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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	125469
Submission Date(s)	September 18, 2013; April 22, 2014
Brand Name	(b) (4)
Generic Name	Dulaglutide [rDNA origin] injection
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OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Elli Lilly
Submission Type	Standard
Formulation; Strength(s)	0.75 mg and 1.5 mg, prefilled syringe or single-use pen
Indication	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) and Division of Pharmacometrics (OCP/DPM) have reviewed BLA 125469 for (b) (4)™ (dulaglutide [rDNA origin] injection) and recommend approval with the following recommendations:

1. OCP recommends approval of both 0.75 mg and 1.5 mg doses. Both 0.75 and 1.5 mg doses had superior efficacy compared to placebo and active comparators in 5 Phase 3 studies. Compared to 0.75 mg, patients on 1.5 mg achieved a greater HbA1c and weight reduction and a higher proportion of patients reached HbA1c targets. Overall safety profile was comparable between two doses, with dose-dependent differences in heart-rate increase (1.9 to 2.7 bpm vs. 3.7 to 4.6 bpm), GI side effects (e.g., 6.0% vs. 12.6% for vomiting), and discontinuations due to GI disorders (1.3% vs. 3.5%) for 0.75 mg vs. 1.5 mg dose, respectively. Although these rates are not unusually high relative to other approved GLP1 analogs, GI tolerability is an issue with this entire class of drugs. Therefore, to maximize patient compliance and to inform physicians about both dose options, we propose following two alternatives for labeling :
   a. Initiate patients at 0.75 mg dose per week. Dose should be increased to 1.5 mg per week after 4 weeks in patients who are able to tolerate the lower dose.

      OR

   b. Initiate patients at 0.75 mg or 1.5 mg dose per week. The 1.5 mg dose is more efficacious than the 0.75 dose; however, the frequency of GI related or other side effects was relatively low for the 0.75 mg dose.

   Note that our recommendation is to consider the 1.5 mg dose based on tolerability, and not necessarily wait for assessment of efficacy. This recommendation is supported by data demonstrating better efficacy for the 1.5 mg dose than the 0.75 mg dose. Therefore, if a patient is able to tolerate the lower dose they should be considered for the higher dose after 4 weeks (i.e., the time by which dulaglutide concentrations will reach steady-state) to offer maximum benefit.
2. OCP concurs with the sponsor's proposal for the 'missed dose' and 'change in weekly dosing schedule', as below:

   "(b) (4) if a dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days remain before the next scheduled dose, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

   (b) (4) the day of weekly administration can be changed if necessary as long as the last dose was administered 3 or more days before."
3. OCP proposes that the dulaglutide should be used with caution in patients with severe renal impairment. Although dulaglutide exposures are not altered in these patients, long-term safety profiles after dulaglutide treatment in these patients is under evaluation. Since patients with severe renal impairment are at high risk of side effects such as acute kidney failure, caution is recommended while using dulaglutide.

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4. No dose adjustment is recommended for other intrinsic (e.g., injection sites, BMI, age or hepatic impairment) and extrinsic (e.g., drug interactions) factors.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor has submitted the BLA 125469 for [redacted] (b) (4) ™ (dulaglutide [rDNA origin] injection) for the indication of an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D).

Dulaglutide is a glucagon-like peptide (GLP-1) receptor agonist. It consists of 2 identical polypeptide chains. Each chain contains a human GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small peptide linker, and 2 chains are linked by 2 disulfide bonds. [redacted] (b) (4) . A total of 5 GLP-1 agonist products are currently available in the world market (see Table 1).

Table 1 List of GLP-1 agonist Products available to the world market

Product name	Active ingredient (No. of amino acid)	Dosing recommendation in labeling	Approval date in US
Byetta	Exenatide (39-amino acid)	• 5 mcg twice daily • Based on clinical response the dose can be increased to 10 mcg twice daily after 1 month of therapy.	4/28/2005
Victoza	Liraglutide (32-amino acid + palmitic acid)	• 0.6 mg once daily • After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.	1/25/2010
Bydureon	Exenatide ER for injectable suspension (39-amino acid)	• 2 mg once weekly	1/27/2012
Tanzeum	Albiglutide (30-amino acid-30-amino acid-albumin)	• 30 mg once weekly • The dosage may be increased to 50 mg once weekly if the glycemic response is inadequate.	4/15/2014
Lyxumia	Lixisenatide (44-amino acid)	• 10 mcg once daily • After 2 weeks, increase the dose to 20 mcg once daily.	• approved in EU • Application was withdrawn in US before FDA's action.

Note: GLP-1-(7-37) or GLP-1-(7-36)NH_2 are known to be active forms.

A total of 30 clinical studies have been conducted for the development of dulaglutide and clinical pharmacology information has been evaluated in 21 studies as follows:

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Based on the 5 Phase 3 studies of 52 to 104 weeks controlled duration, the efficacy of dulaglutide was evaluated as monotherapy and as add-on to multiple different orally administered anti-diabetic drugs or insulin lispro in patients across different stages of T2DM. Dulaglutide was compared to placebo as well as multiple different active comparators, including metformin, sitagliptin, exenatide BID, and insulin glargine. Both the proposed dose of 1.5 mg once weekly and the 0.75 mg dose demonstrated superior efficacy compared to placebo and active comparators. Comparing with the 0.75 mg dose, integrated efficacy analyses demonstrated that 1.5 mg achieved greater HbA1c reduction, a greater proportion of patients reaching HbA1c targets and greater weight reduction.

The overall safety profile was similar between the two doses for the majority of safety measures. A dose-dependent increase in heart rate (range: 2 to 4.6 bpm) was observed with dulaglutide treatment versus placebo in phase-2 study GBDN. The mean increases were greater for the dulaglutide 1.5 mg dose compared with the dulaglutide 0.75 mg dose from week 4 through week 26. The range of distribution of heart rate increases for two groups were highly overlapping. However, there is trend in clinically relevant heart rate increases (heart rate >100 bpm and an increase from baseline ≥15 bpm). The proportion of patients with clinically relevant heart rate increase was low, but numerically higher in patients on 1.5 mg (2.2%) compared to 0.75 mg dose (1.3%) and placebo (0.7%). The 1.5 mg dose was associated with higher risk of GI disorders and discontinuation rate at the beginning of treatment (first 2 weeks). Dose-dependent increases in GI adverse events were most notably nausea (12% for 0.75 to 21% for 1.5 mg) and vomiting (6% for 0.75 and 13% for 1.5 mg). Overall discontinuation rate was low due to GI disorders but was higher in the 1.5 mg dose group (3.5%) compared with the 0.75 mg (1.3%). Dose-dependent increase in pancreatic enzymes was also observed; however in the absence of any other clinical symptoms, these increases may not be clinically relevant.

Pharmacodynamics:

Glycemic control – Dulaglutide lowered fasting glucose on Day 3 (i.e., at the t_{max} for dulaglutide) after the first dose, and glycemic reductions were apparent after 1.5 mg administered every-week (QW) for 6 weeks as measured by reductions in fasting glucose (FPG, -26.6 mg/dL), 2-hour postprandial glucose (-59.5 mg/dL), and postprandial glucose AUC (-197 mg/dL) compared to those of placebo in T2D (Study GBCT). The glycemic reductions were also observed in a placebo controlled dulaglutide monotherapy Phase 3 study GBDC, as follows: the mean postprandial glucose (PPG, self-monitored) and FPG reductions from baseline were -43.38 mg/dL and -28.98 mg/dL, respectively, compared to reductions of -41.40 and -26.28 mg/dL, respectively for metformin, the active comparator in this study.

Insulin and Glucagon Secretion – Dulaglutide stimulates insulin secretion and reduces glucagon secretion. Insulin and C-peptide area under the curves (AUCs) were increased by 211 and 540 pmol*h/L, respectively after 1.5 mg QW for 6 weeks in T2D (Study GBCT). Glucose-dependent increase in insulin secretion rate was shown in a meal challenge study, performed as a subset of a Phase 3 study (Study GBDC). Fasting glucagon and postprandial glucagon AUC (0-3 hours) reductions from baseline were observed with magnitudes of -2.05 pmol/L and -5.91 pmol*h/L, respectively, in this study.

Gastric Emptying – In the dulaglutide program, gastric emptying was assessed in a scintigraphy study and 2 acetaminophen pharmacokinetics (PK) studies. In the scintigraphy study, gastric emptying time was measured from the gastric emptying rates of a radiolabeled meal in the presence

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and absence of dulaglutide. One of the primary derived parameters was the time required for 50% of total administered radio-activity to empty from the stomach (t_{50}), which is regarded as a direct measure of gastric emptying time. Dulaglutide delayed the gastric emptying time by about 2 hours in T2D after the first dulaglutide dose based on the results from a scintigraphy study. The delay following administration of 2nd, 3rd, and 4th dose of 1.5 mg was 88%, 87%, and 84% of the delay after the first dose, respectively.

Acetaminophen PK is regarded as the surrogate measure for the gastric emptying time. Dulaglutide delayed acetaminophen t_{max} by 1 hour in healthy volunteers following administration of acetaminophen on day 3 post 1 mg dulaglutide administration (i.e., administration of acetaminophen at approximately t_{max} for dulaglutide). However, the acetaminophen t_{max} delay was negligible (i.e., 0.016 hour) on Day 3 after 4th dulaglutide dose.

Reasons for the difference in the magnitude of delay in gastric emptying time between the scintigraphy and acetaminophen studies are not clearly understood as major study designs such as the primary endpoints and subject types were significantly different between studies. However, results from acetaminophen studies, which measures change in systemic exposures, seem more relevant to extrapolate the effect of dulaglutide on other drugs' systemic exposures.

Cardiac Electorphysiology (QTc) - Dulaglutide did not show significant effect on the QT/QTc prolongation at supratherapeutic doses of 4 mg and 7 mg. In addition, there was no significant positive correlation between dulaglutide plasma concentrations and change from the baseline in QTc interval.

Immunogenicity - There was no treatment-emergent dulaglutide anti-drug antibodies (ADA) in the clinical pharmacology studies, defined as a 4-fold increase compared with the baseline. 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). According to the preliminary analysis, there was no difference in dulaglutide plasma concentrations between negative and positive ADA tiers.

Pharmacokinetics;

Absorption, Distribution and Elimination

Absolute bioavailability (BA) was 44.3% in healthy subjects. The time to reach maximum concentration (t_{max}) was 48 hours. There was no significant difference in dulaglutide PK after SC administration to injection sites of abdomen, arm, and thigh. There was no significant difference in PK between healthy volunteers and T2D. Accumulation was approximately 1.6-fold after multiple dose administration. Dulaglutide PK was slightly less proportional to doses with the slopes for area under concentration curve (AUC) and maximum concentration (C_{max}) of 0.9 and 0.8, respectively, in a power model (PK parameter = a * Dose ^{slope}), following multiple doses in T2D. The mean volume of distribution (5.3 L) is close to the typical adult blood volume. Dulaglutide is expected to follow the general protein catabolic pathways. Mean terminal half-life ($t_{1/2}$) was 4.5 days. Dulaglutide PK characteristics, such as a relatively long $t_{1/2}$ (i.e., 4.5 days), t_{max} of 2 days and accumulation by 1.6-fold, support the proposed once weekly dosing schedule.

Effect of Intrinsic and Extrinsic Factors

No dose adjustment is recommended for dulaglutide based on tested intrinsic and extrinsic factors because dulaglutide exposure changes with these factors were not clinically relevant (see Figure 1

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and Figure 2). Dulaglutide did not significantly affect PK of digoxin, lisinopril, metformin, oral contraceptives, sitagliptin, and warfarin. Dulaglutide decreased atorvastatin AUC and C_{max} by 21 and 70%, respectively. However, atorvastatin dose adjustment may not be needed because no dose adjustment is recommended in the atorvastatin prescribing information for a mean change in atorvastatin exposure of up to 41% and clinical relevance of atorvastatin C_{max} decrease is not known. Dulaglutide delayed t_{max} of most co-administered drugs because of delay in gastric emptying time, which is a GLP-1 agonist class effect. However, delay in t_{max} of co-administered drugs may not matter for most drugs after steady-state concentrations are reached. Plasma concentrations of drugs for which delay in t_{max} may have clinical relevance, such as drugs with narrow therapeutic index (e.g., digoxin, warfarin), are usually monitored until a stable clinical effect is attained.

Bridging Between Single-pen and Prefilled Syringe

The sponsor proposes two delivery devices; the prefilled syringe (PFS), which has been evaluated in Phase 3 trials with the proposed commercial formulation, and a single-use pen, a new delivery device. The pivotal comparability study demonstrates that dulaglutide PK using the single-pen is comparable to that of PFS. Office of Scientific Investigation (OSI) inspection for this comparability study is pending.

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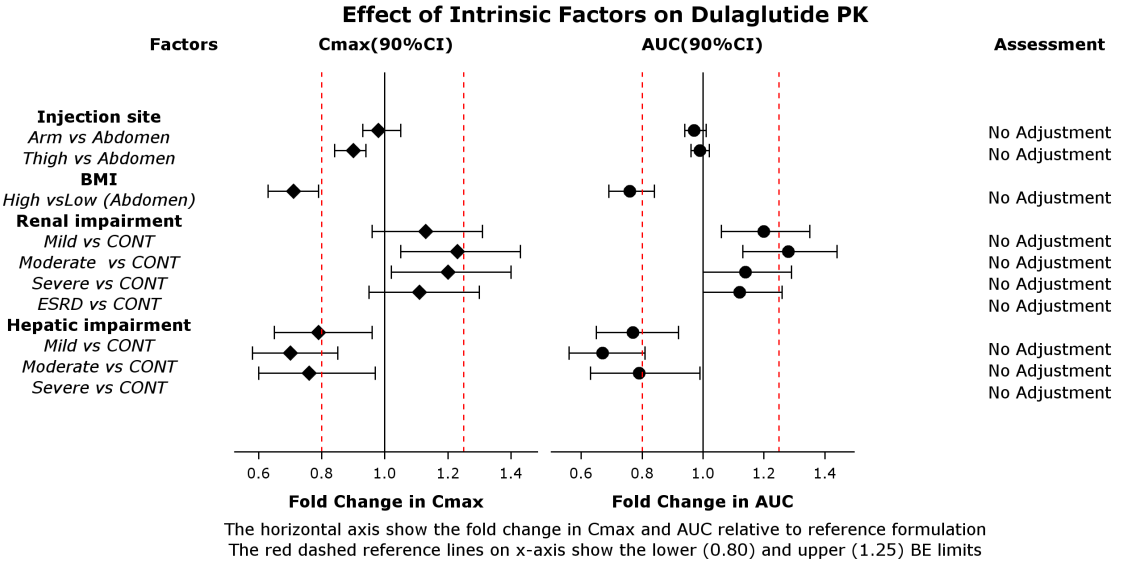

Figure 1 **Effect of intrinsic factors on dulaglutide PK**

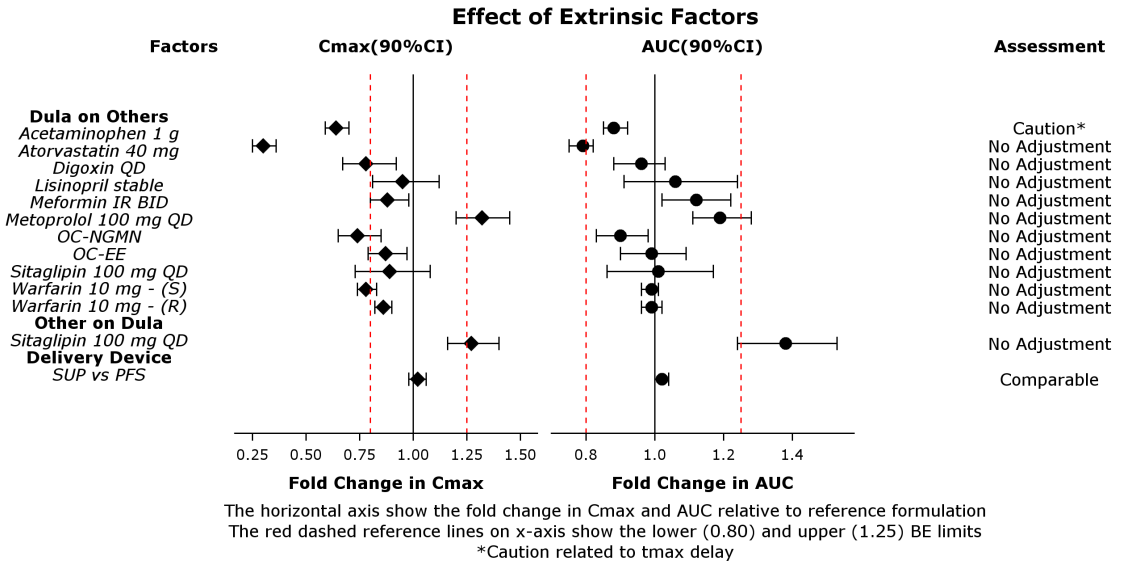

Figure 2 **Effect of extrinsic factors including deliver device comparability**

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2 Question Based Review

2.1 General attributes

2.1.1 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

Drug Substance:

Dulaglutide has been developed as a long acting GLP-1 receptor agonist and it is composed of 2 identical chains. (b) (4) The sponsor indicates that the GLP-1 analog portion of dulaglutide is approximately 90% homologous to native human GLP-1 (7-37) (b) (4)

(b) (4)

Molecular weight: 62,561 Da (b) (4)

Figure 3 A schematic diagram of dulaglutide

Drug Product:

Dulaglutide formulations used in the pivotal clinical trials were either 0.75 mg/0.5 mL or 1.5 mg/0.5 mL. The formulations were available as a semi-finished syringe (SFS), which was to be assembled into either a single-use pen (SUP) or a prefilled syringe (PFS) (see Figure 4). The components and composition of dulaglutide formulations are summarized in Table 2.

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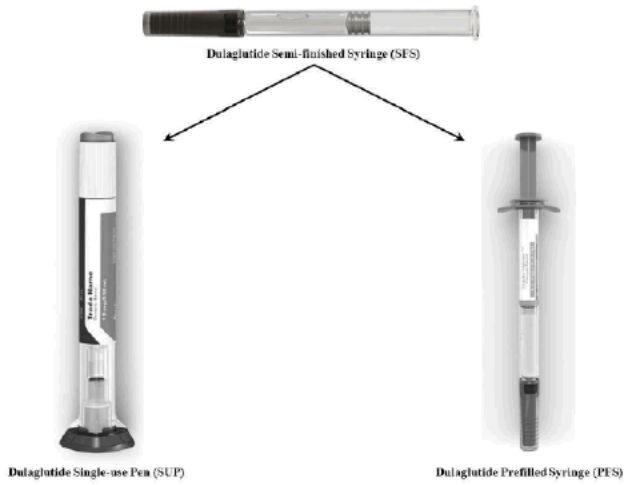

Figure 4 Schematic summary of semi-finished syringe (SFS), single-use pen (SUP), and prefilled syringe (PFS)

Table 2 Components and Composition of Dulaglutide Formulations

Ingredient	Quantity (mg) per Syringe		Function	Reference to Standards
	Low Strength	High Strength		
Active Ingredient				
Dulaglutide	0.75	1.5	Active Ingredient	Internal Standard
Other Ingredients				
Trisodium Citrate Dihydrate	1.37	1.37	(b) (4)	USP, Ph.Eur., JP
Citric Acid Anhydrous	0.07	0.07		USP, Ph.Eur., JP
Mannitol	23.2	23.2		USP, Ph.Eur., JP
Polysorbate 80	0.10	0.10		NF, Ph.Eur., JP
Water for Injection	(b) (4)			USP, Ph.Eur., JP

2.1.2 *What is the mechanism of action and therapeutic indication?*

As the GLP-1 agonist, dulaglutide is expected to activate the GLP-1 receptors in pancreatic beta cell membrane and control the glucose excursion following meals through concerted actions such as stimulation of insulin secretion, inhibition of glucagon secretion, and delay of gastric emptying. Dulaglutide potency seems to be similar to that of native GLP-1 according to *in vitro* study results (see the non-clinical review for details)

2.1.3 *What are the proposed dosage and route of administration?*

Dulaglutide 1.5 mg in 0.5 mL solution is available as SFS, and the SFS is to be assembled into SUP or PFS (see Figure 4) before it is subcutaneously administered once weekly.

The sponsor's proposed labeling for the dosage and administration is as follows:

(b) (4)

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(b) (4)

2.1.4 *Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?*

The OSI inspection was requested for the pivotal comparability study (Study GBDT) for SUP, a new additional commercial delivery device, referencing PFS, which has been evaluated in Phase 3 studies. The report of the OSI inspection is pending at the time of writing this review.

2.2 General clinical pharmacology

2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

It appears that dulaglutide PK has been adequately characterized (see Table 3) and reasonably streamlined supporting the proposed once weekly dosing. A few highlights are as follows:

- Systemic disposition data obtained following intravenous (IV) administration (Study GBDR) were supplemental data for understanding on potential variability from the absorption processes compared to that in the systemic PK parameters (e.g., CL, Vd) following SC administration, especially where typical data such as the mass balance study or metabolic clearance are not available. In addition, the available systemic disposition data in combination with PK from a different route (i.e., intramuscular (IM)) or injection sites indicate the low variability potential in absorption process. Overall, the above mentioned supplemental data support that dulaglutide PK characteristics after SC administration are adequate information.
- The dulaglutide PK data were found to be adequate information and supports conducting a meta-analysis or population analysis. For example, modeling and simulation was the key component of an adaptive, dose-finding, seamless Phase 2/3 trial.
- Study design for drug interaction with a long acting drug or formulation requires special attention on the timing for co-administration of drugs because the magnitude of drug interaction can be sensitive to the time window with maximum exposure between drugs/formulations. Overall time of administration in drug interaction studies reasonably coincide with the t_{max} of dulaglutide.
- Overall, clinical studies were conducted with once weekly administration which is adequate based on the dulaglutide PK data such as half-life (4.7 days), t_{max} (48 hours) and clearance (0.107 L/hr) as reported in section 2.4.

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Table 3 Overview of dulaglutide clinical development programs

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.

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2.3 Exposure-Response

1.1.1 Does the efficacy (HbA1c and body weight reduction) and safety (HR increase and GI tolerability) profile support the proposed dose of 1.5 mg once weekly dosing regimen?

Yes. The proposed dose of dulaglutide 1.5 mg once weekly is supported by the efficacy and safety profiles. Both the 1.5 mg and 0.75 mg dose demonstrated superior efficacy compared to placebo and active comparators, with 1.5 mg being numerically better in efficacy compared to 0.75 mg dose. However, sponsor proposes to include only 1.5 mg dose in the label. It is important to note that the data indicates that 1.5 mg is associated with higher risk of GI disorders and discontinuation rate at the beginning of treatment (first 2 weeks). Furthermore, there is trend in clinically relevant heart rate increases (heart rate >100 bpm and an increase from baseline ≥15 bpm). The proportion of patients with clinically relevant heart rate increase was low, but numerically higher in patients on 1.5 mg compared to 0.75 mg dose with 2.2, 1.3 and 0.7% for placebo, 0.75 and 1.5 mg dose, respectively. Considering the totality of evidence, the reviewer recommends approval for both doses and presents the following two options for the dosage and administration section in the label. The labeling for the dosage and administration section will be finalized after discussion with the clinical review team:

- 0.75 mg as the starting dose which can be titrated to 1.5 mg after 4 weeks based on GI tolerability.

  OR
- Option of starting with either 0.75 or 1.5 mg dulaglutide with adequate language indicating that both doses are efficacious with a description stating that the lower dose offers a better GI tolerability profile and causes lower incidences of clinically relevant heart rate increases (cross reference to section 14 of the label). This will allow physicians to have option of starting at either 0.75 or 1.5 mg after considering benefit-risk profile of dulaglutide.

Note that we are not recommending a dose-titration based on efficacy, but only safety. Data clearly demonstrates that 1.5 mg dose is more efficacious than 0.75 mg. Therefore, if a patient is able to tolerate the lower dose they should be up-titrated to the higher dose to offer maximum benefit. The time point of 4 weeks is recommended for titration because the dulaglutide concentrations will reach steady-state by this time and simulations show that GI related side effects will be minimal with titration after this time period (simulations are shown in the end of this response).

Rationale for selecting 0.75 and 1.5 mg weekly dose for registration trials

The dose-finding stage of Study GBCF demonstrated that the dulaglutide 1.5 mg dose had optimal clinical utility (a multifactorial index defined by Hb1Ac, fasting serum glucose, body weight, sitting Pulse Rate, and blood pressure) and therefore was further evaluated in Phase 3 studies (**Table 4**). Based on FDA recommendation, the 0.75 mg dose was also investigated as a contingency, should the 1.5 mg dose have an unforeseen safety signal.

The phase 2 dose-response in efficacy and safety was also supported by the exposure-response relationships which indicated that higher exposure results in larger reduction in HbA1c, fasting plasma glucose, body weight and increase in heart rate (Figure 50,

and **Figure 7**).

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Table 4. Dose of 1.5 mg weekly was identified as the optimal dose based on both efficacy and safety measures in the dose-finding stage of study GBCF

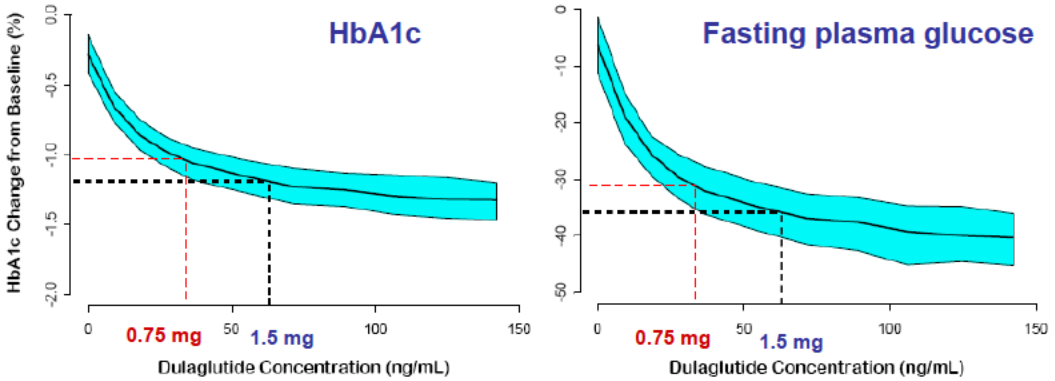
Variable[b] (Units)	Mean (Standard Deviation)[a] Change from Baseline								
	PL/Sit (N=38)	Sit (N=42)	Dula_0.25 (N=24)	Dula_0.5 (N=25)	Dula_0.75 (N=21)	Dula_1.0 (N=10)	Dula_1.5 (N=25)	Dula_2.0 (N=30)	Dula_3.0 (N=15)
HbA1c (%)	-0.06 (0.64)	-0.76 (0.86)	-0.70 (0.49)	-0.94 (0.65)	-1.02 (0.99)	-0.98 (0.47)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

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.

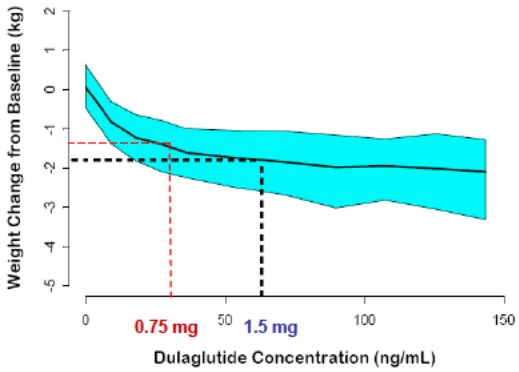
[b] HbA1c, body weight, pulse rate, and DBP were components of the clinical utility index used in the dose selection algorithm based on non-validated data collected up to Decision Point.

(*Source: Sponsor's Clinical Study Report for Trial GBCF, Table GBCF.11.3.)*



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: Sponsor's Clinical Pharmacology Review, Figure 2.7.2.21.)

Figure 5. Exposure-response relationships for change from baseline in HbA1c and fasting plasma glucose at 52 weeks



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: Sponsor's Clinical Pharmacology Review, Figure 2.7.2.27.)

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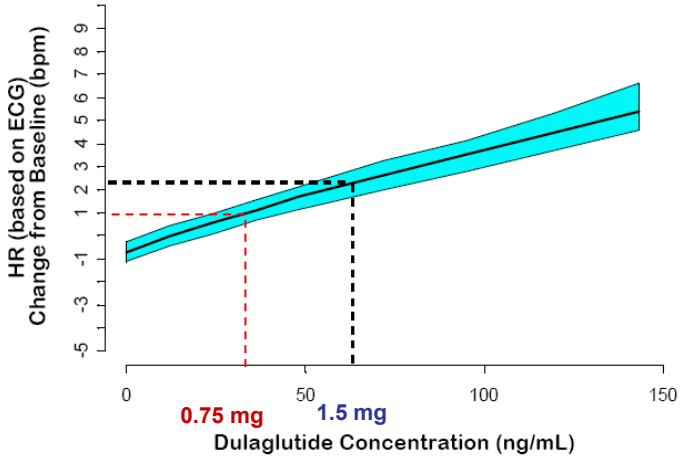
Figure 6. Exposure-response relationships for change from baseline in body weight at 52 weeks



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: Sponsor's Clinical Pharmacology Review, Figure 2.7.2.30.)

Figure 7. Exposure-response relationships for change from baseline in heart rate at 52 weeks

Efficacy Considerations

Based on the 5 Phase 3 studies of 52 to 104 weeks controlled duration, the efficacy of dulaglutide was evaluated as monotherapy and as add-on to multiple different OAMs (Oral Anti-hyperglycemic Medication) and insulin lispro in patients across different stages of T2DM. Dulaglutide was compared to placebo as well as multiple different active comparators, including metformin, sitagliptin, exenatide BID, and insulin glargine.

Both dulaglutide 0.75 and 1.5 mg consistently demonstrated superior efficacy, as measured by change in HbA1c, to placebo and each active comparator evaluated (**Figure 8)**. In addition, in all 5 Phase 3 studies, dulaglutide 1.5 mg resulted in weight reduction from baseline that was sustained through the final time point (**Figure 9**). Dulaglutide 0.75 mg was superior to placebo and the active comparator in 4 of the 5 studies and noninferior to insulin glargine in 1 study, as measured by HbA1c. In 3 of the 5 Phase 3 studies, dulaglutide 0.75 mg was associated with weight reduction over the duration of the studies.

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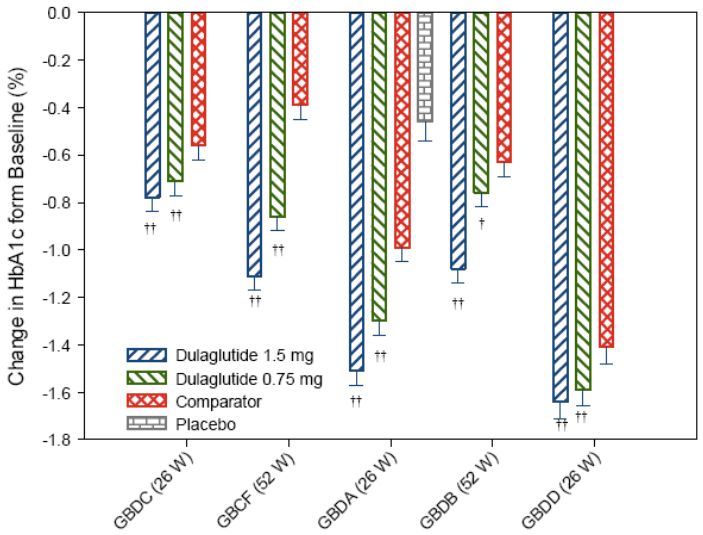
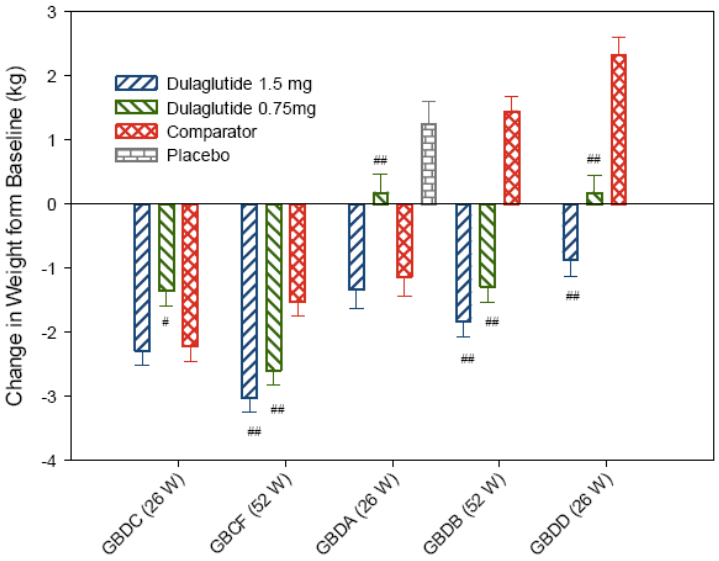


Abbreviations: BID = twice daily injection; HbA1c = glycosylated hemoglobin A1c; SE = standard error; W=weeks. †multiplicity adjusted 1-sided p-value <.025, for noninferiority, ††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to comparator (GBDC=metformin; GBCF=-sitagliptin; GBDA=exenatide BID; GBDB=insulin glargine; GBDD=insulin glargine), assessed only for HbA1c. *(Source: Sponsor's Clinical Review, Figure 2.5.4.1.)*

Figure 8. Mean change in HbA1c (SE) from baseline at primary efficacy time point, dulaglutide 1.5 mg, dulaglutide 0.75 mg, and active comparator

In addition to the Hb1Ac, other efficacy endpoints were also evaluated, such as reduction in fasting plasma glucose, and proportion of patients reaching HbA1c Targets of <7.0% and ≤6.5%, and the results was quite consistent, with the 1.5 mg dose robustly demonstrating superior efficacy compared to placebo and each active comparator evaluated, and also had numerically better efficacy compared to the lower dose of 0.75 mg.



Abbreviations: BID = twice daily injection; SE = standard error; W=weeks. #p<.05, ##p<.001 dulaglutide treatment group compared to active comparator (GBDC=metformin; GBCF=-sitagliptin; GBDA=exenatide BID; GBDB=insulin glargine; GBDD=insulin glargine). *(Source: Sponsor's Clinical Review, Figure 2.5.4.2.)*

Figure 9. Mean change in body weight (SE) from baseline at primary time point, dulaglutide1.5 mg, dulaglutide 0.75 mg, and active comparator

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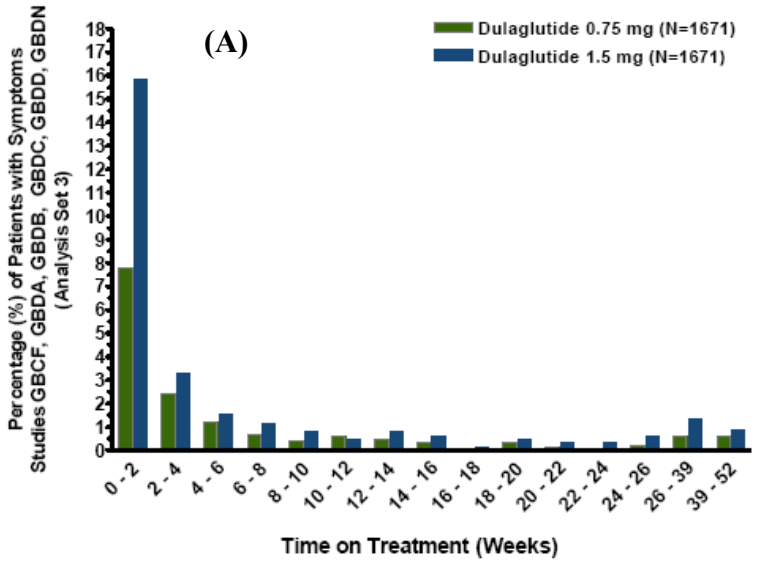
Safety Considerations

Overall the safety profile with dulaglutide is consistent with other marketed GLP-1 receptor agonists. The most commonly reported adverse events are GI related and dose-dependent, most notably nausea and vomiting **(Table 5)**. The onset of nausea and vomiting usually occurs early after drug initiation (the first 2 weeks of exposure) and declines quickly (by week 6 of treatment). As shown in **Figure 10**, the onset (A) and proportion of patients experiencing nausea (B) were also dose-dependent, peaked in the first 2 weeks and declined after. In addition, the overall discontinuation rate due to GI disorders was higher in the 1.5 mg dose group (3.5%) compared with the 0.75 mg (1.3%).

Table 5. Dose-dependant GI adverse events occurring in placebo-controlled studies with 0.75 mg and 1.5 mg dulaglutide (safety population AS1, studies GBCF, GBDA, GBDN)

	Through 26 Weeks of Planned Treatment Period[a]			
System Organ Class Preferred Term	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)**
Gastrointestinal disorders	121 (21.3)	264 (31.6)	342 (41.0)	606 (36.3)
Nausea	30 (5.3)	104 (12.4)	176 (21.1)	280 (16.8)
Diarrhoea	38 (6.7)	74 (8.9)	105 (12.6)	179 (10.7)
Vomiting	13 (2.3)	50 (6.0)	105 (12.6)	155 (9.3)
Dyspepsia	13 (2.3)	34 (4.1)	48 (5.8)	82 (4.9)

(Source: Sponsor's Summary of Clinical Safety, Table 2.7.4.11.)



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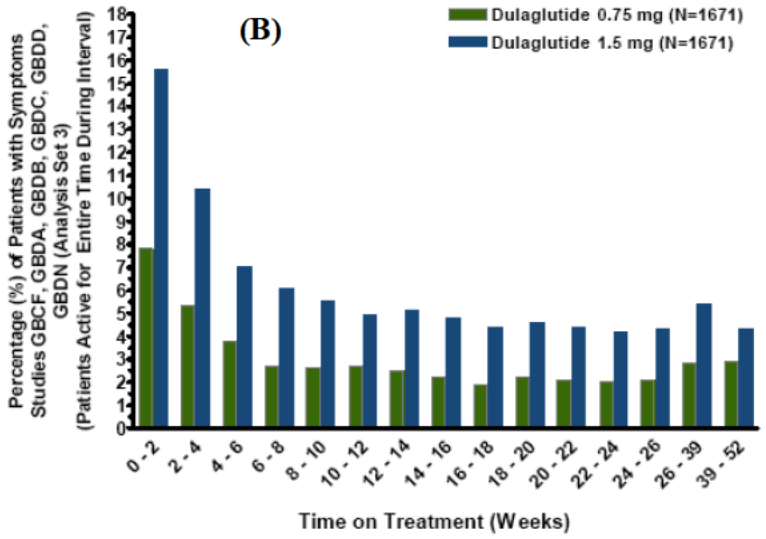

Abbreviations: N = number of patients in specified treatment group of the analysis set.
Specific nausea symptom preferred terms: nausea, procedural nausea.
(Source: Sponsor's Summary of Clinical Safety, Figure 2.7.4.6, Figure 2.7.4.7.)

Figure 10. (A) Onset of specific nausea symptoms (B) Prevalence of specific nausea symptoms in patients active for the entire time during discrete interval

There was a dose-dependent increase in heart rate (2 to 4.6 bpm) with dulaglutide treatment versus placebo in dedicated phase 2 study GBDN for cardiovascular safety (**Figure 7**). These mean increases were greater for 1.5 mg compared with 0.75 mg from week 4 through week 26. However, the ranges of distribution for two groups were highly overlapping, which is consistent with the findings from the phase 3 studies.

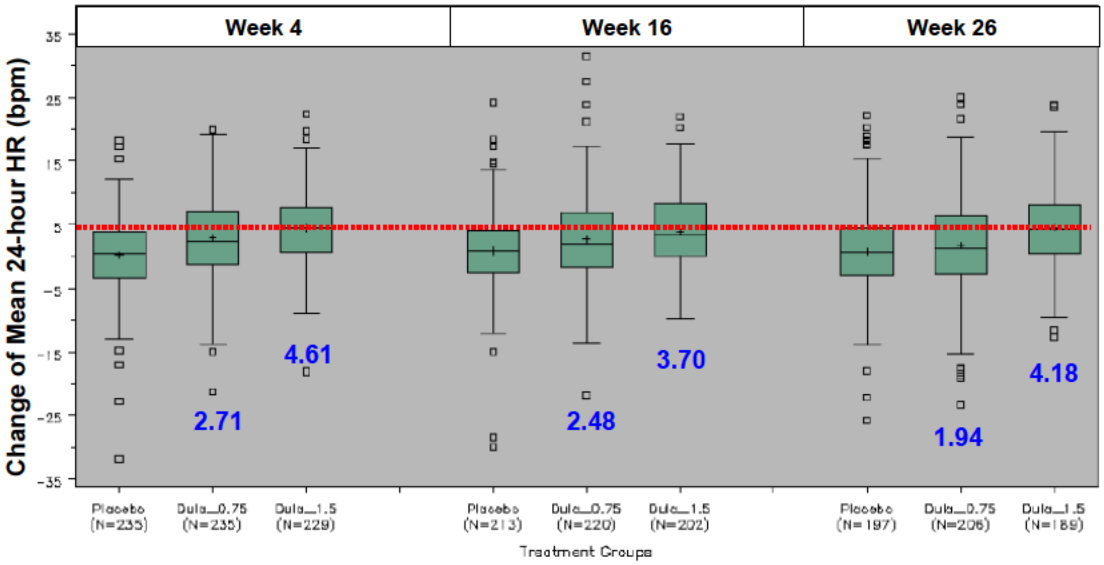

Figure 11. Mean increase from baseline in 24-hour heart rate (bpm) of dulaglutide 1.5 mg, dulaglutide 0.75 mg, and placebo at week4, 16 and 26 (study GBDN)

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Categorical threshold analyses for high heart rate were performed on pooled safety population (studies GBCF, GBDA, GBDN) based on the definition of heart rate >100 bpm and an increase from baseline ≥15 bpm. This definition of clinically relevant heart rate increase was decided after discussions with the clinical reviewer. The overall incidence of treatment-emergent clinically relevant heart rate increase was low, but numerically higher in patients from the 1.5 mg group (2.2%) than 0.75 mg (1.3%) and placebo (0.7%).

An elevation in pancreatic enzymes was also observed and generally higher for dulaglutide 1.5 mg than 0.75 mg, based on an integrated analysis from multiple studies (GBCF, GBDA, GBDB, GBDC, GBDD, GBDN). For lipase, the mean increase from baseline ranged from approximately 11-17% with 0.75 mg and 16-20% with 1.5 mg over time. The mean increase for pancreatic amylase ranged from approximately 14-17% with 0.75 mg and 18-21% with 1.5 mg. For total amylase, the mean increase ranged from approximately 8-11% with 0.75 mg and 10-13% with 1.5 mg.

Given the observed dose-response in AEs, along with previous experience of titration dosing for other approved GLP-1 analogues, implementing a dose titration strategy would be expected to decrease these symptoms and improve overall patient compliance.

Phase 2 Study to evaluate the effect of dose titration on GI tolerability

The effect of dose titration on the incidence of GI events was evaluated in a phase 2 study GBCJ in obese and overweight patients. Patients were assigned to 1 of 4 treatment sequences (1 placebo sequence and 3 dulaglutide sequences); they received the first dose weekly for 4 weeks and a second dose weekly for the following 12 weeks. The sequences were as follows: placebo to placebo; dulaglutide 0.5 mg to 1.0 mg; dulaglutide 1.0 mg to 1.0 mg; and dulaglutide 1.0 mg to 2.0 mg. While the titration was not studied at the proposed dose level, starting at 0.5 mg and escalating to the 1 mg doses after 4 weeks did reduce the incidence of nausea by half at week 4 (**Table 6**Table 6. Incidence of nausea and vomiting, and change from baseline in heart rate following 4 treatments (study GBCJ)).

Table 6. Incidence of nausea and vomiting, and change from baseline in heart rate following 4 treatments (study GBCJ)

Dose	Change from baseline Heart Rate (bpm)			Nausea (%)				Vomiting (%)			
	Week			Week				Week			
	4	8	16	4	8	12	16	4	8	12	16
Placebo	-1.66	-1.75	-0.89	3	4.5	3	0	0	0	1.5	1.5
0.5/1.0 mg	0.95	4.18	5.04	6.1	7.6	9.1	4.5	3	1.5	3	0
1.0/1.0 mg	5.19	3.44	3.4	12.3	9.2	7.7	7.7	1.5	0	0	0
1.0/2.0 mg	3.04	5.43	4.98	9.2	9.2	4.6	6.2	4.6	4.6	3.1	4.6

In addition, simulations were conducted based on exposure-response models for GI events to determine if patients would benefit by using dose titration. The simulated probability of nausea and vomiting following different titration regimens (initiate at 0.75 mg and continue once weekly for 1 to 4 weeks before starting 1.5 mg doses versus treatment initiate with the 1.5 mg dose) is shown in

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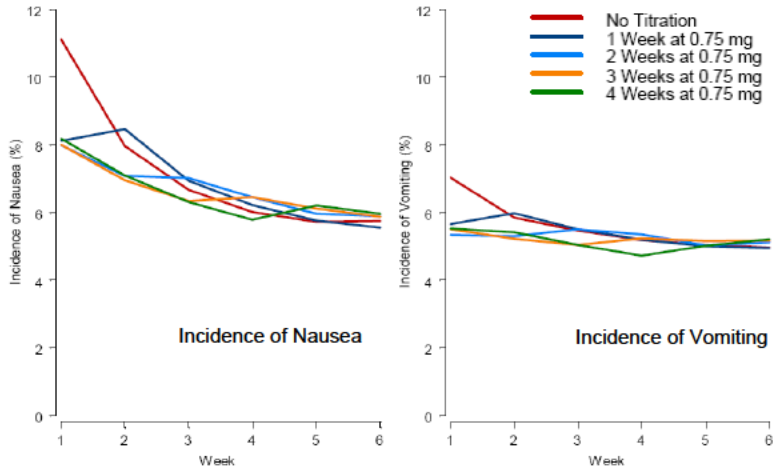
Figure 12. Compared to the titration regimens, starting with 1.5 mg resulted in an increased incidence of nausea (11%) and vomiting (7%) per week after the first dose. Initiating with 0.75 mg and continuing for 4 weeks is associated with lowest rates of initial GI symptoms.



(Source: Sponsor's Summary of Clinical Safety, Figure 2.7.4.8.)

Figure 12. Model-estimated incidence of nausea (left) and vomiting (right) per week for 1.5 mg dulaglutide with no titration and after titrating with 0.75 mg for 1, 2, 3 and 4 weeks

2.3.1 *Does this drug prolong the QT or QTc interval?*

The effect of dulaglutide on QT interval was assessed in a single-blind, randomized, placebo-, and positive-controlled design for 4 mg and 7 mg doses. It was concluded that there was no significant effect of dulaglutide on QT prolongation (see Table 7). There was no significant positive correlation between dulaglutide plasma concentrations and change from the baseline in QTc interval (see Figure 13). Please see the review by QT IRT under IND 70930 dated September 14, 2009 for more details.

Table 7 Statistical Comparison of Mean Changes from Control in QTc Intervals Between 7 mg Dulaglutide and Placebo from Study H9X- MC-GBCC

Parameter (ms)	Time (h)	Least squares mean change from control (90% CI) 7 mg LY2189265 (N=53)	Placebo (N=109)	Least squares mean difference (90% CI) LY2189265 - Placebo
Model based QTc[a]	24	-7.3 (-9.5, -5.2)	-5.5 (-6.9, -4.2)	-1.8 (-4.2, 0.6)
	48	-5.8 (-7.8, -3.8)[c]	0.9 (-0.5, 2.2)	-6.6 (-8.9, -4.3)
	72	-4.9 (-6.9, -3.0)[c]	1.1 (-0.2, 2.4)	-6.0 (-8.3, -3.7)
QTcF[b]	24	-7.1 (-9.0, -5.1)	-5.8 (-7.1, -4.4)	-1.3 (-3.6, 1.0)
	48	-6.3 (-8.3, -4.4)[c]	0.7 (-0.7, 2.0)	-7.0 (-9.3, -4.7)
	72	-5.2 (-7.2, -3.3)[c]	1.1 (-0.3, 2.4)	-6.3 (-8.6, -4.0)
QTcI[b]	24	-11.7 (-13.8, -9.7)	-6.0 (-7.5, -4.6)	-5.7 (-8.1, -3.3)
	48	-8.3 (-10.3, -6.2)[c]	0.0 (-1.4, 1.5)	-8.3 (-10.7, -5.9)
	72	-6.8 (-8.9, -4.8)[c]	0.2 (-1.2, 1.7)	-7.1 (-9.5, -4.7)
QTcP[b]	24	-9.3 (-11.2, -7.4)	-6.2 (-7.6, -4.8)	-3.1 (-5.4, -0.8)
	48	-7.3 (-9.3, -5.4)[c]	0.4 (-1.0, 1.8)	-7.8 (-10.0, -5.5)
	72	-6.0 (-7.9, -4.0)[c]	0.9 (-0.5, 2.2)	-6.9 (-9.2, -4.6)

Control = Mean of the predose values for Day -1 and Day 1 of the relevant period.
Abbreviations: CI = confidence interval; N = number of subjects; QTcF = Fridericia QT correction; QTcI = individual QT correction; QTcP = population QT correction.

[a] Model: Change from control in QTc Interval = Change from control in RR + Treatment + Period + Sequence + Timepoint + Treatment*Timepoint + Subject + Subject*Treatment + Subject*Timepoint + Random Error. Least squares means are estimated at the change from control in RR=0 at each timepoint for model based correction.

[b] Model: Change from control in QTcF, QTcI or QTcP Interval = Treatment + Period + Sequence + Timepoint + Treatment*Timepoint + Subject + Subject*Treatment + Subject*Timepoint + Random Error.

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[c] N=52

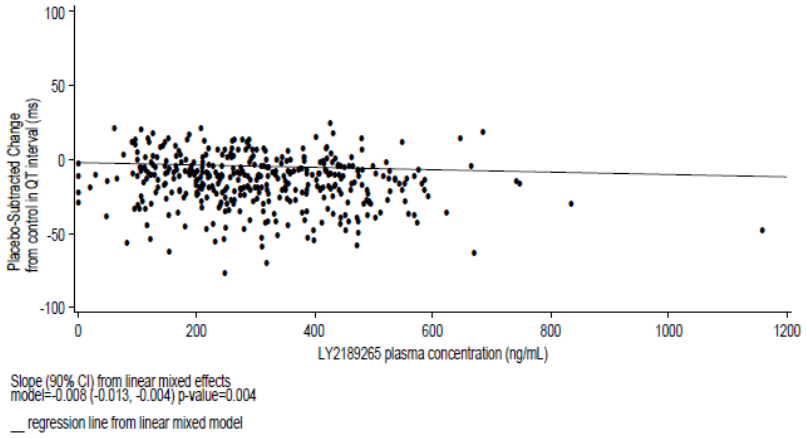

Figure 13 **Scatterplot of placebo-subtracted changes from control in model based QTc interval versus plasma concentrations of dulaglutide following single doses of 4 and 7 mg dulaglutide – Study GBCC.**

2.4 PK Characteristics of Dulaglutide

2.4.1 *What are the single and multiple dose PK characteristics of the drug?*

Single Dose PK:

Dulaglutide PK was characterized after a single ascending dose (SAD) in the range of 0.1 to 12 mg in healthy volunteers (HV, n=22) (Study GBCA). Doses up to 6 mg were tolerated but all subjects in 12 mg dose group experienced vomiting. The overall t_{max} and $t_{1/2}$ were approximately 48 hours and 3.7 days, respectively (see Appendix 4.1.1 for study design and detail of PK parameters). Dulaglutide PK was apparently proportional to single ascending doses in a power model (PK parameter = a * Dose ^{slope}) though proportionality was not concluded. (see Table 8).

Dulaglutide PK was also characterized after a single ascending dose (SAD) in the range of 0.3 to 6 mg in Japanese T2D (n=30, Study GBCB). Doses up to 6 mg were tolerated. The overall t_{max} and $t_{1/2}$ were approximately 48 hours and 3.7 days, respectively (see Appendix 4.1.2 for study design and detail PK parameters). Dulaglutide PK was slightly less than proportional to single ascending doses in the power model (see Table 8). The $AUC_{0\text{-}168}$ was 67% of $AUC_{0\text{-}\infty}$. Therefore, $AUC_{0\text{-}\infty}$ should be the primary parameter for any AUC based analysis unless $AUC_{0\text{-}last}$ is appropriate such as AUC at steady-state.

Table 8 Statistical Results for Dose Proportionality following Single Doses

	PK Parameter (unit)	Power Model Equation	Ratio of Dose Normalized Geometric Mean and 90% C.I.	Increase per doubling the dose and 90% C.I.
HV	**C_{max} (ng/mL)**	**64.7*Dose^0.9**	**0.80 (0.63, 1.02)**	**1.88 (1.76, 2.01)**
	AUC(0-inf) (ng*h/mL)	**10908*Dose^0.9**	**0.74 (0.63, 0.88)**	**1.84 (1.76, 1.93)**
Japanese T2D	**C_{max} (ng/mL)**	**70.6*Dose^0.7**	**0.36 (0.25, 0.51)**	**1.68 (1.58, 1.79)**
	AUC(0-inf) (ng*h/mL)	**15396.5*Dose^0.7**	**0.26 (0.12, 0.56)**	**1.59 (1.40, 1.81)**

Abbreviation: C.I.=Confidence Interval

Proportionality was concluded over the dose range if the 90% CI for the ratio of dose normalized geometric means was entirely contained within (0.7, 1.43). If the 90% CI was completely outside of this interval, 'Not proportional' was concluded. In other cases, the result was 'Inconclusive'.

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Multiple Dose PK:

Dulaglutide PK was characterized following 0.05 to 8 mg once weekly (QW) for 5 weeks in T2D (n=28, Study GBCD). Doses up to 8 mg were tolerated. The overall t_{max} and $t_{1/2}$ were 48 hours and 4.0 days, respectively, at Week 5 (see Appendix 4.1.3 for study design and detail PK parameters). Accumulation index (AI, $AUC_{0\text{-}168h,\ Week5}$ / $AUC_{0\text{-}168h,\ Week1}$) was 1.43. Dulaglutide PK was apparently proportional to multiple ascending dose in the power model though proportionality was not concluded because of wide 90% CI for the slopes. (see Table 9).

Table 9 Statistical Results for Dose Proportionality following Single Doses

	PK Parameter (unit)	Power Model Equation	Ratio of Dose Normalized Geometric Mean and 90% C.I.	Increase per doubling the dose and 90% C.I.
T2D	C_{max} (ng/mL)	59.9*Dose^0.8	0.39 (0.27, 0.57)	1.76 (1.67,1.85)
	AUC(0-168) (ng*h/mL)	6820.9*Dose^0.9	0.72 (0.54,0.96)	1.86 (1.75, 1.98)

Abbreviation: C.I.=Confidence Interval
Proportionality was concluded over the dose range if the 90% CI for the ratio of dose normalized geometric means was entirely contained within (0.7, 1.43). If the 90% CI was completely outside of this interval, 'Not proportional' was concluded. In other cases, the result was 'Inconclusive'.

Dulaglutide PK was characterized following 1 and 1.5 mg QW for 5 weeks in Japanese T2D (n=14, Study GBCL). The overall t_{max} and $t_{1/2}$ were 48 hours and 4.5 days, respectively, at Week 5 (see Appendix 4.1.4 for study design and detail PK parameters). The AIs were 1.51 and 1.57 for 1 and 1.5 mg, respectively.

Reviewer's Comments:

- There was no apparent difference in dulaglutide PK between HV and Japanese T2D after SAD (see Figure 14). The PK data support the proposed QW dosing schedule.
- The PK characteristics after multiple doses were comparable to those of single doses. It indicates that there was no apparent time-dependent non-linearity in dulaglutide PK. Overall, multiple dose PK support the proposed dosing schedule.

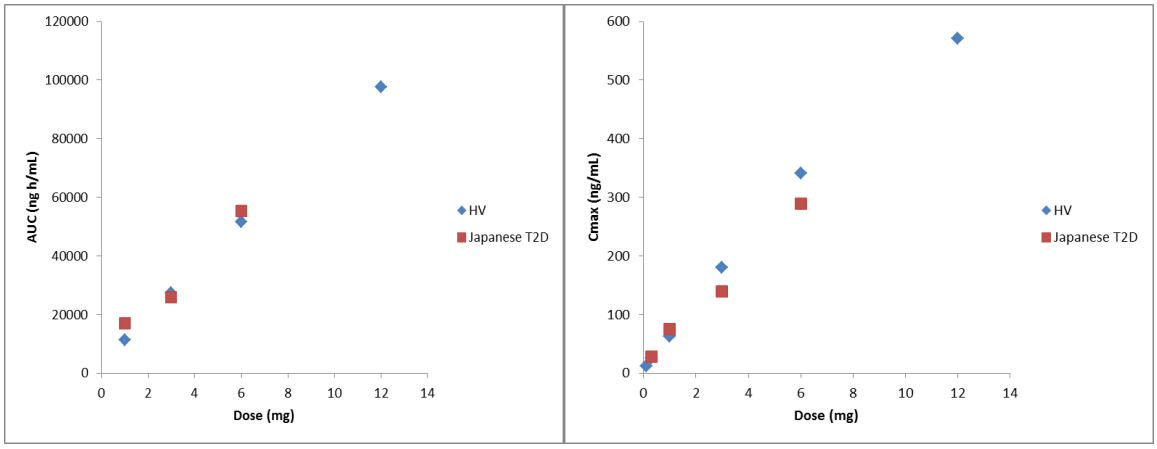

Figure 14 Dose-$AUC_{0\text{-}\infty}$ (left panel) or Cmax (right panel) in HV (blue symbol) and Japanese T2D (red symbol)

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2.4.2 *What are the characteristics of drug absorption, distribution and elimination?*

Absolute bioavailability ($F_{absolute}$) of SC 1.5 mg referencing 0.1 mg IV infusion over 30 minutes was estimated in healthy volunteers (Study GBDR). The mean plasma-concentration time profiles are shown in Figure 15 and PK parameters are summarized in Table 10.

The $F_{absolute}$ was 44.3%. The volume of distribution was 5.3 L and it is comparable to the adult blood volume, which is compatible with that of biologics based on the human anti-body.

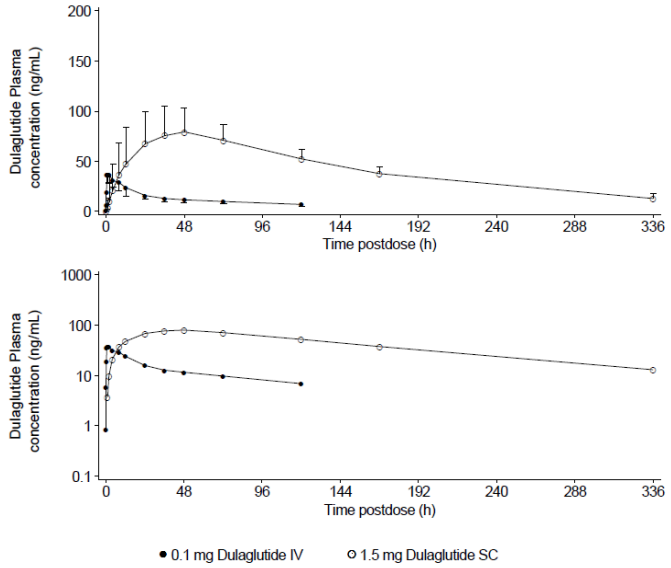

Figure 15 Arithmetic mean (+SD) plasma concentration-time profiles of dulaglutide following 0.1 mg dulaglutide via IV infusion over 30 minutes and 1.5 mg dulaglutide via SC injection (upper panel: linear scale; lower panel: semi-logarithmic scale).

Table 10 Summary of the PK Parameters of Dulaglutide in Plasma Following Administration of 0.1 mg Dulaglutide via IV Infusion and 1.5 mg Dulaglutide via SC Injection

	Geometric Mean (Geometric CV%)	
Parameter	1.5 mg Dulaglutide SC (N=16)	0.1 mg Dulaglutide IV[a] (N=22)
AUC(0-∞) (ng·h/mL)	15400 (21)	2350[b] (41)
AUC(0-168) (ng·h/mL)	9430 (22)	1740 (27)
C_{max} (ng/mL)	80.7 (32)	NA
t_{max}[c] (h)	48.0 (24.0, 72.0)	NA
$t_{1/2}$[d] (h)	107 (87.3, 153)	86.6[e] (37.9, 229)
CL or CL/F (L/h)	0.0975 (21)	0.0426 (41)
V_z or V_z/F (L)	15.1 (17)	5.32 (17)
$F_{absolute}$ [AUC(0-∞)]	0.443 (33)	NA
$F_{absolute}$ [AUC(0-168)]	0.371 (25)	NA

Abbreviations: AUC(0-168) = area under the concentration versus time curve (AUC) from time zero to 168 hours postdose; AUC(0-∞) = AUC from zero to infinity; CL = total body clearance of drug calculated after intravenous administration; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; C_{max} = maximum observed drug concentration; CV% = coefficient of variation; $F_{absolute}$ [AUC(0-168)] = absolute bioavailability based on AUC(0-168); $F_{absolute}$ [AUC(0-∞)] = absolute bioavailability based on AUC(0-∞); IV = intravenous; N = number of subjects; NA = not applicable; SC = subcutaneous; $t_{1/2}$ = apparent plasma terminal elimination half-life; t_{max} = time of maximum observed drug concentration; V_z = volume of distribution calculated after intravenous administration; V_z/F = apparent volume of distribution calculated after extra-vascular administration.

[a] Includes data for subjects from Parts A and B combined; [b] For individual AUC(0-∞) values for all subjects, the percentage of extrapolation was greater than 20%; [c] Median (range); [d] Geometric mean (range); [e] Individual $t_{1/2}$ values for all subjects were estimated over less than 2 half-lives.

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Relative bioavailability of SC 0.75 mg was estimated as 95.8% referencing IM 0.75 mg (Study GBDR) (see detailed PK parameters in Appendix 4.1.5). In addition, dulaglutide PK was comparable after administration to different SC injection sites (i.e, abdomen, arm and thigh, Study GBCN) (see Table 11).

Table 11 Statistical Assessment of the PK Parameters in Plasma Following SC **1.5 mg** (across both BMI Groups) (GBCN)

BMI Group	Parameter	Location of Administration	Geometric LS Means (90% CI)	Ratio of Geometric LS Means (vs. Abdomen) (90% CI)
Overall	AUC(0-∞) (ng·h/mL)	Abdomen (N=43)	14959 (14225, 15730)	
		Arm (N=40)	14557 (13834, 15319)	0.973 (0.941, 1.01)
		Thigh (N=39)	14800 (14064, 15574)	0.989 (0.956, 1.02)
	AUC(0-168) (ng·h/mL)	Abdomen (N=43)	9317 (8869, 9788)	
		Arm (N=40)	9129 (8678, 9605)	0.980 (0.934, 1.03)
		Thigh (N=44)	8580 (8169, 9010)	0.921 (0.879, 0.964)
	C_{max} (ng/mL)	Abdomen (N=43)	76.0 (71.8, 80.5)	
		Arm (N=40)	74.8 (70.5, 79.4)	0.984 (0.925, 1.05)
		Thigh (N=44)	67.7 (63.9, 71.6)	0.890 (0.838, 0.944)

Abbreviations: AUC(0-∞) = area under the plasma concentration-time curve from time zero to infinity; AUC(0-168) = area under the plasma concentration-time curve from time zero up to 168 hours postdose; BMI = body mass index; CI = confidence interval; C_{max} = maximum observed plasma concentration; LS = least squares; N = number of subjects.
Model: Log(PK) = Subject with Sequence and BMI Group + Sequence + BMI Group + Period + Location + BMI Group*Location + Random Error.

Reviewer's Comments:

- The $t_{1/2}$ of SC was apparently parallel to that of IV (see Figure 15) and it indicates that there is no flip-flop in dulaglutide PK after SC. There was numerical difference in $t_{1/2}$ (i.e., 4.6 days for SC vs. 3.6 days for IV) and it may have resulted from the differences in plasma sampling scheme.
- Dulaglutide $t_{1/2}$ is within the range of $t_{1/2}$ for monoclonal human anti-body based biologics and it indicates that IgG4 in the molecule may be a primary PK determinant.
- Dulaglutide PK was comparable between different routes of administration (i.e., IM and SC) and among different SC injection sites (i.e., abdomen, arm and thigh). It indicates that the absorption processes may not significantly contribute to its PK variability. In Phase 3 studies, dulaglutide was injected in the left or right abdominal wall.

2.4.3 *What are the pharmacodynamic properties of dulaglutide in T2DM subjects?*

Glycemic control:

A few glycemic pharmacodynamic measures were evaluated during the clinical development and they are summarized in Table 12. The fasting plasma (FPG) and postprandial (PPG) glucose were routinely measured in the clinical pharmacology and Phase 3 studies. However, the 8-point self-monitored plasma glucose profile (SMPG) was evaluated only in Phase 3 studies. Representative profiles of oral glucose tolerance test (OGTT), postprandial glucose (PPG) after a meal, and SMPG are shown in Appendix 4.1.7.

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Table 12 Summary of glycemic pharmacodynamics parameters used during the dulaglutide clinical development

Categories	Sampling	Parameter
FPG	Blood glucose was measured following an overnight fast condition.	• FPG concentration
PPG	**OGTT**: following an overnight fast, a 75-gram glucose dose was given orally with 300 mL water and the subjects consumed the glucose load within 5 minutes. Blood glucose was measured up to 4 hours after the glucose dose.	• 2-hour PPG concentration (Glucose[2h]) • PPG AUC (gAUC)
	Meal challenge: a standard meal was given followed by measurements of blood glucose (GBCD). Blood glucose was measured up to 4 hours after a meal.	• approximately 2 hours post-meal glucose concentration • PPG AUC (gAUC or $AUC_{glucose}$) • Average of concentrations
	PPG excursion = PPG-FPG	• 2-hour PPG excursion concentration • $AUC_{excusion}$
SMPG	Blood glucose was measured at pre-morning meal, postprandial morning, pre-midday meal, postprandial midday, pre-evening meal, postprandial evening, bedtime, and 0300 hours or 5 hours after bedtime	• mean fasting, preprandial, and postprandial SMPG • mean plasma glucose (PG) from 8-point SMPG profiles

In a study after 1.5 mg QW for 6 weeks, dulaglutide lowered fasting glucose on Day 3 (i.e., at t_{max} for dulaglutide) after the first dose, and glycemic reductions were apparent after 6 weeks as measured by reductions in fasting glucose (FPG, -26.6 mg/dL), 2-hour postprandial glucose (-59.5 mg/dL), and postprandial glucose AUC (-197 mg/dL) compared to those of placebo in T2D (Study GBCT). The glycemic reductions were observed in the 1.5 mg dulaglutide monotherapy Phase 3 study at 26 weeks (Study GBDC) as follows; the mean gAUC after a meal and FPG reductions from baseline were -170.5 mg*hr/dL (-9.46 mmol*hr/L) and -29 mg/dL (-1.61 mmol/L), respectively, compared to reductions of -131.0 mg*hr/dL (-7.27 mmol/L) and -24 mg/dL (-1.34 mmol/L), respectively for metformin.

There were background therapies for Phase 3 studies other than GBDC (Table 13), and there was dose dependent FPG reduction in all Phase 3 studies (Figure 16). In addition, FPG reduction was maintained during the treatment (Figure 17).

Table 13 Overview of Phase 3 studies

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

Abbreviations: BID = twice daily injection; MET=metformin; SU= sulfonylurea; TZD = thiazolidinedione; NA = 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).

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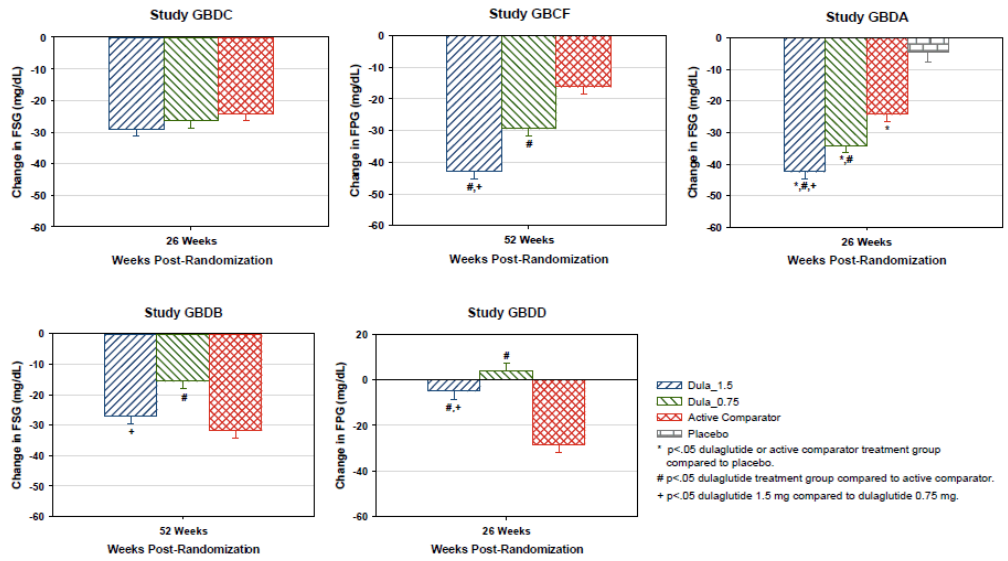
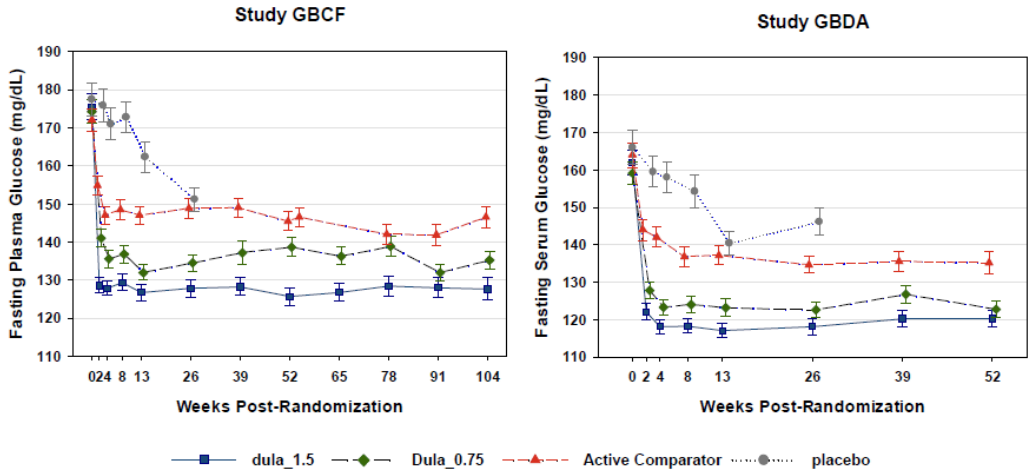


Abbreviations: BID = twice daily; FPG = fasting plasma glucose; FSG = fasting serum glucose (central laboratory); ITT = intent-to-treat; LS = least-squares; QD = once daily.
Note: Dula_x.x refers to dulaglutide x.x mg once weekly.
Note: Active comparator doses: GBDC metformin, 1500 to 2000 mg QD; GBCF 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).
Source: home/lillyce/prd/ly2189265/integrations/submission/programs_stat/tfl_output/efficacy/T_Col_FPG_PPG_Conv_A3.rtf.

Figure 16 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 (Source Figure 2.7.3.18).



Abbreviations: BID = twice daily; ITT = intent-to-treat; LS = least-square; QD = once daily.
Note: Dula_x.x refers to dulaglutide x.x mg once weekly.
Note: Study GBDA active comparator is exenatide, 10 mcg BID; Study GBCF active comparator is sitagliptin, 100 mg QD.
Note: Figure APP.2.7.3.5 contains figure with data reported in mmol/L. Values were converted from mmol/L to mg/dL (mmol/L*18=mg/dL) and standard error was derived from standard deviation.
Sources: home/lillyce/prd/ly2189265/h9x_mc_gbda/final/programs_stat/tfl_output/rmglya61.rtf; home/lillyce/prd/ly2189265/h9x_mc_gbcf/final/programs_stat/tfl_output/rmeffb11.rtf.

Figure 17 Summary of mean (± SE) fasting blood glucose (mg/dL) over time through final time point, ITT, Studies GBDA and GBCF. (Source: Figure 2.7.3.19)

Reviewer's Comments:

- Study designs for the glycemic PD measures were significantly different among studies as highlighted below. Therefore, there should be caution at evaluating the glycemic PD parameters using cross-study comparison.

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- Postprandial glucose measures are dependent on the components and composition of meals in addition to the drug treatment effect, and meals were heterogeneous among studies as follows;
  - Test meal content of breakfast for Study GBCT (elderly T2D): target calorific content of breakfast (total energy content; 640 Kcal) was 12 g of fat content, 20 g of protein content, and 114 g of carbohydrate content
  - Test meal content for Study GBDC (Phase 3): cereal and milk (45 g carbohydrate content in the cereal and 30 g carbohydrate content in the milk, for a total of 75 g carbohydrates)
- Blood sampling schedules were different among studies: up to 4 hours in the clinical pharmacology studies versus 3 hours in Phase 3 studies

Insulin and Glucagon Secretion – Dulaglutide stimulates insulin secretion and reduces glucagon secretion. Insulin and C-peptide, a surrogate for insulin secretion, AUCs were increased by 211 and 540 pmol*h/L, respectively after 1.5 mg QW for 6 weeks in T2D (Study GBCT). Glucose-dependent increase in insulin secretion rate was shown in a meal challenge study as a subset of Phase 3 dulaglutide monotherapy study (Study GBDC). Fasting glucagon and postprandial glucagon AUC (0-3 hours) reductions from baseline were observed by -2.05 pmol/L and -5.91 pmol*h/L, respectively, at Week 26 in a Phase 3 (Study GBDC).

A mechanistic study was conducted to evaluate the effect of dulaglutide on the insulin secretion in response to IV glucose challenge in T2D compared to that of HV (Study GBCI, Synopsis in Appendix 4.1.8). Results indicate that dulaglutide stimulate the insulin secretion at the first as well as second-phase in T2D (Figure 18).

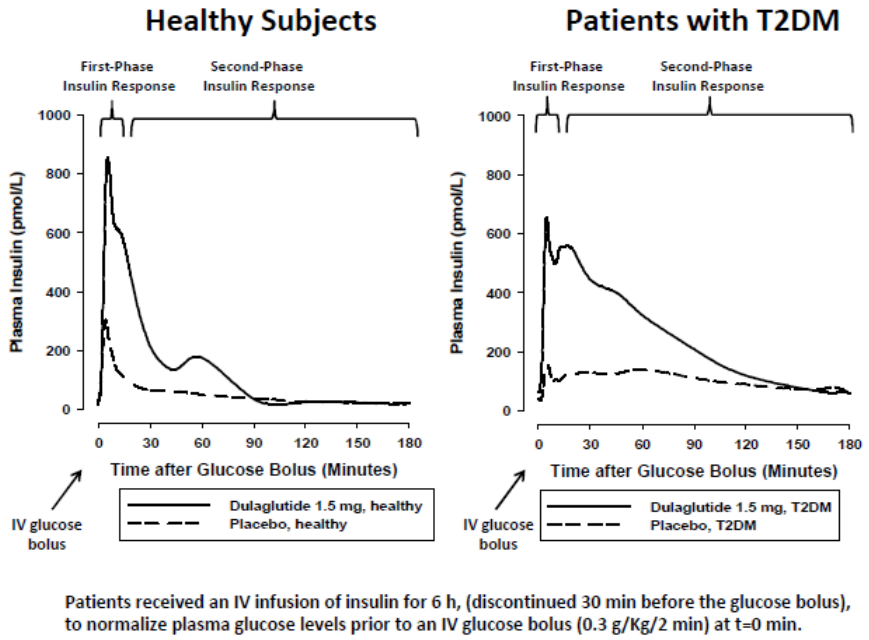

Figure 18 Mean plasma insulin concentrations after dulaglutide or placebo administration to healthy subjects (left panel) and patients with type 2 diabetes (Study GBCI)

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2.5 Intrinsic Factors

2.5.1 *What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

Body mass index (BMI):

The effect of BMI on dulaglutide PK was evaluated as a built in covariate for the injection sites study (Study GBCN). There were two BMI sub-groups; low (18-27 kg/m^2, n=25) and high (30-45 kg/m^2, n=20). Ratios (high/low BMI) of geometric least square means for $AUC_{0-\infty}$ were 0.761, 0.767 and 0.806 for abdomen, arm and thigh injection sites, respectively, and the corresponding values were 0.705, 0.747 and 0.770 for C_{max}.

To evaluate the clinical relevance of the observed PK difference by BMI, potential exposure difference was simulated using population analysis and results indicate that the exposure of 120 kg subject appears to overlap with that of typical population (see Figure 19). In addition, body weight was not the significant covariate for the HbA1c response in Phase 3 studies.

Therefore, the effect of BMI on dulaglutide exposure may not be clinically relevant.

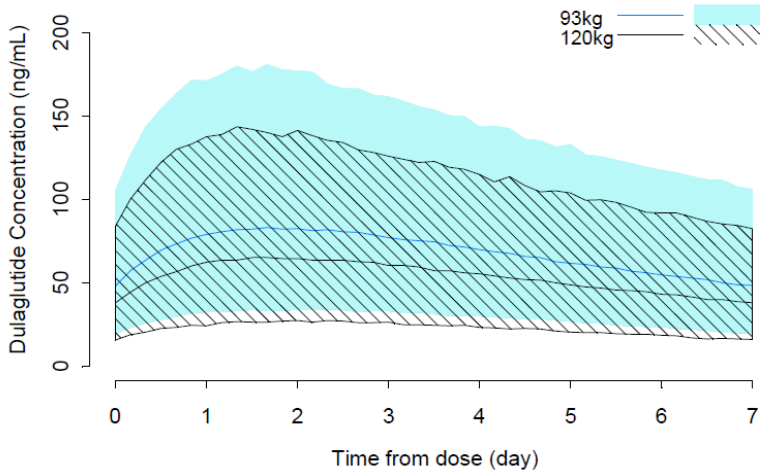

Figure 19 Dulaglutide steady-state concentrations following 1.5 mg for patients with T2DM with higher body weight (120 kg) fall within the 90% prediction interval for the T2DM population. (Source: Figure 2.7.2.39.)

Blue line and shaded area represent the median and 90% prediction interval for concentrations, respectively, after dosing of 1.5 mg dulaglutide at steady state in patients with T2DM and a body weight of 93 kg (represents population median). The black middle line and the hashed area represent the median concentrations and the 90% prediction interval, respectively, for patients with diabetes and body weight of 120 kg.
Source: Phase 3 popPK/PD report

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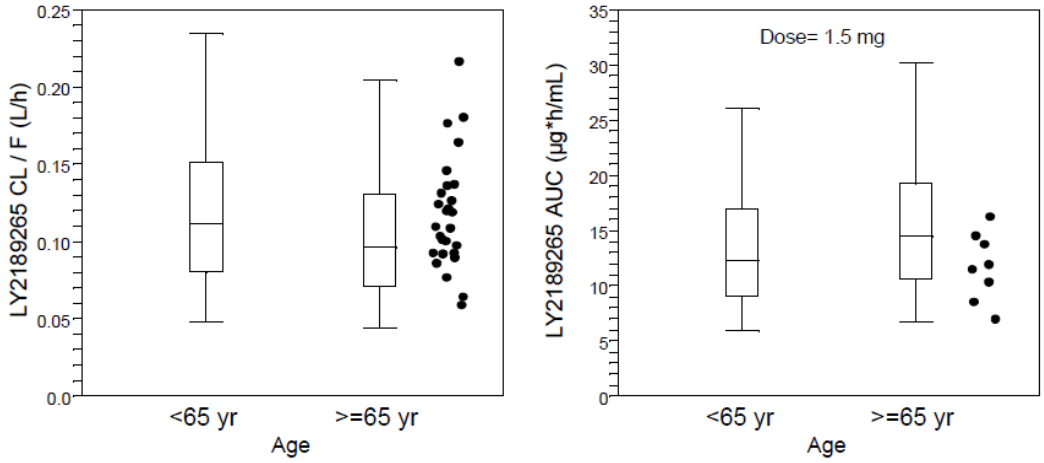
Dulaglutide PK in Elderly T2D:

Dulaglutide PK was characterized after placebo (n=8), 0.5 (n=9), 0.75 (n=11), and 1.5 mg (n=9) in elderly T2D (Study GBCT). The elderly PK was compared to historic data from subjects <65 years old in Phase 1 and 2 trials using a population PK/PD analysis, and it indicates that there is no significant difference in PK between two groups (see Figure 20).



Key: LY2189265 = dulaglutide.
Note: Solid circles represent apparent clearance (CL/F) and area under the concentration versus time curve (AUC) calculated by non-compartmental methods in Study GBCT. Left plot includes subjects in all dulaglutide dose groups; right plot includes subjects in the 1.5 mg dose group only.
Source: CSR GBCT, Figure GBCT.11.2.

Figure 20 Population PK model estimated dulaglutide CL/F (left panel) and AUC (right panel), at steady state, following 1.5 mg once weekly subcutaneous dosing, by age group (<65 years and ≥65 years old)

Renal impairment:

The effect of renal impairment on dulaglutide exposure was evaluated in sub-groups categorized by the estimated creatinine clearance (CrCL) per the renal Guidance (Study GBCM). Dulaglutide AUC was increased by 20, 28, 14 and 12% compared to that of control for mild, moderate, severe, and ESRD renal impairment sub-groups, respectively. The corresponding values for C_{max} were 13, 23, 20 and 11% (see Table 14). There was no meaningful relationship between dulaglutide PK parameters and CrCL as values of r^2 were 0.0686 and 0.0636 for AUC and C_{max}, respectively (see Figure 21).

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Table 14 Statistical Comparison between Renal Groups for the PK Parameters of Dulaglutide following Single Doses of 1.5 mg Dulaglutide

Parameter	Renal Group	N	Geometric LS Mean (90% CI)	Ratio (90% CI) versus Control	p-value
$AUC_{(0\text{-}168)}$ (ng·h/mL)	Control	16	9470 (8792, 10200)	-	-
	Mild Impairment	8	10634 (9566, 11821)	1.12 (0.987, 1.28)	0.139
	Moderate Impairment	8	11355 (10222, 12613)	1.20 (1.05, 1.36)	0.022
	Severe Impairment	8	10835 (9722, 12074)	1.14 (1.00, 1.30)	0.092
	ESRD	8	10174 (9154, 11307)	1.07 (0.944, 1.22)	0.356
AUC(0-∞) (ng·h/mL)	Control	15	15951 (14867, 17114)	-	-
	Mild Impairment	8	19148 (17376, 21100)	1.20 (1.06, 1.35)	0.014
	Moderate Impairment	8	20383 (18509, 22446)	1.28 (1.13, 1.44)	0.001
	Severe Impairment	7	18167 (16323, 20218)	1.14 (1.00, 1.29)	0.095
	ESRD	8	17891 (16238, 19711)	1.12 (0.995, 1.26)	0.115
C_{max} (ng/mL)	Control	16	74.7 (68.3, 81.7)	-	-
	Mild Impairment	8	84.1 (74.0, 95.5)	1.13 (0.963, 1.31)	0.209
	Moderate Impairment	8	91.7 (80.8, 104)	1.23 (1.05, 1.43)	0.031
	Severe Impairment	8	89.4 (78.5, 102)	1.20 (1.02-1.40)	0.062
	ESRD	8	82.9 (73.0, 94.1)	1.11 (0.950, 1.30)	0.267

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; C_{max} = maximum observed drug concentration; CI = confidence interval; ESRD = end-stage renal disease; LS = least squares; N = number of subjects.

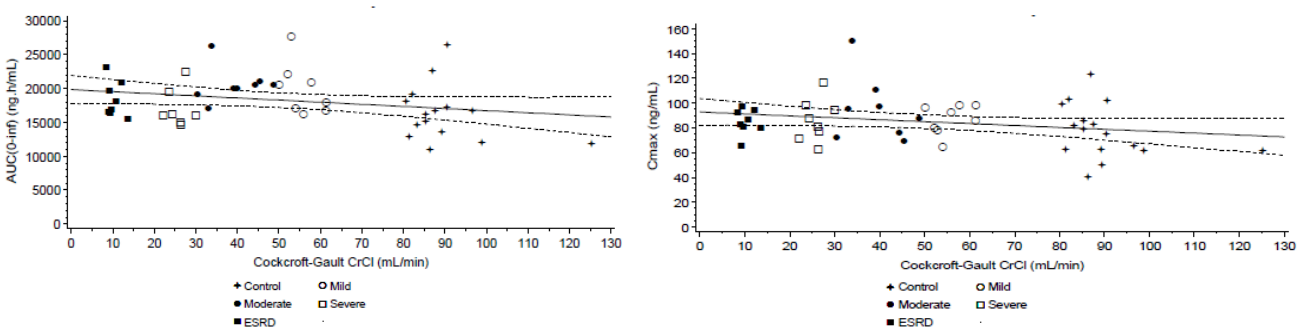

Figure 21 Relationship between AUC(0-∞) (left panel) or Cmax (right panel) of dulaglutide and creatinine clearance (CrCL) based on Cockcroft-Gault

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Reviewer's Comments:

- The data indicate that the dulaglutide exposure change with the renal function may not be clinically relevant as there was no statistically significant difference in GI adverse events by renal function sub-group based on available limited data from patients with renal impairment (see Table 15). Therefore, no dose adjustment is warranted. However, dulaglutide exposure data from patients with severe renal impairment in Phase 3 studies are extremely sparse (see Table 16). A renal safety study following dulaglutide administration is currently on-going to address this gap. Therefore, till more data becomes available, it is recommended that the dulaglutide should be used with caution in patients with severe renal impairment.

Table 15 **Incidence of Nausea, Diarrhea, and Vomiting by Renal Impairment, 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)** (Source: 4/22/2014 submission)

Preferred Term	Renal Impairment	Placebo (N=568) m/ M (%)	DU 0.75 mg (N=836) m/ M (%)	DU 1.5 mg (N=834) m/ M (%)	All DU (N=1670) m/ M (%)	Within-Level Comparison p-value	Treatment by Subgroup Interaction p-value
Nausea	Yes	2/ 40 (5.0)	8/ 52 (15.4)	10/ 47 (21.3)	18/ 99 (18.2)	0.042	0.854
	No	28/ 528 (5.3)	96/ 784 (12.2)	166/ 786 (21.1)	262/ 1570 (16.7)	<0.001	
Diarrhea	Yes	5/ 40 (12.5)	8/ 52 (15.4)	8/ 47 (17.0)	16/ 99 (16.2)	0.612	0.668
	No	33/ 528 (6.3)	66/ 784 (8.4)	97/ 786 (12.3)	163/ 1570 (10.4)	0.003	
Vomiting	Yes	2/ 40 (5.0)	3/ 52 (5.8)	4/ 47 (8.5)	7/ 99 (7.1)	0.559	0.166
	No	11/ 528 (2.1)	47/ 784 (6.0)	101/ 786 (12.8)	148/ 1570 (9.4)	<0.001	

Abbreviations: DU = dulaglutide once weekly dose; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; M = number of patients in the subgroup within specified treatment group; m = number of patients with at least one treatment-emergent adverse event; N = total number of patients in specified treatment group; UACR = urine albumin to creatinine ratio.

Note: For renal impairment, "yes" includes patients with eGFR (CKD-EPI) <60 mL/min/1.73 m^2 or macroalbuminuria (UACR >300 mg/g) at baseline.

Source: Integrated Summary of Safety (Table ISS.APP.598).

Table 16 Summary of Renal Characteristics At Baseline for All Patients from Phase 2 and 3 Trials (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN) (Source: Table ISS 6.118)

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 m^2	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 m^2 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 m^2 group.

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Hepatic impairment:

The effect of hepatic function on dulaglutide exposure was evaluated in sub-groups categorized with Child-Pugh classification per the Hepatic Guidance (Study GBDO). Dulaglutide exposure decreased to 77.4, 66.9 and 79.1% to that of control for mild, moderate and severe hepatic impairment groups, respectively, and C_{max} was decreased to the similar magnitude (see Table 17). There was no apparent trend for change in dulaglutide PK parameters among mild, moderate and severe hepatic impairment sub-groups (see Figure 22).

An approximate 20-30% reduction in dulaglutide exposure may not be clinically relevant. If only the high 1.5 mg dose is approved as proposed by the sponsor; the observed lower exposures may not be of concern because 0.75 mg dose is also shown to be effective. If the titration based dosing regimen is adopted, patients with inadequate efficacy because of lower exposures will have the option to be up-titrated to the high 1.5 mg dose. Therefore, no dose adjustment is recommended in patients with hepatic impairment.

Table 17 Effect of Hepatic Function on Dulaglutide PKs following a Single Subcutaneous Dose of Dulaglutide

Parameter (unit)	Hepatic Group	N	Geometric LS Mean (90% CI)	Ratio (90% CI) versus Control
AUC(0-∞) (ng·h/mL)	Control	11	16084 (14501, 17840)	
	Mild Hepatic Impairment	6	12446 (10815, 14323)	0.774 (0.649, 0.922)
	Moderate Hepatic Impairment	5	10763 (9215, 12572)	0.669 (0.556, 0.805)
	Severe Hepatic Impairment	3	12722 (10441, 15503)	0.791 (0.632, 0.989)
C_{max} (ng/mL)	Control	11	82.5 (73.7, 92.3)	
	Mild Hepatic Impairment	6	65.2 (56.0, 76.0)	0.791 (0.654, 0.957)
	Moderate Hepatic Impairment	6	57.9 (49.8, 67.5)	0.703 (0.582, 0.849)
	Severe Hepatic Impairment	3	62.8 (50.6, 77.8)	0.761 (0.597, 0.971)

Abbreviations: AUC(0-∞) = area under the plasma concentration versus time curve (AUC) from time zero to infinity; C_{max} = maximum observed drug concentration; CI = confidence interval; LS = least squares; N = number of subjects.

Model: Log(PK) = group + weight + random error.

Source: CSR GBDO, Table GBDO.7.2

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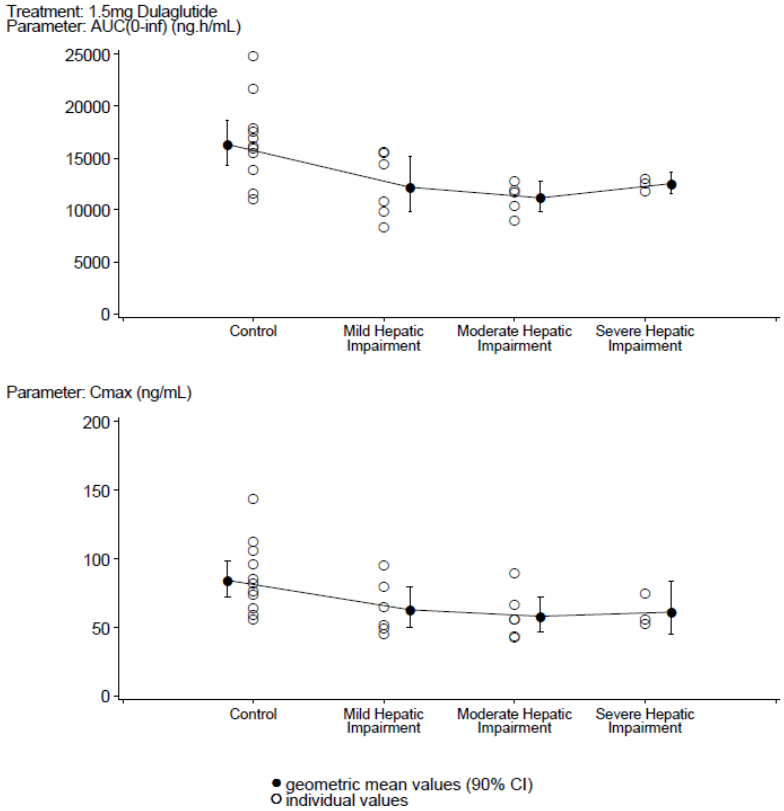

Figure 22 relationship between AUC (upper) or Cmax (lower) and hepatic impairment study sub-groups

2.6 Extrinsic Factors

2.6.1 *What are the results of drug-drug interaction studies?*

Drug interaction was evaluated as follows:

- The effect of dulaglutide on PK of other drugs; acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, oral contraceptive, sitagliptin, and warfarin
- The effect of sitagliptin on dulaglutide PK

Results of *in vivo* drug interaction studies are summarized in Table 18. In general, dulaglutide did not significantly affect exposure of co-administered drugs except that of atorvastatin.

Reviewer's Comments:

- Dulaglutide decreased atorvastatin AUC and C_{max} by 21 and 70%, respectively, but atorvastatin dose adjustment may not be needed because no dose adjustment is recommended in the atorvastatin prescribing information for a mean change in atorvastatin exposure of up to 41% and clinical relevance of atorvastatin C_{max} decrease is not known.
- There is noticeable delay in t_{max} of co-administered drugs (i.e., ≥ 2 hours) when taken with dulaglutide, e.g., for warfarin, atorvastatin and its major metabolite, lisinopril and an active component of oral contraceptive. Caution should be exercised as clinical relevance of t_{max} delay for these drugs may not be known. However, delay in t_{max} of co-administered drugs may not matter for most drugs after steady-state concentrations are reached. Plasma concentrations of drugs for which delay in t_{max} may have clinical relevance, such as drugs with narrow

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therapeutic index (e.g., digoxin, warfarin), are usually monitored until a stable clinical effect is attained. For example, warfarin labeling recommends daily INR determinations upon warfarin initiation until they become stable in the therapeutic range.

- Sitagliptin may reduce the metabolic clearance of GLP-1 analog part of dulaglutide molecule because DPP-4 enzyme is responsible for GLP-1 metabolism and sitagliptin is an inhibitor of DPP-4. Dulaglutide AUC and C_{max} were increased by 38 and 27%, respectively following administration with sitagliptin (see Table 18). If only the high 1.5 mg dose is approved as proposed by the sponsor; based on available dose-response data safety with 40% increase in dulaglutide exposure will not be unacceptably worse. If the titration based dosing regimen is adopted, it will take care of the increased exposures as dose will only be up-titrated if patients who are able to tolerate higher exposures. Therefore, a dose adjustment for dulaglutide is not recommended for co-administration with sitagliptin.

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Table 18 Results of *in vivo* drug interaction studies (Dulaglutide 1.5 mg except with APAP)

Study	Dosing Regimen, primary PK sampling	Primary PK	GMR (90% CI)		
			AUC	C_{max}	Tmax[&]
GBCP	Dula: Day 1, Atorvastatin: 40 mg before Dula and on Day 3 after Dula (n=27 HV)	Atorvastatin (before vs. Day 3)	0.786 (0.752, 0.821)*	0.296 (0.246, 0.355)	2.5
		o-hydorxy	0.937 (0.887, 0.990)*	0.393 (0.330, 0.467)	5
GBCO	Dula: QW for 4 weeks, Lisinopril PK on Day -1, Day 3 and Day 24 (n=8 PL, Dula=23)	Lisinopril (Day -1 vs. Day 3) (n=22)	1.0632 [#] (0.9107, 1.2412)	0.9538 [#] (0.8116, 1.1211)	2 (1.00, 2.00)
	Dula: Day 5, Metoprolol: 100 mg QD for 7 days (n=20 HV; 2D6 EM=4, PM=14)	Metoprolol (Day 4 vs. Day 7)	1.19 (1.11, 1.28)	1.32 (1.20, 1.45)	1.00 (0, 3.00)
GBCQ	Dula: on Day 19, Ortho-Cyclen[$]: PK on Day 21 before Dula (n=19) vs. with Dula (n=14)	Norelgestromin[$]	0.903 (0.832, 0.980)**	0.740 (0.648, 0.845)	2 (0, 2)
		Ethinyl estradiol (EE)	0.991 (0.901, 1.09)**	0.874 (0.790, 0.967)	0.3 (0,2)
GBCR	Dula: on Day 8 and 15, Digoxin: 0.5 mg BID for Day 1, 0.25 mg QD for Day 2-17 Digoxin PK on Day 7, 10 (n=21 HV), 17 (n=20 HV)	Digoxin (Day 7 vs. Day 10)	0.955 (0.884, 1.03)	0.782 (0.666, 0.919)	0.5 (0, 1.5)
		Digoxin (Day 10 vs. Day 17)	1.01 (0.932, 1.09)	1.06 (0.901, 1.25)	0
GBCS	Dula: Day 1, Warfarin: 10 mg (n=28) before Dula and Day 3 (n=25 HV)	(S)-warfarin	0.986 (0.959, 1.01)*	0.783 (0.737, 0.833)	4.02 (3,5)
		(R)-warfarin	0.989 (0.958, 1.02)*	0.857 (0.817, 0.900)	5.5 (4,8)
		INR	1.02 (1.01, 1.03)	1.02 (0.977, 1.07)	6 (0, 12)
GBDW	Dula: Day 1 (treatment 1), Sita: 100 mg sita Day 1-18 + Dula Day 5 and 12 (treatment 2) Sita PK on Day 4, Day 6, Day 13 (n=29 T2D) Dula PK	Sita (Day 4 vs. Day 6)	1.01 (0.862, 1.17)	0.889 (0.729, 1.08)	0.5 (0, 1.02)
		Sita (Day 4 vs. Day 13)	0.926 (0.791, 1.09)	0.768 (0.627, 0.941)	0.5 (0, 1.00)
		Dula (Day 5 vs. Day 12)	1.38 (1.24, 1.53)	1.27 (1.16, 1.40)	72.0 (Day 5) to 59.8 (Day 12)
GBCH	Dula: 1 (n=22 HV) or 3 mg (n=8 HV) QW for 4 weeks APAP: 1 g (oral solution) Day 3, Day 24, Day 36	APAP[@] (Day -1 vs. Day 3)	0.884 (0.854, 0.915)	0.644 (0.591, 0.702)	1 (0.733, 1.73)
		APAP[@] (Day -1 vs. Day 24)	1.05 (1.01, 1.08)	0.943 (0.865, 1.03)	0.016
GBDM[!]	Dula: PL Week1 and then QW for 4 weeks Metformin: IR BID on Day 3 (PL), Day 17 (2nd Dula dose) and Day 31 (3rd Dula dose) (n=12 T2D)	Metformin (Day 3 vs. Day 17)	1.12 (1.02, 1.22)	0.88 (0.80, 0.98)	0.02 (-0.05, 1.03)

Abbreviation: HV=healthy volunteer, Dula=dulaglutide, Sita=sitagliptin, APAP=acetaminophen, PL=placebo

*: $AUC_{0-\infty}$, otherwise $AUC_{0-\tau}$

**: pg*h/mL, otherwise ng*h/mL

$: Ortho-Cyclen: 0.25 mg norgestimate + 0.035 mg ethinyl estradiol; norelgestromin is one of major metabolite of norgestimate and surrogate for norgestimate PK

#: dose normalized PK parameters as patients with different stable lisinopril doses for at least 1 month

&: median difference except dula for GBDW

@: Dula 1 mg

!: One subject took metformin ER and tmax was 3.97, 2.07 and 4 hours on Day 3, 17 and 31, respectively.

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2.6.2 *What is the effect of dulaglutide on the gastric emptying time?*

Scintigraphy in T2D:

Scintigraphy assessments occurred on Days 3, 10, 17, 24, and 31 to coincide with dulaglutide t_{max} after dulaglutide 1.5 mg QW for 5 weeks in T2D (Study GBDM). Patients consumed a radiolabeled breakfast within 15 minutes, and scintigraphy assessments began 15 minutes after breakfast consumption started (t_0= start of breakfast). One of the primary parameters was the time required for 50% of activity to empty from the stomach (t_{50}), and results indicate that dulaglutide delayed t_{50} from 1.72 to 3.77 and that effect remained significant during the subsequent dulaglutide dosing (see Table 19).

Table 19 Statistical Analysis in t10, t50, and t90 Following Administration of 1.5 mg Dulaglutide or Placebo

Treatment	Parameter (unit)	Day	N	Geometric LS Mean (90% CI)	Ratio of Geometric LS Means: Day 3 (90% CI) [p-value]
Placebo	t_{10} (h)	3	10	0.54 (0.45, 0.64)	
		10	10	0.54 (0.45, 0.65)	1.01 (0.84, 1.21) [0.928]
		17	9	0.59 (0.50, 0.71)	1.11 (0.92, 1.34) [0.359]
		24	9	0.51 (0.42, 0.61)	0.95 (0.79, 1.15) [0.654]
		31	10	0.59 (0.49, 0.70)	1.09 (0.91, 1.31) [0.420]
Placebo	t_{50} (h)	3	10	1.44 (1.22, 1.69)	
		10	10	1.41 (1.20, 1.66)	0.98 (0.86, 1.13) [0.852]
		17	9	1.60 (1.36, 1.89)	1.12 (0.97, 1.29) [0.204]
		24	9	1.47 (1.25, 1.73)	1.02 (0.89, 1.18) [0.783]
		31	10	1.46 (1.24, 1.71)	1.01 (0.88, 1.17) [0.867]
Placebo	t_{90} (h)	3	10	2.87 (2.48, 3.32)	
		10	9	2.71 (2.34, 3.14)	0.94 (0.87, 1.02) [0.227]
		17	9	3.05 (2.63, 3.53)	1.06 (0.98, 1.15) [0.201]
		24	9	2.80 (2.42, 3.25)	0.98 (0.90, 1.06) [0.631]
		31	10	2.93 (2.53, 3.38)	1.02 (0.95, 1.10) [0.665]
1.5 mg Dulaglutide	t_{10} (h)	3	15	0.59 (0.46, 0.76)	
		10	15	1.13 (0.88, 1.46)	1.93 (1.40, 2.65) [0.001]
		17	14	1.18 (0.91, 1.52)	2.00 (1.44, 2.77) [<0.001]
		24	14	1.28 (0.99, 1.66)	2.18 (1.57, 3.02) [<0.001]
		31	13	1.32 (1.01, 1.72)	2.24 (1.60, 3.12) [<0.001]
1.5 mg Dulaglutide	t_{50} (h)	3	15	1.72 (1.43, 2.06)	
		10	15	3.77 (3.15, 4.51)	2.19 (1.83, 2.62) [<0.001]
		17	14	3.32 (2.76, 4.00)	1.94 (1.61, 2.33) [<0.001]
		24	14	3.28 (2.72, 3.94)	1.91 (1.59, 2.29) [<0.001]
		31	13	3.15 (2.61, 3.81)	1.84 (1.52, 2.22) [<0.001]
1.5 mg Dulaglutide	t_{90} (h)	3	15	3.50 (2.99, 4.11)	
		10	11	6.57 (5.53, 7.81)	1.88 (1.59, 2.21) [<0.001]
		17	12	6.68 (5.64, 7.91)	1.91 (1.63, 2.24) [<0.001]
		24	13	6.19 (5.25, 7.31)	1.77 (1.51, 2.06) [<0.001]
		31	13	6.13 (5.20, 7.23)	1.75 (1.50, 2.04) [<0.001]

Abbreviations: CI = confidence interval; LS = least squares; N = number of patients; t_{10} = time required for 10% of activity to empty from the stomach; t_{50} = time required for 50% of activity to empty from the stomach; t_{90} = time required for 90% of activity to empty from the stomach.

Source: GBDM CSR, Table GBDM.7.8

Reference ID: 3520514

Acetaminophen Study in Healthy Volunteers:

Dulaglutide effect on acetaminophen was evaluated following administration of dulaglutide 1 or 3 mg once weekly for 4 weeks. Acetaminophen 1 g (oral solution) was administered on Day -1, Day 3 (1st Dula dose), Day 24 (4th Dula dose) and Day 36, approximately 15 minutes after a standardized breakfast in healthy volunteers (Study GBCH). Results are summarized in Table 20. Acetaminophen AUC and C_{max} after dulaglutide 1 mg on Day 3 were 88.4 and 64.4%, respectively, to those without dulaglutide. Dulaglutide 1 mg delayed acetaminophen t_{max} from 3 to 2 hours. However, the effect of dulaglutide on acetaminophen PK was almost negligible after 4th dose of dulaglutide (see Table 20). Results of dulaglutide 3 mg were parallel to those of 1 mg except acetaminophen t_{max} delay was still observed after dulaglutide 4th dose.

Table 20 Effect of Dulaglutide on Acetaminophen PK

Study Design	Dulaglutide Dose	PK parameter	Day	Ratio of GLSM to Day -1 (90% CI)
Dula 1 mg QW for 4 weeks, APAP 1 g as oral solution on Day -1, Day 3 (Dula 1st dose), Day 24 (Dula 4th dose) and Day 36	1 mg (n=22)	AUC0-24 (ng h/mL)	-1	
			3	0.884 (0.854, 0.915)
			24	1.05 (1.01, 1.08)
			36	0.998 (0.964, 1.03)
		Cmax (ng/mL)	-1	
			3	0.644 (0.591, 0.702)
			24	0.943 (0.865, 1.03)
			36	1.04 (0.957, 1.14)
	3 mg (n=8)	AUC0-24 (ng h/mL)	-1	
			3	0.855 (0.825,0.949)
			24	1.13 (1.05, 1.23)
			36	1.05 (0.971, 1.14)
		Cmax (ng/mL)	-1	
			3	0.503 (0.433, 0.585)
			24	0.964 (0.816, 1.14)
			36	0.968 (0.819, 1.14)

Parameter	Dulaglutide Dose	Day	Median	Median difference relative to Day -1 (90% CI)
t_{max} (hour)	1 mg	-1	2.00	
		3	3.00	1.00 (0.733, 1.73)
		24	2.07	0.016 (-0.500, 0.533)
		36	2.00	-0.016 (-0.500, 0.091)
	3 mg	-1	2.00	
		3	4.00	2.15 (1.02, 3.97)
		24	3.00	0.967 (0, 1.48)
		36	2.00	0.492 (-0.033, 1.02)

Acetaminophen Study in T2D:

The effect of dulaglutide on acetaminophen PK was evaluated as part of multiple ascending dose study (Study GBCD). Acetaminophen 480 mg elixir was administered on Day -1 and Day 3 to coincide with dulaglutide t_{max}. Statistically significant difference in the observed t_{max} for acetaminophen between Day -1 and Day 3 was only observed in the 8 mg dose group (see Table 21).

Reference ID: 3520514

Table 21 Least-square Mean Ratio and Difference to Placebo of Acetaminophen PKs Prior to and Following the First Dose of LY2189265

Acetaminophen t_{max} (h)			Comparison to Placebo		
Treatment	n	Geometric Mean Ratio	Relative Change	90% C.I.	P-value
Placebo	11	1.11			
0.05 mg LY	3	0.84	0.76	(0.35, 1.63)	0.54
0.3 mg LY	6	0.94	0.85	(0.46, 1.55)	0.65
1 mg LY	5	0.98	0.89	(0.47, 1.67)	0.76
3 mg LY	3	1.47	1.33	(0.62, 2.85)	0.53
5 mg LY	9	1.38	1.25	(0.73, 2.12)	0.49
8 mg LY	6	2.55	2.31	(1.28, 4.18)	0.02
Acetaminophen C_{max} (µg/mL)			Comparison to Placebo		
Treatment	n	Geometric Mean Ratio	Relative Change	90% C.I.	P-value
Placebo	11	0.92			
0.05 mg LY	3	1.39	1.51	(1.00, 2.27)	0.10
0.3 mg LY	6	0.96	1.04	(0.76, 1.40)	0.85
1 mg LY	5	0.80	0.87	(0.63, 1.20)	0.46
3 mg LY	3	0.83	0.90	(0.61, 1.34)	0.66
5 mg LY	9	0.38	0.41	(0.31, 0.53)	<.01
8 mg LY	6	0.66	0.71	(0.53, 0.97)	0.07
Acetaminophen AUC(0-12) (µg h/mL)			Comparison to Placebo		
Treatment	n	Geometric Mean Ratio	Relative Change	90% C.I.	P-value
Placebo	11	0.99			
0.05 mg LY	3	1.14	1.15	(0.89, 1.50)	0.37
0.3 mg LY	6	0.92	0.93	(0.78, 1.12)	0.52
1 mg LY	5	0.85	0.86	(0.71, 1.05)	0.21
3 mg LY	3	0.99	1.00	(0.79, 1.26)	0.99
5 mg LY	7	0.51	0.52	(0.44, 0.62)	<.01
8 mg LY	6	0.99	1.00	(0.83, 1.21)	0.98
Model: log(Day 3 PK) - log(Day -1 PK) = log(Day -1 PK) + Dose + (error)					

Abbreviations: AUC = area under the concentration versus time curve, CI = confidence interval, Cmax = observed maximum concentration, tmax = time of observed maximum concentration.

Reviewer's Comments:

- The effect of dulaglutide on the gastric emptying time differs between studies, indicating that study design features, such as the primary endpoint, dose, types of subjects, meal conditions, affect the outcome as follows:
    - Results of the scintigraphy study in T2D indicate that the gastric emptying time delay is about 2 hour (i.e., t_{50} from 1.72 to 3.77 hours) after the first dulaglutide 1.5 mg dose, and the delay persists after multiple dose administration.
    - Results of acetaminophen study in HV indicate the gastric emptying time delay is about 1 hour (i.e., t_{max} from 2 to 3 hours) after the first dulaglutide 1.0 mg dose (close to the proposed dose), which does not persist (i.e., eliminated) after multiple dose administration.
    - Results of acetaminophen study in T2D indicate the gastric emptying time delay is not significant (i.e., t_{max} from 1.05 and 0.87 hours) after the first dulaglutide 1 mg dose, which is close to the proposed dose.

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- Study results with acetaminophen in HV and T2D are perhaps more clinically relevant because it informs about the possible systemic exposure change when a drug is coadministered with dulaglutide.
- Based on available knowledge effect of GLP-1 agonist on gastric emptying is more pronounced with the short-acting analogs than the long-acting analogs because of infrequent administration required for long-acting analogs.

2.7 General Biopharmaceutics

2.7.1 *What is the comparability of new additional commercial delivery device to that of clinical trial delivery device?*

The proposed commercial formulation and pre-filled syringe (PFS) as a delivery device have been evaluated in clinical studies including Phase 3 studies. The sponsor proposes a single-use pen (SUP) as an additional commercial delivery device (see Figure 4) and conducted the pivotal comparability study to bridge SUP with PFS (Study GBDT). Dulaglutide PK using SUP was comparable to that of PFS (see Table 22). Therefore, it is concluded that SUP is equivalent to PFS from the clinical pharmacology perspectives.

Table 22 Statistical Comparison between AI and Manual Syringe Administration for the PK Parameters of Dulaglutide Following Single Doses of 1.5 mg Dulaglutide

Parameter	Device	N	GLSM	Ratio (AI:MS) of GLSM (90% CI for the ratio)
AUC(0-∞) (ng·h/mL)	Auto-injector	47	16483	1.02 (0.998, 1.04)
	Manual Syringe	47	16150	
AUC(0-336) (ng·h/mL)	Auto-injector	47	14717	1.02 (1.00, 1.05)
	Manual Syringe	47	14379	
C_{max} (ng/mL)	Auto-injector	47	90.8	1.02 (0.983, 1.06)
	Manual Syringe	48	88.8	

Abbreviations: AI = Auto-injector; AUC(0-336) = area under the concentration versus time curve from time zero to 336 hours postdose; AUC(0-∞) = area under the concentration versus time curve from zero to infinity; BMI = body mass index; CI = confidence interval; C_{max} = maximum observed drug concentration; h = hours; LS = least squares; N = number of subjects; PK = pharmacokinetics; t_{max} = time of C_{max}.

Model for AUC(0-∞), AUC(0-336), and C_{max}: Log(PK) = Subject(Sequence) + Sequence + Device + Period + BMI + Random Error.

t_{max} was analyzed using the method outlined by Hauschke et al. (Hauschke et al. 1990).

2.8 Analytical Section

2.8.1 *What bioanalytical methods are used to assess concentrations?*

The sponsor described the bioanalytical methods as follows, and it is acceptable pending review of the OSI inspection:

The samples were analyzed for dulaglutide using a validated radioimmunoassay (RIA) method. The lower limit of quantitation was 5.00 ng/mL, and the upper limit of quantitation was 50.0 ng/mL.

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Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range. The inter-assay accuracy (% relative error) during validation ranged from -6.72% to 2.86%. The inter-assay precision (% relative standard deviation) during validation ranged from 6.73% to 22.2%. Dulaglutide was stable for up to 363 days when stored at approximately -20°C and up to 735 days when stored at approximately -70°C. QC samples were 3.00, 12.0 and 30.0 ng/mL.

The RIA was designed [redacted] (b) (4) [redacted] Sample concentrations were determined by interpolation from the standard curve, which had been fit using a four-parameter algorithm with $1/ratio^2$ weighting. The amount of tracer bound to antibody decreased as the concentration of unlabeled antigen increased. This assay required a 0.200 mL sample volume. The calibration range was 0.500 to 50.0 ng/mL. The range of quantification was 2.50 to 50.0 ng/mL. Samples were stored at a nominal temperature of -80°C prior to analysis.

Reference ID: 3520514

3 Labeling Recommendations

(Please refer a separate file for clinical pharmacology labeling comments.)

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4 Appendices

4.1 Summary of Individual Study Design and Results

4.1.1 Study GBCA: SAD in HV

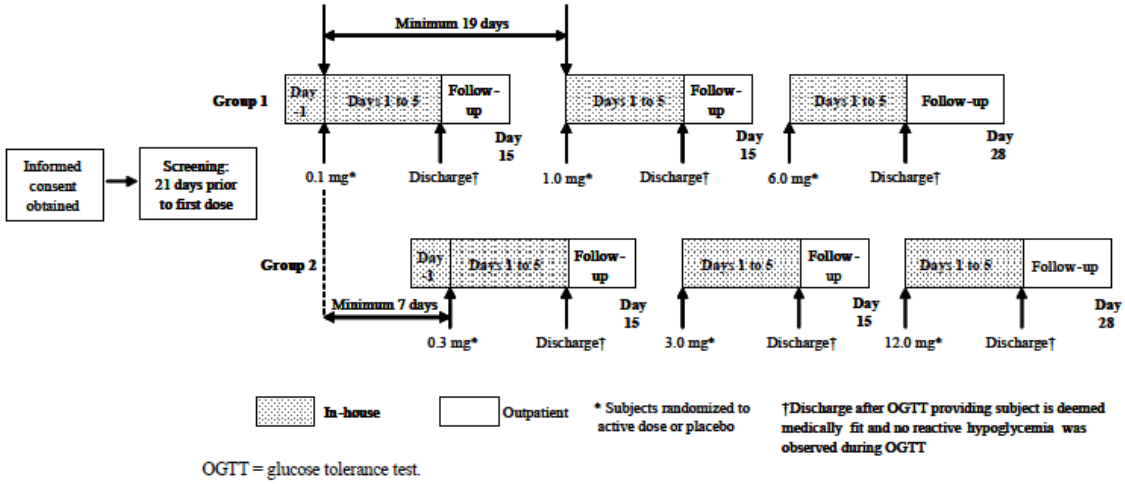

Figure 23 **Study design (GBCA)**

Table 23 **Dose regimens (GBCA)**

	Period 1	Period 2	Period 3
Group 1	Dose 1 0.1 mg LY2189265 or Placebo	Dose 3 1.0 mg LY2189265 or Placebo	Dose 5 6.0 mg LY2189265 or Placebo
Group 2	Dose 2 0.3 mg LY2189265 or Placebo	Dose 4 3.0 mg LY2189265 or Placebo	Dose 6 12.0 mg LY2189265 or Placebo

Table 24 **Summary of Subject Demographics (GBCA)**

Treatment Group	Statistics	Age (years)	Screening Weight (kg)	Screening Height (cm)	BMI Body Mass Index (kg/m**2)
All subjects	Mean	32	74.6	174.3	24.5
	Standard Deviation	9.9	9.92	5.94	2.27
	Median	31	73.7	172.5	24.4
	Minimum	19	61.0	166.0	21.3
	Maximum	52	96.6	189.0	29.8
	N	20	20	20	20

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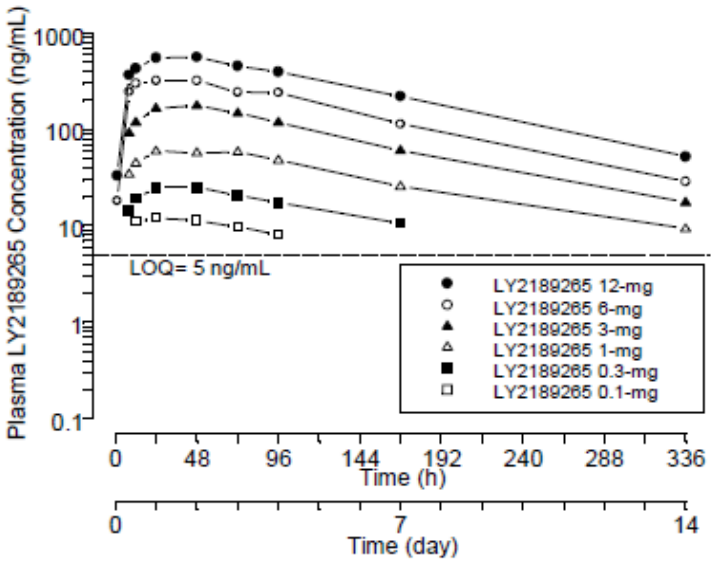


Figure 24 Mean plasma concentration-time profiles (GBCA)

Table 25 Summary of PK parameters following a single dose in HV (Study GBCA)

	LY2189265 Dose						
Parameter	**0.1-mg [n = 6] [b]**	**0.3-mg [n = 6] [b]**	**1-mg [n = 6]**	**3-mg [n = 4]**	**6-mg [n = 6]**	**12-mg [n = 6] [c]**	**Overall [n = 22] [d]**
C_{max} (ng/mL) [a]	11.6 (35.1)	26.2 (12.0)	62.7 (32.3)	180 (25.6)	341 (26.5)	571 (21.4)	--
t_{max} (h) [e]	24.03 (24.00 – 48.00)	36.04 (24.00 – 48.17)	48.00 (24.00 – 72.00)	36.03 (24.00 – 48.03)	36.00 (12.00 – 95.83)	36.00 (12.35 – 72.00)	47.99 (12.00 – 95.83)
$t_{1/2}$ (h) [f]	--	--	102 (90.4 – 139)	88.4 (80.9 – 94.2)	80.4 (70.1 – 94.1)	89.2 (77.8 – 110)	89.9 (70.1 – 139)
AUC (0-t_{last}) (ng h/mL) [a]	1240 (89.8)	3010 (34.7)	10000 (23.9)	25400 (25.0)	48400 (22.0)	83200 (20.2)	--
AUC (0-∞) (ng h/mL) [a]	--	--	11300 (26.5)	27500 (26.1)	51700 (20.5)	97600 (9.00)	--
CL/F (L/h) [a]	--	--	0.0881 (26.5)	0.109 (26.1)	0.116 (20.5)	0.123 (9.01)	0.107 (24.2)
V_z/F (L) [a]	--	--	13.0 (21.1)	13.9 (19.7)	13.4 (29.6)	15.8 (10.6)	13.9 (21.6)

Abbreviations: C_{max} = observed maximum concentration, t_{max} = time of observed maximum concentration, $t_{1/2}$ = LY2189265 half-life, AUC(0-t_{last}) = area under the curve from 0 to time of last quantifiable concentration, AUC(0-∞) = area under the curve from 0 to infinity, CL/F = apparent clearance, V_z/F = apparent volume.

a. Geometric mean (CV%).

b. Parameters ($t_{1/2}$, $AUC_{(0-\infty)}$, CL/F, and V_z/F) could not be estimated in the 0.1-mg and 0.3-mg dose groups due to insufficient quantifiable concentrations in terminal phase for all subjects, except for Subject 1018 and Subject 1049. C_{max} could be identified for all subjects in the 0.1 and 0.3 mg dose groups.

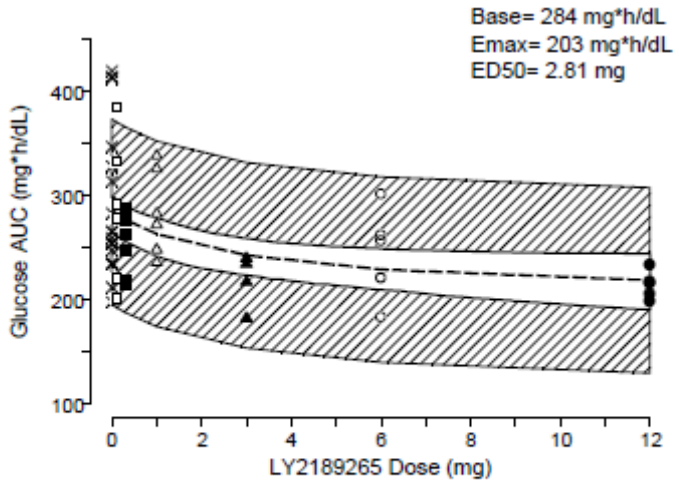
c. Parameters ($t_{1/2}$, $AUC_{(0-\infty)}$, CL/F, and V_z/F) are based on n=5 since the parameters for Subject 1069 could not be estimated due to insufficient quantifiable concentrations in terminal phase.

d. Summary statistics exclude dose groups 0.1- and 0.3-mg.

e. Median (range).

f. Geometric mean (range).

Reference ID: 3520514



Note: E_{max} model predicted mean (dashed line) and 90% CI of the mean predicted response (solid white shaded area) and population response (shaded area); symbols are observed individual responses.

Figure 25 OGTT Glucose AUC - LY2189265 dose response: median and 90% CI of the model predicted.

Reference ID: 3520514

4.1.2 Study GBCB: SAD in Japanese T2D

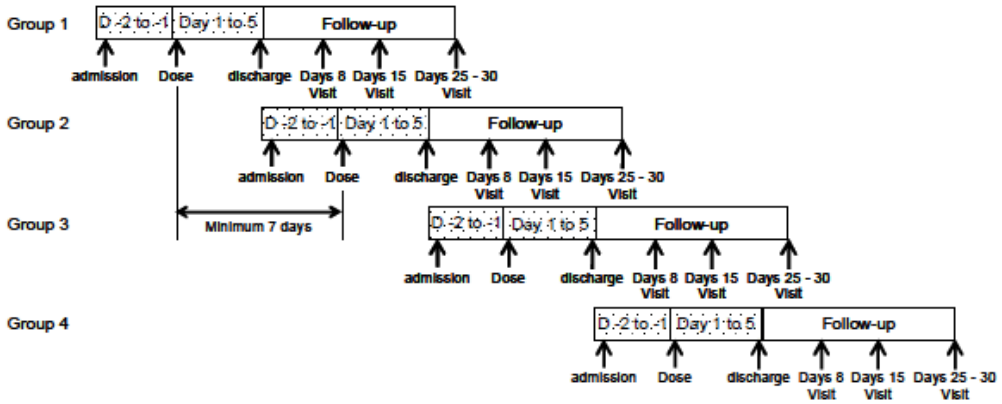


Figure 26 **Study design (GBCB)**

Table 26 **Dose regimens (GBCB)**

Group[a]	Number of Patient	Day 1
1	8	LY2189265 0.3 mg
	2	Placebo
2	8	LY2189265 1 mg
	2	Placebo
3	8	LY2189265 3 mg
	2	Placebo
4	8	LY2189265 6 mg
	2	Placebo

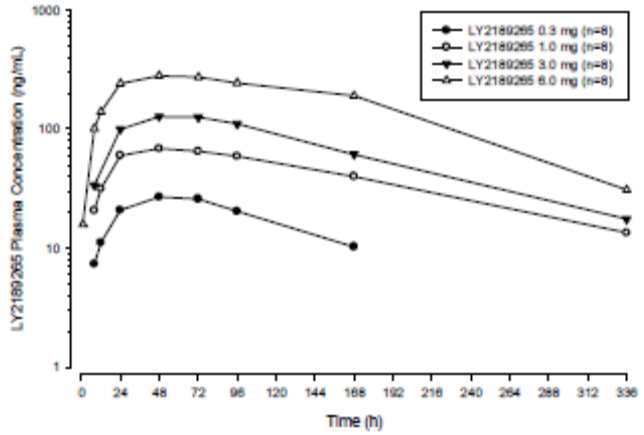


Figure 27 Arithmetic mean plasma concentration-time profiles following subcutaneous doses (GBCB).

Table 27 **Summary of PK parameters following a single dose in Japanese T2D (Study GBCB)**

Parameter	0.3 mg (n=8)	1 mg (n=7) [e]	3 mg (n=7) [e]	6 mg (n=8)	Overall (n=30)

Reference ID: 3520514

C_{max} (ng/mL) [a]	28.3 (29.1)	75.8 (47.3)	140 (35.3)	289 (21.7)	-- [d]
t_{max} (h) [b]	60 (48-72)	48 (24-96)	72 (48-96)	48 (24-72)	48 (24-96)
$t_{1/2}$ (h) [c]	-- [d]	115 (74.9-213) [f]	85.0 (70.9-102) [g]	77.8 (65.8-84.7)	87.6 (65.8-213) [h]
AUC(0-168) (ng·h/mL) [a]	2990 (23.6)	8470 (31.3)	15500 (43.5)	36900 (20.4)	-- [d]
AUC(0-∞) (ng·h/mL) [a]	-- [d]	17100 (56.7) [f]	26000 (17.0) [g]	55400 (17.3)	-- [d]
CL/F (L/h) [a]	-- [d]	0.0586 (56.7) [f]	0.116 (17.0) [g]	0.108 (17.3)	0.0955 (40.4) [h]
V_z/F (L) [a]	-- [d]	9.74 (9.37) [f]	14.2 (14.9) [g]	12.2 (23.8)	12.1 (22.8) [h]

Abbreviations: AUC(0-168) = area under the concentration-time curve from zero to 168 hours after dose, which is calculated using plasma concentrations at pre-dose, 12, 24, 72, 96 and 168 hours post-dose; AUC(0-∞) = area under the concentration-time curve from zero to infinity; CL/F = apparent total body clearance of drug; C_{max} = observed maximum concentration;
$t_{1/2}$ = half-life associated with the terminal rate constant (lambda z) in non-compartmental analysis; t_{max}= time of maximum observed drug concentration; V_z/F = apparent volume of distribution during the terminal phase.

a. Geometric mean (CV%)

b. Median (range)

c. Geometric mean (range)

d. Parameter was not calculated.

e. Parameters in Patient 2001 (1 mg) and 3002 (3 mg) were not calculated due to insufficient data.

f. n=4

g. n=5

h. n=17

Reference ID: 3520514

4.1.3 Study GBCD: MAD in T2D

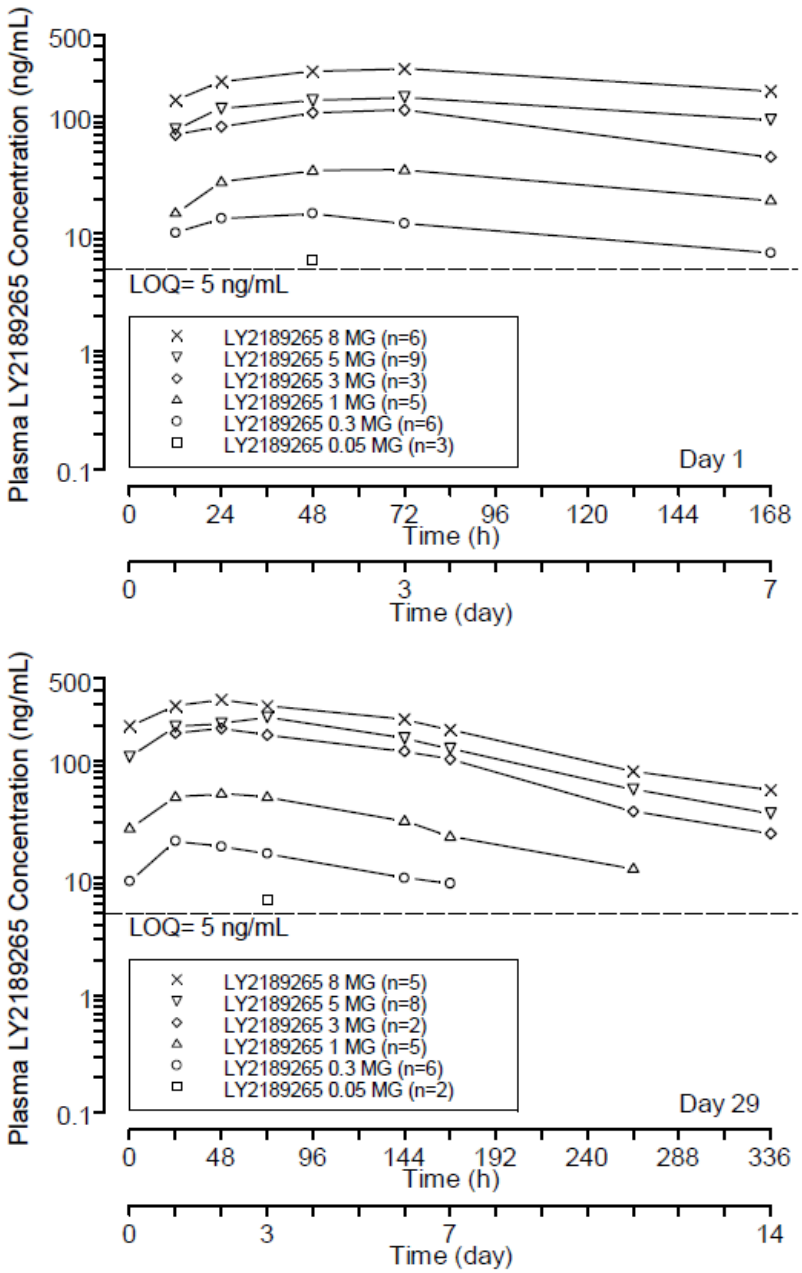


Figure 28 Arithmetic mean plasma concentration-time profiles following subcutaneous doses (GBCD).

Reference ID: 3520514

Table 28 Summary of **PK** Parameters by Dose Group following DULAGLUTIDE Administered at Week 1 (GBCD)

Week 1 LY2189265 Geometric mean (CV%)			
Dose (mg)	**C_{max} (ng/mL)**	**t_{max} [a] (h)**	**AUC(0-168) (ng•h/mL)**
0.05 (n=2)	5.9 (18)	48.00 (48.00 – 48.00)	878 [b] (NC)
0.30 (n=6)	15.4 (31)	47.87 (12.08 – 48.00)	1700 [c] (33)
1.00 (n=5)	37.2 (13)	72.00 (48.00 – 72.50)	4190 [c] (10)
3.00 (n=3)	111 (45)	71.92 (48.00 – 72.00)	12200 (48)
5.00 (n=9)	124 (76)	72.00 (48.00 – 72.25)	20600 [d] (42)
8.00 (n=6)	255 (25)	60.06 (48.00 – 72.00)	31900 [e] (37)
Overall (n=31)	NC	69.75 (12.08 – 72.5)	NC

Abbreviations: AUC(0-168) = area under the curve during one dosing interval, i.e. the interval from time of dose to 168 hours post dose, Cmax = observed maximum concentration, CV = coefficient of variation, h = hour, NC = not calculated, tmax = time of observed. maximum concentration.

[a] Median (minimum – maximum).

[b] The individual estimate for Patient 2001.

[c] n=4

[d] n=6

[e] n=5

Table 29 Summary of P**K** Parameters by Dose Group following DULAGLUTIDE Administered at Week 5 (GBCD)

Week 5 LY2189265 Geometric mean (CV%)							
Dose (mg)	**C_{max} (ng/mL)**	**t_{max} [a] (h)**	**$t_{1/2}$ [b] (h)**	**CL_{ss}/F (L/h)**	**$V_{z,ss}/F$ (L)**	**AUC(0-168) (ng•h/mL)**	**Accum. Index**
0.05 (n=2) [c]	7.47 (32)	58.89 (48.00 – 69.78)	NC	NC	NC	NC	NC
0.30 (n=6)	19.7 (34)	24.00 (24.00 – 72.05)	108 (85.2 – 156)	0.13 (27)	20.3 (25)	2310 (27)	1.53 (15)
1.00 (n=5)	51.7 (37)	48.00 (24.00 – 72.00)	97.2 (83.8 – 121)	0.154 (32)	21.7 (44)	6480 (32)	1.44 (8)
3.00 (n=2)	176 (59)	36.04 (24.00 – 48.08)	82.9 (71.3 – 96.4)	0.131 (57)	15.7 (86)	22900 (57)	1.33 (10)
5.00 (n=8)	234 (29)	71.94 (24.00 – 72.00)	95.4 (79.6 – 117)	0.166 (23)	22.8 (23)	30100 (23)	1.42 (7)
8.00 (n=5) [d]	330 (44)	48.00 (47.92 – 48.00)	82.4 (62.1 – 99.1)	0.204 (54)	24.3 (36)	39100 (54)	1.33 (9)
Overall (n=28) [e]	NC	48.00 (24.00 – 72.05)	95.4 (62.1 – 156)	0.157 (35)	21.5 (34)	NC	1.43 (11)

Abbreviations: AUC(0-168) = area under the curve during one dosing interval, i.e. the interval from time of dose to 168 hours post dose, Accum. Index = accumulation index, CLss/F = steady-state apparent clearance, Cmax = observed maximum concentration, CV% = coefficient of variation, h = hour, tmax = time of observed maximum concentration, t1/2 = LY2189265 half-life, Vz,ss/F = steady-state apparent volume, NC = not calculated.

[a] Median (minimum – maximum).

[b] Geometric mean (minimum – maximum).

[c] Parameters (t1/2, CLss/F, Vz,ss/F, AUC(0-168), and Accum. Index) could not be estimated in the 0.05-mg dose group due to insufficient quantifiable concentrations in terminal phase for all subjects.

[d] n=4. The tmax from Patient #2020 was excluded because no samples were available between time of dose and 144 hours postdose. The parameters (t1/2, CLss/F, Vz,ss/F, AUC(0-168), and Accum. Index) for Patient #2013 were excluded due to insufficient quantifiable concentrations in terminal phase.

[e] n=27 for tmax; n = 25 for parameters t1/2, CLss/F, Vz,ss/F, and Accum. Index.

Reference ID: 3520514

4.1.4 Study GBCL: MAD in Japanese T2D

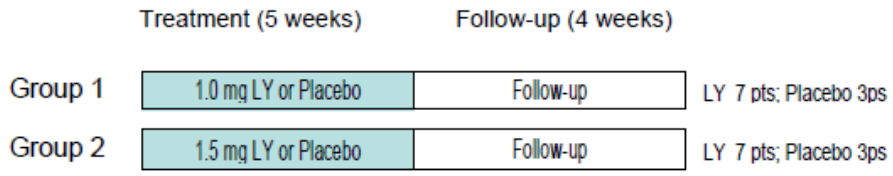


Figure GBCL.5.1. Dosing Groups

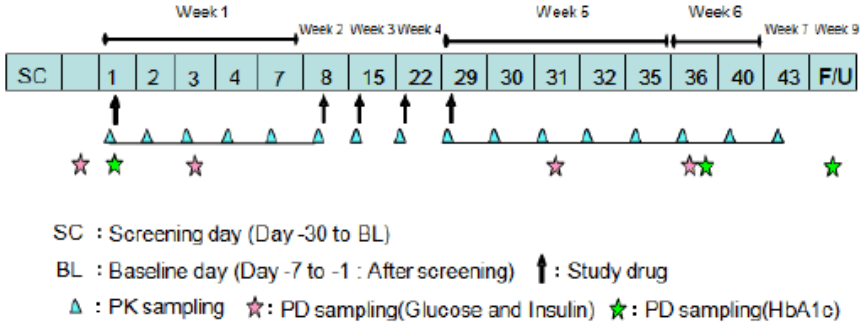


Figure 29 Study design (GBCL)

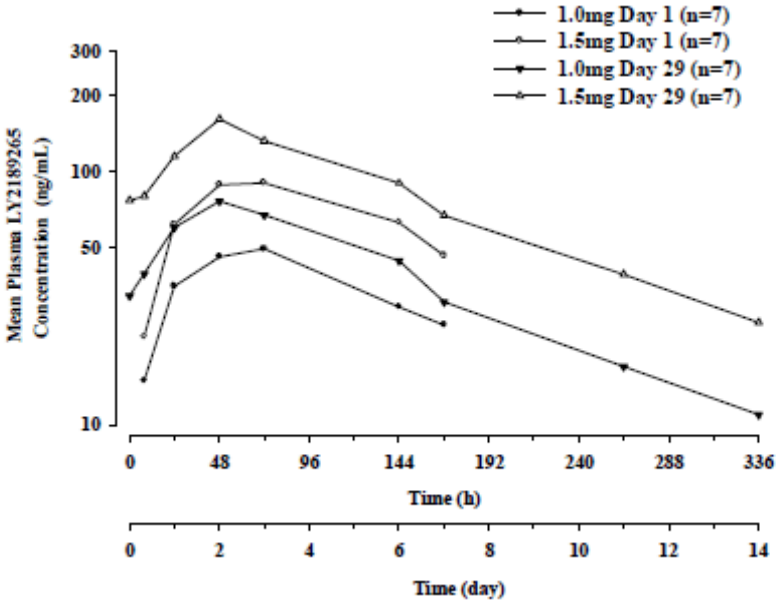


Figure 30 DULAGLUTIDE arithmetic mean plasma concentration-time profiles following subcutaneous doses of DULAGLUTIDE (GBCL)

Table 30 Summary of PK Parameters following a dose of DULAGLUTIDE by Dose Group on Day 1 and Day 29. (GBCL)

Reference ID: 3520514

Geometric Mean (CV%)						
	DULAGLUTIDE		DULAGLUTIDE		Overall	
	Day 1	Day 29	Day 1	Day 29	Day 1	Day 29
N	7	7	7	7	14	14
C_{max} (ng/mL)	52.4 (43)	71.8 (43)	87.8 (39)	152 (40)	NC	NC
t_{max} [a] (h)	72.00 (48.00 - 144.00)	48.00 (48.00 - 144.00)	72.00 (48.00 - 72.00)	48.00 (48.00 - 72.00)	72.00 (48.00 - 144.00)	48.00 (48.00 - 144.00)
$t_{1/2,ss}$ [b] (h)	NC	110 (86.5 - 221)	NC	108 (94.3 - 131)	NC	109 (86.5 - 221)
$AUC_{(0-168h)}$ (ng•h/mL)	5750 (28)	8690 (41)	10900 (33)[c]	18000 (31)	NC	NC
$AUC_{(0-\infty)}$ (ng•h/mL)	NC	13700 (33)	NC	28900 (30)	NC	NC
CL_{ss}/F (L/h)	NC	0.115 (41)	NC	0.0834 (31)	NC	0.0979 (39)
V_{ss}/F (L)	NC	20.1 (63)	NC	15.0 (38)	NC	17.4 (52)
R_A	NC	1.51 29	NC	1.64 (18)[c]	NC	1.57 (24)[d]

Abbreviations: $AUC_{(0-168h)}$ = area under the concentration-time curve from time zero to 168 hours (one dosing interval) after dose, which is calculated using plasma concentrations at pre-dose, 8, 24, 48, 72,144 and 168 hours post-dose; $AUC_{(0-\infty)}$ = area under the concentration-time curve from zero to infinity; CL_{ss}/F = apparent total body clearance of drug at steady state; C_{max} = observed maximum concentration; NC = parameter not calculated; RA = accumulation ratio calculated using AUC(0-168h)Week 5/AUC(0-168h)Week 1; $t_{1/2ss}$ = half-life associated with the terminal rate constant (lambda z) in non-compartmental analysis at steady state; t_{max} = time of maximum observed drug concentration; V_{ss}/F = apparent volume of distribution during the terminal phase at steady state.

[a] Median (range)

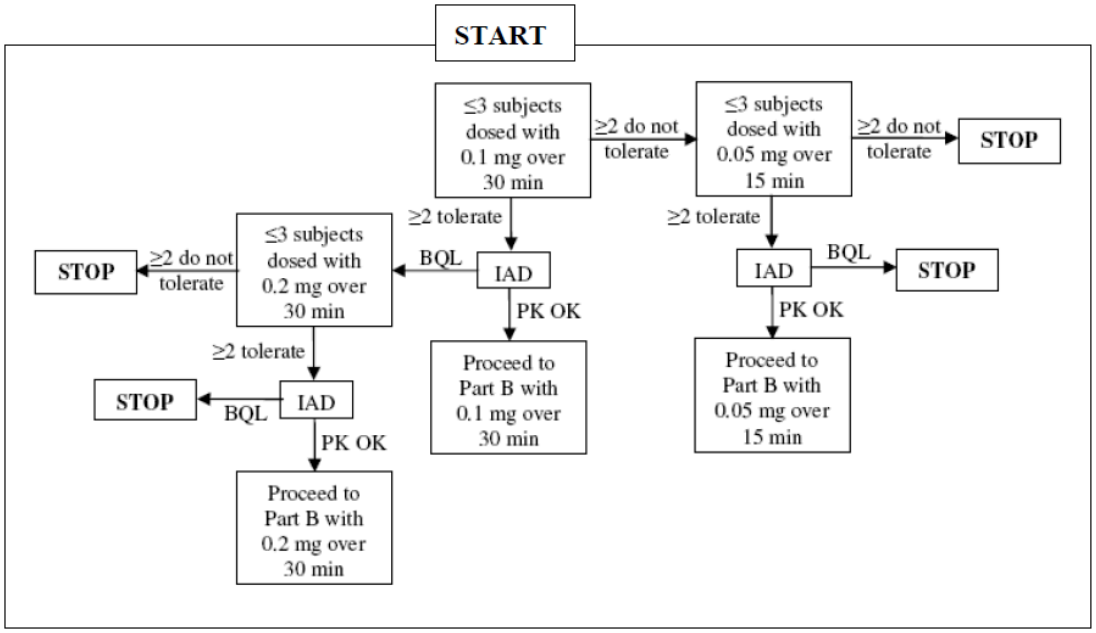
[b] Geometric mean (range)

[c] n = 6. AUC for Subject 106 was not calculated because t_{last} was at 144h.

[d] n = 13. AUC for Subject 106 was not calculated because t_{last} was at 144h.

Reference ID: 3520514

4.1.5 Study GBDR: absolute and relative bioavailability



Abbreviations: BQL = below the quantifiable limit; IAD = interim analysis of data; PK = pharmacokinetics; STOP = do not proceed to Part B

Figure 31 Study design (GBDR)

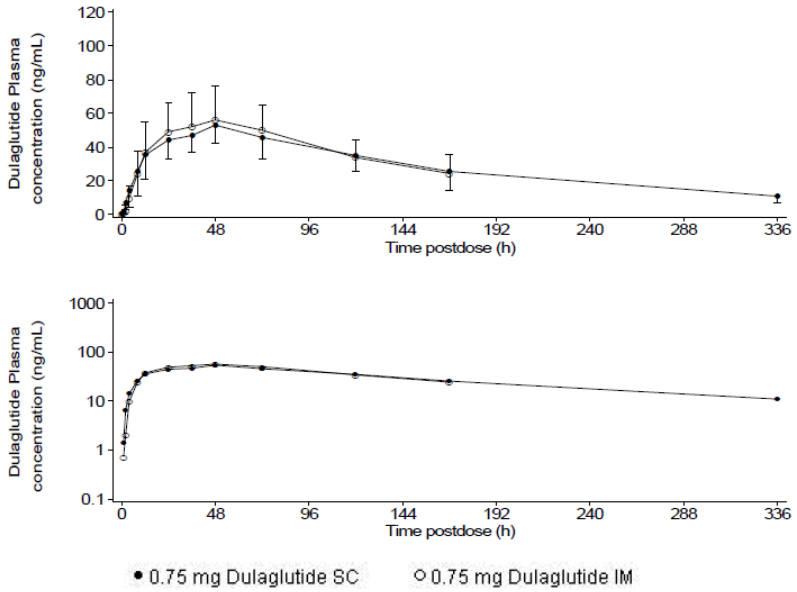


Figure 32 Arithmetic mean (+SD) plasma concentration versus time profiles of dulaglutide following administration of 0.75 mg dulaglutide via SC and IM injection (upper panel: linear scale; lower panel: semi-logarithmic scale) (GBDR)

Table 31 Summary of the PK Parameters of Dulaglutide in Plasma Following Administration of 0.75 mg Dulaglutide via SC and IM Injection (GBDR)

Reference ID: 3520514

Parameter	Geometric Mean (Geometric CV%)	
	0.75 mg Dulaglutide IM (N=7)	0.75 mg Dulaglutide SC (N=8)
AUC(0-∞) (ng·h/mL)	9730 (44)	10200 (36)
AUC(0-168) (ng·h/mL)	6370 (30)	6220 (25)
C_{max} (ng/mL)	57.2 (30)	54.2 (18)
t_{max}[a] (h)	48.0 (12.0, 72.0)	48.0 (12.0, 48.0)
$t_{1/2}$[b] (h)	95.5 (54.8, 138)	107 (49.1, 150)
CL/F (L/h)	0.0771 (44)	0.0734 (36)
V_z/F (L)	10.6 (19)	11.3 (24)
$F_{relative}$ [AUC(0-∞)]	0.958 (14)	

Abbreviations: AUC(0-168) = area under the concentration versus time curve (AUC) from time zero to 168 hours postdose; AUC(0-∞) = AUC from 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; $F_{relative}$ [AUC(0-∞)] = relative bioavailability (IM versus SC dose routes) based on AUC(0-∞); IM = intramuscular; N = number of subjects; NA = not applicable; SC = subcutaneous; $t_{1/2}$ = apparent plasma terminal elimination half-life; t_{max} = time of maximum observed drug concentration; V_z/F = apparent volume of distribution calculated after extra-vascular administration.

[a] Median (range); [b] Geometric mean (range).

Reference ID: 3520514

4.1.6 Study GBCN: comparability among injection sites and effect of BMI

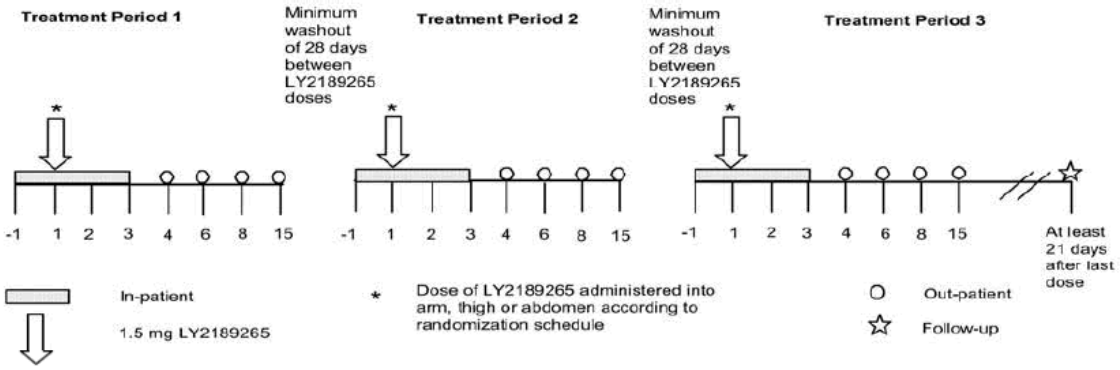


Figure 33 Study Design (GBCN)

Table 32 Subject Demographics (GBCN)

		1.5 mg LY2189265		
		Low BMI (N=25)	High BMI (N=20)	Overall (N=45)
Age (years)	Mean (SD)	45.8 (17.3)	43.8 (10.9)	44.9 (14.6)
	Range	19-71	22-67	19-71
Sex	Male	15	14	29
	Female	10	6	16
Race	White	24	19	43
	Black or African American	1	1	2
Body weight (kg)	Mean (SD)	70.83 (12.55)	101.66 (12.50)	84.53 (19.83)
	Range	52.2-104.8	83.4-123.3	52.2-123.3
BMI (kg/m^2)	Mean (SD)	24.41 (2.02)	34.13 (3.51)	28.73 (5.61)
	Range	19.4-27.0	30.7-44.7	19.4-44.7

Abbreviation: BMI = body mass index; N = number of subjects; SD = standard deviation

Reference ID: 3520514

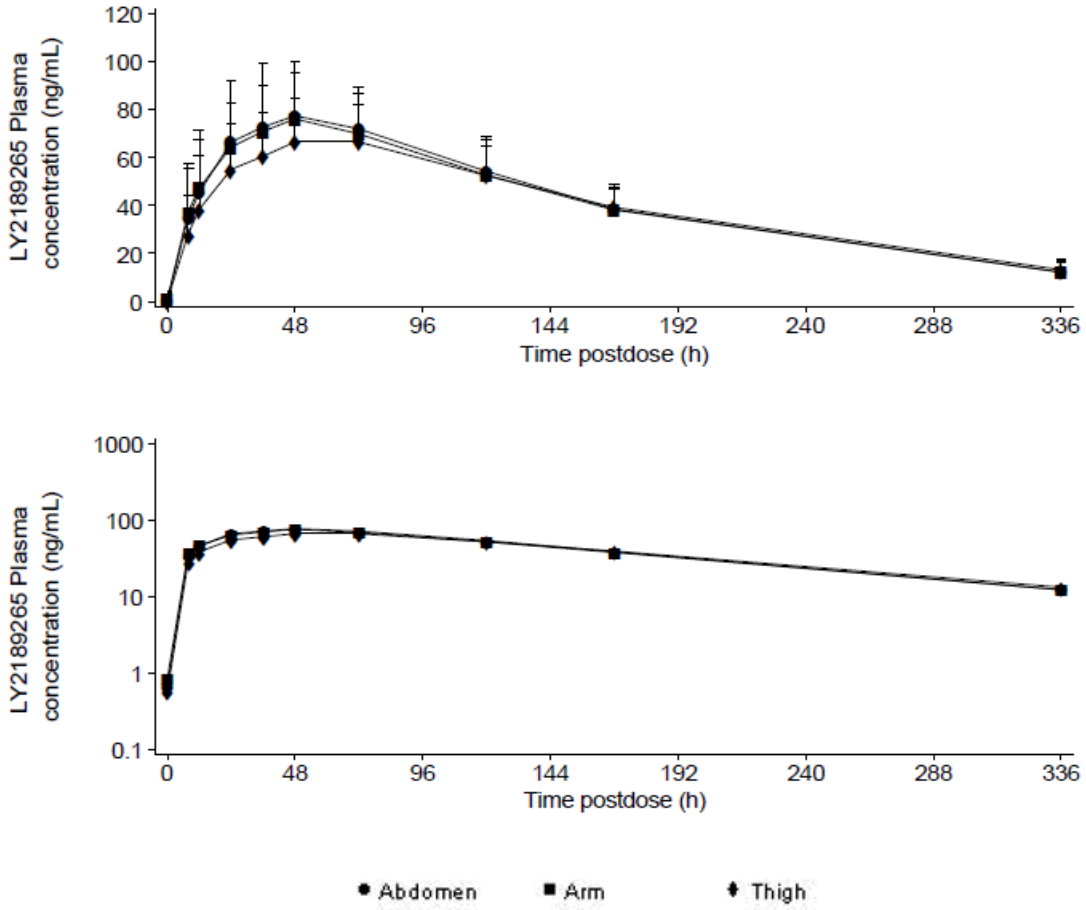


Figure 34 Arithmetic mean (+SD) plasma concentration versus time profiles across BMI **groups and administration sites** following single dose administration of 1.5 mg by **SC** injection (upper panel: linear scale; lower panel: semi-logarithmic scale).

Reference ID: 3520514

Table 33 Summary of the PK Parameters in Plasma Following SC **1.5 mg** (across both BMI Groups) (GBCN)

	Geometric Mean (CV%)		
	Overall BMI		
Parameter	Abdomen (N=43)	Arm (N=40)	Thigh (N=44)
$AUC(0\text{-}t_{last})$ (ng·h/mL)	13200 (24)	13000 (24)	12600 (21)
$AUC(0\text{-}\infty)$ (ng·h/mL)	15100 (24)	14800 (25)	14600 (18)
AUC(0-168) (ng·h/mL)	9410 (26)	9270 (24)	8660 (24)
C_{max} (ng/mL)	76.9 (30)	76.1 (25)	68.5 (27)
t_{max}[a] (h)	48.0 (24.0, 72.0)	48.0 (12.0, 72.0)	48.0 (12.0, 120)
$t_{1/2}$[b] (h)	102 (80.7, 155)	103 (75.0, 146)	107[d] (75.6, 194)
CL/F (L/h)	0.0996 (24)	0.101 (25)	0.101[d] (20)
V_z/F (L)	14.6 (28)	15.0 (26)	15.5[d] (25)
F_{rel} (arm/abdomen) (%)	NA	96.6[c] (14)	NA
F_{rel} (thigh/abdomen) (%)	NA	NA	99.0[e] (13)

Abbreviations: $AUC(0\text{-}t_{last})$ = area under the plasma concentration-time curve from time zero up to the last quantifiable concentration; $AUC(0\text{-}\infty)$ = area under the plasma concentration-time curve from time zero to infinity; AUC(0-168) = area under the plasma concentration-time curve from time zero up to 168 hours postdose; BMI = body mass index; CL/F = apparent total plasma clearance; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; F_{rel} (arm/abdomen) = relative bioavailability of LY2189265 after subcutaneous injection into the arm compared to the abdominal wall; F_{rel} (thigh/abdomen) = relative bioavailability of LY2189265 after subcutaneous injection into the thigh compared to the abdominal wall; N = number of subjects; NA = not applicable; $t_{1/2}$ = apparent plasma terminal elimination half-life; t_{max} = time of maximum observed plasma concentration; V_z/F = apparent volume of distribution during the terminal phase.
[a] Median (range); [b] Geometric mean (range); [c] N=39; [d] N=41; [e] N=40.

Reference ID: 3520514

Table 34 Summary of the PK Parameters in Plasma Following SC **1.5 mg** (by BMI Group) (GBCN)

	Geometric Mean (CV%)					
	Low BMI			High BMI		
Parameter	Abdomen (N=23)	Arm (N=22)	Thigh (N=24)	Abdomen (N=20)	Arm (N=18)	Thigh (N=20)
AUC(0-t_{last}) (ng·h/mL)	15000 (22)	14800 (21)	14100 (16)	11400 (16)	11100 (17)	11100 (19)
AUC(0-∞) (ng·h/mL)	17000 (22)	16800 (23)	15800[c] (16)	13100 (18)	12700 (18)	13300[e] (17)
AUC(0-168) (ng·h/mL)	10900 (23)	10600 (20)	9690 (18)	7950 (17)	7870 (16)	7580 (22)
C_{max} (ng/mL)	90.3 (27)	86.9 (20)	77.1 (22)	64.0 (20)	64.7 (20)	59.5 (26)
t_{max}[a] (h)	48.0 (24.0, 72.0)	48.0 (12.0, 72.0)	48.1 (12.0, 120)	48.0 (36.0, 72.0)	48.0 (24.0, 72.0)	48.0 (36.0, 120)
$t_{1/2}$[b] (h)	100 (80.7, 146)	102 (75.0, 146)	103[d] (75.6, 194)	103 (81.7, 155)	104 (83.2, 133)	111[f] (87.1, 186)
CL/F (L/h)	0.0881 (22)	0.0891 (23)	0.0927[d] (19)	0.115 (18)	0.118 (18)	0.112[f] (17)
V_z/F (L)	12.7 (26)	13.1 (25)	13.8[d] (21)	17.1 (19)	17.7 (17)	17.9[f] (21)
F_{rel} (arm/abdomen) (%)	NA	96.5[c] (17)	NA	NA	96.8 (9)	NA
F_{rel} (thigh/abdomen) (%)	NA	NA	96.2[c] (16)	NA	NA	102[f] (9)

Abbreviations: AUC(0-t_{last}) = area under the plasma concentration-time curve from time zero up to the last quantifiable concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero to infinity; AUC(0-168) = area under the plasma concentration-time curve from time zero up to 168 hours postdose; BMI = body mass index; CL/F = apparent total plasma clearance; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; F_{rel} (arm/abdomen) = relative bioavailability of LY2189265 after subcutaneous injection into the arm compared to the abdominal wall; F_{rel} (thigh/abdomen) = relative bioavailability of LY2189265 after subcutaneous injection into the thigh compared to the abdominal wall; N = number of subjects; NA = not applicable; $t_{1/2}$ = apparent plasma terminal elimination half-life; t_{max} = time of maximum observed plasma concentration; V_z/F = apparent volume of distribution during the terminal phase.
[a] Median (range); [b] Geometric mean (range); [c] N=21; [d] N=22; [e] N=18; [f] N=19.

Table 35 Statistical Assessment of the PK Parameters in Plasma Following SC **1.5 mg** (by BMI Group) (GBCN)

BMI Group	Parameter	Location of Administration	Geometric LS Means (90% CI)	Ratio of Geometric LS Means (vs. Abdomen) (90% CI)	Ratio of Geometric LS Means (vs. Low BMI) (90% CI)
Low BMI	AUC(0-∞) (ng·h/mL)	Abdomen (N=23)	17146 (16025, 18344)		
		Arm (N=22)	16620 (15528, 17789)	0.969 (0.926, 1.01)	
		Thigh (N=21)	16490 (15398, 17659)	0.962 (0.918, 1.01)	
	AUC(0-168) (ng·h/mL)	Abdomen (N=23)	10958 (10250, 11715)		
		Arm (N=22)	10566 (9875, 11306)	0.964 (0.903, 1.03)	
		Thigh (N=24)	9722 (9102, 10385)	0.887 (0.833, 0.945)	
	C_{max} (ng/mL)	Abdomen (N=23)	90.5 (83.8, 97.8)		
		Arm (N=22)	86.6 (80.0, 93.7)	0.956 (0.880, 1.04)	
		Thigh (N=24)	77.1 (71.5, 83.2)	0.852 (0.785, 0.924)	
High BMI	AUC(0-∞) (ng·h/mL)	Abdomen (N=20)	13051 (12113, 14061)		0.761 (0.688, 0.842)
		Arm (N=18)	12750 (11818, 13755)	0.977 (0.930, 1.03)	0.767 (0.693, 0.849)
		Thigh (N=18)	13283 (12315, 14327)	1.02 (0.969, 1.07)	0.806 (0.727, 0.892)
	AUC(0-168) (ng·h/mL)	Abdomen (N=20)	7922 (7367, 8520)		0.723 (0.655, 0.798)
		Arm (N=18)	7888 (7316, 8505)	0.996 (0.928, 1.07)	0.747 (0.675, 0.826)
		Thigh (N=20)	7571 (7040, 8142)	0.956 (0.893, 1.02)	0.779 (0.706, 0.859)
	C_{max} (ng/mL)	Abdomen (N=20)	63.9 (58.7, 69.4)		0.705 (0.629, 0.791)
		Arm (N=18)	64.7 (59.3, 70.6)	1.01 (0.925, 1.11)	0.747 (0.664, 0.840)
		Thigh (N=20)	59.4 (54.6, 64.6)	0.930 (0.852, 1.01)	0.770 (0.687, 0.862)

Abbreviations: AUC(0-∞) = area under the plasma concentration-time curve from time zero to infinity; AUC(0-168) = area under the plasma concentration-time curve from time zero up to 168 hours postdose; BMI = body mass index; CI = confidence interval; C_{max} = maximum observed plasma concentration; LS = least squares; N = number of subjects.
Model: Log(PK) = Subject with Sequence and BMI Group + Sequence + BMI Group + Period + Location + BMI Group*Location + Random Error.

Table 36 Variability Estimates of the PK Parameters in Plasma Following SC **1.5 mg (GBCN)**

Reference ID: 3520514

Parameter	CV% (90% CI)	
	Between-subject	Within-subject
AUC(0-∞) (ng·h/mL)	17.8 (14.7, 22.7)	9.03 (7.94, 10.5)
AUC(0-168) (ng·h/mL)	14.6 (11.7, 19.6)	12.9 (11.4, 15.0)
C_{max} (ng/mL)	15.2 (12.0, 21.3)	16.7 (14.7, 19.3)

Abbreviations: AUC(0-∞) = area under the plasma concentration-time curve from time zero to infinity; AUC(0-168) = area under the plasma concentration-time curve from time zero up to 168 hours postdose; CI = confidence interval; C_{max} = maximum observed plasma concentration; CV = coefficient of variation.
Model: Log(PK) = Subject with Sequence and BMI Group + Sequence + BMI Group + Period + Location + BMI Group*Location + Random Error.

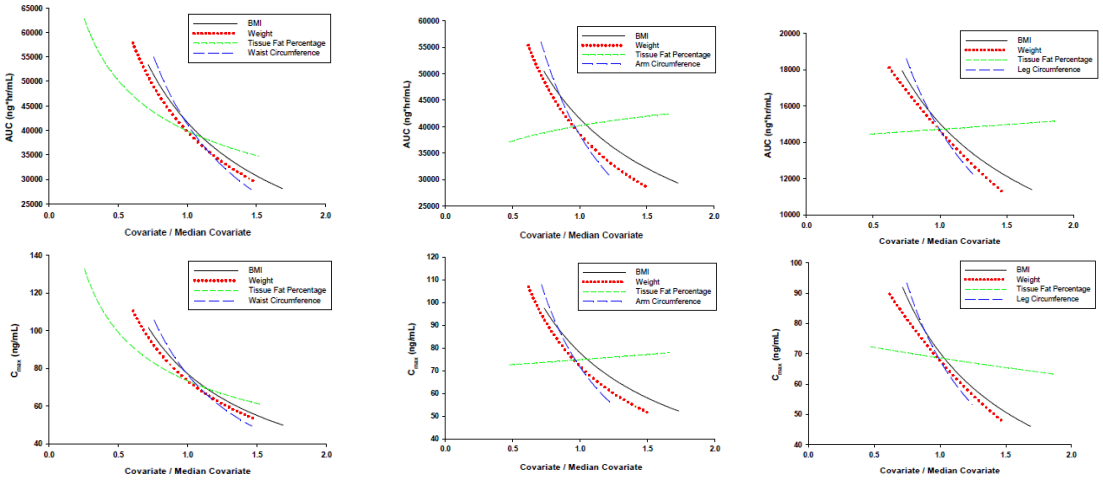


Figure 35 The relationship between AUC(0-∞) (upper panel) and C_{max} (lower panel) and the 4 covariates (BMI, wei**ght, tissue fat percentage, and** waist circumference, expressed as fraction of median) for the lower abdomen (left), upper arm (center), and upper leg (right) injection sites.

Reference ID: 3520514

4.1.7 Pharmacodynamic Studies and Results

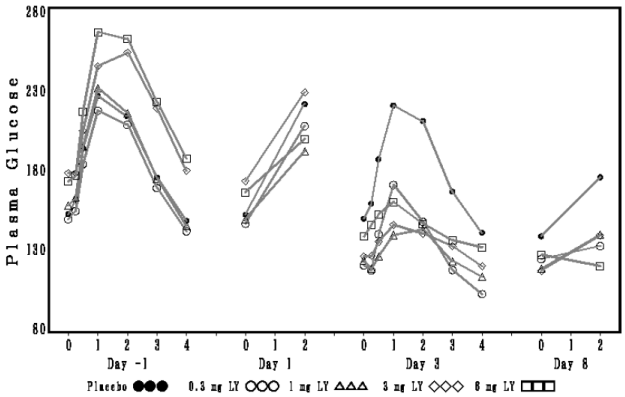


Figure 36 Mean plasma glucose concentration versus time profiles after a single dose (Day 1) of placebo, 0.3, 1, 3 and 6 mg **dulaglutide** 15 minutes prior to breakfast to Japanese patients with type 2 diabetes (Study GBCB)

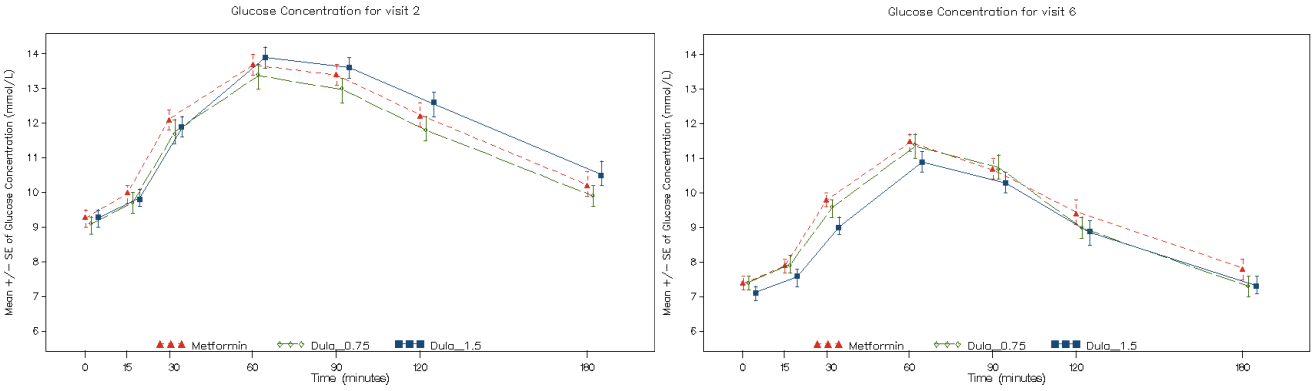


Figure 37 Glucose concentration curves (means ±SE) by treatment: at Visit 2 (baseline, upper) and Visit 6 (26 week, lower, Source: Figure GBDC.11.6)

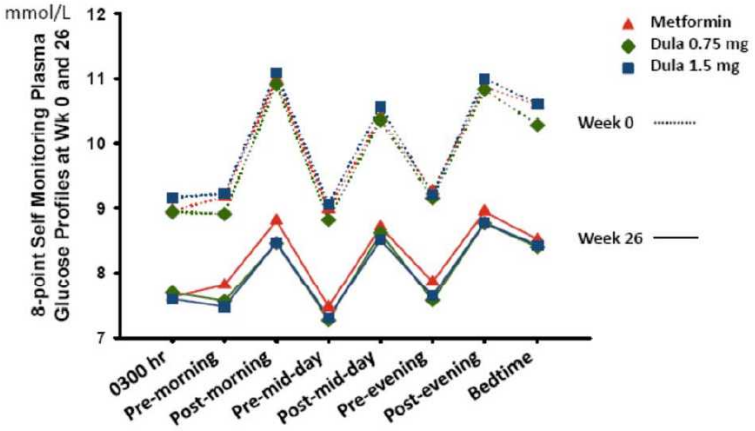


Figure 38 8-point self-monitoring plasma glucose profiles at baseline (Week 0) and Week 26 (Intent-to-Treat Population). (Source: Figure GBDC.11.2)

Reference ID: 3520514

Table 37 Least-squares **(LS)** Mean Differences of Glucose AUC Following OGTT Relative to Placebo (GBCD)

			Comparison to Placebo		
Treatment	n	LS Mean	Diff.	90% C.I.	P-value
Placebo	11	558.50			
0.05 mg LY	3	635.68	77.17	(-41.94, 196.28)	0.28
0.3 mg LY	6	543.40	-15.11	(-107.92, 77.70)	0.78
1 mg LY	4	534.12	-24.39	(-131.16, 82.38)	0.70
3 mg LY	3	391.17	-167.33	(-286.44, -48.22)	0.02
5 mg LY	8	315.99	-242.52	(-327.49, -157.54)	<.01
8 mg LY	6	324.27	-234.23	(-327.04, -141.42)	<.01
Model: Value = Dose + (error)					

Table 38 Summary and Analysis of Fasting Blood Glucose, MMRM by Treatment Group and Visit from Baseline to 52 Weeks, Intent-to-Treat Population without Post-Rescue Values (GBDC)

Variable analyzed: Fasting Blood Glucose (mmol/L)

Visit (Week)	Treatment	N	Actual value Mean	SD	Min	Median	Max	Change from Baseline Mean	SD	Min	Median	Max	LSM	SE
Baseline	Metformin	264	8.96	2.40	4.60	8.40	18.50							
	Dula_0.75	265	8.93	2.63	4.00	8.30	20.30							
	Dula_1.5	267	9.12	2.79	4.60	8.50	23.30							
6 (26)	Metformin	245	7.50	1.92	4.10	7.10	18.30	-1.34	2.10	-9.90	-1.10	8.30	-1.34	0.13
	Dula_0.75	247	7.37	2.00	1.10	6.90	16.20	-1.42	2.09	-10.10	-1.20	7.70	-1.46	0.13
	Dula_1.5	244	7.27	2.15	4.20	6.80	20.40	-1.70	2.50	-11.50	-1.60	13.40	-1.61	0.13
	Pairwise p-value, 95% CI*a							vs Metformin			vs Dula_0.75			
	Dula_0.75							.451, (-0.43, 0.19)						
	Dula_1.5							.079, (-0.59, 0.03)			.313, (-0.47, 0.15)			
8 (52)	Metformin	194	7.60	2.15	4.40	7.10	19.80	-1.18	2.25	-9.10	-1.15	7.90	-1.15	0.14
	Dula_0.75	210	7.82	2.25	4.20	7.25	15.40	-0.98	2.13	-7.90	-0.90	6.60	-1.00	0.14
	Dula_1.5	207	7.20	2.01	3.40	6.70	18.90	-1.64	2.16	-10.70	-1.50	5.10	-1.56	0.14
	Pairwise p-value, 95% CI*a							vs Metformin			vs Dula_0.75			
	Dula_0.75							.402, (-0.20, 0.51)						
	Dula_1.5							.025, (-0.76, -0.05)			.002, (-0.91, -0.21)			

Table 39 Summary and Analysis of AUC Glucose (0-3hrs) ANCOVA at 26 Weeks and 52 Weeks Test Meal Population without Post-Rescue Values **(Source: Table GBDC 11.10)**

Variable analyzed: AUC Glucose (mmol*hr/L)

Visit (Week)	Treatment	N	Actual value Mean	SD	Min	Median	Max	Change from Baseline Mean	SD	Min	Median	Max	LSM	SE
Baseline	Metformin	132	38.27	10.78	20.56	36.18	73.85							
	Dula_0.75	125	37.18	11.20	22.34	34.50	77.68							
	Dula_1.5	125	38.99	11.04	20.68	36.63	87.30							
6 (26)	Metformin	94	29.83	7.77	18.13	28.44	71.80	-7.27	9.03	-39.19	-6.41	29.01	-7.65	0.77
	Dula_0.75	99	29.37	8.34	16.14	27.99	60.14	-7.30	7.80	-25.71	-6.44	21.14	-8.01	0.76
	Dula_1.5	96	28.83	8.66	12.83	25.98	53.95	-9.46	7.18	-34.05	-8.68	5.99	-9.24	0.76
	Pairwise p-value, 95% CI*a							vs Metformin			vs Dula_0.75			
	Dula_0.75							.706, (-2.23, 1.52)						
	Dula_1.5							.099, (-3.47, 0.30)			.195, (-3.09, 0.63)			
8 (52)	Metformin	83	31.32	8.37	20.24	29.45	61.40	-6.24	8.52	-39.30	-6.24	15.78	-7.00	0.95
	Dula_0.75	88	30.33	8.72	16.71	28.58	54.30	-4.94	7.73	-24.66	-5.38	20.04	-6.89	0.93
	Dula_1.5	88	28.90	8.13	13.13	27.26	58.40	-8.96	8.98	-36.30	-8.74	16.81	-9.43	0.91
	Pairwise p-value, 95% CI*a							vs Metformin			vs Dula_0.75			
	Dula_0.75							.919, (-2.02, 2.24)						
	Dula_1.5							.024, (-4.54, -0.32)			.017, (-4.63, -0.45)			

Reference ID: 3520514

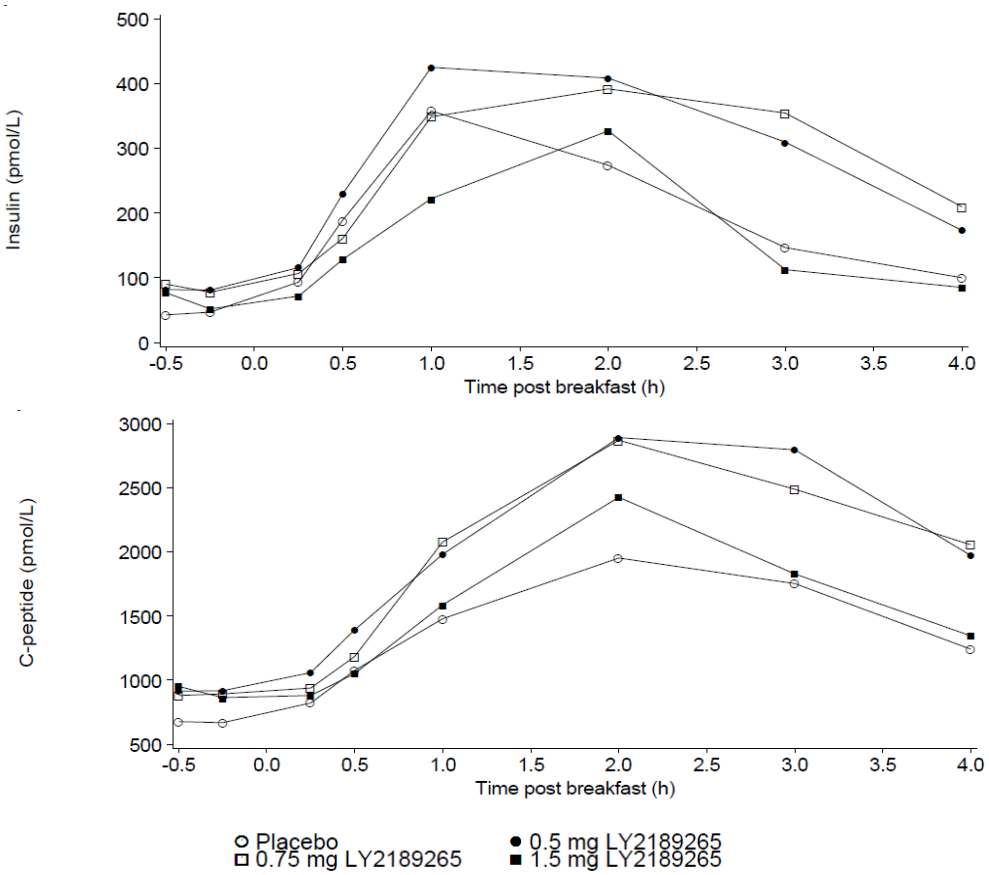


Figure 39 Arithmetic mean plasma insulin (upper) and C-peptide (lower) concentration versus time profiles **on** Day 3 following subcutaneous administration of LY2189265 or placebo on Day 1 (Study GBCT)

Reference ID: 3520514

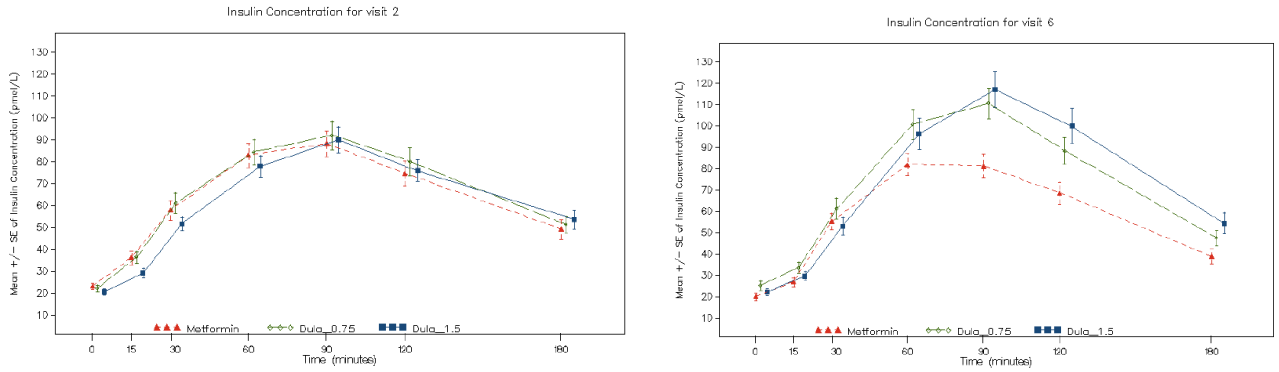


Figure 40 Insulin concentration curves (means ±SE) by treatment: at Visit 2 (baseline, upper) and Visit 6 (26 week, lower) (Study GBDC)

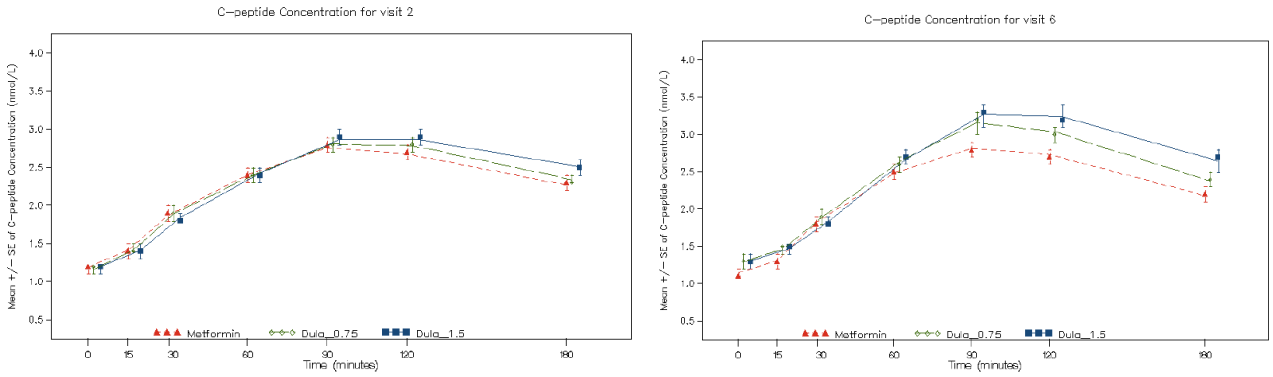


Figure 41 C-peptide concentration curves (means ±SE) by treatment: at Visit 2 (baseline, upper) and Visit 6 (26 week, lower) (Study GBDC)

Reference ID: 3520514

4.1.8 Study GBCI: Insulin Secretion in Response to IV Glucose

Title of Study: The Effect of Dulaglutide (LY2189265) on Insulin Secretion in Response to Intravenous Glucose Infusion	
Number of Investigators: This single-center study included 1 principal investigator, Christoph Kapitza, MD, who was responsible for entering all subjects into the study.	
Study Center: This study was conducted at Profil Institute, Neuss, Germany.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first subject visit: 14 February 2011 Date of last subject visit: 25 August 2011	**Phase of Development:** 1
Objectives: The primary objective of the study was to assess the effect of dulaglutide (LY2189265) on first- and second-phase insulin secretion in response to intravenous (IV) glucose challenge in subjects with type 2 diabetes mellitus (T2DM). The secondary objectives were to assess the effect of dulaglutide on insulin sensitivity; to assess the effect of dulaglutide on β-cell function; and to further evaluate the safety and tolerability of dulaglutide.	
Study Design: A single-center, randomized, placebo-controlled, subject and investigator blinded, single-dose, 2-period crossover study in male and female subjects who were either diagnosed with T2DM or healthy subjects with normal glucose tolerance. Subjects were randomized to receive the following 2 treatments in 2 different periods, with a washout period of at least 28 days between doses: dulaglutide administered as a subcutaneous injection of 1.5 mg; and placebo administered as a subcutaneous injection. On Day 1 of Periods 1 and 2, all subjects were to receive a single subcutaneous injection of either dulaglutide or placebo. On Day 3 of each period, subjects were resident in the clinical research unit (CRU) and underwent a 6-hour insulin infusion titrated to normalize their blood glucose, followed by an IV glucose bolus administered as dextrose solution, which served to stimulate first- and second-phase insulin secretion. Three hours later, subjects were administered a second dextrose bolus followed immediately by an infusion of 20% dextrose and, 15 minutes after the start of the 20% dextrose infusion, by a glucagon bolus to assess the effects of dulaglutide on the β-cell insulin response to glucagon stimulation in comparison to placebo.	
Number of Subjects: Planned: Up to 35 subjects were to be enrolled, so that approximately 24 subjects (16 subjects with T2DM and 8 healthy subjects) completed the study. Enrolled: 32 subjects (10 healthy subjects, 22 subjects with T2DM) Treated (at least 1 dose): 32 subjects (10 healthy subjects, 22 subjects with T2DM) Completed: 29 subjects (10 healthy subjects, 19 subjects with T2DM)	
Diagnosis and Main Criteria for Inclusion: Subjects were required to be men or women aged between 18 and 65 years, inclusive. Subjects were required to be overtly healthy and with a body mass index (BMI) between 19 and 25 kg/m^2, inclusive (healthy group), or diagnosed with T2DM within the past 10 years and with a BMI between 22 and 40 kg/m^2 (T2DM group). Subjects from each population (T2DM or healthy subjects) were aged-matched, as far as possible, such that the mean ages for each group differed from each other by no more than 10 years. Subjects with T2DM were either managed by diet and exercise or receiving a stable dose of metformin for at least 4 weeks prior to the study. Subjects treated with metformin were required to abstain from taking their metformin beginning on Day -3 (prior to dosing) in each period through Day 4 when they were allowed to restart their metformin.	
Study Drug, Dose, and Mode of Administration: Dulaglutide was provided as single-use syringes for subcutaneous injection. Syringes contained 0.5 mL of 3 mg/mL dulaglutide solution (1.5 mg), supplied from lot number CT555819.	

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Reference Therapy, Dose, and Mode of Administration: Injectable placebo was provided as a matching single-use syringe for subcutaneous injection. Placebo syringes contained all of the inactive ingredients found in the dulaglutide solution, but did not contain any active drug.

Duration of Treatment:
Subjects were administered a single injection of dulaglutide or placebo in each of Study Periods 1 and 2. During each period, overnight stays in the CRU on Days -1 and 3 were optional at the discretion of the investigator; however, all subjects were required to stay in the CRU overnight on Day 2. Dulaglutide or placebo was administered on Day 1 of each period. There was a washout period of at least 28 days between doses of study drug. The poststudy follow-up visit occurred at least 21 days after the subject's last dosing day, or at the end of the subject's participation in the study. The total study duration was approximately 2 months for each subject who completed the study.

Variables:
Pharmacokinetic: Blood samples were taken prior to dosing in Period 2 and 48 hours postdose in Periods 1 and 2 for the measurement of plasma concentrations of dulaglutide.
Pharmacodynamic: Venous blood samples were collected for the assessment of hemoglobin A1c (HbA1c), plasma glucose, insulin, C-peptide, glucagon-like peptide-1, lipid panel, and glucagon.
Safety: Adverse events (AEs), vital signs, single safety electrocardiogram (ECG), laboratory tests, physical examination, dulaglutide antibody sampling, amylase, lipase.

Evaluation Methods:
Bioanalytical: Plasma concentrations of dulaglutide were determined using a validated radioimmunoassay.
Pharmacokinetic: Plasma concentrations of dulaglutide were listed and summarized by subject group.
Pharmacodynamic:
Primary Pharmacodynamic Parameters
For the calculation of all primary pharmacodynamic (PD) parameters (for both first and second phase insulin secretion), data were baseline corrected prior to parameter calculation. The baseline was the mean of the insulin concentrations obtained between -30 and 0 minutes relative to the first dextrose bolus (at 360 and 390 minutes post the start of the insulin infusion).
The primary PD parameters to assess first-phase insulin response on Day 3 were baseline-corrected area under the plasma insulin concentration-time curve from 0 to 10 minutes following the first dextrose bolus (i.e. from 390 to 400 minutes post insulin infusion; $INSAUC_{390-400}$) and baseline-corrected maximum insulin concentration from 0 to 10 minutes following the first dextrose bolus ($INSC_{max390-400}$). The primary PD parameters to assess second-phase insulin response were baseline-corrected area under the plasma insulin concentration-time curve from 10 to 180 minutes following the first dextrose bolus (i.e. from 400 to 570 minutes post insulin infusion; $INSAUC_{400-570}$) and baseline-corrected maximum insulin concentration from 10 to 180 minutes following the first dextrose bolus ($INSC_{max400-570}$). The insulin area under the curve (AUC) was calculated using the linear trapezoidal method.
Secondary Pharmacodynamic Parameters for Assessment of First- and Second-Phase Insulin Secretion For the calculation of all secondary PD parameters post first glucose challenge (except glucose disappearance constant [Kg]), data were baseline corrected prior to parameter calculation. For the plasma C-peptide parameters (for both first- and second-phase insulin secretion), the baseline was the mean of the C-peptide concentrations obtained between -30 and 0 minutes relative to the first dextrose bolus (i.e. at 360 and 390 minutes post the start of the insulin infusion). For the plasma glucose parameters (for both first- and second-phase insulin secretion), the baseline was the mean of the plasma glucose concentrations obtained between -15 and 0 minutes relative to the first dextrose bolus (i.e. at 380, 385, and 390 minutes post the start of the insulin infusion).
The secondary PD parameters calculated after the first glucose challenge were as follows: baseline-corrected area under the plasma C-peptide and glucose concentration-time curves from 0 to 10 minutes following the first dextrose bolus ($CpepAUC_{390-400}$ and $GluAUC_{390-400}$, respectively); baseline-corrected maximum C-peptide and glucose concentrations from 0 to 10 minutes following the first dextrose bolus ($CpepC_{max390-400}$; $GluC_{max390-400}$, respectively); baseline-corrected area under the plasma C-peptide and glucose concentration-

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Summary:

A total of 32 subjects (22 male and 10 female) between the ages of 43 and 63 years participated in this study. Ten subjects (7 males and 3 females, aged 43 to 59 years) were healthy subjects and 22 subjects (15 males and 7 females, aged 44 to 63 years) had T2DM. The subjects with T2DM in this study had baseline (Period 1, Day -1) HbA1c values between 6.1% and 8.8% (normal reference range 4% to 6%) and durations of diabetes of approximately 3 months to 12 years at the time of signing the informed consent form. At the predose assessments on Day 1 of each period, subjects with T2DM had mean plasma glucose concentrations between 7.62 and 7.80 mmol/L. Thirteen of the 22 subjects with T2DM were on metformin therapy; the remaining T2DM subjects were on diet and exercise treatment only.

A total of 29 subjects completed the study in accordance with the protocol, and 3 subjects (all of whom had T2DM) did not complete the study. Subject 3008 withdrew her consent during Period 1 for personal reasons. Subjects 3005 and 3022 were withdrawn by the investigator due to AEs that were not considered related to study drugs. **Pharmacokinetics:**

Plasma concentrations of dulaglutide were consistent with the expected values for a 1.5 mg dose for all subjects: mean (±standard deviation) plasma dulaglutide values were 90.4 ± 24.4 ng/mL and 55.9 ± 21.9 ng/mL for healthy subjects and subjects with T2DM, respectively.

Pharmacodynamics:

A 2-sided alpha level of 0.05 was used for the comparisons between treatments and between populations. For all comparisons between healthy and T2DM groups, the results should be interpreted with caution because of the large difference in sample size between the groups.

First- and Second-Phase Insulin Levels

In 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 subcutaneous (SC) administration of 1.5 mg dulaglutide, as compared with placebo. Mean glucose levels following a dextrose bolus appeared to return to baseline more rapidly following administration of 1.5 mg dulaglutide, as compared with placebo, in both groups of subjects.

In both healthy subjects and subjects with T2DM, baseline-corrected first-phase (measured as $INSAUC_{390\text{-}400}$ or $INSC_{max390\text{-}400}$) and second-phase (measured as $INSAUC_{400\text{-}570}$ or $INSC_{max400\text{-}570}$) insulin secretion in response to a 50% dextrose bolus were statistically significantly different following administration of 1.5 mg dulaglutide, as compared with placebo, with the response following 1.5 mg dulaglutide much higher than that of placebo. The fold increase in $INSAUC_{390\text{-}400}$ following administration of dulaglutide versus placebo was greater in subjects with T2DM than in healthy subjects (7.92- and 3.09-fold increase relative to placebo, respectively).

Following administration of placebo, mean $INSAUC_{390\text{-}400}$ and $INSC_{max390\text{-}400}$ were statistically significantly different between subject groups, with mean values being much lower in subjects with T2DM than in healthy subjects. However, a statistically significant difference between subject groups was not observed following administration of 1.5 mg dulaglutide. Mean $INSAUC_{390\text{-}400}$ was approximately 1.8-fold higher in subjects with T2DM treated with dulaglutide compared with healthy subjects on placebo. Following administration of placebo or 1.5 mg dulaglutide, mean $INSAUC_{400\text{-}570}$ was statistically significantly different between subject groups, with higher values observed in subjects with T2DM than in healthy subjects. Mean $INSAUC_{400\text{-}570}$ was approximately 5.2-fold higher in subjects with T2DM treated with dulaglutide compared with healthy subjects on placebo. There were no statistically significant differences in $INSC_{max400\text{-}570}$ between subject groups.

First- and Second-Phase C-Peptide Levels

In healthy subjects and subjects with T2DM, mean baseline-corrected first-phase C-peptide secretion (measured as $CpepAUC_{390\text{-}400}$ and $CpepC_{max390\text{-}400}$) was statistically significantly different between treatments, with much higher values observed following administration of 1.5 mg dulaglutide compared with placebo. The fold increase in $CpepAUC_{390\text{-}400}$ and $CpepC_{max390\text{-}400}$ following administration of dulaglutide versus placebo was greater in subjects with T2DM than in healthy subjects (5.09- and 2.50-fold increase relative to placebo, respectively, for $CpepAUC_{390\text{-}400}$, and 4.06- and 2.48-fold increase relative to placebo, respectively, for $CpepC_{max390\text{-}400}$).

In subjects with T2DM, mean baseline-corrected second-phase C-peptide secretion (measured as $CpepAUC_{400\text{-}570}$) was statistically significantly different between treatments, with higher values observed following administration of 1.5 mg dulaglutide compared with placebo. There was no statistically significant difference in healthy subjects for $CpepAUC_{400\text{-}570}$; although C-peptide levels following administration of dulaglutide appeared to be higher, as compared with placebo, until 480 minutes post the start of the insulin infusion, and the geometric

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LS mean was 28% higher than that of placebo. This is likely due to the high variability (within-subject coefficient of variation of 38.9%) in this measure. In healthy subjects and subjects with T2DM, mean $CpepC_{max400-570}$ was statistically significantly different between treatments, with higher values observed following administration of 1.5 mg dulaglutide compared with placebo.

Following administration of placebo, mean $CpepAUC_{390-400}$ and $CpepC_{max390-400}$ were statistically significantly different between subject groups, with much lower values observed in subjects with T2DM compared with healthy subjects. However, a statistically significant difference between subject groups was not observed following administration of 1.5 mg dulaglutide. $CpepAUC_{390-400}$ and $CpepC_{max390-400}$ were approximately 1.3- and 1.5-fold higher, respectively, in subjects with T2DM treated with dulaglutide compared with healthy subjects on placebo. Following administration of 1.5 mg dulaglutide, mean $CpepAUC_{400-570}$ was statistically significantly different between subject groups, with higher values observed in subjects with T2DM compared with healthy subjects. $CpepAUC_{400-570}$ was not statistically significantly different between subject groups following administration of placebo. There were no statistically significant differences in $CpepC_{max400-570}$ between subject groups.

First- and Second-Phase Glucose Levels

In subjects with T2DM, baseline-corrected plasma glucose levels during first-phase insulin secretion (measured as $GluAUC_{390-400}$) were statistically significantly different between treatments, at the 5% significance level, with higher values observed following administration of 1.5 mg dulaglutide compared with placebo. There was no statistically significant difference in this parameter between treatments in healthy subjects.

Baseline-corrected second-phase plasma glucose levels (measured as $GluAUC_{400-570}$) in healthy subjects and subjects with T2DM were statistically significantly different between treatments, with lower values observed following administration of 1.5 mg dulaglutide compared with placebo. The percentage decrease in $GluAUC_{400-570}$ following administration of dulaglutide versus placebo was greater in healthy subjects than in subjects with T2DM (56% and 29% decrease compared with placebo, respectively). There were no statistically significant differences in $GluC_{max390-400}$ or $GluC_{max400-570}$ between treatments.

Following administration of placebo or 1.5 mg dulaglutide, $GluAUC_{390-400}$ and $GluC_{max390-400}$ were not statistically significantly different between healthy subjects and subjects with T2DM. Following administration of placebo, $GluAUC_{400-570}$ was not statistically significantly different between subject groups. Following administration of 1.5 mg dulaglutide, $GluAUC_{400-570}$ was statistically significantly different between subject groups, being *higher* in subjects with T2DM compared with healthy subjects, consistent with the observation that glucose levels appeared to decrease faster in healthy subjects than in subjects with T2DM. However, $GluAUC_{400-570}$ values were similar between subjects with T2DM treated with dulaglutide and healthy subjects treated with placebo. There were no statistically significant differences in $GluC_{max400-570}$ between subject groups.

In healthy subjects and subjects with T2DM, Kg measured following an IV 50% dextrose bolus was statistically significantly different between treatments, with higher values observed following administration of 1.5 mg dulaglutide compared with placebo. The absolute increase in Kg following administration of dulaglutide versus placebo was greater in healthy subjects than in subjects with T2DM (increases relative to placebo of 1.37 and 0.337, respectively). Following administration of placebo, there was no statistically significant difference in Kg between subject groups. Following administration of 1.5 mg dulaglutide, Kg was statistically significantly different between subject groups, being approximately 50% lower in subjects with T2DM compared with healthy subjects. Mean Kg in subjects with T2DM following administration of dulaglutide was comparable to that in healthy subjects on placebo.

HOMA-B Assessment of β-Cell Function

Mean HOMA-B measured predose on Day 1 showed a trend towards being higher in healthy subjects than in subjects with T2DM, although this was not statistically tested. In subjects with T2DM, 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 with placebo. In healthy subjects, HOMA-B was not statistically significantly different between treatments. HOMA-B was not statistically significantly different between subjects with T2DM and healthy subjects following administration of dulaglutide or placebo.

Assessment of Baseline Insulin Sensitivity

Geometric mean HOMA-IR measured predose on Day 1 was approximately 2.4- to 2.9-fold higher (and geometric mean HOMA-S was approximately 2.4- to 3.0-fold lower) in subjects with T2DM than in healthy subjects. Arithmetic mean QUICKI was approximately 1.3-fold lower in subjects with T2DM than in healthy subjects.

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Assessment of β-Cell Function (Maximal Secretory Capacity)

In healthy subjects and subjects with T2DM, mean plasma insulin and C-peptide concentrations in response to a glucagon challenge were higher following administration of 1.5 mg dulaglutide, as compared with placebo. Mean concentration-time profiles for plasma insulin and C-peptide after a glucagon bolus were similar between healthy subjects and subjects with T2DM following administration of placebo, but showed different responses to dulaglutide.

In healthy subjects and subjects with T2DM, insulin secretion following a glucagon bolus (measured as $INSAUC_{585\text{-}607}$ and $INSC_{max585\text{-}607}$) was statistically significantly different between treatments, with higher values observed following administration of 1.5 mg dulaglutide compared with placebo. The fold increases in $INSAUC_{585\text{-}607}$ and $INSC_{max585\text{-}607}$ following administration of dulaglutide versus placebo were greater in subjects with T2DM than in healthy subjects (1.75- and 1.43-fold increases in $INSAUC_{585\text{-}607}$ relative to placebo, respectively, and 1.39- and 1.22-fold increases in $INSC_{max585\text{-}607}$ relative to placebo, respectively). Mean $INSAUC_{585\text{-}607}$ in subjects with T2DM following administration of dulaglutide was approximately 1.7-fold higher than in healthy subjects following administration of placebo.

In healthy subjects and subjects with T2DM, C-peptide secretion following a glucagon bolus (measured as $CpepAUC_{585\text{-}607}$ and $CpepC_{max585\text{-}607}$) was statistically significantly different between treatments, with higher values observed following administration of 1.5 mg dulaglutide compared with placebo. The fold increase in $CpepAUC_{585\text{-}607}$ appeared to be greater in subjects with T2DM than in healthy subjects (1.48- and 1.33-fold increase relative to placebo, respectively). Mean $CpepAUC_{585\text{-}607}$ in subjects with T2DM following administration of dulaglutide was approximately 1.5-fold higher than in healthy subjects following administration of placebo.

In subjects with T2DM, plasma glucose levels following a glucagon bolus (measured as $GluAUC_{585\text{-}607}$ and $GluC_{max585\text{-}607}$) were statistically significantly different between treatments, with lower values observed following administration of 1.5 mg dulaglutide compared with placebo. In healthy subjects, $GluAUC_{585\text{-}607}$ and $GluC_{max585\text{-}607}$ values were not statistically significantly different between treatments.

For each treatment, there were no statistically significant differences between healthy subjects and subjects with T2DM with respect to the β-cell parameters of insulin, C-peptide, or glucose.

Safety:

The percentage of subjects reporting treatment-emergent AEs across treatments was similar between healthy subjects and subjects with T2DM. Adverse events that were considered by the investigator to be related to study drug (1.5 mg dulaglutide or placebo) were more commonly reported following administration of dulaglutide (reported by 50% of healthy subjects and approximately 33% of subjects with T2DM) than following administration of placebo (reported by 10% of healthy subjects and approximately 14% of subjects with T2DM). All treatment-emergent AEs reported by healthy subjects or subjects with T2DM were mild or moderate in severity. No severe AEs or serious AEs were reported.

The most common drug-related AEs reported by healthy subjects were hypoglycaemia (4 subjects), which occurred on Day 3 of the period in which dulaglutide was administered (following the 50% dextrose bolus infusions), and vomiting (2 subjects). The most common drug-related AEs reported by subjects with T2DM were vomiting (4 subjects), decreased appetite (3 subjects), nausea (2 subjects), and headache (2 subjects).

Four healthy subjects experienced episodes of hypoglycaemia (defined as a blood glucose reading ≤70 mg/dL and/or symptoms of hypoglycaemia including dizziness, faintness, and sweating) following treatment with 1.5 mg dulaglutide. For all 4 subjects, hypoglycaemia occurred on Day 3 of the period in which dulaglutide was administered, following the 50% dextrose bolus infusions that occurred at approximately 390 and 570 minutes post the start of the insulin infusion. All subjects who experienced hypoglycaemia were capable of treating themselves, and the hypoglycaemia resolved following treatment with IV glucose 20%. The hypoglycaemic episodes were all considered by the investigator to be mild in severity and related to dulaglutide.

During the course of the study, there were no clinically significant changes in the clinical chemistry, hematology, or urinalysis data. Isolated values outside the reference range were noted for some subjects, but none of these findings were considered by the investigator to be clinically significant.

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There were no trends in the median amylase or lipase data following administration of 1.5 mg dulaglutide or placebo. There were no changes in amylase or lipase levels for individual subjects that were considered clinically significant by the investigator. No subjects had amylase values more than 3 × the upper limit of normal (ULN) at any time during the study. Three subjects had lipase values more than 3 × ULN during the study, but these occurred at isolated time points only. Since all subjects' lipase values had returned to <2 × ULN within the algorithm-specified 24- to 72-hour retest window, no additional pancreatic assessment was considered necessary. There were no trends in the mean sitting systolic blood pressure or diastolic blood pressure data during the study. Following injection of 1.5 mg dulaglutide SC, an increase in mean pulse rate was observed on Study Days 3 (30 minutes pre insulin infusion) and 4 (discharge) that was not observed following injection of placebo. The maximum observed increase in mean pulse rate was observed on Day 4, and was 11.2 bpm in healthy subjects and 10.9 bpm in subjects with T2DM. Mean pulse rate had returned to predose values by the time of the follow-up visit for both subject groups.

There were no changes in vital signs parameters, ECG parameters, or body weight in individual subjects that were considered clinically significant by the investigator.

No subject developed treatment-emergent dulaglutide anti-drug antibodies (ADAs; defined as a 4-fold increase compared with baseline). No dulaglutide ADA titers were detected in any subject at any time during the study. **Conclusions:**

- Dulaglutide restored first-phase insulin secretion in response to an IV 50% dextrose bolus in subjects with T2DM to a level that exceeded that observed in healthy subjects on placebo.
- Dulaglutide increased second-phase insulin response to an IV dextrose bolus in subjects with T2DM.
- Dulaglutide appears to increase maximal insulin secretion from the β-cells, based on the response to a 1-mg glucagon bolus.
- A single dose of 1.5 mg dulaglutide enhanced β-cell function as assessed by HOMA-B in subjects with T2DM as compared with placebo.
- Dulaglutide was well tolerated in healthy subjects and subjects with T2DM. Gastrointestinal events were the most commonly reported type of AEs by subjects with T2DM.
- There were no safety concerns in terms of clinical laboratory findings, amylase and lipase findings, 12-lead ECGs, or dulaglutide ADAs in subjects exposed to dulaglutide during this study.

4.1.9 Study GBCT: Elderly T2D

Table 40 Patient Demographics (GBCT)

		Treatment (once a week for 6 weeks)			
		Placebo (N=8)	0.5 mg LY2189265 (N=9)	0.75 mg LY2189265 (N=11)	1.5 mg LY2189265 (N=9)
Age[a] (years)	Mean (SD)	67.5 (2.4)	68.9 (3.1)	68.5 (2.7)	68.1 (4.0)
	Range	64[b]-71	65-74	64[b]-74	64[b]-76
Sex	Male	6	7	5	7
	Female	2	2	6	2
Race	White	8	9	11	9
Body weight (kg)	Mean (SD)	91.73 (5.07)	85.19 (15.74)	80.51 (11.95)	86.68 (8.27)
	Range	83.1-98.7	68.0-119.5	64.0-102.0	75.7-102.9
BMI (kg/m^2)	Mean (SD)	30.87 (2.49)	29.01 (4.11)	28.67 (3.79)	29.09 (1.66)
	Range	28.3-34.6	23.6-34.4	22.7-33.1	25.8-31.5
Duration of T2DM (years)	Mean (SD)	8.81 (2.44)	15.52 (6.44)	9.05 (4.03)	10.09 (8.04)
	Range	5.3-13.3	5.3-27.3	3.3-15.4	4.3-30.3
Screening HbA_{1c} (%)	Mean (SD)	6.73 (0.29)	7.34 (1.07)	6.96 (0.42)	6.83 (0.44)
	Range	6.2-7.2	6.1-9.7	6.1-7.5	6.2-7.4

Abbreviations: BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; N = number of patients; SD = standard deviation; T2DM = type 2 diabetes mellitus.

[a] Minimum age was 65; to minimize the risk of a breach in patient privacy, day and month of birth were not captured on Case Report Form, and for the purpose of the study, all patients' date of birth were defaulted to 01 July followed by the actual year of birth and the patient's age was derived from this date. As a result, patients born in 1945 with an actual birthday before 01 July appeared to be 1 year younger than their actual age and would have appeared to be too young to be enrolled into the study if screened before 01 July 2010. The investigator confirmed that all patients born in 1945 who enrolled into the study before 01 July 2010 had an actual birthday before 01 July 1945 and were therefore eligible to participate in the study.

[b] Patients confirmed as being 65 years old at time of enrolment into the study.

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Table 41 Summary of the PK Parameters of DULAGLUTIDE in Plasma Following Subcutaneous Administration of DULAGLUTIDE as Once-weekly Doses for 6 weeks (GBCT)

	Geometric Mean (CV%)					
	0.5 mg LY2189265		0.75 mg LY2189265		1.5 mg LY2189265	
Parameter	Day 1 (N=9)	Day 36 (N=9)	Day 1 (N=11)	Day 36 (N=11)	Day 1 (N=9)	Day 36 (N=8)
AUC_τ (ng·h/mL)	3160 (41)	4680 (42)	4630 (31)	6730 (32)	7700 (22)	11300 (29)
C_{max} (ng/mL)	24.8 (44)	34.6 (37)	37.7 (33)	51.6 (30)	62.2 (23)	89.4 (30)
t_{max}[a] (h)	72.0 (48.0, 95.5)	48.0 (12.0, 72.0)	71.7 (12.0, 95.2)	48.0 (24.0, 72.5)	48.0 (24.0, 95.8)	48.0 (24.0, 72.0)
$t_{1/2}$[b] (h)	NC	123[c] (113, 134)	NC	131[d] (107, 189)	NC	117 (98.1, 147)
CL/F (L/h)	NC	0.107 (42)	NC	0.111 (32)	NC	0.133 (29)
V_z/F (L)	NC	18.0[c] (21)	NC	19.2[d] (19)	NC	22.5 (24)
RA_{Obs}	NC	1.48 (17)	NC	1.45 (17)	NC	1.51 (19)

Abbreviations: AUC_τ = area under the plasma concentration versus time curve during one dosing interval (for this study, the dosing interval τ is 168 hours [1 week]); CL/F = apparent total plasma clearance; C_{max} = maximum observed drug concentration; CV = coefficient of variation; N = number of patients; NC = not calculated; RA_{Obs} = observed accumulation ratio; $t_{1/2}$ = apparent plasma terminal elimination half-life; t_{max} = time of maximum observed drug concentration; V_z/F = apparent volume of distribution during the terminal phase

[a] Median (range); [b] Geometric mean (range); [c] N=7; [d] N=9

Table 42 Statistical assessment of the PK parameters on Day 36 as once-weekly doses for 6 weeks (GBCT)

Table GBCT.7.2. Statistical Assessment of the Pharmacokinetic Parameters of LY2189265 on Day 36 Following Subcutaneous Administration of LY2189265 as Once-weekly Doses for 6 weeks

Parameter	90% CI of Exponent	Treatment	Predicted Dose Normalized Geometric Means	Ratio of Dose Normalized Geometric Means (1.5 mg vs. 0.5 mg) (90% CI)	Estimated increase for a doubling of dose (90% CI)
AUC_τ (ng·h/mL)	(0.551, 1.04)	0.5 mg LY2189265 (N=9)	9524		
		0.75 mg LY2189265 (N=11)	8774		
		1.5 mg LY2189265 (N=8)	7626	0.801 (0.610, 1.05)	1.74 (1.46, 2.06)
C_{max} (ng/mL)	(0.624, 1.09)	0.5 mg LY2189265 (N=9)	70.8		
		0.75 mg LY2189265 (N=11)	66.8		
		1.5 mg LY2189265 (N=8)	60.5	0.854 (0.662, 1.10)	1.81 (1.54, 2.13)

Abbreviations: AUC_τ = area under the plasma concentration versus time curve during one dosing interval (for this study, the dosing interval τ is 168 hours [1 week]); CI = confidence interval; C_{max} = maximum observed drug concentration; N = number of patients

Table GBCT.7.3. Statistical Assessment of the Dose Normalized Pharmacokinetic Parameters of LY2189265 on Day 36 Following Subcutaneous Administration of LY2189265 as Once-weekly Doses for 6 weeks

Parameter	Treatment	Geometric Means (90% CI)	Ratio of Geometric Means (1.5 mg vs. 0.75 mg) (90% CI)
AUC_τ (ng·h/mL)/mg	0.75 mg LY2189265 (N=11)	8976 (7662, 10516)	
	1.5 mg LY2189265 (N=8)	7539 (6261, 9077)	0.840 (0.658, 1.07)
C_{max} (ng/mL)/mg	0.75 mg LY2189265 (N=11)	68.8 (59.0, 80.2)	
	1.5 mg LY2189265 (N=8)	59.6 (49.8, 71.4)	0.867 (0.684, 1.10)

Abbreviations: AUC_τ = area under the plasma concentration versus time curve during one dosing interval (for this study, the dosing interval τ is 168 hours [1 week]); CI = confidence interval; C_{max} = maximum observed drug concentration; N = number of patients

Reference ID: 3520514

Table 43 Variability Estimates of the PK Parameters of DULAGLUTIDE in Plasma on Days 1 and 36 Following Subcutaneous Administration of DULAGLUTIDE as Once-weekly Doses for 6 weeks (GBCT)

	CV% (90% CI)	
Parameter	Between-patient	Within-patient
AUC_τ (ng·h/mL)	30.4 (24.3, 41.4)	12.5 (10.1, 16.3)
C_{max} (ng/mL)	28.8 (22.7, 40.2)	15.8 (12.8, 20.7)

Abbreviations: AUC_τ = area under the plasma concentration versus time curve during one dosing interval (for this study, the dosing interval τ is 168 hours [1 week]); CI = confidence interval; C_{max} = maximum observed drug concentration; CV = coefficient of variation.

Reference ID: 3520514

4.1.10 Study GBCM: Renal impairment

Table 44 Categories of Chronic Kidney Disease Staging (Source: Table ISS 6.117)

CKD Stage	eGFR[a] (mL/min/1.73 m^2)	Macroalbuminuria (UACR >300 mg/g)[b]
Normal	≥60	–
Stage 1	≥90	+
Stage 2	≥60 to <90	+
Stage 3A	≥45 to <60	+/–
Stage 3B	≥30 to <45	+/–
Stage 4	≥15 to <30	+/–
Stage 5	<15 (or dialysis)	+/–

Abbreviations: + = attribute present; – = attribute absent; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urine albumin-to-creatinine ratio.

a Calculated using Chronic Kidney Disease Epidemiology Collaboration equation.

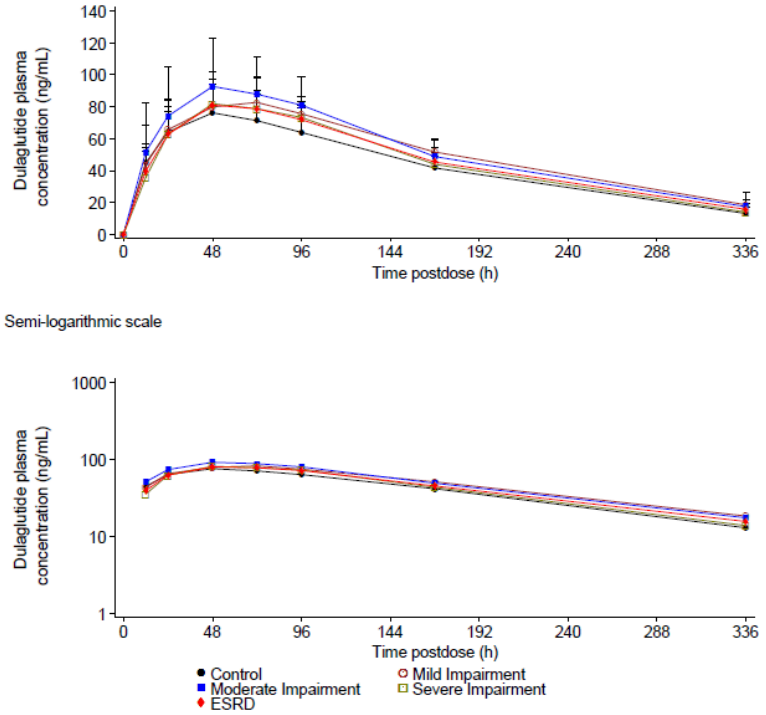
b Based on spot urine collection.

Table 45 Subject Demographics (GBCM)

		Control N=16	Mild Impairment N=8	Moderate Impairment N=8	Severe Impairment N=8	ESRD N=8	Overall N=48
T2DM		0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	2 (4.2%)
Age (years)	Mean	56.4	62.0	62.4	66.5	50.0	59.0
	SD	8.9	6.5	12.1	7.4	12.2	10.6
	Range	38-72	49-70	43-76	56-80	28-65	28-80
Sex	Male	10 (62.5%)	5 (62.5%)	5 (62.5%)	5 (62.5%)	5 (62.5%)	30 (62.5%)
	Female	6 (37.5%)	3 (37.5%)	3 (37.5%)	3 (37.5%)	3 (37.5%)	18 (37.5%)
Race	White	16 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	48 (100.0%)
Weight (kg)	Mean	79.59	75.59	78.25	80.70	75.58	78.22
	SD	11.60	12.88	9.83	17.22	9.18	11.95
	Range	62.6-103.1	60.2-100.9	67.9-95.4	61.4-114.2	66.6-95.8	60.2-114.2
Height (cm)	Mean	173.19	171.00	172.63	168.88	171.50	171.73
	SD	10.07	8.64	7.71	10.01	9.87	9.17
	Range	158.0-186.0	159.0-186.0	160.0-184.0	152.0-181.0	156.0-180.0	152.0-186.0
BMI (kg/m^2)	Mean	26.47	25.68	26.24	28.08	25.79	26.45
	SD	2.54	2.13	2.23	3.93	2.98	2.78
	Range	22.0-31.8	23.1-29.2	22.4-29.1	24.1-36.9	21.5-30.0	21.5-36.9
Estimated CrCL (mL/min)	Mean	89.9	55.7	39.3	25.8	10.3	51.8
	SD	10.7	4.19	6.56	2.45	1.77	31.3
	Range	80.6-125	50.1-61.4	30.4-48.7	22.1-30.0	8.39-13.6	8.39-125

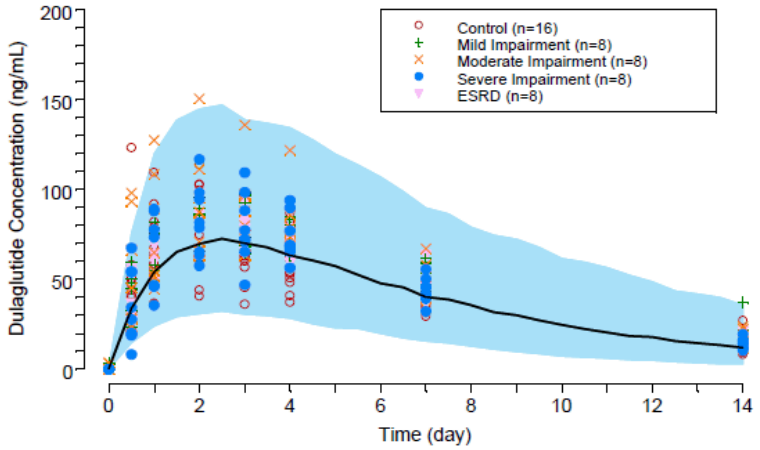
Abbreviations: BMI = body mass index; CrCL = creatinine clearance; ESRD = end-stage renal disease; N = number of subjects; SD = standard deviation; T2DM = type 2 diabetes mellitus.

Reference ID: 3520514



Abbreviations: ESRD = end-stage renal disease; SD = standard deviation.

Figure 42 Arithmetic mean (+SD) plasma dulaglutide concentration-time profiles following single doses of 1.5 mg dulaglutide [upper panel: linear scale; bottom panel: semi-logarithmic scale].



Abbreviations: CI = confidence interval; PK = pharmacokinetics; PopPK = population pharmacokinetics.

Note: The solid black line is the median of the simulations and the blue area is the 90% CI from the simulation.

Figure 43 Comparison of individual PK profiles from subjects in the control and renal impairment groups to the PopPK model-predicted population median and 90% CI.

Reference ID: 3520514

Table 46 Summary of Dulaglutide PK Parameters following Single Doses 1.5 mg Dulaglutide for Each Renal Function Group

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

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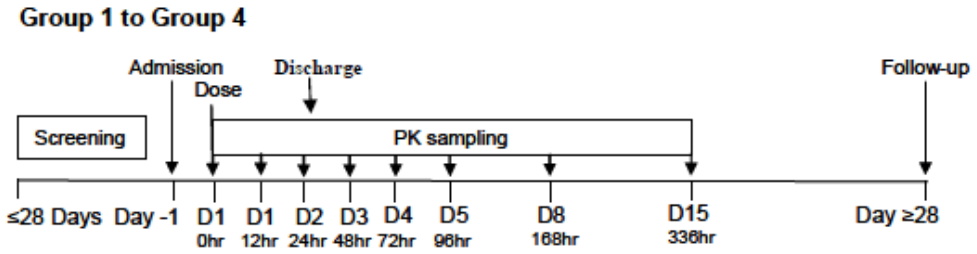
4.1.11 Study GBDO: Hepatic impairment



Abbreviation: PK = pharmacokinetic.

Figure 44 **Study design (GBDO)**

Table 47 Child-Pugh Classification of Hepatic Impairment (Child and Turcotte 1964; Pugh et al. 1973)

Parameter	1 Point	2 Points	3 Points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prolonged prothrombin time (s)	<4	4 to 6	>6
or			
Prothrombin time INR (ratio)	<1.70	1.7 to 2.3	>2.30
Ascites [a]	Absent	Slight	Moderate
Encephalopathy [b]	Grade 0	Grade 1 or 2	Grade 3 or 4

Child-Pugh A: 5 or 6 points; Child-Pugh B: 7 to 9 points; Child-Pugh C: 10 to 15 points (scores are the sum of the 5 parameters).

Abbreviations: INR = international normalized ratio (subject prothrombin time/normal plasma pool prothrombin time).

[a] Ascites is graded according to the following criteria:

Absent: No ascites detectable by manual and also not by ultra sound investigation.

Minimal: Ascites palpitation doubtful, but ascites measurable by ultrasound investigation.

Moderate: Ascites detectable by palpitation and by ultra sound investigation.

Severe: Necessity of paracentesis, does not respond to medication treatment.

[b] Encephalopathy is graded according to the following criteria:

Grade 0: Normal consciousness, personality, neurological examination, and electroencephalogram.

Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves.

Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.

Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity.

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Table 48 Summary of Dulaglutide PK Parameters Following a Single Subcutaneous Dose of 1.5 mg Dulaglutide for Each Hepatic Function Group (Geometric mean (%CV)) (GBDO)

Parameter	Control	Mild Hepatic Impairment	Moderate Hepatic Impairment	Severe Hepatic Impairment
N	11	6	6	3
AUC(0-168) (ng·h/mL)	10200 (26)	7670 (27)	7220 (19)	7660 (13)
AUC(0-∞) (ng·h/mL)	16300 (24)	12200 (26)	11200[c] (14)	12500 (5)
C_{max} (ng/mL)	84.5 (29)	63.0 (30)	58.1 (28)	61.3 (18)
t_{max}[a] (h)	48.00 (24.02-72.02)	48.01 (47.95-72.02)	59.96 (47.10-95.97)	71.93 (71.90-71.98)
$t_{1/2}$[b] (h)	104 (88.6-116)	101 (86.2-116)	88.2[c] (75.1-104)	99.2 (76.4-121)
CL/F (L/h)	0.0920 (24)	0.123 (26)	0.135[c] (14)	0.120 (5)
V_z/F (L)	13.8 (27)	17.9 (27)	17.1[c] (20)	17.1 (24)

Abbreviations: AUC(0-168) = area under the concentration versus time curve (AUC) from time zero to 168 hours; AUC(0-∞) = AUC from 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; 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 = 5.

Table 49 Statistical Comparison Between Hepatic Groups for the PK Parameters of Dulaglutide Following a Single Subcutaneous Dose of Dulaglutide (GBDO)

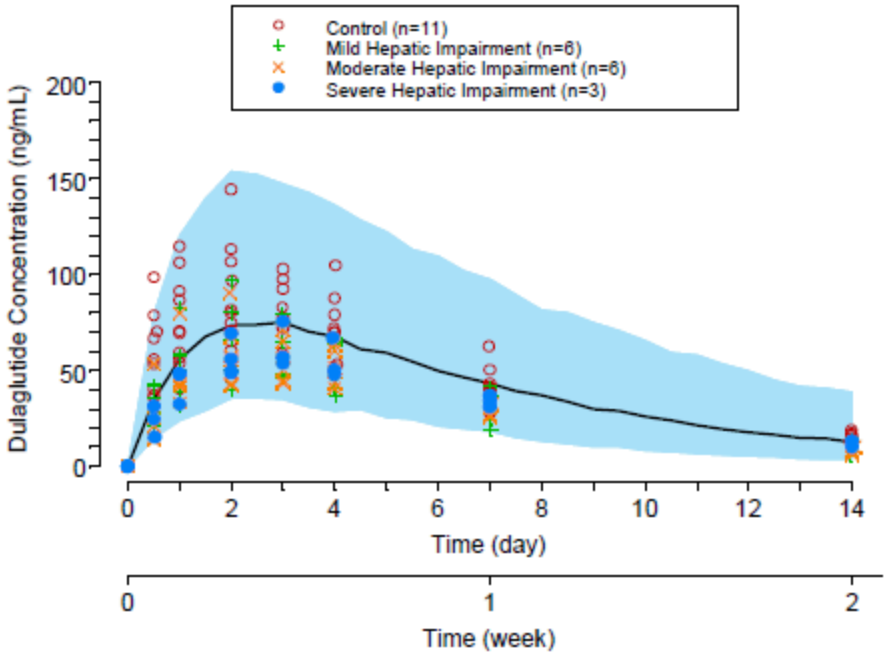
Reference ID: 3520514

Parameter	Hepatic Group	N	Geometric LS Mean (90% CI)*	Ratio (90% CI) versus Control
AUC(0-∞) (ng·h/mL)	Control	11	16084 (14501, 17840)	
	Mild Hepatic Impairment	6	12446 (10815, 14323)	0.774 (0.649, 0.922)
	Moderate Hepatic Impairment	5	10763 (9215, 12572)	0.669 (0.556, 0.805)
	Severe Hepatic Impairment	3	12722 (10441, 15503)	0.791 (0.632, 0.989)
C_{max} (ng/mL)	Control	11	82.5 (73.7, 92.3)	
	Mild Hepatic Impairment	6	65.2 (56.0, 76.0)	0.791 (0.654, 0.957)
	Moderate Hepatic Impairment	6	57.9 (49.8, 67.5)	0.703 (0.582, 0.849)
	Severe Hepatic Impairment	3	62.8 (50.6, 77.8)	0.761 (0.597, 0.971)
CL/F (L/h)	Control	11	0.0933 (0.0841, 0.103)	
	Mild Hepatic Impairment	6	0.121 (0.105, 0.139)	1.29 (1.08, 1.54)
	Moderate Hepatic Impairment	5	0.139 (0.119, 0.163)	1.49 (1.24, 1.80)
	Severe Hepatic Impairment	3	0.118 (0.0968, 0.144)	1.26 (1.01, 1.58)
V_z/F (L)	Control	11	14.1 (12.7, 15.7)	
	Mild Hepatic Impairment	6	17.3 (15.0, 20.0)	1.23 (1.03, 1.47)
	Moderate Hepatic Impairment	5	18.1 (15.4, 21.2)	1.28 (1.06, 1.55)
	Severe Hepatic Impairment	3	16.7 (13.7, 20.5)	1.19 (0.945, 1.49)

Abbreviations: AUC(0-∞) = area under the plasma concentration versus time curve (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; CI = confidence interval; LS = least squares; N = number of subjects; V_z/F = apparent volume of distribution during the terminal phase after extra-vascular administration.

* At arithmetic mean weight.

Model: Log(PK) = group + weight + random error.



Note: The solid black line is the median of the simulations and the blue area is the 90% prediction interval from the simulation.

Figure 45 Comparison of individual PK profiles from subjects in the control and hepatic impairment groups to the PopPK model-predicted population median and 90% prediction interval.

Reference ID: 3520514

4.1.12 Study GBDM: Scintigraphy study and metformin PK

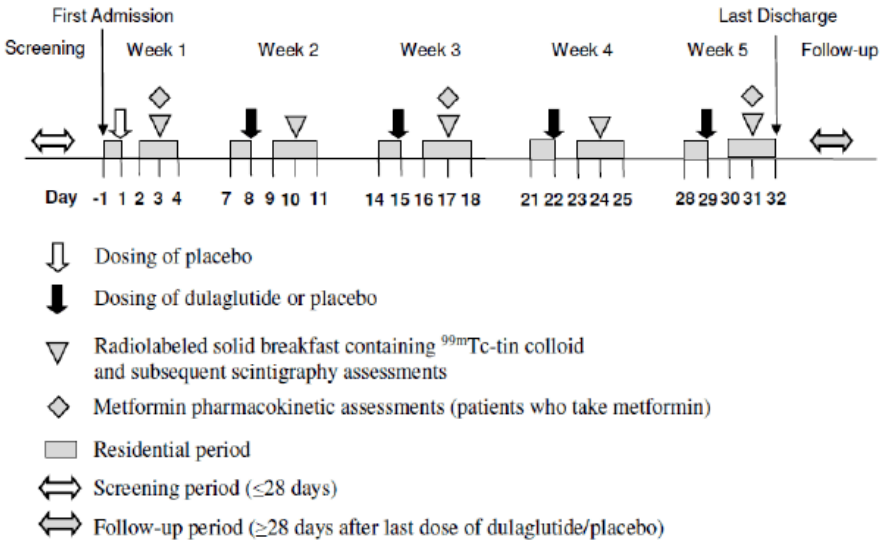


Figure 46 Study design (Study GBDM)

Table 50 Patient demographics (GBDM)

		Placebo (N=13)	1.5 mg Dulaglutide (N=25)	Overall (N=38)
Age (years)	Mean (SD)	52.0 (14.0)	58.9 (9.8)	56.5 (11.7)
	Range	18-76 *	30-73	18-76 *
Sex	Male	11 (84.6%)	20 (80.0%)	31 (81.6%)
	Female	2 (15.4%)	5 (20.0%)	7 (18.4%)
Ethnicity	Hispanic or Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Hispanic or Latino	13 (100.0%)	25 (100.0%)	38 (100.0%)
Race	White	10 (76.9%)	24 (96.0%)	34 (89.5%)
	Asian	3 (23.1%)	1 (4.0%)	4 (10.5%)
Body weight (kg)	Mean (SD)	91.01 (15.04)	92.04 (12.18)	91.69 (13.03)
	Range	61.7-127.5	68.3-110.8	61.7-127.5
BMI (kg/m^2)	Mean (SD)	30.16 (3.88)	32.32 (3.60)	31.58 (3.79)
	Range	25.7-39.9	26.0-38.6	25.7-39.9
Metformin type	Immediate release	8 (61.5%)	15 (60.0%)	23 (60.5%)
	Extended release	0 (0.0%)	4 (16.0%)	4 (10.5%)

Abbreviations: BMI = body mass index; N = number of patients; SD = standard deviation

* Patient confirmed as being 75 years old at the time of screening.

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Table 51 Summary of derived Scintigraphy Parameters (GBDM)

		Geometric Mean (CV%)			
Treatment	Day	AUC (%.h)	t_{10} (h)	t_{50} (h)	t_{90} (h)
Placebo (N=10)	3	132.12 (30.7)	0.536 (25.96)	1.435 (28.44)	2.868 (29.71)
	10	131.10 (30.0)	0.541 (43.46)	1.413 (28.30)	2.635 (18.86)[a]
	17	150.71 (31.5) [a]	0.613 (28.01) [a]	1.662 (38.52) [a]	3.193 (22.62) [a]
	24	131.97 (31.1) [a]	0.504 (38.07) [a]	1.475 (29.49) [a]	2.837 (25.48) [a]
	31	132.48 (29.6)	0.585 (28.93)	1.456 (24.68)	2.925 (28.38)
1.5 mg Dulaglutide (N=15)	3	160.07 (27.5)	0.589 (28.25)	1.717 (32.18)	3.503 (27.42)
	10	379.53 (43.0)	1.134 (76.03)	3.767 (46.55)	6.266 (39.50) [b]
	17	333.35 (51.1) [c]	1.176 (74.81) [c]	3.326 (49.97) [c]	6.449 (51.43) [d]
	24	322.28 (42.7) [c]	1.282 (48.36) [c]	3.278 (48.52) [c]	6.027 (32.99) [e]
	31	306.84 (41.7) [e]	1.342 (81.50) [e]	3.180 (39.29) [e]	5.941 (38.18) [e]

Abbreviations: AUC = area under the concentration versus time curve (residual activity); CV = coefficient of variation; N = number of patients; t_{10} = time required for 10% of activity to empty from the stomach; t_{50} = time required for 50% of activity to empty from the stomach; t_{90} = time required for 90% of activity to empty from the stomach.

[a] N = 9; [b] N = 11; [c] N = 14; [d] N = 12; [e] N = 13

Reference ID: 3520514

Table 52 Statistical Analysis in t10, t50, and t90 Following Administration of 1.5 mg Dulaglutide or Placebo (GBDM)

Treatment	Parameter	Day	N	Geometric LS Mean (90% CI)	Ratio of Geometric LS Means: Day 3 (90% CI) [p-value]
Placebo	t_{10} (h)	3	10	0.54 (0.45, 0.64)	
		10	10	0.54 (0.45, 0.65)	1.01 (0.84, 1.21) [0.928]
		17	9	0.59 (0.50, 0.71)	1.11 (0.92, 1.34) [0.359]
		24	9	0.51 (0.42, 0.61)	0.95 (0.79, 1.15) [0.654]
		31	10	0.59 (0.49, 0.70)	1.09 (0.91, 1.31) [0.420]
Placebo	t_{50} (h)	3	10	1.44 (1.22, 1.69)	
		10	10	1.41 (1.20, 1.66)	0.98 (0.86, 1.13) [0.852]
		17	9	1.60 (1.36, 1.89)	1.12 (0.97, 1.29) [0.204]
		24	9	1.47 (1.25, 1.73)	1.02 (0.89, 1.18) [0.783]
		31	10	1.46 (1.24, 1.71)	1.01 (0.88, 1.17) [0.867]
Placebo	t_{90} (h)	3	10	2.87 (2.48, 3.32)	
		10	9	2.71 (2.34, 3.14)	0.94 (0.87, 1.02) [0.227]
		17	9	3.05 (2.63, 3.53)	1.06 (0.98, 1.15) [0.201]
		24	9	2.80 (2.42, 3.25)	0.98 (0.90, 1.06) [0.631]
		31	10	2.93 (2.53, 3.38)	1.02 (0.95, 1.10) [0.665]
1.5 mg Dulaglutide	t_{10} (h)	3	15	0.59 (0.46, 0.76)	
		10	15	1.13 (0.88, 1.46)	1.93 (1.40, 2.65) [0.001]
		17	14	1.18 (0.91, 1.52)	2.00 (1.44, 2.77) [<0.001]
		24	14	1.28 (0.99, 1.66)	2.18 (1.57, 3.02) [<0.001]
		31	13	1.32 (1.01, 1.72)	2.24 (1.60, 3.12) [<0.001]
1.5 mg Dulaglutide	t_{50} (h)	3	15	1.72 (1.43, 2.06)	
		10	15	3.77 (3.15, 4.51)	2.19 (1.83, 2.62) [<0.001]
		17	14	3.32 (2.76, 4.00)	1.94 (1.61, 2.33) [<0.001]
		24	14	3.28 (2.72, 3.94)	1.91 (1.59, 2.29) [<0.001]
		31	13	3.15 (2.61, 3.81)	1.84 (1.52, 2.22) [<0.001]
1.5 mg Dulaglutide	t_{90} (h)	3	15	3.50 (2.99, 4.11)	
		10	11	6.57 (5.53, 7.81)	1.88 (1.59, 2.21) [<0.001]
		17	12	6.68 (5.64, 7.91)	1.91 (1.63, 2.24) [<0.001]
		24	13	6.19 (5.25, 7.31)	1.77 (1.51, 2.06) [<0.001]
		31	13	6.13 (5.20, 7.23)	1.75 (1.50, 2.04) [<0.001]

Abbreviations: CI = confidence interval; LS = least squares; N = number of patients; t_{10} = time required for 10% of activity to empty from the stomach; t_{50} = time required for 50% of activity to empty from the stomach; t_{90} = time required for 90% of activity to empty from the stomach.

Reference ID: 3520514

Table 53 Summary of Metformin Noncompartmental PK Parameters (GBDM)

Parameter	Geometric Mean (%CV)								
	Placebo			1.5 mg Dulaglutide					
	Day 3	Day 17	Day 31	Day 3		Day 17		Day 31	
Metformin type	IR	IR	IR	IR	ER	IR	ER	IR	ER
N	6	6	6	12	1[c]	12	1[c]	11	1[c]
AUCτ (ng·h/mL)	13600 (49)	14600 (47)	14600 (47)	13700 (40)	10700	15300 (43)	NC	15800 (43)	15900
C_{max} (ng/mL)	1610 (48)	1690 (48)	1770 (46)	1690 (47)	1083.15	1500 (53)	778.18	1680 (44)	1151.86
t_{max}[a] (h)	1.00 (1.00-2.03)	2.02 (1.02-8.00)	1.53 (0.98-4.00)	2.02 (1.00-4.10)	3.97	2.05 (0.96-4.02)	2.07	2.02 (1.00-4.03)	4.00
$t_{1/2}$[b] (h)	5.52 (4.95-6.66)	5.47 (5.06-6.32)	5.19 (4.29-6.24)	4.94 (4.00-6.21)	5.14	5.34 (3.63-6.87)	NC	5.14 (3.40-6.43)	5.26
CL/F (L/h)	49.3 (18)	46.4 (24)	46.3 (20)	48.9 (21)	88.4	42.9 (26)	NC	40.6 (21)	59.1
V_z/F (L)	392 (16)	366 (20)	347 (8)	349 (24)	656	331 (23)	NC	301 (21)	449

Abbreviations: AUCτ = area under the concentration versus time curve during one dosing interval; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; ER = extended release; IR = immediate release; N = number of patients; NC = not calculated; $t_{1/2}$= half-life associated with the terminal rate constant (λ_Z) in noncompartmental analysis; t_{max} = time of C_{max}; V_z/F = apparent volume of distribution at steady state during the terminal phase after extra-vascular administration.

[a] Median (range)

[b] Geometric mean (range)

[c] Values from Patient 1002 only are presented for 1.5 mg dulaglutide and metformin ER

Table 54 Statistical Analysis of Metformin AUC τ (ng· h/mL) and Cmax (ng/mL) Following Coadministration of 1.5 mg Dulaglutide and Metformin IR (GBDM)

Parameter	Study Day	N	Geometric LS Means (90% CI)	Ratio (90% CI) versus Day 3	p-value
AUCτ	3	12	13744 (11228, 16824)		
	17	12	15330 (12523, 18766)	1.12 (1.02, 1.22)	[0.044]
	31	11	15857 (12941, 19429)	1.15 (1.05, 1.26)	[0.013]
Cmax	3	12	1694 (1342, 2139)		
	17	12	1498 (1186, 1891)	0.88 (0.80, 0.98)	[0.043]
	31	11	1677 (1326, 2119)	0.99 (0.89, 1.10)	[0.862]

Abbreviations: AUCτ = area under the concentration versus time curve during one dosing interval; CI = confidence interval; C_{max} = maximum observed drug concentration; IR = immediate release; LS = least squares; N = number of patients.

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Table 55 Median Differences From Baseline in Metformin tmax (h) Following Coadministration of 1.5 mg Dulaglutide and Metformin IR (GBDM)

Study Day	N	Wilcoxon Signed Rank Median	Differences (90% CI) versus Day 3	p-value
3	12	2.02		
17	12	2.05	0.02 (-0.05, 1.03)	[0.748]
31	11	2.02	-0.02 (-1.03, 1.02)	[0.941]

Abbreviations: CI = confidence interval; IR = immediate release; N = number of patients; t_{max} = time of maximum observed drug concentration.

Table 56 Comparison of Change from Baseline by Treatment for Metformin AUC τ (ng· h/mL) and Cmax (ng/mL) Following Administration of 1.5 mg Dulaglutide or Placebo (placebo corrected) (GBDM)

Parameter	Study Day	Treatment	N	Geometric LS Means of ratio versus Day 3	Ratio of LS Means for dulaglutide versus placebo (90% CI) [p-value]
AUCτ	17	Placebo	6	1.07	
		1.5 mg Dulaglutide	12	1.12	1.04 (0.91, 1.19) [0.588]
	31	Placebo	6	1.07	
		1.5 mg Dulaglutide	11	1.16	1.08 (0.94, 1.24) [0.344]
C_{max}	17	Placebo	6	1.04	
		1.5 mg Dulaglutide	12	0.884	0.85 (0.74, 0.97) [0.045]
	31	Placebo	6	1.10	
		1.5 mg Dulaglutide	11	1.00	0.91 (0.80, 1.05) [0.280]

Abbreviations: AUCτ = area under the concentration versus time curve during one dosing interval; CI = confidence interval; C_{max} = maximum observed drug concentration; LS = least squares; N = number of patients.

Table 57 Comparison of Change from Baseline by Treatment for Metformin tmax (h) Following Administration of 1.5 mg Dulaglutide or Placebo (placebo corrected) (GBDM)

Study Day	Treatment	N	Median Difference	Difference versus placebo (90% CI) [p-value]
17	Placebo	6	0.517	
	1.5 mg Dulaglutide	12	0.0167	-0.0750 (-2.98, 0.0333) [0.425]
31	Placebo	6	0.525	
	1.5 mg Dulaglutide	11	-0.0167	-0.950 (-2.05, 0.983) [0.512]

Abbreviations: CI = confidence interval; N = number of patients; t_{max} = time of maximum observed drug concentration.

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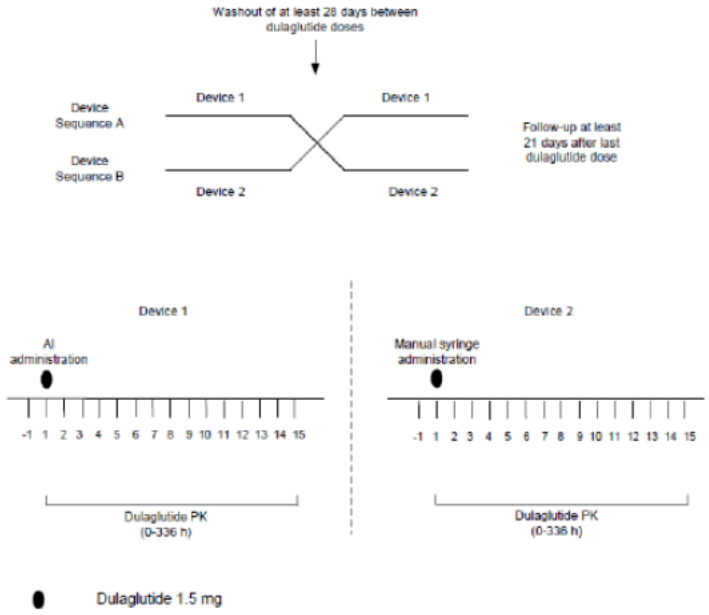
4.1.13 Study GBDT: pivotal comparability study



Abbreviations: AI = Auto-injector; h = hours; PK = pharmacokinetics.

Figure 47 **Study design (GBDT)**

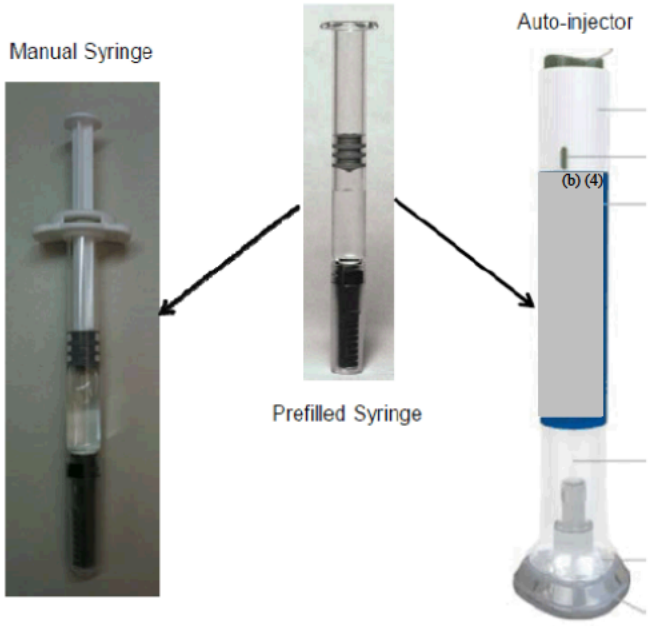


Figure 48 Prefilled syringe component of manual syringe and AI.

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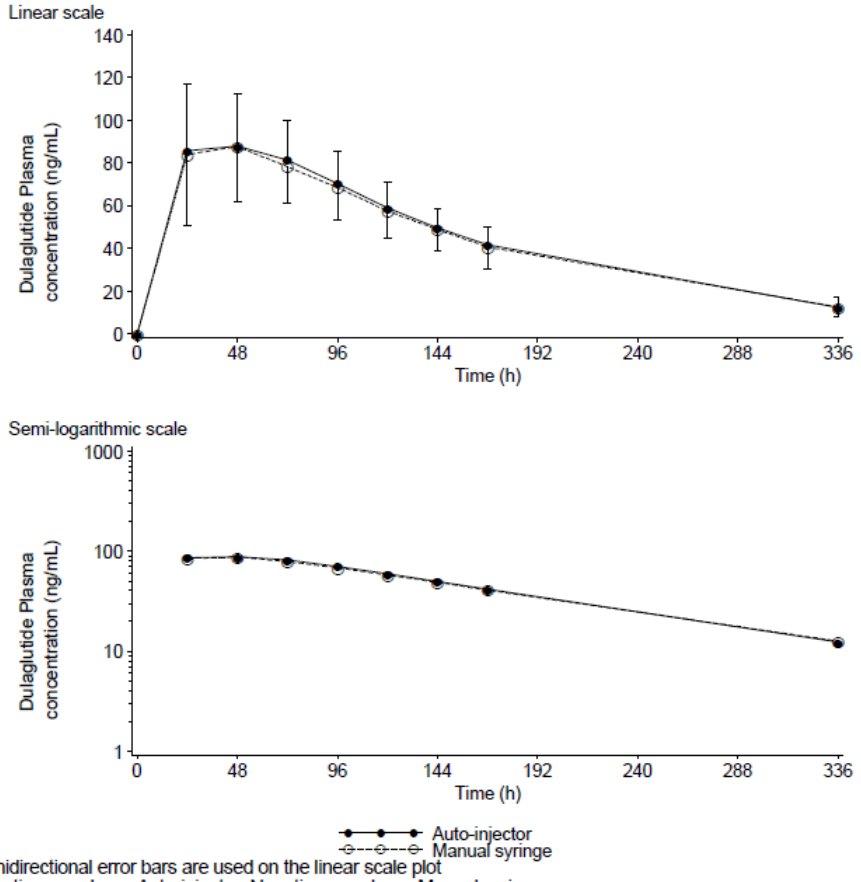
Table 58 Patient demographics (GBDT)

		Auto-injector (N=47)	Manual Syringe (N=49)	Overall (N=50)
Age (years)	Mean (SD)	42.5 (17.6)	42.8 (17.0)	42.3 (17.2)
	Range	19-77	19-77	19-77
Sex	Male	39 (83.0%)	39 (79.6%)	40 (80.0%)
	Female	8 (17.0%)	10 (20.4%)	10 (20.0%)
Ethnicity	Hispanic or Latino	14 (29.8%)	14 (28.6%)	14 (28.0%)
	Not Hispanic or Latino	33 (70.2%)	35 (71.4%)	36 (72.0%)
Race	Black or African American	12 (25.5%)	11 (22.4%)	12 (24.0%)
	White	32 (68.1%)	35 (71.4%)	35 (70.0%)
	Multiple	3 (6.4%)	3 (6.1%)	3 (6.0%)
Body weight (kg)	Mean (SD)	80.86 (10.72)	81.15 (10.33)	80.87 (10.41)
	Range	62.2-103.3	62.2-103.3	62.2-103.3
Body Mass Index (kg/m^2)	Mean (SD)	27.21 (2.94)	27.30 (2.87)	27.21(2.90)
	Range	20.4-31.9	20.4-31.9	20.4-31.9

Abbreviations: N = number of subjects; SD = standard deviation.



Unidirectional error bars are used on the linear scale plot
Postive error bars=Auto-injector; Negative error bars=Manual syringe;

Abbreviations: h = hours; SD = standard deviation.

Figure 49 Arithmetic mean (±SD) plasma dulaglutide concentration-time profiles following single doses of dulaglutide via AI or manual syringe administration [upper panel: linear scale; bottom panel: semi-logarithmic scale].

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Table 59 Summary of Dulaglutide Noncompartmental PK Parameters Following Single Dos**es of 1.5 mg Dulaglutide via AI** or Manual Syringe Administration (GBDT)

Parameter	Geometric Mean (%CV)	
	Auto-injector	Manual syringe
N	47	48
AUC(0-168) (ng·h/mL)	10700 (24)	10300 (26) [a]
AUC(0-336) (ng·h/mL)	14700 (22)	14300 (24) [a]
AUC(0-∞) (ng·h/mL)	16400 (22)	16000 (25) [a]
C_{max} (ng/mL)	91.1 (31)	88.2 (32)
t_{max} [b] (h)	48.0 (24.0-96.0)	48.0 (24.0-96.0)
$t_{1/2}$ [c] (h)	94.2 (71.0-157)	95.7 (59.0-174) [a]
CL/F (L/h)	0.0913 (22)	0.0936 (25) [a]
V_z/F (L)	12.4 (25)	12.9 (25) [a]

Abbreviations: AUC(0-168) = area under the concentration versus time curve from time zero to 168 hours postdose; AUC(0-336) = area under the concentration versus time curve from time zero to 336 hours postdose; AUC(0-∞) = area under the concentration versus time curve from 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; N = number of subjects; $t_{1/2}$ = half-life associated with the terminal rate constant (λ_z) in noncompartmental analysis; t_{max} = time of C_{max}; V_z/F = apparent volume of distribution during the terminal phase after extra-vascular administration.

[a] N = 47.

[b] Median (range).

[c] Geometric mean (range).

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4.2 PHARMACOMETRIC REVIEW

4.2.1 Summary of Findings

4.2.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

4.2.1.1.1 Does the efficacy (HbA1c and body weight reduction) and safety (HR increase and GI tolerability) profile support the proposed dose of 1.5 mg once weekly dosing regimen?

Yes. The proposed dose of dulaglutide 1.5 mg once weekly is supported by the efficacy and safety profiles. Both the 1.5 mg and 0.75 mg dose demonstrated superior efficacy compared to placebo and active comparators, with 1.5 mg being numerically better in efficacy compared to 0.75 mg dose. However, sponsor proposes to include only 1.5 mg dose in the label. It is important to note that the data indicates that 1.5 mg is associated with higher risk of GI disorders and discontinuation rate at the beginning of treatment (first 2 weeks). Furthermore, there is trend in clinically relevant heart rate increases (heart rate >100 bpm and an increase from baseline ≥15 bpm). The proportion of patients with clinically relevant heart rate increase was low, but numerically higher in patients on 1.5 mg compared to 0.75 mg dose with 2.2, 1.3 and 0.7% for placebo, 0.75 and 1.5 mg dose, respectively. Considering the totality of evidence, the reviewer recommends approval for both doses and presents the following two options for the dosage and administration section in the label. The labeling for the dosage and administration section will be finalized after discussion with the clinical review team:

- 0.75 mg is recommended to be the starting dose which can be titrated to 1.5 mg after 4 weeks based on GI tolerability.

  OR
- Option of starting with either 0.75 or 1.5 mg dulaglutide with adequate language indicating that both doses are efficacious with a clear description stating that the lower dose offers a better GI tolerability profile and causes lower incidences of clinically relevant heart rate increases (cross reference to section 14). This will allow physicians to have option of starting at either 0.75 or 1.5 mg after considering benefit-risk profile of dulaglutide.

<u>Rationale for selecting 0.75 and 1.5 mg weekly dose for registration trials</u>

The dose-finding stage of Study GBCF demonstrated that the dulaglutide 1.5 mg dose had optimal clinical utility (defined by Hb1Ac, fasting serum glucose, body weight, sitting Pulse Rate, and blood pressure) and therefore was further evaluated in Phase 3 studies (Table 60). The 0.75 mg dose was also investigated as a contingency, should the 1.5 mg dose have an unforeseen safety signal.

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Table 60. Dose of 1.5 mg weekly was identified as the optimal dose based on both efficacy and safety measures in the dose-finding stage of study GBCF

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

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.

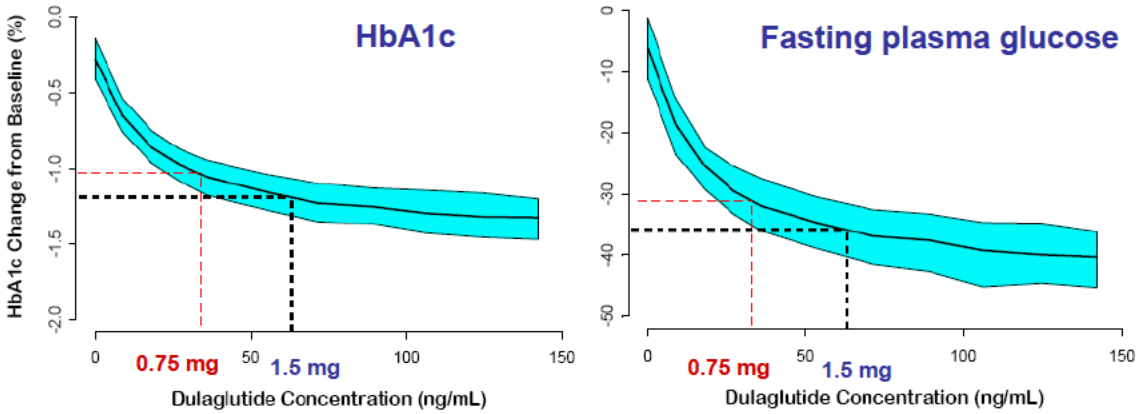
[a] Least squares means and confidence intervals could not be produced due to the lack of data at 6 months.

[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.

(*Source: Sponsor's Clinical Study Report for Trial GBCF, Table GBCF.11.3.*)

The phase 2 dose-response in efficacy and safety was also supported by the exposure-response relationships which indicated that higher exposure results in larger reduction in HbA1c, fasting plasma glucose, body weight and increase in heart rate (Figure 50, **Figure 51** and **Figure 52**).

Figure 50. Exposure-response relationships for change from baseline in HbA1c and fasting plasma glucose at 52 weeks



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: Sponsor's Clinical Pharmacology Review, Figure 2.7.2.21.)

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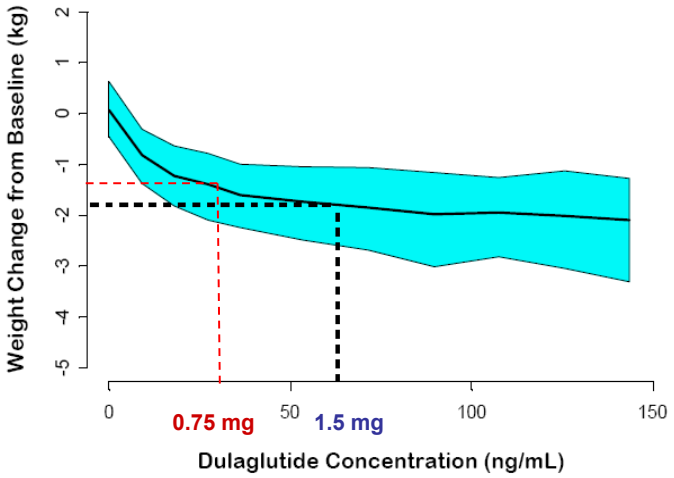
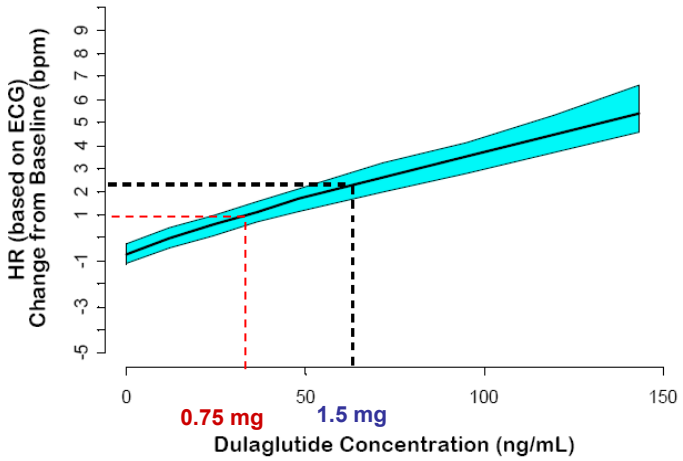
Figure 51. Exposure-response relationships for change from baseline in body weight at 52 weeks



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: Sponsor's Clinical Pharmacology Review, Figure 2.7.2.27.)

Figure 52. Exposure-response relationships for change from baseline in heart rate at 52 weeks



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: Sponsor's Clinical Pharmacology Review, Figure 2.7.2.30.)

Efficacy Considerations

Based on the 5 Phase 3 studies of 52 to 104 weeks controlled duration, the efficacy of dulaglutide was evaluated as monotherapy and as add-on to multiple different OAMs (Oral Anti-hyperglycemic Medication) and insulin lispro in patients across different

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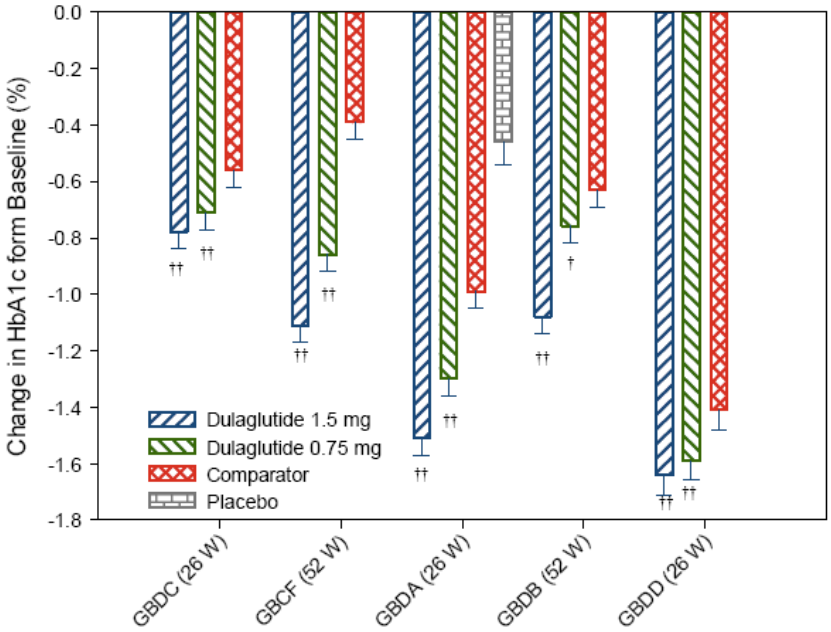
stages of T2DM. Dulaglutide was compared to placebo as well as multiple different active comparators, including metformin, sitagliptin, exenatide BID, and insulin glargine. **Both dulaglutide 0.75 and 1.5 mg consistently demonstrated superior efficacy, as measured by measured by change in HbA1c, to placebo and each active comparator evaluated (Figure 53). In addition, in all 5 Phase 3 studies, dulaglutide 1.5 mg resulted in weight reduction from baseline that was sustained through the final time point (**

Figure 54). Dulaglutide 0.75 mg was superior to placebo and the active comparator in 4 of the 5 studies and noninferior to insulin glargine in 1 study, as measured by HbA1c. In 3 of the 5 Phase 3 studies, dulaglutide 0.75 mg was associated with weight reduction over the duration of the studies.

Figure 53. Mean change in HbA1c (SE) from baseline at primary efficacy time point, dulaglutide 1.5 mg, dulaglutide 0.75 mg, and active comparator



Abbreviations: BID = twice daily injection; HbA1c = glycosylated hemoglobin A1c; SE = standard error; W=weeks. †multiplicity adjusted 1-sided p-value <.025, for noninferiority, ††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to comparator (GBDC=metformin; GBCF=-sitagliptin; GBDA=exenatide BID; GBDB=insulin glargine; GBDD=insulin glargine), assessed only for HbA1c.
(Source: Sponsor's Clinical Review, Figure 2.5.4.1.)

In addition to the Hb1Ac, other efficacy endpoints were also evaluated, such as reduction in fasting plasma glucose, and proportion of patients reaching HbA1c Targets of <7.0% and ≤6.5%, and the results was quite consistent, with the 1.5 mg dose robustly demonstrating superior efficacy compared to placebo and each active comparator evaluated, and also had numerically better efficacy compared to the lower dose of 0.75 mg.

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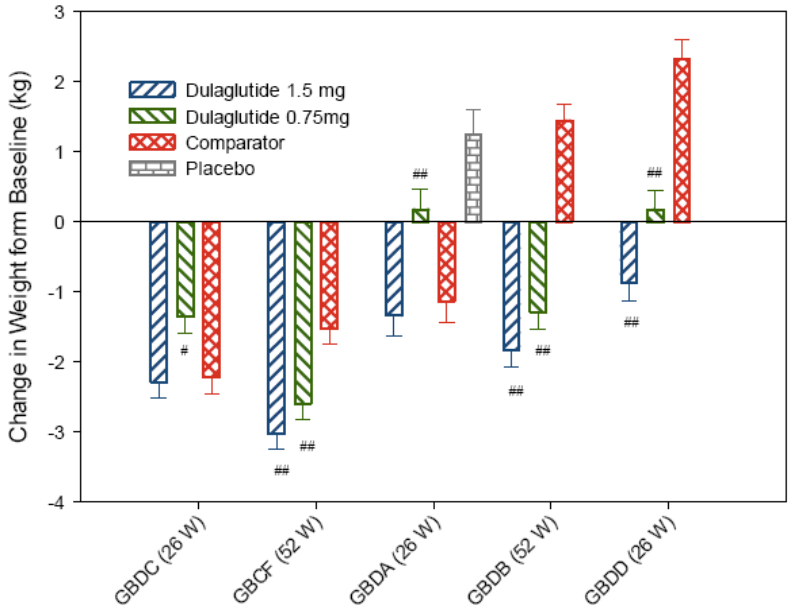
Figure 54. Mean change in body weight (SE) from baseline at primary time point, dulaglutide1.5 mg, dulaglutide 0.75 mg, and active comparator



Abbreviations: BID = twice daily injection; SE = standard error; W=weeks. #p<.05, ##p<.001 dulaglutide treatment group compared to active comparator (GBDC=metformin; GBCF=-sitagliptin; GBDA=exenatide BID; GBDB=insulin glargine; GBDD=insulin glargine).
(Source: Sponsor's Clinical Review, Figure 2.5.4.2.)

Safety Considerations

Overall the safety profile with dulaglutide is consistent with other marketed GLP-1 receptor agonists. The most commonly reported adverse events are GI related and dose-dependent, most notably nausea and vomiting (Table 61). The onset of nausea and vomiting usually occurs early after drug initiation (the first 2 weeks of exposure) and declines quickly (by week 6 of treatment). As shown in Figure 55, the onset (A) and proportion of patients experiencing nausea (B) were also dose-dependent, peaked in the first 2 weeks and declined after. In addition, the overall discontinuation rate due to GI disorders was higher in the 1.5 mg dose group (3.5%) compared with the 0.75 mg (1.3%).

Table 61. Dose-dependant GI adverse events occurring in placebo-controlled studies with 0.75 mg and 1.5 mg dulaglutide (safety population AS1, studies GBCF, GBDA, GBDN)

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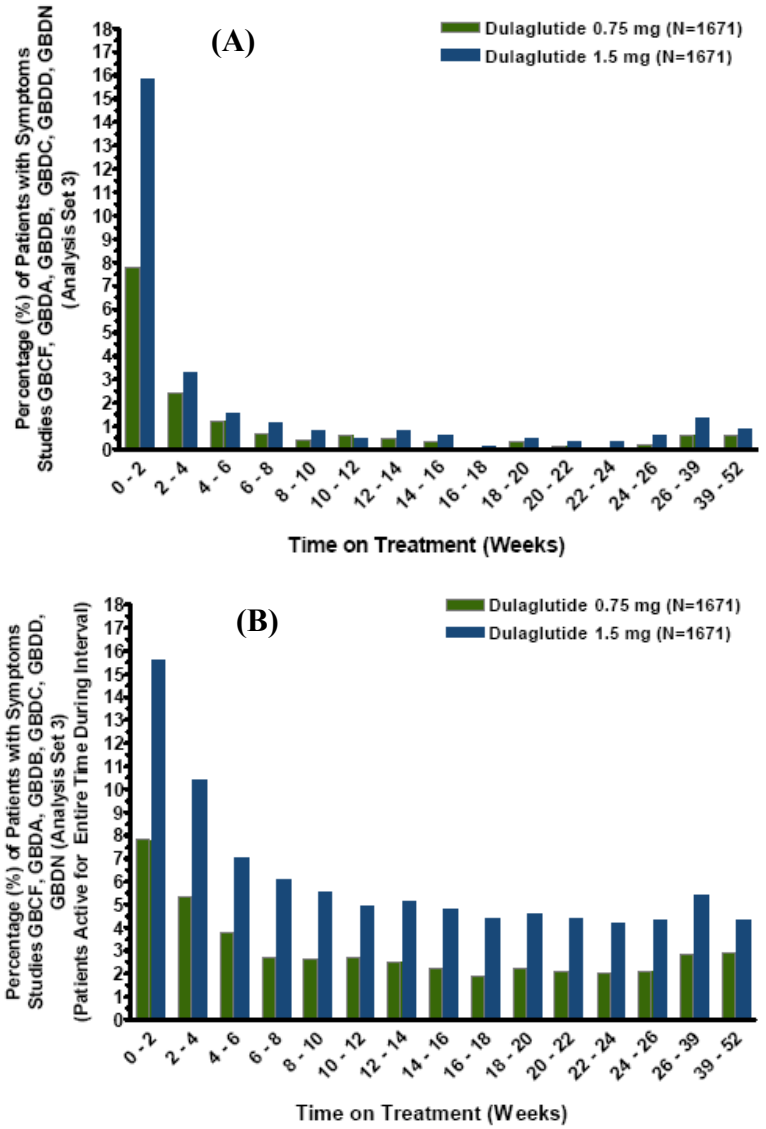
System Organ Class Preferred Term	Through 26 Weeks of Planned Treatment Period[a] Pbo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)
Patients with ≥1 TEAE	**379 (66.7)**	**569 (68.1)**	**597 (71.6)**	**1166 (69.8)**
Gastrointestinal disorders	121 (21.3)	264 (31.6)	342 (41.0)	606 (36.3)
Nausea	30 (5.3)	104 (12.4)	176 (21.1)	280 (16.8)
Diarrhoea	38 (6.7)	74 (8.9)	105 (12.6)	179 (10.7)
Vomiting	13 (2.3)	50 (6.0)	105 (12.6)	155 (9.3)
Dyspepsia	13 (2.3)	34 (4.1)	48 (5.8)	82 (4.9)

(Source: Sponsor's Summary of Clinical Safety, Table 2.7.4.11.)

Figure 55. (A) Onset of specific nausea symptoms (B) Prevalence of specific nausea symptoms in patients active for the entire time during discrete interval



Abbreviations: N = number of patients in specified treatment group of the analysis set.
Specific nausea symptom preferred terms: nausea, procedural nausea.
(Source: Sponsor's Summary of Clinical Safety, Figure 2.7.4.6, Figure 2.7.4.7.)

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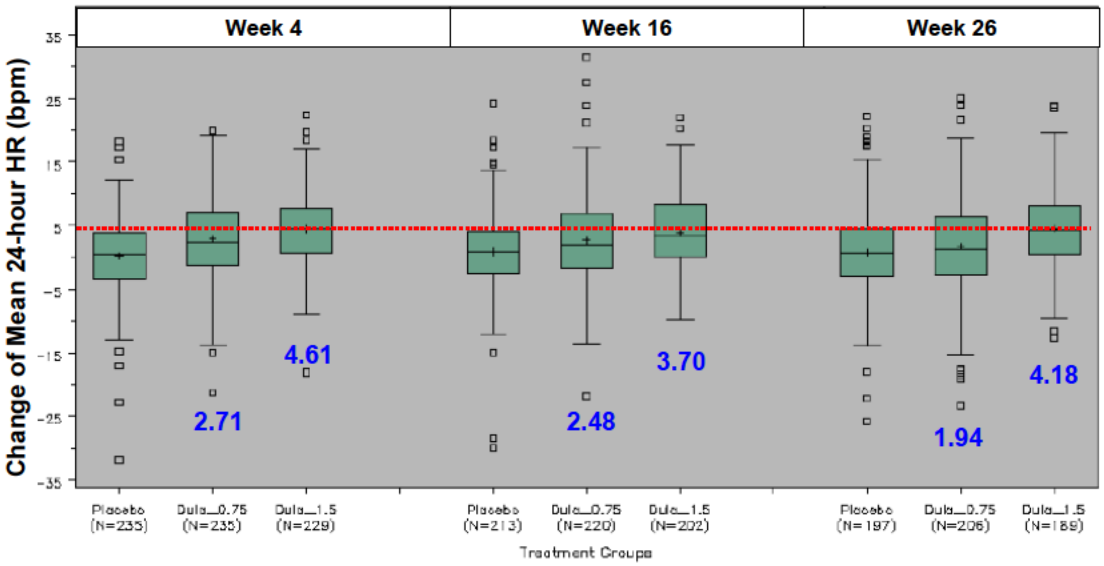
There was a dose-dependent increase in heart rate (2 to 4.6 bpm) with dulaglutide treatment versus placebo in dedicated phase 2 study GBDN for cardiovascular safety (Figure 56). These mean increases were greater for 1.5 mg compared with 0.75 mg from week 4 through week 26. However, the ranges of distribution for two groups were highly overlapping, which is consistent with the findings from the phase 3 studies.

Figure 56. Mean increase from baseline in 24-hour heart rate (bpm) of dulaglutide 1.5 mg, dulaglutide 0.75 mg, and placebo at week4, 16 and 26 (study GBDN)



Categorical threshold analyses for high heart rate were performed on pooled safety population (studies GBCF, GBDA, GBDN) based on the definition of heart rate >100 bpm and an increase from baseline ≥15 bpm. This definition of clinically relevant heart rate increase was decided after discussions with the clinical reviewer. The overall incidence of treatment-emergent clinically relevant heart rate increase was low, but numerically higher in patients from the 1.5 mg group (2.2%) than 0.75 mg (1.3%) and placebo (0.7%).

An elevation in pancreatic enzymes was also observed and generally higher for dulaglutide 1.5 mg than 0.75 mg, based on an integrated analysis from multiple studies (GBCF, GBDA, GBDB, GBDC, GBDD, GBDN). For lipase, the mean increase from baseline ranged from approximately 11-17% with 0.75 mg and 16-20% with 1.5 mg over time. The mean increase for pancreatic amylase ranged from approximately 14-17% with 0.75 mg and 18-21% with 1.5 mg. For total amylase, the mean increase ranged from approximately 8-11% with 0.75 mg and 10-13% with 1.5 mg.

Given the observed dose-response in AEs, along with previous experience of titration dosing for other approved GLP-1 analogues, implementing a dose titration strategy would be expected to decrease these symptoms and improve overall patient compliance.

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Phase 2 Study to evaluate the effect of dose titration on GI tolerability

The effect of dose titration on the incidence of GI events was evaluated in a phase 2 study GBCJ in obese and overweight patients. Patients were assigned to 1 of 4 treatment sequences (1 placebo sequence and 3 dulaglutide sequences); they received the first dose weekly for 4 weeks and a second dose weekly for the following 12 weeks. The sequences were as follows: placebo to placebo; dulaglutide 0.5 mg to 1.0 mg; dulaglutide 1.0 mg to 1.0 mg; and dulaglutide 1.0 mg to 2.0 mg. While the titration was not studied at the proposed dose level, starting at 0.5 mg and escalating to the 1 mg doses after 4 weeks did reduce the incidence of nausea by half at week 4 (Table 62Table 6. Incidence of nausea and vomiting, and change from baseline in heart rate following 4 treatments (study GBCJ)).

Table 62. Incidence of nausea and vomiting, and change from baseline in heart rate following 4 treatments (study GBCJ)

Dose	Change from baseline Heart Rate (bpm)			Nausea (%)				Vomiting (%)			
	Week			Week				Week			
	4	8	16	4	8	12	16	4	8	12	16
Placebo	-1.66	-1.75	-0.89	3	4.5	3	0	0	0	1.5	1.5
0.5/1.0 mg	0.95	4.18	5.04	6.1	7.6	9.1	4.5	3	1.5	3	0
1.0/1.0 mg	5.19	3.44	3.4	12.3	9.2	7.7	7.7	1.5	0	0	0
1.0/2.0 mg	3.04	5.43	4.98	9.2	9.2	4.6	6.2	4.6	4.6	3.1	4.6

In addition, simulations were conducted based on exposure-response models for GI events to determine if patients would benefit by using dose titration. The simulated probability of nausea and vomiting following different titration regimens (initiate at 0.75 mg and continue once weekly for 1 to 4 weeks before starting 1.5 mg doses versus treatment initiate with the 1.5 mg dose) is shown in Figure 57. Compared to the titration regimens, starting with 1.5 mg resulted in an increased incidence of nausea (11%) and vomiting (7%) per week after the first dose. Initiating with 0.75 mg and continuing for 4 weeks is associated with lowest rates of initial GI symptoms.

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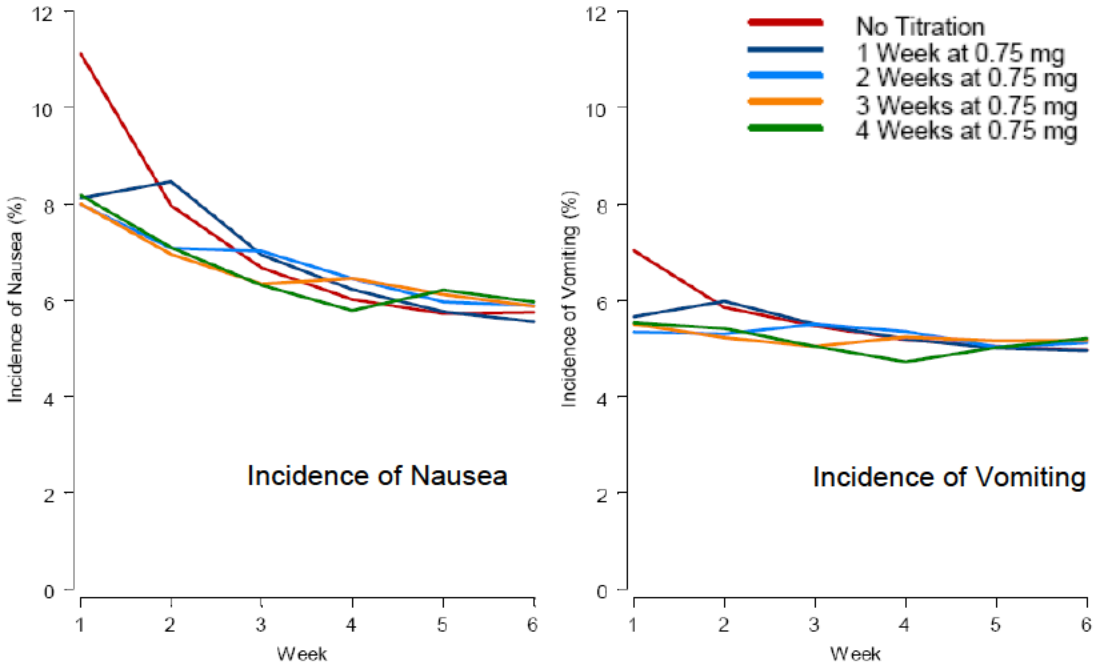
Figure 57. Model-estimated incidence of nausea (left) and vomiting (right) per week for 1.5 mg dulaglutide with no titration and after titrating with 0.75 mg for 1, 2, 3 and 4 weeks



(Source: Sponsor's Summary of Clinical Safety, Figure 2.7.4.8.)

4.2.1.2 Recommendations

Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this BLA and recommends approval. We recommend both the doses (0.75 and 1.5 mg once weekly) be approved and included in the label. However, given the dose-dependent increase in GI related AEs and clinically relevant heart rate increases, the following two options are presented for the dosing and administration section of the label:

- Dose of 0.75 mg is recommended to be the starting dose which can be titrated to 1.5 mg after 4 weeks based on GI tolerability. This is consistent with a titration based dosing regimen that has been implemented for other GLP-1 analogues (Exenatide, Liraglutide and Albiglutide).

  OR
- Option of starting with 0.75 or 1.5 mg dulaglutide with adequate labeling indicating that both doses are efficacious with a description stating that the lower dose offers a better GI tolerability profile and causes lower incidences of clinically relevant heart rate increases (cross reference to section 14 of the label). This will allow physicians to start with either 0.75 or 1.5 mg after weighing benefit risks.

4.2.1.3 Label Statements

Refer to the QBR section 3 for detailed labeling recommendations.

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4.2.2 Pertinent regulatory background

Eli Lily and Company is seeking FDA approval for [redacted] (b) (4) ™ (dulaglutide [rDNA origin] injection) for the indication of an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Dulaglutide is a glucagon-like peptide (GLP-1) receptor agonist. It consists of 2 identical polypeptide chains. Each chain contains a human GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small peptide linker, and 2 chains are linked by 2 disulfide bonds. (b) (4) [redacted]

Sponsor conducted several pivotal trials (monotherapy and background therapy) with two dose levels of dulaglutide (0.75 and 1.5 mg once weekly). Both doses were found to be effective with 1.5 mg having numerically higher reduction in HbA1c and other efficacy parameters. However, there was some dose dependence of clinically relevant heart rate increase and also GI related adverse events. It is worth noting that sponsor proposes to only include 1.5 mg dose in the proposed label.

4.2.3 Results of Sponsor's Analysis

Population PK/PD models were developed to evaluate the exposure-response relationships for efficacy parameters (FPG, HbA1c, and body weight), and safety parameters (HR, nausea and vomiting).

The relationship of BP, amylase (pancreatic and total), lipase, and calcitonin to dulaglutide concentrations were examined graphically. No relationships were observed for any of these measures in this population; therefore, PK/PD models were not developed.

Sponsor's conclusion from population PKPD analysis:

The PK of dulaglutide increased proportionally from the 0.75-mg to 1.5-mg dose. The following covariates were identified as being significant to explain dulaglutide variability in the respective models: baseline weight on bioavailability in the PK model; and baseline FPG, and coadministration of thiazolidinediones (TZDs) use on the HbA1c response to dulaglutide in the FPG-HbA1c model. No covariates were retained on dulaglutide-related parameters for the weight or the HR models. No clinically relevant relationships were observed between amylase, lipase, calcitonin, or antibodies and dulaglutide concentrations.

4.2.3.1 Exposure-response relationship for FPG, HbA1c, heart rate and body weight

The analyses used PK and PD data from three Phase 3 studies GBCF, GBDA, and GBDC, which included 0.75-mg and 1.5-mg weekly doses for 1 to 2 years of treatment.

The Monte Carlo importance sampling (IMP) estimation method was used for all PK/PD models. First, a base structural model was established for each of the measures. Next, covariates prospectively selected for their clinical relevance and/or interest were individually tested on relevant model parameters and baselines. The validity of the final

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models was evaluated with a bootstrap analysis to ensure that all parameters were well estimated. The models were also qualified using a VPC, comparing the range of model predicted values from the population model to those in the observed dataset.
The models described the observed data well. Two covariates explained the variability of the FPG-HbA1c response to dulaglutide in the final model: baseline FPG and co-medication with TZD on HLIM.

4.2.3.2 Exposure-response relationship for Nausea and Vomiting

Exposure-response models for nausea and vomiting were developed with data from 4 clinical pharmacology studies in healthy subjects and patients with T2DM (Studies GBCA, GBCB, GBCD, and GBCT). Both nausea and vomiting were modeled using a Markov Chain approach with a one hour time interval. For each endpoint, each patient's status at any time was divided into three categories: normal, mild, or moderate/severe, based upon their adverse event incidence over the course of that hour. Probabilities were then estimated, using a logit transformation, for remaining in the current state, or transitioning between states, as shown in Figure 58.
The model-predicted dulaglutide concentration at the mid-point of each one hour interval was assessed as a covariate on the transition probabilities. In addition, concentration-based tolerance relationships were evaluated on the transition probabilities, using an effect compartment model to estimate lag time.
For the nausea endpoint, increasing dulaglutide concentration was found to increase the probability of nausea, regardless of the previous state. Increasing dulaglutide concentration was also found to increase the probability of remaining in a state of moderate/severe nausea. Sustained exposure to dulaglutide concentration was found to cause tolerance, decreasing the probability of nausea. This tolerance effect lagged the concentration of dulaglutide with a halflife of approximately 990 hours.
For the vomiting endpoint, it was found that the probability of starting to vomit depended on the previous nausea state, with a higher probability of vomiting following previous nausea. Increasing dulaglutide concentrations were also found to increase the probability of starting to vomit. Sustained exposure to dulaglutide was found to cause tolerance, decreasing the probability of starting to vomit. This tolerance effect lagged dulaglutide concentration with a half-life of approximately 5.2 hours. The transition probabilities once vomiting commenced were not affected by dulaglutide concentration or previous nausea state.

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Figure 58. Markov chain model for nausea and vomiting

(b) (4)

(Source: Sponsor's Appendix to the Summary of Clinical Pharmacology, Figure APP.2.7.2.5.27.)

Reviewer's Comments:

- *The sponsor's population PK/PD analyses overall appear adequate for describing the exposure-response relationship for main efficacy and safety endpoints.*
- *Baseline FPG and coadministration of TZD significantly affected the glycemic response. Patients starting with a higher baseline FPG or taking a TZD would be expected to derive a greater benefit from the treatment:*
    - *an additional 0.17% decrease in HbA1c for each 10-mg/dL increase in baseline FPG;*
    - *a larger change at 1 year for patients on TZDs relative to those not taking TZDs, for both FPG (-35.9 mg/dL and -28.1 mg/dL, respectively) and HbA1c (-1.22% and -0.93%, respectively).*
- *These analyses support the 1.5 mg once weekly dose as an optimal dose based on benefit-risk profile.*
- *No dose adjustment is apparently required for any patient factors.*

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4.2.3.3 Population pharmacokinetic model

The population PK model was developed using a dataset of all available observations from 1067 patients in the Phase 3 Studies GBDA and GBDC combined with the 0.75-mg and 1.5-mg data from the Phase 2/3 Study GBCF.

A two-compartment model with first-order absorption was identified to best describe the population PK of dulaglutide using data from the absolute bioavailability study (GBDR). Thus, a two-compartment model was used for the PK analysis in the current analysis. The model is parameterized in terms of relativxe bioavailability (F1), rate constant of absorption (KA), clearance (CL), volume of the central and peripheral compartments (V2 and V3), and inter-compartmental clearance (Q). Inter-patient variability on KA was fixed to the final estimated value from Study GBDR. Inter-patient variability was estimated for CL and V2, using an omega block to quantify covariance between the 2 parameters. A proportional residual error model was used. The first-order conditional estimation method (FOCE) with interaction was used.

The results of previous analyses, including the bioavailability study, demonstrated that dulaglutide bioavailability decreases with increasing dose. The bioavailability of the 1.5-mg dose was fixed to 47%, the final estimate from Study GBDR, while the bioavailability of the 0.75-mg dose was estimated using a continuous function.

(b) (4)

Where FMAX is the maximum decrease in bioavailability, FD50 is the dose at which half-maximal decrease occurs, F1 is relative bioavailability, and F0 is the bioavailability without dose effect.

Informative priors based upon the final GBDR PK model were used for the structural parameters (KA, CL, V2, Q, and V3) based upon the final GBDR PK model.

The covariates tested on the population PK model were age, body weight, BMI, sex, race/ethnicity, serum creatinine, dose, smoking, DPP-IV coadministration, renal function, and macroalbuminuria. The only study- or patient-specific factor retained in the final model was baseline weight on bioavailability (F).

The parameter estimates for the final base and final PK models are listed in Table 63 and VPC plots are shown in Figure 59.

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Table 63. PK and covariate parameters in the base and final model

Parameter Description	Final Base		Final Model	
	Population Estimate (%SEE)	Inter-Patient Variability[a] (%SEE)	Population Estimate (%SEE)	Inter-Patient Variability[a] (%SEE)
Relative Bioavailability				
Parameter for F1 for 0.75 mg Dose	0.474 (2.57)	---	0.476 (2.33)	---
Parameter for F1 for 1.5 mg Dose	0.470 (Fixed)	---	0.470 (Fixed)	---
Effect of Baseline WT on F1[b]			-0.00877 (6.61)	---
Rate of Absorption				
Parameter for Ka (hr^{-1})	0.00705 (15.6)	39.9% (18.9)	0.00769 (18.3)	40.5% (20.7)
Clearance				
Parameter for CL (L/hr)	0.0604 (1.90)	39.4% (8.75)	0.0593 (1.74)	33.8% (11.2)
Volume of Central Compartment				
Parameter for V2 (L)	2.12 (16.9)	68.7% (41.3)	2.25 (19.2)	55.6% (57.2)
Inter-Compartmental Clearance				
Parameter for Q (L/hr)	0.0145 (42.8)	---	0.0201 (38.4)	---
Volume of Peripheral Compartment				
Parameter for V3 (L)	3.18 (14.2)	---	3.75 (13.5)	---
Inter-Patient Variability Interaction Term (CL and V2)	0.220 (22.4)		0.155 (31.0)	
Residual Error (proportional)	28.5% (5.01)		28.7% (4.97)	

Abbreviations: CL = clearance; F1=relative bioavailability; Ka = absorption rate constant; Q = inter-compartmental clearance; SEE = standard error of the estimate; V2 = volume of the central compartment; V3 = volume of the peripheral compartment.

a %CV = (SQRT(EXP(OMEGA(variance estimate))-1))*100%.

b Described as: F1*EXP($\theta_{WT\text{-}F1}$• (Weight - 92.5 kg)).

(Source: Sponsor's Phase 3 Combined Population PK/PD Report, Table 9.2)

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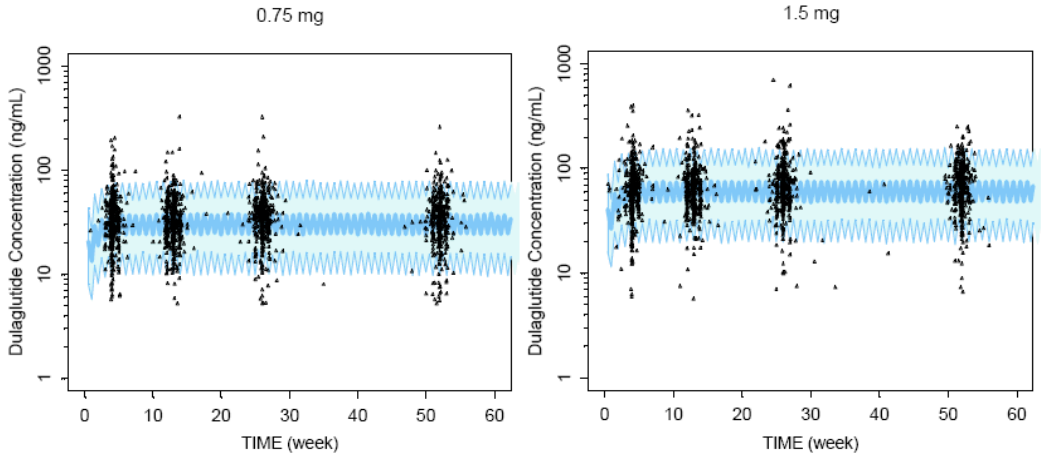
Figure 59. VPC plots for the final model following 0.75 mg (left panel) and 1.5 mg (right panel) of dulaglutide.



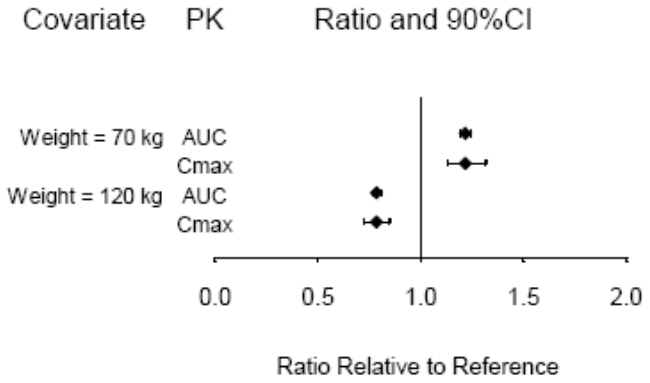
(Source: Sponsor's Phase 3 Combined Population PK/PD Report, Figure 9.5)

Sponsor's Justification for No Dose Adjustment by Body Weight

(1). Effect of Body Weight on PK is not clinically relevant

As shown in **Figure 60**, over a wide range (10 to 90%) of body weights in phase 3 population, the change in AUC and Cmax was not significant. In addition, the model-estimated concentrations for patients at the 90th percentile of body weight fall within the 90% prediction interval for the median weight (93 kg) T2DM population; therefore, patients with higher body weights would have concentrations that are comparable to those expected in the majority of the patient population (**Figure 61**) .

Figure 60. Forest plot of effect of body weight on the pharmacokinetics of dulaglutide from the combined Phase 3 population analysis.



The reference for the ratios was the population median (weight = 93 kg). The weight values chosen (70 and 120 kg) represent the 10th and 90th percentiles of weight in this population.
(Source: Sponsor's Clinical Pharmacology Summary, Figure 2.7.2.38.)

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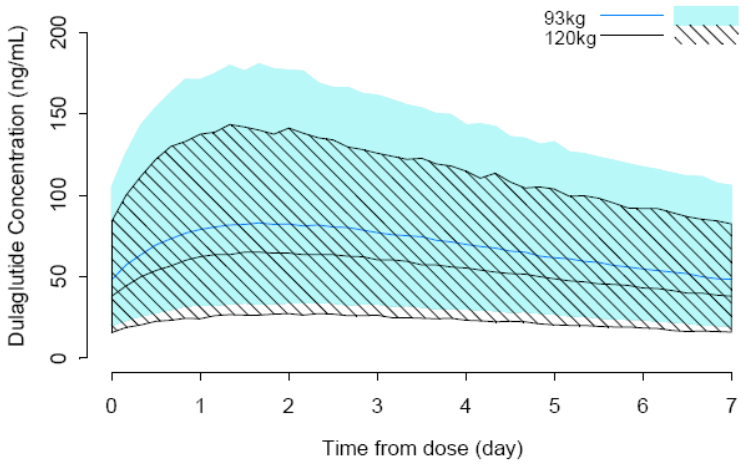
Figure 61. Dulaglutide steady-state concentrations following 1.5 mg for patients with T2DM with higher body weight (120 kg) fall within the 90% prediction interval for the T2DM population.



Blue line and shaded area represent the median and 90% prediction interval for concentrations, respectively, after dosing of 1.5 mg dulaglutide at steady state in patients with T2DM and a body weight of 93 kg (represents population median). The black middle line and the hashed area represent the median concentrations and the 90% prediction interval, respectively, for patients with diabetes and body weight of 120 kg.
(Source: Sponsor's Clinical Pharmacology Summary, Figure 2.7.2.39.)

(2). Body Weight does not appear to have effect on glycemic control

The average concentrations at steady state (Cavg,ss) following 1.5 mg and 0.75 mg dulaglutide doses in the combined Phase 3 PK/PD population were 74.0 ng/mL and 37.5 ng/mL, respectively, which are both greater than the concentration needed to achieve a minimal clinically significant reduction in HbA1c (as prospectively defined as -0.4%, ~ 10 ng/mL). In addition, the predicted Cavg,ss following 1.5 mg and 0.75 mg and dulaglutide doses for a 120 kg patient, which represents the 90th percentile of weight in the combined Phase 3 PK/PD population, were 55.6 ng/mL and 28.2 ng/mL, respectively, which are also greater than 10 ng/mL.

In addition, given the high variability in PK and HbA1c, there does not appear to be any trend of loss in efficacy in higher body weight patients (**Figure 62**). In the Phase 3 studies, 1.5 mg and 0.75 mg dulaglutide demonstrated effective HbA1c reductions in both patients who weighed <90 kg and ≥90 kg.

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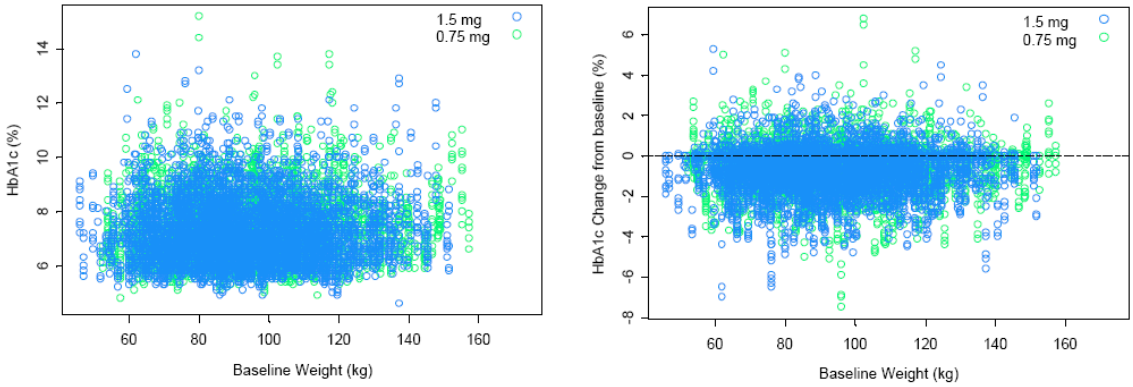
Figure 62. Individual observed absolute HbA1c (left) and HbA1c change from baseline (right) by baseline weight from the combined Phase 3 analysis.

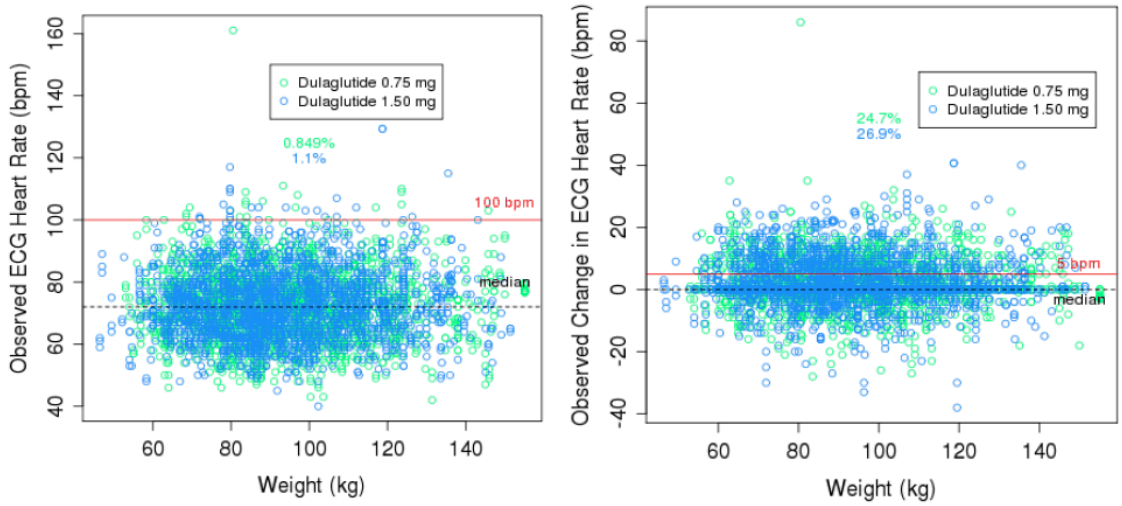


(Source: Sponsor's Clinical Pharmacology Summary, Figure 2.7.2.40.)

(3). Body weight does not appear to have an effect on heart Rate

The observed HR data from Phase 3 showed no relationship between the HR changes from baseline and body weight for both the 1.5 mg and 0.75 mg doses (**Figure 63**).

Figure 63. Individual observed absolute heart rate (left) and heart rate change from baseline (right) in heart rate data versus weight from the combined Phase 3 analysis



For the 0.75 mg and 1.5 mg doses respectively, 0.849 % and 1.1 % of the data were above the 100 bpm threshold for absolute heart rate, and 24.7 % and 26.9 % of the data were above the 5 bpm threshold for heart rate change from baseline.

(Source: Sponsor's Clinical Pharmacology Summary, Figure 2.7.2.41.)

The population PK/PD modeling determined that although exposure affected HR, the magnitude of this effect was small (2.1 bpm at 52 weeks based on Phase 3 data) and did not result in a clinically meaningful change (median change from baseline in HR < 5 bpm).

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Reviewer's Comments:

- *The sponsor's population PK analysis appears appropriate for evaluating the effects of potential covariates on dulaglutide PK.*
- *Baseline body weight was the only covariate retained in the final model. It is important to note that inter-patient variability on CL only decreased by 5% (39% to 34%) with the addition of weight as a covariate on F1, which leaves a large amount of inter-patient variability unexplained.*
- *Sponsor's justification for no dose adjustment by body weight is acceptable, given overlapping PK by body weight and no apparent effect on glycemic control and heart rate.*

4.2.4 Reviewer's Analysis

4.2.4.1 Introduction

The reviewer's independent analysis was mainly focusing on the heart rate increase in the dose-titration study GBCJ.

4.2.4.2 Objectives

Analysis objective is to understand the distribution of heart rate change from baseline in individual patients.

4.2.4.2.1 Data Sets

Data sets used are summarized in **Table 64.**

Table 64. Analysis Data Sets

Study Number	Name	Link to EDR
Study GBCJ	vs.xpt	\\cdsesub1\bla\ectd_submissions\stn125469\0000\m5\datasets\h9x-mc-gbcj\tabulations\sdtm\vs.xpt
Study GBCJ	dm.xpt	\\cdsesub1\bla\ectd_submissions\stn125469\0000\m5\datasets\h9x-mc-gbcj\tabulations\sdtm\dm.xpt

4.2.4.2.2 Software

Data preparation and analysis was conducted using SAS 9.2.

4.2.4.3 Results

The needle plots in Figure 64 were generated from individual patient level data from study GBCJ, depicting the distribution of change from baseline in heart rate in each treatment group over time.

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- At all time points, there were larger proportions of patients with heart rate increase in the dulaglutide treatment group compared to the placebo, and the magnitude of increase was also higher than placebo.
- The number of patients with heart rate increase seems to increase over time for all treatment groups.
- The magnitude of the increase was highest in the highest dosing group 1.0→2.0 mg at week 4, compared to the lower dosing groups. The difference decrease over time and was no longer seen at week 12.
- The distributions of heart rate change are generally comparable between the 0.5→1.0 mg group and 1.0 fixed dose group. One patient was associated with a significant heart rate reduction at week 4, which may explain the major difference in mean increase between these two groups, as seen in Table 62.
- Overall the titration effect was not evident on change from baseline in heart rate.

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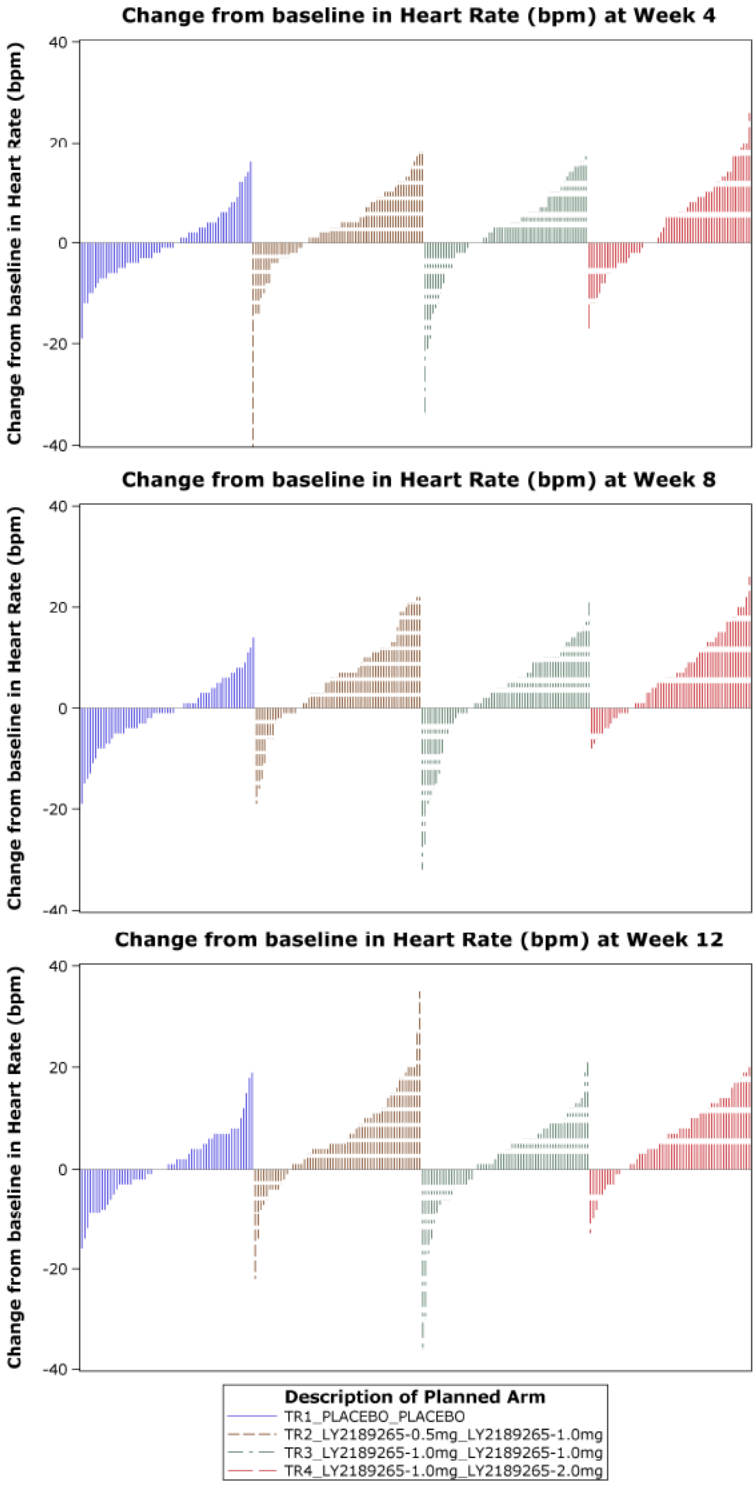

Figure 64. Needle plot comparing the change from baseline in heart rate (bpm) in placebo vs. three dulaglutide treatment groups at week 4, 8 and 12. Each vertical line represents one patient.

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4.2.5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
HR.gbcj.sas		\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Dulaglutide_BLA_125469_LM\ER Analyses\Code

Reference ID: 3520514

4.3 FILING MEMO

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	BLA 125469	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Dulaglutide
Medical Division	DMEP	Drug Class	Glucagon-like peptide (GLP-1) receptor agonist
OCP Reviewer	Sang Chung	Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
OCP Team Leader	Lokesh Jain	Dosage Form	Solution
Pharmacometrics Reviewer	Lian Ma	Dosing Regimen	1.5 mg once weekly
Date of Submission	9/18/2013	Route of Administration	Subcutaneous
Estimated Due Date of OCP Review	7/18/2014	Sponsor	Eli Lilly and Company
Medical Division Due Date		Priority Classification	Standard
4.3.1.1 PDUFA Due Date	9/18/2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any (Study Name)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-				
single dose:	X	1	1	GBCA
multiple dose:				
Patients-				
single dose:	X	1	1	GBCB
multiple dose:	X	2	2	GBCD, GBCL
Dose proportionality -	X			
fasting / non-fasting single dose:	X	1	1	GBCA
fasting / non-fasting multiple dose:	X	2	2	GBCD, GBCL
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1	1	GBDW
In-vitro:	X	8	8	GBCH, GBCD, GBCP, GBCO, GBCQ, GBCR, GBCS, GBDW
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1	1	GBCT
renal impairment:	X	1	1	GBCM

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hepatic impairment:	X	1	1	GBDO
PD -				
Phase 2:	X			
Phase 3:	X			
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability	X	1	1	GBDR
Relative bioavailability -				
solution as reference:	X	2	2	GBCN (im), GBCN (injection sites)
alternate formulation as reference:				
Bioequivalence/Comparability studies -				
traditional design; single / multi dose:	X	1		GBDT
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		21	21	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			To-be-marketed formulation has been evaluated in Phase 3 studies. The pivotal comparability study for an additional commercial deliver device was conducted.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it	X			

Reference ID: 3520514

	have appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X		A partial waiver in patients less than 10 years; deferral in children between 10 years and younger than 18 years
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

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If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Sang Chung, Ph.D.	10/30/2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain, Ph.D.	10/30/2013
Team Leader/Supervisor	Date

RECOMMENDATIONS:

- This NDA application is fileable from a clinical pharmacology perspective
- No comments in the 74-day letter
- OSI inspection will be requested for the pivotal comparability study (Study GBDT)

Reference ID: 3520514

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANG M CHUNG
06/06/2014

LIAN MA
06/06/2014

NITIN MEHROTRA
06/06/2014

LOKESH JAIN
06/06/2014