.14]	6.5 [0.19]
Severe	[0.01]	0 [0.0]a	0 [0.0]
In Combination with MET+SU (78 weeks; Study GBDB)	**Insulin glargine (N=262)**	**Dulaglutide 0.75 mg (N=272)**	**Dulaglutide 1.5 mg (N=273)**
Total	71.4 [6.90]	56.6 [4.18]	58.6 [4.27]
Documented symptomatic	51.1 [3.02]	39.0 [1.67]	40.3 [1.67]
Severe	0.8 [0.01]	0 [0.0]	0.7 [0.01]b
In Combination with Insulin lispro±MET(52 weeks; Study GBDD)	**Insulin glargine (N=296)**	**Dulaglutide 0.75 mg(N=293)**	**Dulaglutide 1.5 mg (N=295)**
Total	89.9 [57.17]	90.1 [48.38]	86.1 [41.74]
Documented symptomatic	83.4 [40.95]	85.3 [35.66]	80.0 [31.06]
Severe	5.1 [0.09]	2.4 [0.05]	3.4 [0.06]

a An event of severe hypoglycemia was also reported by a patient in the placebo/dulaglutide 0.75 mg treatment arm during the dulaglutide 0.75 mg period after the patient had initiated rescue therapy with a sulphonylurea.
b An event of severe hypoglycemia was reported by a patient in the dulaglutide 1.5 mg treatment arm while receiving metformin, approximately 7 weeks after discontinuing concomitant glimepiride.

Dulaglutide vs Placebo

Studies GBCF (background metformin) and GBDA (background metformin plus TZD) were summarized for patients receiving placebo and dulaglutide 0.75 mg or 1.5 mg doses (separately and combined) through 26 weeks. In dulaglutide-treated patients the estimated rates of hypoglycaemic events/patient/year were small, but numerically higher, than those on placebo in each study. With concomitant metformin in Study GBCF, 5.9% of dulaglutide-treated patients reported hypoglycaemia through 26 weeks of treatment (0.28 events/patient/year) compared with 1.1% of placebo-treated patients (0.08 events/patient/year). A similar pattern was observed in patients receiving concomitant metformin plus TZD in Study GBDA. No events of severe hypoglycaemia were reported for placebo or dulaglutide in Study GBCF or Study GBDA through 26 weeks.

Dulaglutide 1.5mg vs 0.75mg

The incidence and estimated rates of total hypoglycaemia were similar for dulaglutide 0.75 mg (22.5%; 1.40 events/patient/year) and dulaglutide 1.5 mg (23.7%; 1.42 events/patient/year). Two patients (0.2%) treated with dulaglutide 1.5 mg reported severe hypoglycaemia but none of patients who received dulaglutide 0.75 mg.

Dulaglutide vs Active Comparators

In Studies GBDC, GBCF, and GBDA, the incidence of total hypoglycaemia during the full treatment and the rate of hypoglycaemia with dulaglutide was numerically lower than that of exenatide BID, similar to that of sitagliptin, and higher than that of metformin (Table 40 above).

Two studies compared dulaglutide to insulin glargine, Study GBDB and GBDD. The incidence of total hypoglycaemia was lower with dulaglutide 0.75 and 1.5 mg versus insulin glargine in Study GBDB and similar in Study GBDD. For the entire treatment period, the rates were lower in both studies for the dulaglutide 1.5 mg dose versus insulin glargine. There were 24 events of severe hypoglycaemia with insulin glargine, 15 events with dulaglutide 0.75 mg, and 13 events with dulaglutide 1.5 mg in these 2 studies. The majority of these events were reported in Study GBDD.

Impact of Concomitant Antihyperglycaemic Treatment

In Studies GBDC (monotherapy), GBCF (concomitant metformin), and GBDA (concomitant metformin plus TZD), the incidence of total hypoglycaemia during the full treatment period for dulaglutide 1.5 mg, the incidence was 12.3%, 12.8%, and 12.5% respectively; for dulaglutide 0.75 mg was slightly lower. Estimated event rate/patient/year of total hypoglycaemia followed a similar pattern.

The addition of dulaglutide 0.75 mg and 1.5 mg to metformin plus glimepiride in Study GBDB was associated with a higher incidence (56.6% and 58.6%, respectively) and rates (4.18 and 4.27 events/patient/year) of total hypoglycaemia compared to Studies GBDC, GBCF, and GBDA, despite similar reduction in HbA1c over time.

In Study GBDD, dulaglutide was combined with titrated pre-meal insulin lispro. Patients were also allowed to use metformin (approximately 73%). This trial was associated with the highest incidence and rate of hypoglycaemia observed in the Phase 3 program which at 52-week for dulaglutide 0.75 mg was 90.1% and for dulaglutide 1.5 mg was 86.1% (48.38 events/patient/year and for dulaglutide 1.5 mg was 41.74 events/patient/year respectively). Seven dulaglutide 0.75 mg-treated patients and 10 dulaglutide 1.5 mg-treated patients reported 11 and 15 events of severe hypoglycaemia, respectively.

Severe Hypoglycaemia

A total of 41 patients (insulin glargine: 18; exenatide BID: 2; dulaglutide 0.75 mg: 9; dulaglutide 1.5 mg: 12) reported 62 events severe hypoglycaemia. Most events (54 of 62) occurred prior to initiation of any rescue therapy. Three patients experienced 8 events of severe hypoglycaemia after initiating a rescue medication.

Rates of severe hypoglycaemia with dulaglutide varied across Phase 3 trials. The majority of patients (34 of 41 [82.9%]) were in Study GBDD and received insulin lispro with or without metformin as concomitant treatment. Of the 55 events in Study GBDD, 48 occurred during the treatment period while patients were receiving their randomized therapies (insulin glargine: 22 events in 15 [5.1%] patients; dulaglutide 0.75 mg: 15 events in 7 [2.4%] patients; dulaglutide 1.5 mg: 11 events in 10 [3.4%] patients). In Study GBDB, 4 patients reported severe hypoglycaemia. Three of the patients (insulin glargine: 2; dulaglutide 1.5 mg: 1) each reported 1 event while receiving concomitant therapy with metformin plus glimepiride. Another dulaglutide-treated patient (1.5 mg) had an event while receiving metformin, approximately 7 weeks after discontinuing concomitant glimepiride. In Study GBDA (concomitant metformin plus TZD), 3 patients reported severe hypoglycaemia (exenatide BID: 2; dulaglutide 0.75 mg: 1). One of these patients (on placebo/dulaglutide 0.75 mg) had the event during dulaglutide treatment after receiving a sulphonylurea (glipizide XL) as rescue therapy.

In general, with regard to the overall risk of hypoglycaemia although differences in the methodologies, measurement time points, study populations and background therapy levels between the dulaglutide studies and previous trials with GLP-1 agonists may not allow straightforward comparisons, the initial data suggested a possibly higher incidence of hypoglycaemia with dulaglutide than other members of the class in different settings, and even more when dulaglutide was combined with SU or insulin. In response to questions on this

subject the Applicant has provided some additional analyses supporting that the hypoglycaemia rates particularly when dulaglutide is combined with a SU or insulin are comparable with other members of the class and rates reported in the literature, especially when taking also into account differences in the definitions of hypoglycaemia between studies.

It is true that the background dose of glimepiride in study GBDB (median 6 mg at all timepoints; in addition to median 2550 mg of metformin) was high (according to the SmPC, 6mg/day is the maximum recommended glimepiride dose, while doses of more than 4mg are recommended only in exceptional cases) and the glycaemic targets in study GBDD might be too stringent for a population with such long-standing diabetes. It is likely that hypoglycaemia would be less frequent if lower doses of glimepiride and insulin were used in the trials but at this point it is difficult to determine to what extent SU and insulin dose adjustments alone would be sufficient to mitigate the risks. Differences between the two dulaglutide doses tested in the studies under question (GBDB and GBDD) were small. This could be explained by the already observed high incidence across all groups, not allowing detecting further small differences between treatments. This may also be possibly explained by higher doses of concomitant insulin lispro required to achieve the target PG values with dulaglutide 0.75 mg compared with dulaglutide 1.5 mg. Still it is not entirely clear if lowering dulaglutide dose could have a significant impact on hypoglycaemia.

The Applicant suggests that the risk of hypoglycaemia attributable to dulaglutide is low and similar to the risk observed with active comparators metformin, sitagliptin and exenatide BID, despite greater glycaemic control with dulaglutide. They also argue that in the two insulin comparator studies treatment with dulaglutide 1.5 mg dose resulted in superior glycaemic control, lower risk of hypoglycaemia and fewer episodes of severe hypoglycaemia (in Study GBDD only) compared to insulin glargine.

The Applicant also submitted a summary of the recently completed of Study H9X-MC-GBDE (please see outline of the study above) comparing the dulaglutide 1.5mg/week with liraglutide 1.8mg/day in adult T2DM with HbA1c ≥7.0% to ≤10% not optimally controlled with diet and exercise and a dose of metformin that was at least 1500 mg/day. At 26 weeks efficacy measures were similar between the two treatments. A total of 43 (7.2%) patients (dulaglutide, 8.7%; and liraglutide, 5.7%) experienced total hypoglycaemia (PG ≤3.9 mmol/L) during the study and 16 patients (dulaglutide, 2.7%; and liraglutide, 2.7%) had documented symptomatic hypoglycaemia. There were no episodes of severe hypoglycaemia.

In general, although there are some limitations (especially with indirect comparisons based on literature data), overall the submitted evidence seems to support the Applicant's arguments and the rates of hypoglycaemia do not appear excessively higher than other relevant therapies for comparable levels of glycaemic control. The new data from GBDE study are consistent with this view.

Certainly the risk is much higher when dulaglutide is given with insulin or a sulphonylurea and the SmPC includes a warning and recommendations for the need of dose adjustment for those cases which is acceptable. Relevant rates are also reported in section 4.8 of the SmPC .

However, there are still uncertainties particularly with respect to the risk of hypoglycaemia in more vulnerable patient groups. The Applicant has provided some analyses for older patients and patients with impaired renal function from the insulin studies but data in very old patients and patients with more severe renal disease are scarce and it is not possible to draw conclusions. The current lack of data with dulaglutide in those groups is reflected in the product information.

Injection Site Reactions

Dulaglutide was supplied in a 3 mL glass vial and administered by a syringe for most of the Phase 2 clinical trials and also for the Phase 2/3 study, Study GBCF. Patients enrolled in the Phase 3 studies were provided with prefilled syringes for ease of administration of study drug.

Across placebo and dulaglutide treatment groups, 44 out of 2916 patients had an injection site adverse event. There were numerically more events in the dulaglutide treatment group (38, 1.7%) compared to placebo (6, 0.9%), but the difference was not statistically significant. Injection site haematoma was the most frequently reported injection site reaction for both the placebo (3, 0.4%) and all dulaglutide (17, 0.8%) treatment groups. Injection site pain (6, 0.3%) and erythema (4, 0.2%) were the next most frequently reported adverse events and were only reported in the dulaglutide treatment groups.

In the AS3 safety set, 63 out of 3342 patients treated with 0.75 mg or 1.5 mg dulaglutide in Phase 2 and 3 studies for the full duration reported injection site reactions. There was no difference in the percentage (1.9% for both) between dulaglutide 1.5- (n=31) and 0.75- (n=32) mg treatment groups. Injection site haematoma, by PT, was the most frequently reported injection site reaction for both. One patient (dulaglutide 1.5 mg), reported a severe TEAE of injection site reaction (injection site rash and injection site swelling and discontinued study drug after 107 days of treatment. This patient was negative for treatment emergent dulaglutide ADA.

Comparisons to other injectable active comparators (studies GBDA, GBDB and GBDD) showed the following results: i. In Study GBDA, after 52 weeks of treatment, 14 (5.1%) patients treated with exenatide BID, 14 (5.0%) patients treated with dulaglutide 0.75 mg, and 8 (2.9%) of patients treated with dulaglutide 1.5 mg reported injection site adverse event; the most common was hematoma (PT); ii. In Study GBDB, after 78 weeks of treatment, 4 (0.5%) patients treated with dulaglutide (2 each in the 0.75 mg and 1.5 mg groups) and none of the insulin glargine-treated patients reported injection site adverse event; iii. In Study GBDD, after 52 weeks of treatment, 4 (1.4%) patients treated with dulaglutide 0.75 mg, 1 (0.3%) patient treated with dulaglutide 1.5 mg, and none of the insulin glargine-treated patients reported an injection site adverse event. Potentially immune-mediated injection site AEs are discussed in *Immunological events* below.

Generally the rate of injection site reactions appears similar if not less than those previously reported with other members of the class. Serious reactions or reactions leading to discontinuations were very rare. The observed rates of injection site reactions are presented in the SmPC.

Cardiovascular Safety

Increases in heart rate (HR) and variable effects on diastolic blood pressure (DBP) were noted in clinical pharmacology studies with dulaglutide. No clinically meaningful effects on SBP were seen. Due to these early findings, both DBP and HR were included among the 4 response measures used in the dose selection and dose adaptation criteria in the dose finding Study GBCF. The dulaglutide dose selected was not to increase mean DBP by more than 2 mm Hg compared with placebo at the predicted 6-month time point. Likewise, the dulaglutide dose selected was not to increase mean HR by more than 5 bpm.

A comprehensive approach was undertaken to assess CV safety in the dulaglutide clinical development program, including: i. The Phase 2 Study GBDN, which assessed the effects of dulaglutide on SBP, DBP, and HR over a 26-week period in 755 patients with T2DM using 24-hour ABPM (see *Pharmacodynamics* above); ii. Sitting vital sign measurements in the Phase 2 and 3 studies; iii. Serum lipids, CPK, and both quantitative ECG assessments of HR, PR interval, QRS complex, QT interval and qualitative ECG assessments of rhythm or conduction abnormalities in Phase 2 and 3 studies; iv. Events associated with cardiac arrhythmias in Phase 2 and 3 studies identified by SMQ and compared in AS1 and AS3 to evaluate for clinical significance of potential numerical findings; v. Major adverse CV events (MACE) in Phase 2 and 3 studies.

Blood Pressure

Table 41 presents mean 24-hour SBP measured with ABPM in Study GBDN. In the primary analysis dulaglutide 1.5 mg significantly decreased SBP from baseline compared to placebo at 16 weeks (difference of -2.8 mm Hg) and 26 weeks (difference of -2.7 mm Hg).

Table 41 Mean 24-Hour Systolic Blood Pressure, Measured with ABPM at 4, 16, and 26 Weeks, Mixed-Model Repeated Measures Analysis (Intent-to-Treat Population, Study H9X-MC-GBDN)

Time	Placebo (N=250)		Dula_0.75 (N=254)		Dula_1.5 (N=251)	
Point	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)
Systolic Blood Pressure (mm Hg)						
Baseline	131.13 (11.23)	--	132.08 (12.97)	--	130.85 (12.14)	--
Week 4	130.84 (11.82)	-0.34 (0.53)	130.39 (11.82)	-1.85 (0.53)	127.10 (12.00)	-3.73 (0.53)
Week 16	130.36 (11.79)	-0.63 (0.59)	130.38 (12.29)	-1.70 (0.58)	127.23 (12.58)	-3.41 (0.61)
Week 26	130.83 (11.63)	0.15 (0.62)	130.67 (12.11)	-1.56 (0.60)	127.75 (11.94)	-2.51 (0.63)

In the safety set AS1, a comparison of dulaglutide to placebo showed significantly greater reductions in mean sitting SBP from baseline for dulaglutide group compared to placebo at each time point through 26 weeks. The comparison between the dulaglutide doses (AS3) showed not significantly different reductions in LS mean sitting SBP from baseline between dulaglutide doses at Weeks 2 to 4 through Week 104. The decrease in SBP was maximal by 2 to 4 weeks (difference in mean change from baseline in all dulaglutide: -2.8 mm Hg).

With regard to DBP, in study GBDN mean 24-hour DBP in the dulaglutide 0.75 mg and 1.5 mg groups were not different from placebo at 16 or 26 weeks (Table 42).

Table 42 Mean 24-Hour Diastolic Blood Pressure, Measured with ABPM at 4, 16, and 26 Weeks, Mixed-Model Repeated Measures Analysis (Intent-to-Treat Population, Study H9X-MC-GBDN

Time	Placebo (N=250)		Dula_0.75 (N=254)		Dula_1.5 (N=251)	
Point	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)
Diastolic Blood Pressure (mm Hg)						
Baseline	75.96 (7.79)	--	76.64 (8.38)	--	76.29 (8.39)	--
Week 4	75.84 (8.13)	-0.06 (0.34)	76.76 (8.15)	0.28 (0.33)	75.83 (8.03)	-0.16 (0.34)
Week 16	75.07 (8.44)	-0.55 (0.37)	76.23 (7.70)	-0.13 (0.37)	75.69 (8.85)	-0.23 (0.38)
Week 26	75.20 (7.91)	-0.24 (0.39)	76.49 (8.33)	-0.09 (0.38)	75.84 (8.40)	0.26 (0.40)

Similar to the findings of Study GBDN, in the integrated safety databases (AS1 and AS3), small non significant changes in DBP (LS mean change from baseline <1 mm Hg) were observed with both placebo and all dulaglutide through 26 weeks of treatment. These reductions were similar between dulaglutide doses through 104 weeks of treatment and were not considered clinically relevant.

Heart rate

In study GBDN, based on MMRM methodology in the ITT population, mean within group 24-hour HR increased significantly for dulaglutide 0.75 mg and 1.5 mg from as early as 4 weeks and continuing to 16 and 26 weeks (Table 43).

Table 43 Mean 24-Hour Heart Rate Measured with ABPM at 4, 16, and 26 Weeks, Mixed-Model Repeated Measures Analysis (Intent-to-Treat Population, Study H9X-MC-GBDN)

Time Point	Placebo (N=250)		Dula_0.75 (N=254)		Dula_1.5 (N=251)	
	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)
Heart Rate (beat per minute)						
Baseline	79.91 (9.97)	--	79.01 (9.75)	--	79.86 (10.83)	--
Week 4	80.07 (9.78)	0.28 (0.40)	81.80 (9.05)	2.71 (0.40)	84.47 (10.51)	4.61 (0.40)
Week 16	80.40 (9.46)	0.86 (0.44)	81.48 (8.99)	2.48 (0.43)	83.65 (10.16)	3.70 (0.45)
Week 26	80.46 (9.64)	0.68 (0.47)	81.00 (9.69)	1.94 (0.46)	83.72 (11.14)	4.18 (0.47)

In the integrated analyses of placebo-controlled studies (AS1) there were no clinically meaningful LS mean changes from baseline for HR in the placebo group. Increases in mean HR from baseline were statistically significantly greater for dulaglutide compared to placebo at each time point up to 26 weeks. The comparison between dulaglutide doses (AS3) showed that LS mean increase was significantly greater for dulaglutide 1.5 mg group compared with the 0.75 mg group with the largest difference at Weeks 2 to 4 (LS mean [95% CI] difference: 1.02 [0.51, 1.53]).

Arrhythmias

There were no important differences in the incidence of abnormal cardiac rhythms between treatment groups in AS1 with the exception of numerically more sinus tachycardia in all dulaglutide (1.8%) compared with placebo (0.4%). There were no differences in reporting of any specific arrhythmia between dulaglutide doses.

Similar proportions of placebo (0.7%) and all dulaglutide-treated (0.5%) patients reported supraventricular arrhythmias over 26 weeks (AS1). Likewise, a similar proportion of patients reported ventricular tachyarrhythmias (placebo: 0.7%; all dulaglutide: 0.2%). A larger proportion of patients in the dulaglutide 1.5 mg than 0.75 mg group reported any supraventricular arrhythmia over the full planned treatment period (1.0% and 0.2%) (AS3). There was no dose difference in the reporting of any ventricular tachyarrhythmia (0.2% with each dose). Three patients on dulaglutide (dulaglutide 1.5mg: 2; dulaglutide 0.75mg: 1) discontinued due to atrial fibrillation and sinus tachycardia but none on placebo, over 26 weeks. There was no difference in the reporting of any bradyarrhythmia for placebo versus all dulaglutide (AS1) or between dulaglutide doses (AS3).

ECG parameters

QTc Interval. The results of the thorough QT study are discussed in *Secondary pharmacology* above. In the clinical program there was no evidence of QT or QTcF prolongation with dulaglutide compared with placebo (AS1) or between dulaglutide 0.75 mg and 1.5 mg (AS3).

QRS complex. No notable differences in QRS between placebo and dulaglutide (AS1) or between dulaglutide 0.75 mg and 1.5 mg (AS3) were observed. As with QTc intervals, treatment-emergent abnormal analyses did not reveal notable differences in QRS complex between placebo and all dulaglutide (AS1) or between dulaglutide doses (AS3).

Heart Rate. Consistent with results of Study GBDN and office-measured HR, in the integrated database, increases in mean ECG-derived HR from baseline were statistically significantly greater for all dulaglutide compared with placebo at Week 2 to 16 (LS mean [95% CI] difference: 3.36 [2.49, 4.23]) and Week 26 week (LS mean [95% CI] difference: 3.56 [2.76, 4.35]). Increases from baseline in HR were observed for both dulaglutide 0.75 mg and 1.5 mg at Week 2 to 16 through Week 104 (AS3) which were greater for dulaglutide 1.5 mg group compared with the 0.75 mg with the largest difference during the first 16 weeks.

PR Interval. Prolongation of PR interval was described in studies GBCO and GBCK. In Study GBDN small LS mean increases from baseline were observed for PR interval at 16 and 26 weeks with both dulaglutide doses that were significantly greater than placebo at both the 16- and 26-week time points. The increases in PR interval were not

significantly different between the doses at either time point. Amongst patients with a normal baseline PR interval, 2% or less developed a treatment-emergent high (>220 msec) PR interval at 16 or 26 weeks (16 weeks:2 placebo, 3 dulaglutide 0.75 mg, 9 dulaglutide 1.5 mg; 26 weeks:0 placebo, 4 dulaglutide 0.75 mg, 8 dulaglutide 1.5 mg).

In the integrated safety databases, statistically significant LS mean increases in PR interval were observed for all dulaglutide versus placebo at both the 16- and 26-week time points (LS mean [95% CI] difference: 2.67 msec [1.30, 4.04]; 3.09 msec [1.88, 4.29], respectively). In AS1 a higher proportion of patients in the all dulaglutide than placebo group (1.4% and 0.6%) had postbaseline PR interval ≥220 msec on 2 consecutive visits. In AS3, increases PR interval from baseline were observed for both dulaglutide 0.75 mg and 1.5 mg treatments groups but were not significantly different between doses except at Week 26.

Atrioventricular Block (AVB). In Study GBDN seventeen patients (2.4%) had some form of AVB, with the majority (16 out of 17 patients) having 1st degree AVB (defined as a PR interval >220 msec) and one having 2nd degree AVB Mobitz Type 1. Eight of these 17 patients had a PR interval change >30 msec at either Week 16 or Week 26. Most of the patients with atrioventricular (AV) conduction abnormalities were in the dulaglutide groups (placebo: 2, dulaglutide 0.75 mg: 6; dulaglutide 1.5 mg: 9).

In the overall Phase 2 and 3 program determined that there were 208 patients (3.5% of the overall program population) who had any postbaseline PR interval value ≥220 msec, indicating AVB. The exposure-adjusted incidence rates for treatment-emergent high PR interval were: dulaglutide (73 patients, 21.5/1000 patient-years), exenatide BID (4 patients, 17.9/1000 patient-years), insulin glargine (6 patients, 10.3/1000 patient-years), metformin (1 patient, 4.9/1000 patient-years), placebo (7 patients, 25.9/1000 patient-years), and sitagliptin (7 patients, 11.3/1000 patient-years).

Thirty-seven patients (placebo: 5 [0.9%]; all dulaglutide: 32 [2.0%]) had some form of treatment-emergent AVB. The event reported in all cases with a single exception was 1st degree AVB. One patient (dulaglutide 0.75 mg) reported Mobitz-1 AVB. In AS3, more patients with normal conduction at baseline who received dulaglutide 1.5 mg than 0.75 mg (6.1% and 4.2%) had postbaseline abnormal conduction. Sixty-three dulaglutide-treated patients (dulaglutide 0.75 mg: 24 [1.5%]; dulaglutide 1.5 mg: 39 [2.5%]) had some form of treatment-emergent AVB. With the exception of 2 patients, these reports were treatment-emergent 1st degree AVB. One patient in each dose group had treatment-emergent 2nd degree Mobitz-1 AVB. In addition, based on qualitative ECG review in AS3 3 dulaglutide-treated patients (dulaglutide 0.75 mg: 1; dulaglutide 1.0 mg: 1; dulaglutide 1.5 mg: 1) were identified with treatment-emergent 2nd degree, 3rd degree/complete, or variable AVB based. Two reports of treatment-emergent variable or 3rd degree AVBs have been identified in patients who received active comparators (exenatide BID: 1; insulin glargine: 1).

Generally, a consistent finding in the clinical program with dulaglutide was a PR interval prolongation and evidence of higher rate of AV conduction abnormalities. However, more serious forms of AV block were very rare and, considering the overall exposure, is it difficult to say whether dulaglutide was different to the active comparators. Of note, an effect on PR interval has also been reported with other members of the class like lixisenatide. Information about the effect on PR and AV block are included in section 4.8 of the SmPC.

Cardiovascular Meta-Analysis

In accordance with regulatory guidance (FDA 2008; EMEA 2012), the applicant conducted a meta-analysis of dulaglutide Phase 2 and 3 clinical study data to exclude a potential unacceptable increase in CV risk.

The analysis included data from 9 controlled clinical studies with different comparators, background medications, and a broad spectrum of the T2DM population. However, patients with a recent history of clinically significant and potentially unstable CV disease were excluded from these studies. In addition, patients with

uncontrolled blood pressure, abnormally elevated serum creatinine, or reduced creatinine clearance or eGFR were also excluded from most studies. Therefore, certain groups with high CV risk may not be represented in the population included in this CV meta-analysis. There was similar use of antihypertensive and lipid-lowering therapies across groups.

The primary analysis population included all randomized patients from phase 2 and 3 trials according to the treatment to which they were assigned. The censoring date for a patient in the completed studies was the date of safety follow-up visit approximately 30 days after the last visit at the end of the treatment period or after early discontinuation. The primary analysis was repeated using the per-protocol (PP) population and completer population from each study included in the meta-analysis.

The primary meta-analysis measure was the time to first occurrence (after randomization) of the 4-component major adverse CV event (MACE) composite of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. Study GBDC did not have any patients with an event, so was combined with Study GBCF into a single stratum. The primary analysis model included treatment as a fixed effect with only 2 levels for the factor (dulaglutide or control).The primary analysis model was a Cox proportional hazards regression model stratified by study (with all phase 2 trials forming one stratum). The model included treatment as a fixed effect with only 2 levels for the factor (dulaglutide or control). The primary meta-analysis objective was to show the upper bound of the (adjusted) 95% CI of the HR is <1.8.

A second meta-analysis was planned to be conducted if the first meta-analysis did not exclude a HR of 1.8 when a minimum total of 180 patients with adjudicated CV events had been observed including additional data from an on-going dulaglutide cardiovascular outcomes study. A Pocock spending function was specified as the method to control the Type I error for multiple analyses; the 95% CI was adjusted accordingly for the primary analysis. For secondary analyses, nominal 95% confidence intervals are reported.

Statistical heterogeneity between the strata was tested by including in the primary analysis model an interaction term between treatment and strata at alpha level 0.10. If significant heterogeneity was present, a random effects model was to be used; this model was to include a random term for the treatment effect in each study (stratum). A data-based decision on the type of analysis (fixed effects or random effects) is not appropriate as the type I error of such a procedure is unknown. The requested random effects analysis was provided. It would have been preferred when the adjusted 95% CIs (nominal 98.02% CIs) were provided as for primary analysis rather than the nominal 95% CIs. However, the results are consistent with the results from the fixed effects model.

A total of 6010 randomized patients (All Comparators arm: 2125; All Dulaglutide arm: 3885) were included in the analysis. Of these, 1228 (20.4%) patients discontinued early before completing the treatment period or the safety follow up period without experiencing the 4-component MACE event (All Comparators: 449 [21.1%]; All Dulaglutide: 779 [20.1%]). The baseline demographics and cardiovascular risk characteristics were comparable between arms. Prior MI at baseline was slightly higher for the All Dulaglutide group compared to the All Comparator group (3.4% vs. 2.4%, p=.049).

A total of 51 patients experienced at least one MACE (Table 3.4.45). The results showed that treatment with dulaglutide was not associated with an increase in the risk of experiencing a 4-component MACE endpoint compared with control therapies (estimated HR: 0.57; adjusted 98.02% CI: [0.30, 1.10]). The upper bound of the adjusted 2-sided 98.02% CI for the HR (1.10) was less than the FDA-stipulated limit of 1.8 for pre-submission (and also less than the FDA stipulated post-submission limit of 1.3). Therefore the primary objective of the meta-analysis was met.

Table 44 Time-to-Event Analysis of Primary CV Endpoint and Individual Components Without Adjudicated Events after Safety Follow-up Period, Alpha = 0.0198; All Randomized Patients

Endpoint Component	All Comparators N=2125 n (%)	All Dula_ N=3885 n (%)	Hazard Ratio*a Est. (adj. 98.02% CI)	Treatment Comparison p-value*a
Primary 4-Component MACE Endpoint	25 (1.18)	26 (0.67)	0.57 (0.30, 1.10)	.046
Death from CV Causes*b	5 (0.24)	3 (0.08)	0.35 (0.07, 1.87)	.119
Nonfatal MI	14 (0.66)	9 (0.23)	0.35 (0.13, 0.95)	.014
Nonfatal Stroke	4 (0.19)	12 (0.31)	1.61 (0.42, 6.20)	.411
Hospitalization for Unstable Angina	6 (0.28)	3 (0.08)	0.28 (0.05, 1.46)	.054

Note: Columns may not add up since patients may have had more than one type of event, but patients are counted only once per event type. Patients are also counted only once for the primary MACE endpoint.
*a: Calculated from a stratified Cox Proportional Hazards regression model: response = treatment. Strata = studies. All phase 2 studies form one stratum, GBDC and GBCF form one stratum. When the total number of outcomes is < 10 or zero is in a cell, survival analysis is not performed. Instead when the total number of outcomes is < 10 and >= 5 and no zero is in a cell, Mantel-Haenszel odds ratio and p-value by Cochran–Mantel–Haenszel test are reported; when the total number of outcomes is < 5 or zero is in a cell, ratio and p-value are not reported.
*b: Death from CV causes is defined as a death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other CV causes.

The primary analysis (adjusted) was repeated for the PP population. The number of events in the PP population was less than in the intent-to-treat (ITT) population. A total of 24 patients (All Comparators: 11 [0.81%]; All Dulaglutide: 13 [0.49%]) experienced a 4-component MACE in the 9 studies. There was no significant difference between the 2 groups (HR: 0.63; 98.02% CI: [0.24, 1.63]; p=.255). Results of various sensitivity analyses with different definitions of the strata, and across various analyses, were consistent with the result of the primary analysis.

Additional endpoints including MACE defined more narrowly (3-component MACE), or broadly (6-component MACE) showed similar results. Evaluation of individual component endpoints showed a significant decrease in the risk for the combined coronary revascularization endpoint (estimated HR: 0.44; 95% CI: [0.21, 0.92]). No significant difference was observed for the heart failure requiring hospitalization endpoint, although the estimated HR was 2.02; 95% CI [0.41, 9.88] (all comparators 2 events vs dulaglutide 7 events).

The overall findings of the CV meta-analyses are reassuring, although the limitations both in terms of the number of events and the exclusion or certain high risk groups like patients with moderate-severe renal impairment or advanced heart failure should be taken into account. Baseline data suggest that >60% were also hypertensive and >50% had hyperlipidaemia while 8-9% had history of CV disease with similar distributions between groups. .

All but two individual endpoints were in favour of dulaglutide; only 'heart failure requiring hospitalisation' and 'nonfatal stroke' (without particularly attributed to any specific type) were numerically more frequent with dulaglutide than with comparator. There were also 5 TIA events, 2 in the dulaglutide and 3 in the All-comparators groups. Generally, the numbers are small and conclusions are difficult to draw but certainly these events will need to be monitored. A large cardiovascular trial (Study GBDJ), with dulaglutide is currently ongoing and is expected to provide a clearer picture of its long term CV potential benefits and risks. This is a Phase 3, randomised, double-blind, placebo controlled study with dulaglutide 1.5 mg on a background standard-of-care treatment. Patient enrolment was completed in Q3 2013. During the study, an independent data monitoring committee (DMC) performs ongoing reviews of safety data. The Applicant indicated that if any safety concerns are raised by the DMC, the Applicant will notify the CHMP as appropriate. Unblinded data will not be available until the final analysis, which is scheduled to occur after 1067 patients have experienced CV events (CV death, nonfatal myocardial infarction, or nonfatal stroke) as confirmed by adjudication. The final report for this study is expected to be available in Q3 2019 but as the primary endpoint of the study and the study duration are event driven, this is an estimate.

Renal Safety

The clinical pharmacology study (H9X-MC-GBCM) that was conducted in renal patients is discussed in the *Pharmacokinetics* section above. The single dulaglutide dose was generally tolerated in all renal function groups. The majority of adverse events were mild and GI in nature, and clinical laboratory assessments, including amylase and lipase, did not worsen following dulaglutide dosing. A Phase 3 study (H9X-MC-GBDX) is currently ongoing to assess the effects of dulaglutide treatment over 52 weeks in patients with T2DM and moderate or severe CKD.

The effects of dulaglutide on renal function both in the overall population and in the renal impairment populations, and dulaglutide safety in patients with renal impairment, were evaluated in the Phase 2 and 3 studies. It should be noted, however, that for most Phase 2 and 3 studies, patients with serum creatinine ≥1.5 mg/dL (males), ≥1.4 mg/dL (females) or eCrCl <60 mL/min were excluded based on label-specific restrictions of concomitant medications (for example, metformin) and limited data available on the use of dulaglutide in patients with renal impairment at the time of these studies.

A summary of the renal baseline characteristics of the Phase 2 and 3 type 2 diabetes population is presented in Table 45. At baseline, 88% (5285 patients) of all randomized patients (6005) had normal kidney function, 4.4% (265) had eGFR <60 mL/min/1.73 m^2, 3% (181) had macroalbuminuria, and 7.1% (425) had eGFR <60 mL/min/1.73 m^2 and/or macroalbuminuria.

Table 45 Summary of Renal Characteristics At Baseline of All Phase 2 and 3 Patients At Baseline (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

Variable	All Randomized Phase 2 (N=1329)	All Randomized Phase 3 (N=4676)	All Randomized Phase 2 and 3 (N=6005)
CKD Stage at Baseline *a			
Normal	973 (73.2)	4312 (92.2)	5285 (88.0)
Stage 1	9 (0.7)	75 (1.6)	84 (1.4)
Stage 2	13 (1.0)	63 (1.3)	76 (1.3)
Stage 3A	69 (5.2)	161 (3.4)	230 (3.8)
Stage 3B	12 (0.9)	23 (0.5)	35 (0.6)
Unknown	253 (19.0)	42 (0.9)	295 (4.9)
Renal Impairment *b	103 (7.8)	322 (6.9)	425 (7.1)
Macroalbuminuria (UACR >300)	28 (2.1)	153 (3.3)	181 (3.0)
eGFR (CKD-EPI) <60 mL/min/1.73 m²	81 (6.1)	184 (3.9)	265 (4.4)

*a CKD Stage as determined by adapted CKD-EPI guidelines, using the highest measured value of eGFR (CKD-EPI) and the lowest measured value of UACR from the baseline period.
*b Patients are included in Macroalbuminuria group if UACR > 300 at all measured timepoints during baseline, included in the eGFR (CKD-EPI) <60 mL/min/1.73 m² group when that criterion is satisfied at all measured timepoints during baseline, and included in the Renal Impairment group if included in either the Macroalbuminia group or the eGFR (CKD-EPI) <60 mL/min/1.73 m² group.

Dulaglutide vs Placebo

In placebo-controlled studies, baseline serum creatinine values were similar in placebo and the all dulaglutide group. Treatment with dulaglutide up to 26 weeks did not alter serum creatinine values. Baseline mean eGFR values were comparable between groups. After treatment, there was a trend toward a greater decrease in eGFR in the all dulaglutide group compared to placebo (Table 46). Additional analysis for eGFR calculated using MDRD equation showed a borderline significantly higher decrease with dulaglutide compared to placebo (p=0.042).

Table 46 ANCOVA Analysis of Baseline to Postbaseline Anchor Timepoint of eGFR CKD-EPI By Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA,GBDN) (AS1)

Variable analyzed: eGFR estimated by CKD-EPI (mL/min/1.73 m^2)

		Actual value							Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Baseline	Placebo	568	89.04		18.85	77.65	90.52	101.68	129.65						
	Dula_0.75	836	89.30		35.61	78.19	91.22	101.48	131.42						
	Dula_1.5	833	89.59		42.63	77.23	92.05	101.84	136.54						
	All_Dula	1669	89.44		35.61	77.62	91.61	101.70	136.54						
16 - 26*	Placebo	551	88.22	86.51	33.23	75.86	90.40	101.61	133.05	-0.82	-42.25	-5.66	-0.37	4.49	71.53
	Dula_0.75	811	87.79		27.50	76.50	90.86	100.48	133.51	-1.37	-62.26	-5.44	-1.02	3.14	27.24
	Dula_1.5	811	87.77		35.74	75.00	89.37	100.32	136.07	-1.90	-48.96	-6.92	-1.08	2.92	36.34
	All_Dula	1622	87.78	85.57	27.50	75.52	90.30	100.40	136.07	-1.64	-62.26	-6.15	-1.05	3.02	36.34
	All_Dula vs Placebo LSM Comparison, p-value*a						.075								

* - Actual timing depending on study, but overall constituting a single anchor time point.
*a - P-value of difference of LS Means is from an ANCOVA model: log(eGFR CKD-EPI) = Treatment + Study + Treatment*Study + log(Min Baseline eGFR CKD-EPI) + log(Max Baseline UACR) + log(Baseline HbA1c) + log(Baseline HbA1c)*Treatment (Type III sums of squares). Estimated LSM is EXP(estimated log(eGFR CKD-EPI)).

In response to treatment with dulaglutide for up to 26 weeks, a lowering of median albuminuria was observed in the dulaglutide group compared to the placebo. In the all dulaglutide group, more patients shifted to lower UACR values (10.6% including 9.4% shifting to normal albuminuria and 1.2% shifting to microalbuminuria) compared to the placebo group (6.9% including 6.1% shifting to normal albuminuria and 0.8% shifting to microalbuminuria). Proportions of patients shifting between CKD stages in response to treatment with placebo or dulaglutide were comparable between groups (AS1). The majority of patients did not change their CKD stage in either group (placebo: 90.1%; all dulaglutide: 91.7%). However, numerically lower proportion of the all dulaglutide group had worsened CKD stage compared to placebo (6.6% and 8.4%) but two dulaglutide-treated patients shifted from normal to CKD stage 4.

Dulaglutide 1.5mg vs 0.75mg (AS3)

In all Phase 2 and 3 studies (treatment period 26 to 104 weeks), baseline serum creatinine values were comparable between the 0.75 mg and 1.5 mg dulaglutide doses. No differences in serum creatinine values (change from baseline) were observed between the 0.75 mg and 1.5 mg dulaglutide groups at 16-26 weeks, at 52 weeks, or at 78-104 weeks of treatment. In the dulaglutide 1.5 mg group, more patients shifted to lower UACR values (10.7% including 9.1% shifting to normal albuminuria and 1.6% shifting to microalbuminuria) compared to the 0.75 mg dulaglutide groups (8.5% including 7.5% shifting to normal albuminuria and 1.0% shifting to microalbuminuria).

The majority of patients in both groups were classified under the normal kidney function category at baseline (dulaglutide 0.75 mg: 93.3% and dulaglutide 1.5 mg: 92.5%). Based on last postbaseline observation, the majority of patients did not change their CKD stage in both groups. However, numerically more patients in the 1.5 mg group had improved their CKD stage compared to dulaglutide 0.75 mg (2.0% vs. 1.4%), and slightly fewer patients in the dulaglutide 1.5 mg group had worsened CKD stage (7.2% vs. 7.9%).

Dulaglutide vs Active Comparators

In all Phase 2 and 3 studies that evaluated dulaglutide versus an active comparator (treatment period 52 to 104 weeks), baseline mean serum creatinine levels were comparable between groups. Throughout the treatment period, no significant difference was observed in serum creatinine between the all dulaglutide group and the active comparator group. Mean baseline eGFR values were similar between groups and no significant difference in eGFR was observed throughout the treatment period. Changes in eGFR from baseline were also comparable between dulaglutide and active comparators throughout the treatment period. UACR values (LS mean at different anchor timepoints) were slightly but significantly smaller in the all dulaglutide group compared to the active comparators group throughout the treatment period.

Acute Renal Failure (ARF)

Throughout Phase 2 and 3 studies, dulaglutide-treated patients who reported ARF included 7 patients in dulaglutide 1.5 mg, 4 patients in dulaglutide 0.75 mg, and 1 patient in dulaglutide 0.5 mg.

In placebo-controlled studies with both dulaglutide doses through 26 weeks of planned treatment (AS1). SMQs searches showed similar numbers of patients in the dulaglutide groups who reported ARF compared to placebo (AS1) [dulaglutide: 2 patients (0.1%); placebo: 2 patients (0.4%)]. No significant difference between dulaglutide 0.75 mg and dulaglutide 1.5 mg was also observed in Phase 2 and 3 studies≥ 26-week planned treatment duration (AS3). However, numerically more patients treated with dulaglutide 1.5 mg reported ARF compared to dulaglutide 0.75 mg (dulaglutide 1.5 mg: 6 patients [0.4%]; dulaglutide 0.75 mg: 3 patients [0.2%]).

Patients with Renal Dysfunction

Renal subpopulations from the Phase 2 and 3 dulaglutide clinical studies were analysed to evaluate renal safety of dulaglutide in patients with various degrees of renal dysfunction. As mentioned, patients with CrCL <60 mL/min were mostly excluded from most dulaglutide studies. The GBDN Study excluded patients with eGFR ≤30 mL/min/1.73m^2, and the GBDD Study excluded patients with creatinine clearance <60 mL/min if they were receiving metformin.

In the remaining patients with renal dysfunction three subpopulations were identified (Table 45 above) as 1) having eGFR <60 mL/min/1.73m^2 (n=265), 2) having macroalbuminuria (UACR >300 mg/g n=181), or 3) having eGFR<60 mL/min/1.73m^2 and/or macroalbuminuria (renal impairment subpopulation; n=425 [7.1%]).

Treatment with dulaglutide did not alter significantly serum creatinine or eGFR in all 3 renal subpopulations compared to placebo. However, dulaglutide was associated with a small but significant decrease in albuminuria compared to placebo. Similar to the overall T2DM population, the most frequently reported TEAEs in the renal impairment subpopulation (renal subpopulation 3) were GI disorders with more dulaglutide than placebo-treated patients reporting these events. Subgroup analysis for patients with renal impairment did not show any treatment by subgroup interactions for TEAE terms except for infections and infestations (lower incidence in the renal population).

With regard to serious adverse events, the incidence of SAEs was numerically higher in the all dulaglutide-treated patients (5 patients, 5.1%) compared to placebo (1 patient, 2.5%) in AS1. In AS3 the dulaglutide 1.5 mg- and 0.75 mg-treated patients reported a similar number of SAEs (10 patients [8.1%] and 12 patients [10.8%]). Dulaglutide treatment of patients with T2DM and renal impairment had generally similar effects on laboratory and cardiac parameters as in the rest of patients.

Overall, there is no clear evidence that dulaglutide has a detrimental effect on renal function in the groups that were studied. Some positive findings were noted with regard to albuminuria but their long term clinical importance is difficult to determine. However, a limitation is, as previously mentioned, the lack of data in patients with more advanced renal disease. Therefore, the safety of dulaglutide in these groups remains uncertain. The SmPC has been updated to reflect more accurately the current limitations and advise that in patients with severe renal failure and end stage disease dulaglutide use is not recommended.

Hepatic Safety

The effect of hepatic impairment on dulaglutide PK was examined in Study GBDO in patients with stable hepatic impairment to that of healthy subjects (see *Pharmacokinetics section* above). To fully evaluate the hepatic safety of dulaglutide in the clinical program, samples were collected through the Phase 2 and 3 studies to assess

hepatic parameters: ALT, AST, total bilirubin, direct bilirubin, GGT, and AP. Integrated analyses of adverse events potentially associated with hepatic injury in these studies were also conducted using SMQs.

Across the Phase 2 and Phase 3 program, dulaglutide was generally not shown to increase transaminases, bilirubin, or markers of cholestasis. The proportion of patients having values exceeding thresholds of concern was comparable between placebo- and all dulaglutide-treated patients and between the dulaglutide 0.75 mg and 1.5 mg dose groups. Moreover, there were no differences between treatment groups in the proportion of patients shifting to higher categories from baseline to postbaseline.

Two cases in the overall safety database fulfilled the criteria for hepatotoxicity/potential drug induced liver injury using Hy's criteria (ALT and/or AST ≥3x ULN and total bilirubin >2x ULN, with AP <2x ULN). In one patient (Placebo/Dulaglutide 1.5 mg) a finding of high baseline GGT was consistent with a preexisting hepatic abnormality and possibly associated with alcohol. The second case (Dulaglutide 0.75 mg) was concluded to be related to acute hepatitis E. Two additional patients had AST or ALT >5x ULN (dulaglutide 0.75 mg) during clinical studies. A persistent elevation of ALT or AST (≥3x ULN during at least 3 consecutive visits/measurements) was observed in 6 cases (placebo: 1; sitagliptin: 2; dulaglutide 0.75 mg: 2; placebo/dulaglutide 1.5 mg: 1).

Three cases of serious hepatic-related events were retrieved from LSS and the clinical studies database. One case concerns a fatal event of hepatic failure. The other events included the patient with acute hepatitis E described above and a case reported as hepatitis (apparently not viral) accompanied by AST >21x ULN. The fatal case concerned a subject with preexisting alcoholic cirrhosis in the hepatic PK study GBDO which the investigator considered the death unrelated to dulaglutide.

Overall, there is no evidence that dulaglutide can adversely affect hepatic function and as shown by study GBDO hepatic impairment is unlikely to have a significant effect on the pharmacokinetics of dulaglutide. The proposed SmPC does not include any relevant information or recommendations. Based on the overall evidence and the PK data this is accepted.

Malignancies

The databases of the Phase 2 and 3 clinical studies were queried for events contained in the malignant and unspecified tumours (narrow) SMQ. The search criteria included terms for pancreatic and thyroid cancers and neoplasms. Table 47 summarizes reported events by anatomical location for placebo, each active comparator, and dulaglutide.

Table 47 Exposure Adjusted Incidence of Patients with Treatment-Emergent Malignancies and Unspecified Tumors, All Postbaseline Observations Through Safety Follow-up – Phase 2 and 3 Studies (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

	Number (%) of Patients [Number of Events/1000 Patient-Years of Exposure]					
		Active Comparator				
Location of Cancer Cancer Type	**Placebo (N=703)**	**Metformin (N=268)**	**Sitagliptin (N=439)a**	**Exenatide (N=276)**	**Insulin Glarg. (N=558)**	**Dulaglutide (N=4006)b**
Patient Year Exposure (pt-yrs)	**284**	**227**	**637**	**236**	**621**	**3531**
Number (%) of patients with any malignancy or unspecified tumor c	**7 (1.0) [24.6]**	**0**	**9(2.1)[14.1]**	**3(1.1)[12.7]**	**12(2.2)[19.3]**	**48 (1.2)d,e [13.6]**
Thyroid	**0**	**0**	**1(0.2)[1.57]**	**1(0.4)[4.23]**	**2(0.4)[3.22]**	**7(0.2)d[1.98]**
Thyroid neoplasm	0	0	1 (0.2) [1.57]	1 (0.4) [4.23]	2 (0.4) [3.22]	5 (0.1) [1.42]
Thyroid cancer	0	0	0	0	0	3 (0.1)h [0.85]
Breast	**0**	**0**	**1(0.2)[1.57]**	**0**	**2(0.4)[3.22]**	**6 (0.1) [1.70]**
Breast cancer	0	0	1 (0.2) [1.57]	0	2 (0.4) [3.22]	4 (0.1) [1.13]
Breast cancer in situ	0	0	0	0	0	1(<0.1)f [0.28]
Breast cancer metastatic	0	0	0	0	0	1 (<0.1) [0.28]

Skin	**4(0.6)[14.08]**	**0**	**1(0.2)[1.57]**	**0**	**1 (0.2) [1.61]**	**10(0.2)[2.83]**
Basal cell carcinoma	0	0	1 (0.2) [1.57]	0	0	7 (0.2)e [1.98]
Neoplasm skin	2 (0.3) [7.04]	0	0	0	0	0
Malignant melanoma	2 (0.3) [7.04]	0	0	0	0	0
Skin cancer	0	0	0	0	1 (0.2) [1.61]	1 (<0.1) [0.28]
Squamous cell carcinoma of skin	0	0	0	0	0	1 (<0.1) [0.28]
Bowen's disease	0	0	0	0	0	1 (<0.1) [0.28]
Ear, nose, or throat	**0**	**0**	**1(0.2)[1.57]**	**0**	**0**	**1(<0.1)[0.28]**
Laryngeal cancer stage 3	0	0	1 (0.2) 1.57]	0	0	0
Vocal cord neoplasm	0	0	0	0	0	1 (<0.1) [0.28]
Gastrointestinal	**1 (0.1) [3.52]**		**1(0.2)[1.57]**	**1(0.4)[4.23]**	**2 (0.4)[3.22]**	**11(0.3)[3.12]**
Tongue neoplasmg	0	0	0	0	0	1 (<0.1) [0.28]
Tongue carcinoma stage 1	0	0	0	0	0	1 (<0.1) [0.28]
Oesoph. adenocarcinoma1	(0.1) [3.52]	0	0	0	0	0
Colon cancer	0	0	0	1 (0.4) [4.23]	0	2 (<0.1) [0.57]
Rectal neoplasm	0	0	0	0	0	1 (<0.1) [0.28]
GI stromal tumour	0	0	0	0	0	1 (<0.1) [0.28]
Gastric neoplasm	0	0	0	0	0	1 (<0.1) [0.28]
Rectal cancer	0	0	0	0	2 (0.4) [3.22]	0
Gallbladder cancer	0	0	0	0	0	1 (<0.1) [0.28]
Gastric cancer	0	0	1 (0.2) [1.57]	0	0	1 (<0.1) [0.28]
Pancreatic carcinoma	0	0	0	0	0	2 (<0.1) [0.57]
Lung	**0**	**0**	**2(0.5)[3.14]**	**0**	**2(0.4) [3.22]**	**2(<0.1)[0.57]**
Lung neoplasm	0	0	2 (0.5) [3.14]	0	1 (0.2) [1.61]	2 (<0.1) [0.57]
Non-small cell cancer of lung	0	0	0	0	1 (0.2) [1.61]	0
Other	**2 (0.3) [7.04]**	**0**	**2(0.5)[3.14]**	**1(0.4)[4.23]**	**3 (0.5) [4.83]**	**12(0.3)[3.40]**
Non-secretory adenoma of pituitary	1 (0.1)f [3.52]	0	0	0	0	0
Chronic lymphocytic leukemia	0	0	0	0	0	1 (<0.1) [0.28]
Prostate cancer	1 (0.1) [3.52]	0	1 (0.2) [1.57]	1 (0.4) [4.23]	1 (0.2) [1.61]	1 (<0.1) [0.28]
Prostate cancer stage 0	0	0	0	0	0	2 (<0.1) [0.57]
Uterine cancer	0	0	1 (0.2) [1.57]	0	0	0
Liposarcoma	0	0	0	0	0	1(<0.1)e[0.28]
Squamous cell carcinoma	0	0	0	0	0	1 (<0.1) [0.28]
Adenocarcinoma	0	0	0	0	0	1 (<0.1) [0.28]
Testicular seminoma (pure)	0	0	0	0	0	1 (<0.1) [0.28]
Transitional cell carcinoma	0	0	0	0	0	1 (<0.1) [0.28]
Multiple myeloma	0	0	0	0	0	1 (<0.1) [0.28]
Non-Hodgkin's lymphoma	0	0	0	0	0	1 (<0.1) [0.28]
Vaginal neoplasm	0	0	0	0	1 (0.2) [1.61]	0
B-cell small lymphocytic lymphoma	0	0	0	0	1 (0.2) [1.61]	0
Renal neoplasm	0	0	0	0	0	1 (<0.1) [0.28]

a Total sitagliptin exposure includes 124 patients who received placebo during the first 26 weeks of Study GBCF.
b Total dulaglutide exposure contains 121 patients who received placebo during the first 26 weeks of Study GBDA.
c Patients were included in this table if they reported events contained in the malignant and unspecified tumors (narrow) standardized MedDRA query in Phase 2 and 3 studies. Patients who participated in crossover treatments and reported multiple qualifying events may be counted in more than 1 treatment group.
d One dulaglutide-treated patient (GBDB-202-2102) reported both a thyroid neoplasm and thyroid cancer.
e One dulaglutide-treated patient (GBDA-033-1609) reported separate events of basal cell carcinoma and liposarcoma. The patient is counted in each location of cancer but only once in the total number of dulaglutide-treated patients with any malignancy or unspecified tumor.
f Reported in safety follow-up period or after study discontinuation.
g Tongue neoplasm (Patient GBCF-013-0715) was reported as a mild tongue lesion that resolved within 1 month of initial report.
h Reported after discontinuation from study, but determined by Lilly to be preexisting

The analyses revealed similar incidence of malignant and unspecified tumours across treatment groups. Most types of cancer and unspecified tumours were reported by only one or two patients. Only breast cancer, basal cell carcinoma, thyroid neoplasm, and thyroid cancer were reported by more than 2 patients in any treatment group.

Thyroid malignancies and neoplasms were reported by 1 patient (0.2%) who received sitagliptin, 1 patient (0.4%) who received exenatide BID, 2 patients (0.4%) who received insulin glargine and 7 (0.2%) who received any dose of dulaglutide. No placebo or metformin-treated patients reported thyroid malignancies or thyroid neoplasms. Three (3) thyroid cancers have been described in the clinical trial database – all in dulaglutide treated patients (see also *Thyroid* section above).

Two pancreatic carcinomas were reported for patients who received dulaglutide in the completed Phase 2 and 3 studies. These patients had a rather short duration (≤3 year) of diabetes and baseline BMI <25 kg/m^2. The first

patient (GBCZ-117- 1712) was diagnosed with a large, non resectable tumour 1 week after his one and only dose of dulaglutide 0.75 mg suggesting that was present prior to use of dulaglutide. The second patient (GBDA-012-0555) was found to have a large tumour that consumed most of the body and tail of her pancreas after approximately 5 months of therapy with dulaglutide.

The two cases of pancreatic carcinomas, taking into account the limited exposure to dulaglutide by the time of diagnosis, are rather unlikely to be causally related to dulaglutide. The thyroid neoplasms and the cases of cancer are more of concern but the numbers are small and the overall incidence with dulaglutide was not greater than the other active comparators. No patients who received placebo or any active comparator reported pancreatic cancers.

Weight Loss

The effects of dulaglutide on body weight and BMI as efficacy parameters are presented in the *Efficacy* section above. From a safety perspective, significant weight loss was explored in dulaglutide-treated patients in the Phase 2 and 3 studies (AS6). A total of 77 (2%) dulaglutide-treated patients showed the greatest weight loss. These patients had 6% reduction in median body weight from baseline by 4 weeks, 9% by 12 to 14 weeks, and 12% by 26 weeks. The remaining patients lost a median of approximately 1% of their body weight through 26 weeks.

At each time point, a numerically larger percentage of patients with the greatest weight loss compared to the rest reported TEAEs. As with the overall dulaglutide-treated population, the most frequent TEAEs were GI disorders, namely nausea, vomiting, and diarrhoea. The events of special interest reported for patients with greatest weight loss were almost exclusively GI disorders, with the exception of one report of cholelithiasis and one report of acute renal failure. The rate of early discontinuation from studies in patients with the greatest weight loss was generally lower than the rest at each time point (although it increased over time for both groups).

Laboratory findings

Clinical laboratory measurements were performed for haematology, chemistry, urinalysis, and special analytes (for example, dulaglutide anti-drug antibodies [ADA]) at time points specified in each protocol in the dulaglutide Phase 2 and 3 studies. The results associated with special topics were presented in the relevant sections (*Adverse events of special interest*) above. In addition, the effect of dulaglutide on lipids and creatine phosphokinase (CPK) were also assessed. Analyses of CPK from Phase 2 and 3 studies showed no notable differences between placebo and all dulaglutide (AS1) or between dulaglutide 0.75 and 1.5 mg (AS3).

With regard to lipids, in AS1 small decreases in total cholesterol, LDL-C, triglycerides, and total cholesterol/HDL-C were observed for all dulaglutide compared to placebo at 16 to 26 weeks of treatment. For the last postbaseline observation of each of these analytes, the LS mean reduction was statistically significant for all dulaglutide compared with placebo. There was a small increase in HDL-C for both placebo and all dulaglutide, but the difference was not statistically different.

Generally, it is reassuring that dulaglutide appears to have a small but overall positive effect on lipid parameters. However, baseline lipid values do not indicate a particularly dyslipidaemic population as one would have expected, especially when it is reported (as in the CV meta-analysis) that more than 50% of the patients were hyperlipidaemic. The Applicant clarified that the definition of 'Hyperlipidaemia' was mostly based on medical history, not necessarily confirmed by lipid tests. The vast majority of patients with such history were on lipid-lowering treatments and most of them had no raised lipid levels, while an approximate 18% with no history

were found to have abnormal lipids. Overall, around 43% of all patients in the CV meta-analysis had abnormal lipid profiles at baseline. The distribution of patients in the different categories appears consistent across treatment groups.

Safety in special populations

The safety profile of dulaglutide was reviewed based on TEAEs and SAEs for placebo and all dulaglutide (AS1) and dulaglutide 0.75 mg and 1.5 mg (AS3) for the following intrinsic factors: age, sex, baseline BMI, race, ethnicity, and duration of diabetes. Treatment-by-subgroup interactions with p<0.10 were considered to be of interest.

Age and baseline BMI subgroup-by-treatment interactions yielded the results of greatest clinical interest. For most other subgroups, the interactions reflected effects similar to those observed for the overall population. Within the subgroups (for example, race or ethnicity), the incidence of TEAEs typically varied by less than 5% across the subgroup-by-treatment combinations. When larger differences were observed within subgroups, the number of patients representing the subgroup populations was typically small. These observations suggest that these interactions are likely to be of little clinical relevance

Age

Table 48 shows the age distribution in Phase 2 and 3 studies.

Table 48 Age (Baseline Characteristics) in All Patients in Phase 2 and 3 Studies (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

Variable	All Randomized Phase 2 (N=1329)	All Randomized Phase 3 (N=4676)	All Randomized Phase 2 and 3 (N=6005)	All Randomized Phase 2 and 3 on dulaglutide (N=4006)
Age (yrs)				
Number of Patients	1329	4676	6005	4006
Mean	56.06	56.11	56.10	56.11
SD	10.36	9.91	10.01	9.97
Minimum	25.72	19.81	19.81	19.81
Median	56.67	56.67	56.67	56.63
Maximum	86.89	86.55	86.89	86.89
Age Group, n (%)				
< 65 (yrs)	1078 (81.1)	3819 (81.7)	4897 (81.5)	3283 (82.0)
>= 65 (yrs)	251 (18.9)	857 (18.3)	1108 (18.5)	723 (18.0)
Age Group, n (%)				
< 75 (yrs)	1297 (97.6)	4590 (98.2)	5887 (98.0)	3930 (98.1)
>= 75 (yrs)	32 (2.4)	86 (1.8)	118 (2.0)	76 (1.9)
Age Group, n (%)				
< 65 (yrs)	1078 (81.1)	3819 (81.7)	4897 (81.5)	3283 (82.0)
>= 65 and < 75 (yrs)	219 (16.5)	771 (16.5)	990 (16.5)	647 (16.2)
>= 75 and < 85 (yrs)	31 (2.3)	84 (1.8)	115 (1.9)	73 (1.8)
>= 85 (yrs)	1 (<0.1)	2 (<0.1)	3 (<0.1)	3 (<0.1)

No subgroup-by-treatment interactions were observed within the <65 years versus ≥65 years group or <75 years versus ≥75 years group comparisons of placebo and all dulaglutide (AS1). In AS3, some interactions were observed. The most notable difference was for decreased appetite for which there was a higher incidence with dulaglutide 1.5 mg than 0.75 mg in both the <65 years group (7.3% and 5.5%, respectively) and ≥65 years groups (9.6% and 3.2%). The incidence of TEAEs was similar for patients <75 years who received dulaglutide 0.75 mg and 1.5 mg but whereas in patients ≥75 years there were more AEs with dulaglutide 1.5 mg than 0.75 mg (90.6% and 66.7%). The GI disorders SOC, nervous system disorders SOC, and decreased appetite PT were primary contributors to the differences between subgroups (although for none p was <0.10).

Body Mass Index

Across Phase 2 and 3 studies, 401 (279 received dulaglutide) patients in Phase 2 and 3 studies had baseline BMI <25 kg/m^2, 1816 (1212 received dulaglutide) had ≥25 and <30 kg/m^2, 1979 (1297 received dulaglutide) had ≥30 and <35 kg/m^2, and 1809 (1218 received dulaglutide) had ≥35 kg/m^2.

In AS1, patients lower BMI groups had a lower reporting of TEAEs overall among the placebo than all dulaglutide group (<25 kg/m^2: 59.0% and 71.0%, respectively; ≥25 and <30 kg/m^2: 56.7% and 68.3%). Patients in the higher BMI groups reported TEAEs at a similar incidence for both placebo and all dulaglutide. In AS3, across the BMI subgroups, nausea was reported at a lower incidence among the dulaglutide 0.75 mg than 1.5 mg groups. The magnitude of differences between dulaglutide 0.75 mg and 1.5 mg were greatest at the lower BMIs. For patients in the higher BMI groups, the difference in incidence of nausea was less pronounced for dulaglutide 0.75 mg and 1.5 mg.

Other subgroups

Safety in patients with renal dysfunction is discussed in the *Renal safety* subsection above.

There were 7 pregnancies in completed studies in the dulaglutide clinical program. Five occurred during dulaglutide treatment and 2 during active comparator treatment (insulin glargine; sitagliptin). For 5 of the 7 pregnancies, women were using a non-hormonal method of contraception and 2 women were using oral or injectable hormonal contraceptives in combination with other contraceptive methods. Fetal exposure was restricted to the first trimester in all cases. Two of the pregnancies were voluntarily terminated. The other 5 pregnancies resulted in live births. No complications were reported for infants. For one mother mild hypertension, cholestasis, and hyperglycaemia were reported. No other maternal complications were observed.

Overall, the subgroup analyses did not identify any specific group at much higher risk of major complications. However, as previously discussed, there is concern about the small number of patients >75 years in the studies, especially when there is some evidence of higher AE reporting rate in this group and greater with dulaglutide 1.5mg than with the lower dose.

Immunological events

Anti-drug Antibodies

The immunogenicity testing strategy for the dulaglutide program was based on the use of a solid phase extraction with acid dissociation (SPEAD) enzyme-linked immunosorbent assay (ELISA) format, and a cell-based assay developed to detect neutralizing ADA (dulaglutide-specific assay; nsGLP-1-specific assay). Blood samples from patients in the Phase 2 and 3 studies were collected and assayed for dulaglutide ADA. Samples with treatment-emergent dulaglutide ADA were then tested for neutralizing activity against dulaglutide and for their potential to bind native GLP-1 (nsGLP-1 cross-reactivity). Lastly, samples with cross-reactivity to nsGLP-1 were further tested for neutralizing activity against nsGLP-1.

At baseline a total of 148 samples had detected dulaglutide ADA, approximately 3% for both the dulaglutide and active comparator treatment groups. These results reflect the background predose assay reactivity in the Phase 2 and 3 study population included in the studies. One patient (dulaglutide 1.5 mg treatment group) who had ADA at baseline had prior exposure to a GLP-1 receptor agonist; 5 other patients with prior exposure to GLP-1 receptor agonist did not have ADA at baseline. The baseline ADA titers for samples from these groups were generally between 1:2 and 1:16. High titers (≥1:128) were seen at baseline in 2 patients from the "other comparator" arm in Study GBCF. Neither of these patients had prior exposure to a GLP-1 receptor agonist.

Post baseline, the incidence of treatment-emergent dulaglutide ADA in dulaglutide-treated patients ranged from 0 (at any dose in Study GBCJ and Study GBCZ) to a maximum of 3.7% (Study GBDB patients randomized to the

0.75 mg dulaglutide dose). Review of the data for all post baseline observations for the "All dulaglutide" treatment group across the Phase 2 and 3 trials, showed that 64 (1.6%) of the patients developed treatment-emergent dulaglutide ADA at least once versus 8 (0.7%) patients in the other comparator treatment group (Table 49). Nine dulaglutide-treated patients with treatment-emergent ADA had detectable ADA prior to exposure. Four 4 patients had high (≥1:128) treatment-emergent dulaglutide ADA titers and none of them had detectable ADA at baseline. One patient had progressive increases in antibody titer over time, but remained in the low range until the completion of the trial.

Table 49 Summary of Patients with Treatment-Emergent Dulaglutide Anti-Drug Antibodies - All Results Available Postbaseline through Follow-Up Period (Safety Population, Studies GBCF, GBCJ, GBCK, GBDZ, GBDA, GBDB, GBDC, GBDD, and GBDN)

Category	All_Dula (N=4006) n (%)	Exenatide (N=276) n (%)	Other Comparator (N=1141) n (%)
Patients with Postbaseline Test *a	3907	270	1114
Patients with >=1 TE Dula ADA *b	64 (1.6)	14 (5.2)	8 (0.7)
TE Dula ADA and Dula Neutralizing	34 (0.9)	13 (4.8)	4 (0.4)
TE Dula ADA and nsGLP1 Cross-Reactive	36 (0.9)	12 (4.4)	3 (0.3)
TE Dula ADA and nsGLP1 Neutralizing	4 (0.1)	7 (2.6)	3 (0.3)
TE Dula ADA and both nsGLP1 Cross-Reactive and Neutralizing	2 (<0.1)	7 (2.6)	2 (0.2)

Abbreviations: ADA = anti-drug antibody; Dula = dulaglutide; N = total number of patients in specified treatment group; n = number of patients in specified category; nsGLP1 = native sequence GLP1; TE = treatment-emergent.
Note: All_Dula refers to all dulaglutide treatment groups combined. Exenatide group is from study GBDA exclusively. Other Comparator is any non-dulaglutide assigned treatment except exenatide, including placebo. Patients in GBDA who received Placebo initially and subsequently received Dulaglutide are included in both the 'Other Comparator' group and the 'All_Dula' group, with treatment-emergence assessed relative to original baseline, in each case. Denominator for percent (%) is the number of patients with postbaseline test result for Dula ADA.
Note: Placebo and active comparator patients in studies GBCF, GBDA, and GBDN were tested for ADA. Active comparator patients in studies GBDB, GBDC, and GBDD were not requested to be tested for ADA, but for some patients testing occurred. In addition to placebo and sitagliptin patients required by protocol to be tested in studies GBCF, GBDA, and GBDN, N for 'Other Comparator' includes any active comparator patients from GBDB, GBDC, and GBDD for whom ADA testing was performed, and results from these tests are included in the table.
*a - All patients with at least one test result for Dula ADA (Detected or Not Detected) at any time during postbaseline, including post-treatment follow-up visit.
*b - A patient is considered to have TE Dula ADA if the patient has at least one titer that is treatment-emergent relative to baseline, defined as a 4-fold or greater increase in titer from baseline measurement. To assess treatment-emergence, baseline titer is imputed if unavailable (1:1 if baseline Dula ADA test is missing or 'Not Detected'; 1:2 if baseline Dula ADA test result was 'Detected' with no titer available).

Of the 64 dulaglutide patients with treatment-emergent ADA, 55 had follow-up testing. Of the 47 patients who developed treatment-emergent ADA during the treatment period, 2 patients were not tested in the follow-up period, 24 patients still exhibited treatment emergent ADA in the safety follow-up period (an indication of "persistent" immune response) and 21 patients demonstrated reverse seroconversion (a possible indication of "intermittent" dulaglutide ADA during the exposure period that was not present upon discontinuation of the study drug).

No dose effect was observed on the incidence of treatment-emergent dulaglutide ADA. The treatment emergent dulaglutide ADA seen with dulaglutide 1.5 mg treatment (26 patients had detected ADA [1.5%]) was comparable to that seen with 0.75 mg (36 patients had detected ADA [2.08%]).

As described above patient samples with treatment-emergent ADA were also assayed to identify their potential specificity for nsGLP-1 molecule. Among the 64 patients treated with dulaglutide and having ADA, 36 patients developed nsGLP-1 cross-reactive (binding) antibodies, 4 patients had nsGLP neutralizing ADA and 2 patients had both nsGLP-1 cross-reactive (binding) and neutralizing antibodies (Table 49 above).

In study Study GBDA patients in the exenatide group were tested for exenatide and dulaglutide treatment-emergent ADA as well as cross-reactive antibodies against nsGLP-1 and neutralizing antibodies against dulaglutide and nsGLP-1. Of the 276 exenatide-treated patients, 130 (47.1%) had detected exenatide ADA during the study. 123 patients (44.6%) had treatment emergent exenatide ADA as determined by at least

4-fold postbaseline increase in titer. A total of 14 patients (5.2%) in the exenatide group developed treatment-emergent dulaglutide ADA. Importantly, all exenatide patients with treatment-emergent dulaglutide ADA also had exenatide ADA. This indicates that the observed dulaglutide ADA activity in patients exposed to exenatide may be related to cross-reactivity of anti-exenatide with exenatide and dulaglutide (shared epitopes). Two of these patients were previously exposed to a GLP-1 receptor agonist. There were no apparent clinical safety consequences related to these cross-reactive antibodies.

Overall, the number of patients who developed anti-dulaglutide antibodies during therapy was small, and in a much lower rate than those reported with the other three currently licensed GLP-1 receptor agonists. The incidence was higher than in patients treated with placebo or non-GLP-1 comparators (1.6% versus 0.7%) but very few patients had high titers. There was no clear relation with dose level. Approximately half (0.9% of the overall population) had dulaglutide neutralizing ADA but their impact on glycaemic control, at least as the Phase 3 data suggest (see Efficacy section) was small and inconsistent. There were four patients with nsGLP-1 neutralizing ADA. The patients had no hypersensitivity or injection suite reactions. There was also no clear evidence of an adverse impact on glycaemic control.

Hypersensitivity TEAEs

TEAEs indicating potential hypersensitivity reactions resulting from the systemic immune response were assessed using specific SMQs (Anaphylactic Reaction, Angioedema or Severe Cutaneous Adverse Reaction narrow terms).

In patients randomized to placebo or dulaglutide in all Phase 2 and 3 placebo-controlled studies (up to 26 weeks of treatment) the number of those with a hypersensitivity adverse event was small (12 out of 2916) and balanced across the placebo (5 [0.7%]) and dulaglutide- (7 [0.3%]) treated patients. Urticaria, was the most frequently reported TEAE for placebo (2, 0.3%) and all dulaglutide (5, 0.2%) treatment groups. The remaining hypersensitivity reactions occurred in ≤0.1% of the patients and included lip swelling, face oedema, pharyngeal oedema, and face swelling.

In AS3 data up to 104 weeks showed more dulaglutide 0.75 mg treated patients (13, 0.8%) than dulaglutide 1.5 mg treated patient (3, 0.2%) reporting systemic hypersensitivity adverse events. For both doses, urticaria was again the most frequently reported AE and was the only PT reported in the dulaglutide 1.5 mg treatment group. There were 3 patients that had either a severe hypersensitivity adverse event or had an adverse event that was considered to be of special interest: Patient GBCF-302-4565 (Stevens Johnson syndrome; dulaglutide 0.75 mg), Patient GBCF-701-6713 (Anaphylactic shock; dulaglutide 0.75 mg); Patient GBCJ-001-0101 (Severe urticaria; dulaglutide 1.0/2.0 mg).

Across all dulaglutide doses in the Phase 2 and 3 studies, 19 (0.5%) patients experienced at least one potential hypersensitivity TEAE. None of them were positive for treatment-emergent dulaglutide ADA suggesting that the appearance of treatment-emergent dulaglutide ADA in patient's serum has a very low potential for causing systemic hypersensitivity adverse events.

Generally hypersensitivity reactions were rare with a rate similar to placebo, and no apparent association with the presence of anti-dulaglutide antibodies. Most common was urticaria. However, there were 3 cases with severe reactions although a clear causal relationship with dulaglutide exposure, at least for the two of them, is difficult to establish. In the first case dulaglutide had been administered for 21 months before the patient developed moderate serious erythema multiforme with bullous changes after receiving oxacillin, which has been associated with such events. In the second case 'anaphylactic shock' moderate in severity and related to food was reported in a 46 years old female with previously reported food allergy, urticaria and allergic dermatitis while on dulaglutide for 32 weeks together with various other medications. None of the above two patients had

anti-dulaglutide antibodies. In the third case an adverse event of severe urticaria was reported after 7 days on therapy with dulaglutide.

Potentially Immune-Mediated Injection Site Adverse Events

Across all dulaglutide doses in the Phase 2 and 3 studies, 20 patients (0.5%) experienced at least one potentially immune-mediated injection site adverse event. Across the dulaglutide treatment groups from the placebo-controlled Phase 2 and 3 studies (AS2), 10 (0.5%) of 2213 patients treated with dulaglutide had an injection site reaction that was potentially immune mediated. There were no such reports in the placebo group. Injection site erythema (4 patients, 0.2%) was the most frequently reported reaction. Injection site-irritation (3 patients, 0.1%) and pruritus (3 patients, 0.1%) were the next most frequently reported adverse events. The remaining adverse events (induration and rash) occurred in $\leqslant$0.1% of the dulaglutide-treated patients.

In AS3 There was no significant difference in the incidence of patients with these events between dulaglutide 1.5 mg treatment group (11 patients, 0.7%) and the 0.75 mg (8 patients, 0.5%) treatment group.

To assess the possible relationship between potentially immune-mediated injection site adverse events and treatment-emergent dulaglutide ADA, patients were also assessed for the presence of treatment-emergent dulaglutide ADA. Of the 20 patients with at least one potentially immune-mediated injection site adverse event across all dulaglutide doses in the Phase 2 and 3 studies, two had also treatment-emergent dulaglutide ADA. Three of the 20 patients, none with treatment-emergent dulaglutide ADA, reported severe potentially immune mediated injection site adverse event.

Patients with treatment-emergent dulaglutide ADA had significantly higher incidence of immune-mediated injection site adverse events (3.1%; 2 of 64 patients) compared to patients who did not develop treatment-emergent dulaglutide ADA (0.5%; 18 of 3843 patients); one more patient with treatment-emergent dulaglutide ADA had application site erythema considered by Lilly as potentially immune mediated injection site adverse event. Two of the 5 dulaglutide-treated patients who had high or progressive antibody titers, had potentially immune mediated injections site adverse events or other possibly related events.

Immunotoxicity

Part of the dulaglutide molecule corresponds to the constant (Fc) part of an IgG4 antibody (heavy chain). The type IgG4 was selected because its interaction with other parts of the immune system is low; e.g., IgG4 does not induce complement activation. Furthermore, the Applicant states that certain positions in the antibody-like part of the dulaglutide molecule were changed to reduce binding to Fc receptors on the surface of immune cells.

There is some indication from AE incidence rates that infectious disorders might be slightly more frequent with dulaglutide than with comparators (see respective sections above). There was concern since dulaglutide is structurally similar to IgG and might therefore influence immune function. The additional data provided by the Applicant for studies of longer duration demonstrate that there is no indication for such an effect. The total rate of infections/infestations is well balanced between treatment groups. Also, no specific type of infection was markedly more frequent in one group as compared to the other groups. Regarding the term "Immune System Disorders", hypersensitivity was numerically more frequent in the Dula 0.75 mg vs. the comparator group (0.5% vs. 0); however, Dula 1.5 mg was again similar to comparator. Therefore, this is regarded as a chance finding.

Safety related to drug-drug interactions and other interactions

As discussed in the *Pharmacokinetics/Interactions* section above, drug-interaction studies were conducted to evaluate the effect of dulaglutide on atorvastatin (Study GBCP), digoxin (Study GBCR), warfarin (Study GBCS), sitagliptin (Study GBDW), metformin (Study GBDM) and oral contraceptives (Study GBCQ).

Study GBCO also examined the PK and PD effect of dulaglutide on concomitant medications with haemodynamic properties (lisinopril in subjects with hypertension and metoprolol in healthy subjects). Multiple doses of dulaglutide were well tolerated when administered in combination with lisinopril in subjects with hypertension. No clinically significant effect on blood pressure was observed following multiple doses of 1.5 mg dulaglutide in hypertensive subjects on lisinopril therapy. However, statistically significant increases in HR compared to placebo were seen using ABPM following a single (LS mean 24-hour change from baseline of 8.10 bpm) and multiple (LS mean 24-hour change from baseline of 6.87 bpm) 1.5 mg doses of dulaglutide in hypertensive subjects on lisinopril therapy. Single 1.5 mg doses of dulaglutide were well tolerated when administered in combination with metoprolol in healthy subjects. When administered in combination with metoprolol, single doses of 1.5 mg dulaglutide resulted in statistically significant increases in HR in healthy subjects.

The Applicant has provided information from the Phase 2 and Phase 3 studies on the potential effects of concomitant use of beta blockers, calcium channel blockers or digoxin on cardiac parameters. Clearly, there are limitations but overall the submitted data are consistent with what was observed in the clinical pharmacology studies and do not raise any new safety concerns about clinically significant drug interactions. The effects of concomitant antidiabetic medication especially with regard to hypoglycaemia are discussed in detail in the relevant sections above.

Discontinuation due to AES

In AS1, more patients in the placebo than all dulaglutide group (7.0% and 4.7%, respectively) discontinued study drug or from the study altogether due to an adverse event. The most notable adverse events that led to discontinuation were GI disorders and metabolism and nutrition disorders. GI disorders led to discontinuation more frequently in the all dulaglutide than placebo group (2.4% and 0.2%, respectively). Only nausea was associated with a significantly greater rate of discontinuation for all dulaglutide compared with placebo (1.1% and 0%). In contrast, metabolism and nutrition disorders led to discontinuation more frequently in the placebo group.

Table 50 Summary and Analysis of Adverse Events Reported as the Reason for Discontinuation of Study Drug or Discontinuation from Study, Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

System Organ Class	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)	Odds Ratio*a	Hetero-geneity p-val.*b	CMH p-val.*c
Pts discontinued due to AE	40 (7.0)	24 (2.9)	55 (6.6)	79 (4.7)	0.66	.0.17	.037
Cardiac disorders	0 (0.0)	1(0.1)	3 (0.4)	4 (0.2)			.242
Eye disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.616
Gastrointestinal disorders	1 (0.2)	11 (1.3)	29 (3.5)	40 (2.4)	13.91	.585	<.001
General disorders and administration site conditions	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.2)			.300
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.482
Immune system disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			.046
Infections and infestations	2 (0.4)	1 (0.1)	0 (0.0)	1 (<0.1)	0.17		.216

Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (<0.1)	1 (0.1)			.616
Investigations	4 (0.7)	6 (0.7)	4 (0.5)	10 (0.6)	0.85	.796	.761
Metabolism and nutrition disorders	19 (3.3)	3 (0.4)	5 (0.6)	8 (0.5)	0.14	.0.35	<.001
Neoplasms benign, malignant/unspecified	3 (0.5)	1 (0.1)	1 (0.1)	2 (0.1)	0.23	.648	.033
Nervous system disorders	3 (0.5)	0 (0.0)	2 (0.2)	2 (0.1)	0.23	.362	.060
Pregnancy, puerperium and perinatal	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)			.319
Renal and urinary disorders	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)			.022
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.482
Skin and subcutaneous tissue disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			.064
Vascular disorders	4 (0.7)	0 (0.0)	3 (0.4)	3 (0.2)	0.25	.316	.144
*a - Mantel-Haenszel Odds Ratio. All_Dula is numerator, Placebo is denominator. *b - Heterogeneity of odds ratios across studies was assessed using the Breslow-Day test. *c - p-values are from Cochran-Mantel-Haenszel (CMH) test comparing All_Dula to Placebo stratified by study.							

In AS3, fewer patients who received dulaglutide 0.75 mg than 1.5 mg (n=128 [7.7%] vs 173 [10.4%], respectively) discontinued study drug or study due to an adverse event. The SOCs with the highest incidences of AEs that led to discontinuation of study drug or study were GI disorders (dulaglutide 0.75 mg: n=41 [2.5%] vs 1.5 mg: n=81 [4.8%]) and metabolism and nutrition disorders (dulaglutide 0.75 mg: n=43 [2.6%] vs 1.5 mg: n=34 [2%] mostly due to Hyperglycaemia). Nausea was reported as a reason for discontinuation less frequently with dulaglutide 0.75 mg than 1.5 mg (1.0% and 1.9%, respectively). Otherwise, adverse events leading to discontinuation of study drug or study were balanced between doses.

Analyses of studies GBDA, GBDB, GBDC, and GBDD revealed that the pattern of adverse events leading to discontinuations with regard to dose level (0.75mg vs 1.5mg) was balanced across concomitant (background) antihyperglycemic treatments. Discontinuation due to GI events was dose dependent but the overall proportions of patients discontinuing due to the events was small and similar across the trials.

The Applicant also provided further summary data about discontinuations in the dulaglutide groups compared to all active comparators As previously noted, the rates of discontinuation in the clinical studies was generally low with the highest ones, as rather expected, seen in the longest 104-week GBCF study. In most studies discontinuations were less likely with the lower 0.75mg dose than with the higher dose. GI events were the primary reason (more often nausea) and with a higher frequency in patients treated with dulaglutide 1.5mg compared to the lower dose. The exception was study CBCF (in which no rescue therapy was allowed) where among the main reasons for discontinuation was hyperglycaemia and in this case the percentages were similar between treatment groups.

The Applicant suggests that the overall rate of discontinuation due to adverse events across the Phase 3 studies are consistent with the GLP-1 class and do not raise major concerns about treatment adherence and this is agreed. It is noted, however, that the findings with the lower dulaglutide dose are generally more favourable compared to the higher one and add to the body of evidence supporting the usefulness of the lower strength formulation.

Monotherapy indication

As mentioned above, the pivotal data for the monotherapy indication come from Study H9X-MC-GBDC. In this study the tolerability and safety profile of dulaglutide was similar to metformin but overall more favourable for

the lower 0.75mg dose, showing generally less GI effects and a lower risk of hypoglycaemia, as outlined in the tables below:

Common TEAEs. Summary of Treatment-Emergent Adverse Events Occurring in at Least 5.0% of Patients in Any Group by Preferred Term, Baseline to 26 Weeks Intent-To-Treat Population

Adverse Event	Dula 1.5 mg (N = 269) n (%)	Dula 0.75 mg (N = 270) n (%)	Metformin (N = 268) n (%)	Total (N = 807) n (%)	Overall p-value[a]
Patients with ≥1 TEAE	163 (60.6)	150 (55.6)	151 (56.3)	464 (57.5)	0.445
Nausea	51 (19.0)	29 (10.7)	39 (14.6)	119 (14.7)	0.027
Diarrhea[b]	27 (10.0)	14 (5.2)	37 (13.8)	78 (9.7)	0.003
Vomiting	23 (8.6)	16 (5.9)	11 (4.1)	50 (6.2)	0.099
Decreased appetite	18 (6.7)	11 (4.1)	12 (4.5)	41 (5.1)	0.330
Headache	9 (3.3)	14 (5.2)	18 (6.7)	41 (5.1)	0.205
Nasopharyngitis[b]	10 (3.7)	7 (2.6)	21 (7.8)	38 (4.7)	0.010
Constipation[b]	17 (6.3)	9 (3.3)	2 (0.7)	28 (3.5)	0.002

Hypoglycaemia. Summary of Total, Documented, and Severe Hypoglycaemia (Plasma Glucose Less than or Equal to 70 mg/dL, Excluding Post-Rescue Visits) – Dulaglutide and Comparator (Safety Population, Studies GBDC)

	Percentage of Patients [Estimated Event Rate/Patient/Year]		
Monotherapy (52 weeks; Study GBDC)	**MET (N=268)**	**Dulaglutide 0.75 mg (N=270)**	**Dulaglutide 1.5 mg (N=269)**
Total	12.7 [0.28]	11.1 [0.47]	12.3 [0.89]
Documented symptomatic	4.9 [0.09]	5.9 [0.15]	6.3 [0.62]
Severe	0 [0.0]	0 [0.0]	0 [0.0]

The percentage of patients who discontinued the study drug or discontinued from study due to adverse events was also lower with the 0.75mg dose (n=10; 3.7%) compared to the 1.5mg dose (n=20; 7.4%) or metformin (n=17; 6.3%)

Taken into account also the efficacy results that showed a very similar performance between the two dulaglutide doses the above data suggest that in a monotherapy setting the 0.75mg dose may have an overall more favourable benefit:risk profile than the higher 1.5mg dose and comparable to metformin.

Further to the dulaglutide effects on glycaemic parameters the Applicant considered various characteristics of patient groups who could potentially receive dulaglutide instead of metformin. Several aspects were discussed and it is true that the concept of using a GLP-1 agonist as monotherapy in T2DM patients who cannot tolerate metformin or have contraindications has already been accepted for another GLP-1 agonist (for albiglutide).

In general, despite some limitations the body of evidence suggests that there are patients among those who cannot receive metformin because of a contraindication or intolerability, who can benefit from dulaglutide treatment and the monotherapy indication can be accepted. The evidence also suggests a better benefit:risk profile for the 0.75mg dose than the 1.5mg .Therefore, 0.75mg is the recommended dose in this setting.

2.6.1. Discussion on clinical safety

The main safety database includes data from the Phase 2 and 3 clinical studies in a total of 6005 patients with T2DM of whom 4006 received at least one dose of dulaglutide. Clinical pharmacology studies also contributed 680 dulaglutide-treated healthy subjects, patients with T2DM, and a small number of special population subjects (including renally or hepatically impaired). The Applicant submitted a comprehensive review of the safety data, detailed assessments of events of special interest across the whole program and narratives for serious cases.

In order to broaden the database for the safety evaluation of dulaglutide the Applicant constructed pooled datasets from the individual studies. The Applicant mainly focused on the pool of placebo-controlled studies (AS1) which included a limited patient number and shorter treatment duration but allows a good evaluation of the true adverse effects attributable to dulaglutide. A broad dataset encompassing all phase 2/3 studies, all comparators and also the extension phases of the trials would be desirable for detection of rare events and of events that require longer treatment duration in order to be detected. Such a dataset was defined (AS7) but not all evaluations were performed on this. The Applicant argued that this set was too heterogeneous because of the active comparators being from very different substance classes. This argument is not fully endorsed since all comparators are established antidiabetics with known AE profiles so that new AEs of dulaglutide would have been detected. A limitation of dataset AS7 is that the Applicant did not distinguish events between the different dulaglutide doses so that dose dependency cannot be examined within this set. Nevertheless, the evaluations performed with AS7, in conjunction with AS1 and AS3, are considered sufficient for a reliable assessment of the dulaglutide safety profile by CHMP although a broad, long-term dataset including all comparators would have been favoured.

The overall exposure to dulaglutide, in terms of number of patients included in the clinical program, is also considered sufficient to characterise its main safety profile. However, it should be noted that a relatively small number of patients were exposed to the drug for more than 1.5-2 years and this is a limitation considering its intended long term use. It is positive, however, that the study population comprised a wide range of diabetic patients both in terms of demographic and disease characteristics as well as common comorbidities and background medications; still, there are areas with little or missing information, which is reflected in the SmPC, including patients older than 75 years and potentially more vulnerable special groups such as patients with severe renal insufficiency/end stage renal disease, patients with advanced heart failure.

As rather expected for a GLP-1 receptor agonist, the most common adverse events were gastrointestinal disorders with a generally higher rate with dulaglutide 1.5mg compared to the lower 0.75mg dose and nausea, diarrhoea and vomiting being the most commonly experienced adverse events. Nevertheless, the data suggest that the likelihood of new GI events diminishes after the first 2-4 weeks of treatment and it is reassuring that although GI tolerability was the most frequent cause of early discontinuations, the overall number of patients who discontinued study drug in the main trials was small and the reported compliance was generally high.

There were only few deaths in the whole program and, as expected for this population, most of them of cardiovascular causes. There was no indication of a higher rate in the dulaglutide groups. Similarly the number of serious adverse events was generally low, with hypoglycaemia consistently reported as the most the common SAE with a slightly higher incidence with dulaglutide 1.5mg. Pneumonia, appendicitis and cholelithiasis were also among the most common although differences between groups were small and conclusions are difficult to draw.

A number of safety topics of special interest in T2DM in general or relevant to the GLP-1 agonist class were reviewed in more detail, including GI tolerability, pancreatitis, thyroid neoplasms, hypersensitivity and/or

immune reactions, hypoglycaemia, cardiovascular events, effects on renal and hepatic function and malignancies.

With regard to pancreas there was a small but clear trend for higher mean amylase and lipase concentrations with dulaglutide compared to placebo (and generally larger for dulaglutide 1.5mg than 0.75mg) but cases of pancreatitis were very rare and the overall incidence was not higher than placebo or sitagliptin. However, a higher rate was observed in the thorough QT study when patients were exposed to doses of 4mg and higher. CHMP now considers pancreatitis as an identified risk of the whole class of incretin mimetics. Thus, although there is currently no clear evidence for an association between dulaglutide treatment and pancreatitis, this AE is therefore included as identified risk in the RMP. Pancreatitis is expected to be assessed in the CV outcome study with dulaglutide. There was also no indication from the submitted data that dulaglutide is associated with pancreatic cancer. However, any association with cancer is difficult to be established or excluded based on premarketing data. CHMP considers pancreatic cancer as a potential risk of the whole class of incretin mimetics. Therefore, this issue again is being considered in the RMP and in the ongoing CV outcome study.

Review of safety data related to the thyroid revealed a number of neoplasms but the incidence was similar between dulaglutide, placebo and active comparators. However, there were three cases of thyroid cancer among the dulaglutide treated patients, although their causal relationship to dulaglutide exposure is uncertain. Otherwise, dulaglutide was not shown to be associated with a higher incidence of malignancies compared to placebo or the active comparators.

In terms of cardiovascular safety, the data suggest a small lowering effect on blood pressure; however, a dose dependent increase in heart rate was a consistent finding across the whole program. Similar effects have been reported with other GLP-1 agonists but their clinical importance remains unclear. A consistent finding was also a P-R interval prolongation and there was evidence of higher rate of AV conduction abnormalities, although more serious forms of AV block were very rare. Due to the low magnitude of these effects, they may not be of concern; so far the data also do not suggest more serious effects in case that dulaglutide is combined with digoxin or calcium antagonists (see also *Clinical Pharmacology* above).

Nevertheless, the overall cardiovascular database, including the findings of a meta-analysis, did not raise any major concerns, with dulaglutide showing a lower incidence of MACE than the comparators. However, there are limitations both in terms of the number of the events and the exclusion or certain high risk groups like patients with advanced renal impairment or heart failure and there was some evidence of a higher rate of strokes in the dulaglutide groups. A large cardiovascular trial is currently ongoing and is expected to provide a clearer picture of the dulaglutide long term potential CV benefits and risks.

There is no clear evidence that dulaglutide adversely affects renal or hepatic function; also renal or hepatic impairment, as shown in the PK studies, are unlikely to have a significant effect on its pharmacokinetics. However, few patients with worse than mild renal disease (and none with severe or end stage renal failure) were examined in the Phase 2 and 3 studies. Therefore, the renal safety of dulaglutide in these special groups has not been fully established and the SmPC has been updated accordingly to reflect these limitations, to ensure the safe use of the drug in such patients.

The immunogenic potential of dulaglutide appears to be low and hypersensitivity reactions were rare with no apparent association with the presence of anti-dulaglutide antibodies, which were detected in a small overall percentage of patients (1.6%). The incidence of injection site reactions with dulaglutide was also low, similar or less than that reported with other agents in this class. Potentially immune-mediated reactions were even less frequent (0.5%) with erythema being the most commonly reported.

The dulaglutide molecule contains the Fc part of an IgG4 antibody heavy chain aiming at prolonging its half-life. There is a theoretical concern that this may exert immunological effects. The Applicant has designed dulaglutide in such a way to minimise such potential interactions. However, immunological effects by yet unrecognised mechanisms cannot be fully excluded. Certain infectious disorders occurred somewhat more frequently in dulaglutide-treated patients, including serious ones (pneumonia and urinary tract infection). One patient in the dulaglutide group died of pneumonia. However, the total rate of infections/infestations was well balanced between treatment groups; also, no specific type of infection was markedly more frequent in one group as compared to the others. The total number of cases was low, and the overall evidence suggests that this is a chance finding.

A safety issue identified in the dulaglutide pivotal trials was the high incidence of hypoglycaemia observed in certain studies. Dulaglutide was shown to be worse than placebo, possibly suggesting a real hypoglycaemic effect but the overall incidence was comparable to metformin or sitagliptin (and better than exenatide BID) with rates similar when administered with non-secretagogues as background therapy. However, the risk increased noticeably when dulaglutide was given with glimepiride (plus metformin) and even further with prandial insulin (with or without metformin) reaching 41.7 events/patient/year for total hypoglycaemia with dulaglutide 1.5mg (and even worse 48.4 events/patient/year with dulaglutide 0.75mg) in study GBDD. There were also 21 cases with severe hypoglycaemia among dulaglutide-treated patients with 18 taking also insulin lispro and two on concomitant glimepiride. In general, despite the high rates and although there are some limitations (especially with indirect comparisons based on literature data), overall the submitted evidence suggests that hypoglycaemia with dulaglutide does not appear excessively higher than other relevant therapies for comparable levels of glycaemic control. Data from the newly completed data from GBDE study (dulaglutide vs liraglutide; see above) are consistent with this view. Certainly, the risk is much higher when dulaglutide is given with insulin or a sulphonylurea and the SmPC includes a warning and recommendations for the need of dose adjustment for those cases which is acceptable. Relevant rates are also reported in section 4.8 of the SmPC.

Remaining uncertainties are particularly with respect to the risk of hypoglycaemia in more vulnerable patient groups. The Applicant has provided some analyses for older patients and patients with impaired renal function from the insulin studies but data in very old patients and patients with more severe renal disease are scarce.

From the safety database adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

A reasonably large safety database has provided sufficient information to determine the key aspects of the dulaglutide safety profile, although there are limitations, including the relatively small number of patients exposed for longer than 18 months and the absence of robust data on older patients and certain special groups.

Overall, the safety profile appears consistent with what has previously been observed in this class and separate analyses of areas of special interest did not reveal any unexpected findings or raise major concerns, including its effect on pancreas and thyroid. Similarly, there was no evidence of an increase in cardiovascular risk or of a detrimental effect on renal or liver function. Immunogenicity was low and hypersensitivity reactions were rare.

The high incidence of hypoglycaemia, in some cases severe, reported in the pivotal trials when dulaglutide was administered with glimepiride and prandial insulin is of concern. However, the evidence suggests that the risk of hypoglycaemia with dulaglutide may not be higher than other relevant therapies for comparable levels of glycaemic control. Still very old patients and other potentially vulnerable groups were underrepresented or

excluded from the studies.These limitations are reflected in the SmPC. Moreover, to alleviate the risk for such vulnerable patients the currently recommended starting dose is 0.75mg.

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.7. Risk Management Plan

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

The PRAC considered that the risk management plan version 1.5 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.6 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 51 Summary of the Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	Hypoglycaemia Acute pancreatitis Gastrointestinal events
Important Potential Risks	Hypersensitivity Thyroid C-cell tumours Pancreatic malignancy Cardiovascular effects Medication errors (more than one injection per week)
Missing Information	Use in children and adolescents <18 years of age Use in pregnant and/or breastfeeding women Use in patients with hepatic impairment Use in patients with severe renal failure Use in patients with congestive heart failure Use in patients aged ≥75 years Confirmation of memory deficits in directly dosed immature rats

Pharmacovigilance plan

Table 52: Ongoing and planned studies in the PhV development plan

Study/Activity **Type, Title and Category (1-3)**	**Objectives**	**Safety Concerns Addressed**	**Status** **(Planned, Started)**	**Date for Submission of Interim or Final Reports** **(Planned or Actual)**
An Active Surveillance Program for Cases of Medullary Thyroid Carcinoma (MTC) (Category 3)	To determine the annual incidence of MTC in the US and to identify any possible increase related to the introduction of liraglutide and other GLP-1 receptor agonists into the US market.	Potential risk of medullary thyroid carcinoma	The MAH plans to join this registry upon approval of dulaglutide by the FDA.	Estimated submission of study report: March 2032
Cardiovascular outcomes study (GBDJ; REWIND) (Category 3)	A large dulaglutide CV outcome study that will also provide data relevant to pancreatic safety	CV effects Acute pancreatitis Pancreatic carcinoma Medullary thyroid cancer and c-cell hyperplasia	Started	Estimated submission of study report: March 2020 No interim reports are planned
Study Comparing the Effect of Once-Weekly Dulaglutide with Insulin Glargine on Glycaemic Control in Patients with Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease (GBDX) (Category 3)	To evaluate the risk/benefit of dulaglutide in patients with T2DM and moderate or severe chronic kidney disease	Evaluate the safety and efficacy of dulaglutide in patients with T2DM and moderate or severe chronic kidney disease	Started	Estimated submission of study report: May 2017
A Drug Utilisation Study (Category 3)	To provide information on the use of dulaglutide after approval in the EU.	Overall utilisation in real world conditions as well as off-label useand use in subpopulations of patients identified as	Planned	Estimated completion: Completion is subject to reimbursement status and use of dulaglutide in the EU. Estimated completion

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
		missing information: • diagnosed with severe renal failure • patients with congestive heart failure • patients with hepatic disease • patients with severe GI disease • use in children and adolescents <18 years of age • use in elderly • use in pregnant and breastfeeding women • medication errors		within 5 years of marketing authorization. The protocol outlines will be submitted within 1 month of approval (Commission Decision) and the protocols within 6 months of approval.
A Prospective Study (Category 3)	To monitor the occurrences of events of interest and ensure that the profile and rate remains consistent with what has been seen in clinical trials	Pancreatitis Hypersensitivity Pancreatic and thyroid cancers CV events including heart rate (tachycardia) and conduction abnormalities (atrioventricular block) GI effects/gastric stenosis	Planned	Estimated completion: not more than 5 years after marketing authorization. The protocol outlines will be submitted within 1 month of approval (Commission Decision) and the protocols within 6 months of approval

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
		Medication errors The above outcomes will also be described in the dulagutide subpopulations identified as missing information		
A Retrospective Study (Category 3)	To estimate the incidence rates of events of interest among T2DM patients treated with dulaglutide compared to other GLP-1 receptor agonists	Pancreatitis Pancreatic and thyroid cancers	Planned	Estimated completion: Completion is subject to reimbursement status and use of dulaglutide in the EU. Data gathered from the aforementioned Drug Utilisation Study will assist in determining when this retrospective study can start and therefore complete. A proposed timeline for start and completion of this Retrospective Study can be proposed after 75% of the required sample size in the Drug Utilisation Study has been achieved. The timeline for start and completion of the Retrospective Study will then be provided within 6 months of this date.
Juvenile Rat Toxicity Study (Category 3)	To determine the potential effects of dulaglutide on neurobehavioral development, including learning and memory, in	Confirmation of memory deficits in directly dosed immature rats	Started	Q2, 2015

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	directly dosed immature rats.			

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the study(ies) in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 53: Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk-Minimisation Measures	Additional Risk-Minimisation Measures
Hypoglycaemia	SmPC wording: SmPC 4.4. Special warnings and precautions for use Hypoglycaemia Patients receiving dulaglutide in combination with sulphonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea or insulin. SmPC 4.8. Undesirable Effects Hypoglycaemia (when used in combination with prandial insulin, metformin [1.5 mg only], or metformin plus glimepiride): Very common Hypoglycaemia (when used as monotherapy or in combination with metformin plus pioglitazone): Common Hypoglycaemia When dulaglutide 0.75 mg and 1.5 mg were used as monotherapy or in combination with metformin alone or metformin and pioglitazone, the incidences of documented symptomatic hypoglycaemia were 5.9% to 10.9% and the rates were 0.14 to 0.62 events/patient/year, and no episodes of severe hypoglycaemia were reported. The incidences of documented symptomatic hypoglycaemia when dulaglutide 0.75 mg and 1.5 mg, respectively, were used in combination with a sulphonylurea (plus metformin) were 39.0% and 40.3% and the rates were 1.67 and 1.67 events/patient/year. The severe hypoglycaemia event incidences were 0% and 0.7%, and rates were 0.00 and 0.01 events/patient/year. The incidences when dulaglutide 0.75 mg and 1.5 mg, respectively, were used in combination with prandial insulin were 85.3% and 80.0% and rates were 35.66 and 31.06 events/patient/year. The severe hypoglycaemia event incidences were 2.4% and 3.4%, and rates were 0.05 and 0.06 events/patient/year.	None
Acute Pancreatitis	SmPC wording: **4.4 Special warnings and precautions for use** *Acute pancreatitis* Use of GLP1 receptor agonists has been associated with a risk of developing acute pancreatitis. In clinical trials, acute pancreatitis has been reported in association with dulaglutide (see Section 4.8). Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued. If pancreatitis is confirmed, dulaglutide should not be restarted. In the absence of other signs and	None

	symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see Section 4.8). **Section 4.8 Undesirable effects** Acute pancreatitis Acute pancreatitis: rare The incidence of acute pancreatitis in Phase II and Phase III clinical studies was 0.07% for dulaglutide compared to 0.14% for placebo and 0.19% for comparators with or without additional background antidiabetic therapy. Pancreatic enzymes Dulaglutide is associated with mean increases from baseline in pancreatic enzymes (lipase and/or pancreatic amylase) of 11% to 21% (see Section 4.4). In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.	
Gastrointestinal Events	SmPC wording: **4.4 Special warnings and precautions for use** Use of GLP 1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function since these events (i.e. nausea, vomiting, and/or diarrhoea), may cause dehydration which could cause a deterioration of renal function. Dulaglutide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients. **4.8 Undesirable effects** Gastrointestinal disorders: Common and very common Gastrointestinal adverse reactions Cumulative reporting of gastrointestinal events up to 104 weeks with dulaglutide 0.75 mg and 1.5 mg respectively included nausea (12.9% and 21.2 %), diarrhoea (10.7% and 13.7%) and vomiting (6.9% and 11.5%). These were typically mild or moderate in severity and were reported to peak during the first 2 weeks of treatment and rapidly declined over the next 4 weeks, after which the rate remained relatively constant. In clinical pharmacology studies conducted in patients with type 2 diabetes mellitus up to 6 weeks, the majority of gastrointestinal events were reported during the first 2-3 days after the initial dose and declined with subsequent doses.	None
Hypersensitivity	SmPC wording: **4.3 Contraindications** Hypersensitivity to the active substance or any of the excipients listed in 6.1. 4.8 Undesirable effects Immunogenicity In clinical studies, treatment with dulaglutide was associated with a 1.6 %	None

	incidence of treatment emergent dulaglutide anti drug antibodies, indicating that the structural modifications in the GLP 1 and modified IgG4 parts of the dulaglutide molecule, together with high homology with native GLP 1 and native IgG4, minimise the risk of immune response against dulaglutide. Patients with dulaglutide anti drug antibodies generally had low titres, and although the number of patients developing dulaglutide anti drug antibodies was low, examination of the Phase 3 data revealed no clear impact of dulaglutide anti drug antibodies on changes in HbA1c. Hypersensitivity In the Phase 2 and Phase 3 clinical studies, systemic hypersensitivity events (e.g., urticaria, edema) were reported in 0.5% of patients receiving dulaglutide. None of the patients with systemic hypersensitivity developed dulaglutide anti drug antibodies.	
Thyroid C-Cell Tumours	SmPC wording: **Section 5.3 Preclinical safety data** Nonclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeat-dose toxicity In a 6-month carcinogenicity study in transgenic mice, there was no tumorigenic response. In a 2-year carcinogenicity study in rats, at ≥ 7 times the human clinical exposure following 1.5 mg dulaglutide per week, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas combined). The clinical relevance of these findings is currently unknown.	None
Pancreatic Malignancy	SmPC wording: None proposed	None
Cardiovascular Effects	SmPC wording: **Section 4.8 Undesirable effects** Sinus tachycardia, first degree atrioventricular block (AVB): common Heart rate increase Small mean increases in heart rate of 2 to 4 beats per minute (bpm) and a 1.3% and 1.4% incidence of sinus tachycardia, with a concomitant increase from baseline ≥15 bpm, were observed with dulaglutide 0.75 mg and 1.5 mg respectively. First degree AV block/PR interval prolongation Small mean increases from baseline in PR interval of 2 to 3 msec and a 1.5% and 2.4% incidence of first-degree AV block were observed with dulaglutide 0.75 mg and 1.5 mg respectively.	None
Medication Errors(more than one injection per week)	**Proposed text in SmPC:** **Section 4.2 Posology and method of administration** *Monotherapy*	None

	The recommended dose is 0.75 mg once weekly *Add-on therapy* The recommended dose is 1.5 mg once weekly. For potentially vulnerable populations, such as patients ≥ 75 years, 0.75 mg once weekly can be considered as a starting dose **PARTICULARS TO APPEAR ON THE OUTER PACKAGING Section 5 Method and route(s) of administration** For single use only Read the package leaflet before use Once weekly (prominently displayed on the front panel of the carton) Mark the day of the week you want to use your medicine to help you remember (calendar provided on the package carton) **MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS** **Section 2. Method of Administration:** Once weekly **Package Leaflet: Information for the patient** **Section 3 How to use Trulicity** When used alone, the recommended dose is 0.75 mg once a week. When used with other medicines for diabetes, the recommended dose is 1.5 mg once a week. In certain situations, for example if you are 75 years or older, your doctor may recommend a starting dose of 0.75 mg once a week. Each pen/syringe contains one weekly dose of Trulicity (0.75 mg or 1.5 mg). You can use your Trulicity at any time of the day, with or without meals. You should use it on the same day each week if you can. To help you may wish to tick the day of the week when you inject your first dose on the box that your Trulicity comes in, or on a calendar. **Instructions for Use** **Trulicity is administered once a week.** You may want to mark your calendar to remind you when to take your next dose	
Missing Information - Use in children and adolescents <18 years of age	SmPC wording: **Section 4.2 Posology and method of administration** Paediatric Population The safety and efficacy of dulaglutide in children aged less than 18 years have not yet been established. No data are available.	None

Missing Information - Use in pregnant and/or breastfeeding women	SmPC wording: **Section 4.6 Fertility, pregnancy, and lactation** Pregnancy There are no or limited amount of data from the use of dulaglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Therefore, the use of dulaglutide is not recommended during pregnancy. Breastfeeding It is unknown whether dulaglutide is excreted in human milk. A risk to newborns/infants cannot be excluded. Dulaglutide should not be used during breastfeeding.	None
Missing Information – Use in patients with hepatic impairment	SmPC wording: **Section 4.2 Posology and method of administration** Patients with hepatic impairment No dosage adjustment is required in patients with hepatic impairment.	None
Missing Information - Use in patients with severe renal failure	SmPC wording: **Section 4.2 Posology and method of administration** Patients with renal impairment No dosage adjustment is required in patients with mild or moderate renal impairment. There is very limited experience in patients with severe renal impairment (eGFR [by CKD EPI] <30 ml/min/1.73 m^2) or end stage renal disease, therefore Trulicity is not recommended in this population (see Section 5.2).	None
Missing Information - Use in patients with congestive heart failure	SmPC wording: **Section 4.4 Special warnings and precautions for use** Populations not studied There is limited experience in patients with congestive heart failure.	None
Missing Information - Use in patients aged ≥75 years	SmPC wording: **Section 4.2 Posology and method of administration** Elderly patients (> 65 years old) No dose adjustment is required based on age. However, the therapeutic experience in patients ≥75 years is very limited (see Section 5.1), and in these patients 0.75 mg once weekly can be considered as a starting dose.	None
Missing Information -Confirmation of memory deficits in directly dosed	SmPC wording: **Section 4.1Therapeutic indications** Trulicity is indicated in adults with type 2 diabetes mellitus to imrove glycaemic control	None

immature rats	**Section 4.2 Posology and method of administration** *Paediatric population* The safety and efficacy of dulaglutide in children less than 18 year have not yet been established. No data are available.	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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

Benefits

Beneficial effects

Dulaglutide is a new long acting GLP-1 receptor agonist, proposed to be used as monotherapy in patients who cannot receive metformin due to intolerance or contraindications, and as second line therapy in adult patients with T2DM in combination with other glucose lowering therapies (oral antidiabetics and/or insulin) together with diet and exercise. Although in recent years a number of different therapeutic options have been made available to the T2DM population, including other GLP-1 agonists, new agents still will have a different benefit:risk profile or may have advantages in terms of ease of use.

The efficacy of dulaglutide was mainly examined in six pivotal trials. A sixth phase 3 study, considered supportive, was submitted during the procedure.Both dulaglutide doses that were tested, 1.5mg and 0.75mg, consistently showed a significant and clinically relevant mean reduction in HbA1c from baseline which was the primary efficacy endpoint. For dulaglutide 1.5mg the mean changes ranged from -0.78% (in the monotherapy Study GBDC) to -1.64% (in the insulin Study GBDD). For dulaglutide 0.75mg treatment the mean changes from baseline ranged from -0.71% to -1.59% respectively. Apart from the monotherapy trial (GBDC), these reductions were achieved when dulaglutide was administered as add-on to other OAMs or prandial insulin, in

patients not adequately controlled on the previous therapy, suggesting a significant incremental effect.

Dulaglutide was also superior to placebo as well as the active comparators that it was tested against in the most trials. In general, active comparators were titrated to sufficiently high doses to achieve full glucose lowering potential. In the pivotal study for the monotherapy indication monotherapy study GBDC both dulaglutide doses showed a significant reduction in HbA1c compared to baseline (-0.71% and -0.78% for 0.75mg and 1.5mg respectively). In addition, the primary objective of the study was achieved showing that both doses were not only non-inferior (the primary objective) but also superior to metformin although by only a small margin.

In study GBCF, dulaglutide 1.5mg was (as add-on to metformin) better in reducing HbA1c than sitagliptin at 12 months by -0.71% [-0.87%, -0.55%], and in study GBDA it was (as add-on to metformin plus pioglitazone) superior to exenatide twice daily by -0.52% [-0.66%, -0.39%]. In the GBDB trial dulaglutide 1.5mg in combination with metformin and glimepiride was more effective than insulin glargine by -0.45% [-0.60%, -0.29%] as was also in study GBDD in combination with insulin lispro (with or without metformin) against the insulin glargine+inslulin lispro regimen by -0.22% [-0.38%, -0.07%]. Dulaglutide 0.75mg, although to a lower degree, showed similar results.

In all main studies dulaglutide 1.5mg also resulted in significantly greater percentages of patients reaching HbA1c <7.0% or ≤6.5% than the comparators and was also better in reducing fasting (apart from insulin glargine) and post-prandial glucose. In addition, dulaglutide therapy had a significant effect on body weight in most trials with mean changes from baseline to primary time point ranging (depending on the characteristics of the population and duration of the observation period) from -0.87kg (Study GBDD, 26 weeks) to -3.03 kg (Study GBCF, 52 weeks). Not unexpectedly, the effect on weight was minimal in patients with long duration of diabetes and on concomitant insulin, but still dulaglutide was superior in weight reduction when compared to insulin and even a small weight loss or even preventing further weight gain in such a population can be important. Of note, most of the observed effects were shown to persist through to the final points of the trials, indicating persistence of the effects. Also, reassuringly, the sensitivity analyses confirmed the findings of the primary analyses. Study data (GBDA, GBDC; DTSQs) also indicated a positive relationship between dulaglutide treatment and patient satisfaction.

In addition, some small but in the right direction effects on systolic blood pressure and lipid parameters were observed, although their clinical significance is uncertain. The subgroup analyses did not identify any particular factor having a negative impact on the efficacy of dulaglutide, including the presence of anti-dulaglutide antibodies, which were detected in only a small number of patients.

Overall, dulaglutide showed a consistent and significant effect on the primary and secondary glycaemic parameters and weight across all main clinical trials, further supported by the findings of the four Phase 2 studies, suggesting that it can be a valuable new agent in the therapy of T2DM. In addition, the once weekly administration can be an attractive feature for many patients and is likely to result in better compliance than other daily injectable products, as also suggested by study GBDA when dulaglutide was compared to exenatide BID.

Uncertainty in the knowledge about the beneficial effects

Although there are no issues with the proposed monotherapy indication, the second line (add-on) indications are very broad. Not all specific combinations of dulaglutide with oral antidiabetics or insulin are supported by specific studies asavailable evidence..

Although it would be unreasonable to expect individual studies for each possible combination the lack of data on

some of them raise some concerns about the generalizability of the findings of the dulaglutide clinical program. For example, there are no data on double therapy in combination with a sulphonylurea or a thiazolidinedione alone, or triple combination with sulphonylurea plus thiazolidinedione. Although these may not be first line combinations, they may be relevant to certain patients. Also the current application does not contain a study investigating dulaglutide in comparison with a SU. An important issue is the lack of efficacy data on the combination of dulaglutide with basal insulin as dulaglutide was only examined (study GBDD) together with prandial insulin (with or without metformin) against a basal+prandial insulin regimen, investigating the place of dulaglutide as basal treatment for glucose control.

Taking into account the totality of the efficacy data and the notable consistency seen across the whole program, considering also the experience so far with other members of the class, there is no reason to believe that dulaglutide would be less efficacious in the combinations under question than in the regimens tested in the clinical trials. However, the lack of efficacy data on certain conditions that dulaglutide is possible to be used in real world, although the extrapolation of the results of the trials seems reasonable, remains an uncertainty. With regard to the reduction in body weight, the clinical relevance of the observed effect size (-0.87 kg to -3.03 kg with dulaglutide 1.5 mg) is unclear.

An additional issue is the minimal or missing information on certain special patient groups such as patients older than 75 years or those with moderate and severe renal insufficiency, patients with hepatic disease or advanced heart failure. There is a lack of robust data to establish the benefits of treatment in these vulnerable groups.

In addition to the above specific issues, there is the wider uncertainly regarding the longer term impact of the therapy on macrovascular complications and whether and to what extent dulaglutide will be able to positively affect the course of the disease. Although, as mentioned above, there is solid evidence of a favourable effect on glycaemic control and other secondary parameters, these remain surrogate measures.

Risks

Unfavourable effects

A reasonably large safety database has provided sufficient information to determine the key characteristics of dulaglutide safety profile, which appears generally consistent with what has previously been observed in this class.

As expected for a GLP-1 receptor agonist, the most common adverse events were gastrointestinal disorders with a higher rate seen with dulaglutide 1.5mg than with the lower 0.75mg dose and nausea, diarrhoea and vomiting being the most commonly experienced adverse events. There were only few deaths in the whole program with no indication of a higher frequency in the dulaglutide groups. Similarly the number of serious adverse events was generally low, with hypoglycaemia consistently reported as the most the common SAE with a slightly higher incidence with dulaglutide 1.5mg. Pneumonia, appendicitis and cholelithiasis were also among the most common although differences between groups were small and conclusions are difficult to draw.

With regard to pancreas there was a small but clear trend for higher enzyme concentrations with dulaglutide compared to placebo but cases of pancreatitis were very rare and the overall incidence was not higher than placebo or sitagliptin. However, a higher rate was observed in the thorough QT study when patients were exposed to doses of 4mg or more, suggesting a potentially small safety margin. Review of thyroid safety data revealed a number of neoplasms but the incidence was similar between dulaglutide, placebo and active comparators. However, there were three cases of thyroid cancer among the dulaglutide treated patients,

although their causal relationship to dulaglutide exposure is uncertain. Otherwise, dulaglutide was not shown to be associated with a higher incidence of serious events, including malignancies compared to placebo or the active comparators. There was also no clear evidence of a detrimental effect on renal or liver function.

In terms of cardiovascular safety, no adverse effect was noted on blood pressure but a dose dependent increase in heart rate was a consistent finding across the whole program. Studies also showed P-R interval prolongation in dulaglutide groups, and there was evidence of higher rate of AV conduction abnormalities, although more serious forms of AV block were very rare. Nevertheless, the overall cardiovascular database, including the findings of a meta-analysis, did not raise any major concerns, with dulaglutide showing an overall lower incidence of MACE than the comparators.

The immunogenic potential of dulaglutide appears to be low and hypersensitivity reactions were rare with no apparent association with the presence of anti-dulaglutide antibodies, which were detected in a small percentage of patients (1.6%). The incidence of injection site reactions with dulaglutide was also low, similar or less than that reported with other agents in this class. Potentially immune-mediated reactions were even less frequent (0.5%) with erythema being the most commonly reported.

A safety issue identified in the dulaglutide pivotal trials was the high incidence of hypoglycaemia observed in certain studies particularly when it was given with glimepiride (plus metformin) and even further with prandial insulin (with or without metformin). However, despite the high rates and although there are some limitations (especially with indirect comparisons based on literature data), overall the submitted evidence suggests that hypoglycaemia with dulaglutide does not appear excessively higher than other relevant therapies for comparable levels of glycaemic control. Data from the newly completed data from GBDE study (dulaglutide vs liraglutide; see above) are consistent with this view.The risk is much higher when dulaglutide is given with insulin or a sulphonylurea and the SmPC includes a warning and recommendations for the need of dose adjustment for those cases which is acceptable. Relevant rates are also reported in section 4.8 of the SmPC.

Uncertainty in the knowledge about the unfavourable effects

As noted above, the safety database was of a reasonable size for this type of medication including a total of 6005 patients with T2DM (with 4006 taking at least one dose of dulaglutide) from the Phase 2 and 3 trials and an additional 680 patients from the clinical pharmacology studies. The overall exposure to dulaglutide, in terms of numbers is considered sufficient to characterise its main safety profile. However, a relatively small number of patients were exposed to the drug for more than 1.5-2 years (≥78 weeks: n= 642; ≥104 weeks: n= 157) and this is a limitation considering that dulaglutide is intended for chronic use.

It is acknowledged that the study population across the main trials comprised a wide range of diabetic patients, but there are areas with little or missing information including, as previously mentioned, patients older than 75 years and other potentially vulnerable special groups such as those with advanced heart failure as well as patients with severe renal insufficiency or with hepatic disease. There was no clear evidence that dulaglutide may adversely affect renal or hepatic function; however, few patients with worse than mild renal disease (and none with severe or end stage renal failure) were examined in the Phase 2 and 3 studies. The same is also true for patients with hepatic disease. Overall, the safety of dulaglutide in the above special groups, particularly in severe renal patients remains uncertain and this is reflected in the product information which advises that dulaglutide is not recommended in such patients.

In addition to the above, although the safety analyses did not identify any specific issue of major concern there are still areas like pancreatic and thyroid safety that are uncertain and remain under monitoring. This is not

specific to dulaglutide but concerns the whole incretin-based class. Based on a recent data review, CHMP considers pancreatic cancer as a potential risk of the whole class of incretin mimetics [Article 5(3) Procedure (EMEA/H/A-5(3)/1369) on pancreatic issues with GLP-1 based therapies]. Therefore, this issue is addressed in the RMP and in the ongoing CV outcome study.

With regard to dulaglutide cardiovascular effects, although as discussed above, the overall data did not identify any particularly new or unexpected issues and the results of the CV meta-analysis were generally reassuring, there are still some uncertainties about specific findings such as the increase in heart rate, the effect on AV conduction and repolarisation that deserve further consideration. Regarding PR interval prolongation, it is uncertain whether more serious effects should be expected if dulaglutide is combined with digoxin or calcium antagonists. In addition, there was an imbalance in the incidence of nonfatal strokes between groups not in favour of dulaglutide; the numbers are small and conclusions are difficult to draw but this is another issue that is monitored. Furthermore, despite the generally encouraging findings of the CV meta-analysis, the long term potential CV benefits and especially risks of dulaglutide are yet to be established as addressed in the ongoing CV outcome trial.

There was an increase in the incidence of certain infectious disorders. The rate for each individual event was small and firm conclusions cannot be drawn. Nevertheless, due to the Fc part of the dulaglutide molecule, a direct effect of dulaglutide on the immune system is theoretically possible. The overall evidence, however, suggests that this is a chance finding.

Benefit-risk balance

Importance of favourable and unfavourable effects

Type 2 diabetes remains one of the leading causes of cardiovascular disease, renal failure, blindness, amputations and hospitalisations and has been associated with a variety of other disorders. Despite recent therapeutic progresses there are areas of unmet need and good glycaemic control, as measured by HbA1c, remains a major focus of therapy aiming at reducing the risk of microvascular and macrovascular complications. In this context, any new therapy that can contribute to these targets can be a valuable asset in the management of the condition.

However, equally important is to ensure that both short and long term safety of the patients is not compromised, and poor tolerability does not affect the patients' quality of life and compliance to a degree that may render the therapy unendurable or ineffective.

These are the main parameters that need to guide the benefit:risk evaluation. For dulaglutide, as discussed in more detail below, there is sufficient evidence to suggest that it is a potent and efficacious antidiabetic agent. However, it is characterised, as the rest of the class, by relatively poor GI tolerability, and there are safety concerns about its administration with certain combinations.

Benefit-risk balance

Based on the current evidence, overall the benefits of dulaglutide outweighs the possible risks in the proposed target population.

Discussion on the benefit-risk assessment

The clinical program has provided sufficient evidence of a significant and clinically relevant effect on the primary and secondary glycaemic and other metabolic parameters suggesting that both 0.75mg and 1.5mg doses of dulaglutide can offer incremental benefits over and above common treatments in the management of a wide range of T2DM patients. Not all potential scenarios were examined in the clinical trials and extrapolations are inevitable but there is no reason to believe, taking also into account the experience with other members of the class, that dulaglutide would perform less well under most possible conditions. Of importance, it appears that in most cases it can do so reasonably safely and without major tolerability issues that could significantly affect the patients' quality of life or compliance. Although still an injectable product, the once weekly administration and the low incidence of injection site reactions are likely to further help to this end.

In terms of safety, there are several uncertainties including the lack of data in certain special groups and the relatively limited duration of exposure that do not permit excluding longer term adverse effects on CV and other systems such as pancreas or thyroid at this stage. Nevertheless, the increasing accumulation of data on GLP-1 agonists and the incretin-based class as a whole, allow a certain amount of confidence in the assessment of the potential risks.

Taking into account all the above, the benefit:risk of dulaglutide under most conditions appears to be favourable. There are still concerns about its use in combination with sulphonylureas or insulin as the risk of hypoglycaemia, sometimes severe, may be high as suggested by the relevant trials. The hazards associated with hypoglycaemia in the T2DM population are well-established and the fact that possibly more vulnerable groups such as very old patients were underrepresented in the studies add to the general uncertainty.

The above points also apply to the monotherapy indication for patients who cannot receive metformin (because of a contraindication or if they cannot tolerate it) with the evidence suggesting that dulaglutide can be a useful alternative. The data indicate that the 0.75mg dose has an overall more favourable benefit:risk profile than the higher 1.5mg dose in this setting and this is the currently recommended posology. Similarly for combination therapies, the lower dose, although less efficacious, may still be useful in certain patients when starting therapy but also for those who in the longer term may not be able to tolerate the higher dose. In this context for dulaglutide as add-on therapy the recommended dose is 1.5mg once weekly but for potentially more vulnerable groups a starting dose with 0.75mg is recommended.

For these reasons, the CHMP requested during the procedure to make the 0.75mg strength formulation available, to which the applicant agreed, thus allowing a greater degree of flexibility to meet the needs of the intended target population. On this basis and in the absence of any major concerns the overall benefits of dulaglutide appear to outweigh the possible risks for the proposed indications.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the

risk-benefit balance of Trulicity in the treatment of type 2 diabetes mellitus is favourable and therefore recommends the granting of the marketing authorisation 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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that dulaglutide is qualified as a new active substance.

CHMP recommendation

Area	Number	Description	Classification*	Due date
Quality	1	*Where previously freeze/thawed drug substance (DS) is used beyond the 24 months' time point, the applicant has agreed to carry out additional tests on the DS and will submit a proposal a suitable testing regimen for this as*	REC	

		recommended by the CHMP.		