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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**BLA #:** 125469

**Drug Name:** Dulaglutide Injection (proposed dose 1.5 mg)

**Indication:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

**Applicant:** Eli Lilly and Company

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## 1 EXECUTIVE SUMMARY

This is a statistical safety review of a cardiovascular (CV) meta-analysis report submitted on September 18, 2013, by Eli Lilly and Company (hereafter referred to as the Applicant) for the Biologics License Application (BLA 125469) for dulaglutide injection. The Applicant is seeking an indication for dulaglutide as an “adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus” (T2DM). The development program assessed the efficacy and safety of multiple doses of dulaglutide; however, the Applicant is proposing to commercialize the 1.5 mg dose only to be administered once weekly. The primary objective of the meta-analysis was to demonstrate that the upper bound of the confidence interval for the hazard ratio (dulaglutide to comparators) was smaller than the pre-market risk margin of 1.8 as stipulated in the FDA Diabetes Guidance<sup>1</sup> for assessing CV safety in new anti-diabetic products. The Applicant planned to conduct at most two meta-analyses to rule out this risk margin prior to the BLA submission. The first meta-analysis was to be based on data from 9 completed Phase 2 and 3 trials, regardless of the number of events observed. If the first meta-analysis did not meet the pre-specified 1.8 risk margin, a second (and final) meta-analysis was to be conducted when 180 primary events were accumulated. The second meta-analysis was to be based on all trials included in the first meta-analysis and interim data from the ongoing CV outcomes trial (REWIND). According to the study report, the first meta-analysis met the FDA requirement by demonstrating that the upper bound of the alpha-adjusted confidence interval for the hazard ratio (HR) was less than 1.8. Therefore, no data from REWIND were included in the meta-analysis included in the BLA submission that is currently under review. Post approval, the Applicant plans to use all the data from REWIND to determine whether the CV risk based on the 1.3 margin can be ruled out.

The meta-analysis was conducted according to an analysis plan (finalized July 2012) that was reviewed and agreed upon by the FDA<sup>2,3</sup>. There were some trials that were complete before finalization of the meta-analysis plan; see Section 3.2.1 for trial completion dates. The agreed upon<sup>4</sup> primary safety endpoint of this meta-analysis was **MACE+**, a composite endpoint comprising CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina. A key secondary endpoint was **MACE**, a composite endpoint comprising CV death, non-fatal MI, or non-fatal stroke. All CV events included in the meta-analysis were based on positively adjudicated events determined by an independent blinded Clinical Event Committee that used standardized definitions for the components of the composite endpoint. The agreed upon population of interest was the intent-to-treat (ITT) population comprising all randomized patients; patients were analyzed according to their assigned treatment group, regardless of actual treatment received. The main treatment groups compared were dulaglutide (pooled doses) and comparator (pooled placebo and active controls). Note that the meta-analysis was not designed to assess CV safety of the individual dulaglutide doses. The pre-specified

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<sup>1</sup> Refer to FDA Guidance for Industry *Diabetes Mellitus –Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* dated December 2008

<sup>2</sup> Refer to Statistical Review by Dr. Lee Ping Pian dated August 19, 2011

<sup>3</sup> Refer to FDA Correspondence dated June 12, 2012

<sup>4</sup> Refer to End-of-Phase 2 meeting minutes dated January 19, 2010.

primary statistical analysis used a stratified Cox proportional hazards model. Because there were two planned analyses to rule out the 1.8 risk margin, the Type I error rate was controlled using the Pocock spending function. Therefore, results of the primary and secondary endpoints presented in this review are based on two-sided alpha-adjusted 98.02% confidence intervals (CIs). The results of subgroup analyses are presented with unadjusted 95% CIs as they are considered exploratory.

For the meta-analysis, a total of 3885 patients were randomized to dulaglutide of which 26 patients (0.7%) experienced a MACE+ event, whereas a total of 2125 patients were randomized to a comparator of which 25 patients (1.2%) experienced a MACE+ event. The estimated hazard ratio for MACE+ across all trials included in the meta-analysis was **0.57** with 98.02% CI (**0.30, 1.10**); the meta-analysis of MACE yielded consistent results, see Table 1. Thus, it can be concluded that the meta-analysis to evaluate cardiovascular safety ruled out the pre-marketing risk margin of 1.8.

Table 1 Summary of Meta-analysis Results of MACE+ and MACE

Outcome	Number of Patients with Events		HR (98.02% CI)
	Dulaglutide <sup>1</sup> , N=3885 n (%)	Comparator <sup>2</sup> , N=2125 n (%)	
MACE+	26 (0.70)	25 (1.20)	0.57 (0.30, 1.10)
MACE	23 (0.60)	21 (1.00)	0.60 (0.30, 1.21)

n=number of patients with outcome, N=number of patients randomized, HR=hazard ratio from stratified Cox model, CI= alpha-adjusted confidence interval based on Pocock spending function

<sup>1</sup>Pooled dulaglutide doses

<sup>2</sup>Pooled active and placebo comparators

Source: Created by the reviewer using dataset “cv\_all.xpt”

Subgroup analyses were also conducted to compare the risk of MACE+ within each dulaglutide dose (1.5 mg or 0.75 mg) relative to all comparators. For the 0.75 mg dose, the HR estimate of MACE+ was 0.56 with 95% CI (0.29, 1.11). For the 1.5 mg dose, the HR estimate was 0.58 with 95% CI (0.30, 1.14).

It is important to note that the dulaglutide meta-analysis comprises trials of various designs (with respect to randomization ratios, blinding strategies, parallel arm, adaptive design, trial durations, etc.), and was designed to test whether the pre-market 1.8 risk margin can be ruled out. As a result, the conclusion is that meta-analysis data was sufficient to show that dulaglutide is not associated with an 80% increase in CV risk. The recommendation is that further evaluation of the CV risk of dulaglutide be based on findings from the REWIND trial, which is designed around the MACE endpoint and conducted in a high risk population with prolonged exposure.

## 2 INTRODUCTION

### 2.1 Product Description and Regulatory Background

Dulaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that increases insulin secretion in the presence of elevated glucose concentrations, decreases glucagon secretion, and slows gastric emptying. The Applicant, Eli Lilly and Company (Lilly), submitted a Biologics License Application, BLA 125469, for dulaglutide injection on September 18, 2013 (PDUFA Goal Date: September 18, 2014) to be indicated as an “adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus” (T2DM). The development program studied efficacy and safety of multiple doses of dulaglutide; however, Lilly is proposing to commercialize the 1.5 mg dose only and it is to be administered as a once weekly subcutaneous (SC) injection. The BLA submission strategy and development program for dulaglutide were discussed with the Division of Metabolism and Endocrinology Products (DMEP) and reflected in End of Phase 2 Meeting Minutes (dated January 19, 2010), Written Responses to Request for Clarification (dated May 5, 2011) and pre-NDA Meeting Minutes (July 23, 2013).

In accordance with the FDA Guidance for Industry *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (dated December 2008), Lilly performed a meta-analysis of clinical trials in their development program to assess whether dulaglutide is associated with an unacceptable increased risk of cardiovascular (CV) disease. In alignment with the guidance, the pre-marketing objective of the meta-analysis was to rule out an excess risk of 80%, as demonstrated by an upper bound of the two-sided 95% confidence interval (CI) for the hazard ratio less than 1.8. The CV meta-analysis that was designed to rule out the 1.8 risk margin is the subject of this statistical safety review. The meta-analysis was conducted according to an analysis plan (finalized July 2012) that was reviewed and agreed upon by the FDA<sup>5,6</sup>. All CV events were adjudicated by an independent Clinical Event Committee (CEC) for inclusion in the statistical analyses. The CEC was governed under a charter and blinded to treatment allocation information for all patients. Note that the original charter was dated November 3, 2008 after commencement of a small Phase 2 trial that started in April 2008. With these dates in mind, it is possible that adjudication was retrospective for this trial; however, this is not expected to impact the findings of the primary endpoint analysis as few events are generally expected to be observed in small Phase 2 trials.

The Applicant had planned to conduct two meta-analyses to assess the 1.8 risk margin prior to the BLA submission. The first meta-analysis was to include data from 9 completed Phase 2 and 3 trials; regardless of the number of events accumulated. If the first meta-analysis did not meet the pre-specified 1.8 risk margin, a second (and final) meta-analysis was to be conducted when 180 primary events were accumulated. The second meta-analysis was to be based on all trials in the first meta-analysis and interim data from the ongoing CV outcomes trial (REWIND). According

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<sup>5</sup> Refer to Statistical Review by Dr. Lee Ping Pian dated August 19, 2011

<sup>6</sup> Refer to FDA Correspondence dated June 12, 2012

to the study report, the first meta-analysis met the FDA requirement by demonstrating that the upper bound of the alpha-adjusted<sup>7</sup> confidence interval for the HR was less than 1.8. Therefore, no data from REWIND were included in the meta-analysis for CV safety at the time of BLA submission that is the subject of this review.

## 2.2 Clinical Trial Overview

The CV meta-analysis was based on data from 9 completed randomized, placebo- or active-controlled Phase 2 and 3 trials: 4 Phase 2 trials (durations: 12-26 weeks) and 5 Phase 3 trials (durations: 52-102 weeks); see Table 2 for summary of trial designs. Section 3.2.1 provides detailed discussion of the study designs and respective patient populations.

## 2.3 Data Sources

The NDA was submitted electronically and included integrated datasets across all the trials included in the CV meta-analysis. All data tabulation datasets were provided in CDISC Study Data Tabulation Model (SDTM) format and all analysis datasets were provided in Lilly's standard Analysis Dataset (ADS) format. Data definition files for all datasets were also included in the application. The CV meta-analysis study report and data relevant for this statistical review can be found at the following location:

CBER EDR: <http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6812e0f42>

In the FDA preliminary responses<sup>8</sup> to the initial preBLA meeting questions, the concern was raised that the ADS format may not be sufficiently similar to the CDISC Analysis Dataset (ADaM) format to allow an FDA reviewer to successfully navigate ADS. A template for the desired structure of the integrated analysis datasets to facilitate review of CV safety was also provided to Lilly in these responses. Note that this initial meeting was cancelled due to insufficient briefing information. In the subsequent briefing information for the actual pre-BLA meeting, Lilly acknowledged FDA's concerns regarding the ADS format and noted that several types of detailed documents will be included in the submission to assist the reviewer with navigating across various formats and datasets and to mitigate the differences between ADS and ADaM. The integrated CV analysis datasets were submitted using the structure requested by the FDA.

The following integrated datasets were used to perform statistical analyses in this review:

- “subjinfo.xpt” which contains the demographic and disposition data
- “cv\_all.xpt” which contains the time to event analysis variables.

A discussion of the data quality is provided in Section 3.1 of this review.

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<sup>7</sup> The Pocock spending rule was used for alpha adjustment to account for two planned meta-analyses for testing the 1.8 risk margin.

<sup>8</sup> Refer to FDA preliminary responses to pre-BLA meeting package, dated May 2, 2013

Table 2 Summary of Trials Included in CV Meta-analysis

Trial ID	Phase	Treatment Duration (in weeks)	Number of Patients Randomized		Dulaglutide Dose (in mg)	Comparator Name
			Dulaglutide	Comparator		
GBCJ	2	16	196	66	0.5→1.0, 1.0, 1.0→2.0	Placebo
GBCK	2	12	135 <sup>2</sup>	32	0.1, 0.5, 1.0, 1.5	Placebo
GBCZ	2	12	108	37	0.25, 0.5, 0.75	Placebo
GBDN	2	26	505	250	0.75, 1.5	Placebo
GBCF <sup>1</sup>	3	104	710	492	Stage 1: 0.25 to 3.0 Stage 2: 0.75,1.5	Placebo/Sitagliptin, Sitagliptin
GBDA	3	52	559	419	0.75, 1.5	Placebo, Exenatide
GBDB	3	78	545	265	0.75, 1.5	Insulin glargine
GBDC	3	52	539	236	0.75, 1.5	Metformin
GBDD	3	52	588	296	0.75, 1.5	Insulin glargine

→ indicates dose titration

<sup>1</sup> GBCF is an adaptive design trial. In stage 1, patients were randomized to one of 7 possible doses of dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, or 3.0 mg), followed by stage 2 where patients were randomized to the 0.75 and 1.5 mg doses only. See Section 3.2.1 for more details of the trial design.

<sup>2</sup> In trial GBCK, the dulaglutide arm includes 3 patients who were randomized to 3.0 mg dose, prior to protocol amendments that changed the maximum dose to 1.5 mg, see Section 3.2.1 for more details of the trial design.

Source: Created by the reviewer using dataset “subjinfo.xpt” and study report Table 1.1 (page 16)

### 3 STATISTICAL EVALUATION

This is a statistical safety review that focuses solely on the cardiovascular safety meta-analysis for dulaglutide. Please refer to separate statistical review by Dr. Bradley McEvoy for overall efficacy and safety evaluation.

#### 3.1 Data and Analysis Quality

The data definition files included in the application provided sufficient details such that the primary endpoint analysis results could be replicated with ease from the submitted analysis datasets. There were no notable data quality or analysis issues discovered in this review that would impact the findings of the primary endpoint analyses for CV safety.

#### 3.2 Evaluation of Safety

##### 3.2.1 Design of Trials Included in Meta-Analysis

All trials in the meta-analysis included adults who had been diagnosed with T2DM, had insufficient glycemic control, and BMI  $\leq 45\text{kg/m}^2$ . Female patients could not participate in any trial if they were pregnant or breast feeding or if they did not use adequate contraceptive methods. With the exception of 2 phase 2 trials (GBCJ and GBCZ), all trials studied the 1.5 mg proposed dose of dulaglutide. The trials had varying design characteristics, such as, randomization ratios and specifications for blinding. The summaries for each of the trials included in the meta-analysis, which were obtained from the respective trial protocols and study reports, are provided in the subsections that follow.

###### 3.2.1.1 Designs of Phase 2 Trials Included in Meta-analysis

**GBCJ:** A multicenter, multiple-titrated and non-titrated dose, placebo-controlled, parallel-group, double-blind study conducted in overweight and obese (BMI range: 27– 40  $\text{kg/m}^2$  inclusive) T2DM patients at least 18 years who are taking any 2 oral antihyperglycemic medications (OAMS) included in the sulfonylurea, biguanide, thiazolidinedione, or DPP4 inhibitor classes, and had  $7.0\% < \text{HbA1c} \leq 10.5\%$ . The primary objective of the trial was to evaluate once-weekly dulaglutide compared to placebo for glycemic control as measured by HbA1c change from baseline to 16 weeks. The trial was composed of a 2-week placebo run-in period followed by a 16-week treatment period in which patients were randomized in a 1:1:1:1 ratio to four possible treatment arms:

- Placebo: Once weekly SC placebo injection for 16 weeks
- Dulaglutide 0.5 mg/1.0 mg: Once weekly SC injection of 0.5mg dulaglutide for 4 weeks followed by once weekly SC injection of dulaglutide 1.0 mg for 12 weeks
- Dulaglutide 1.0 mg: Once weekly SC injections of dulaglutide 1.0mg for 16 weeks

- Dulaglutide 1.0mg/2.0mg: Once weekly SC injection of 1.0 mg dulaglutide for 4 weeks followed by once weekly SC injection of dulaglutide 2.0 mg for 12 weeks

A total of 510 patients were screened for this trial, of which 262 patients were randomized: 66 patients to placebo, 66 patients to the dulaglutide 0.5 mg/1.0mg arm, 65 patients to the dulaglutide 1.0 mg arm, and 65 patients to the dulaglutide 1.0 mg/2.0 mg arm. The trial was conducted between April 17, 2008 and January 9, 2009.

GBCK: A multicenter, parallel-arm, randomized, double-blind, placebo-controlled trial in patients with T2DM who were OAM naïve or who had discontinued metformin monotherapy. Eligible patients were between 18 and 75 years, had  $6.5\% \leq \text{HbA1c} \leq 9.5\%$ , and had BMI 23–40  $\text{kg/m}^2$  for patients who are native to and residing in South or East Asia, or BMI between 25–40  $\text{kg/m}^2$  for all other patients. The primary objective of the trial was to demonstrate a dose-dependent effect of once-weekly dulaglutide compared to placebo as measured by change in HbA1c from baseline to 12 weeks. The trial consisted of 4 periods: a 2-week screening period, a lead-in period to last approximately 4 – 8 weeks (for patients discontinuing metformin there must be an 8-week wash-out period of metformin prior to obtaining qualifying HbA1c measurement, and for OAM naïve patients the lead-in period should be at least 4 weeks), a 12-week treatment period, and a 4-week safety follow-up period. Patients who met all the eligibility criteria after lead-in were randomized in a 1:1:1:1 ratio to placebo or 1 of 4 doses of dulaglutide (0.1, 0.5, 1.0, or 1.5 mg). A total of 460 patients were screened, of which 167 were randomized as follows: 32 patients to placebo, 35 patients to dulaglutide 0.1 mg, 34 patients to dulaglutide 0.5 mg, 29 patients to dulaglutide 1.0mg, 34 patients to dulaglutide 1.5 mg, and 3 patients to dulaglutide 3.0 mg prior to protocol amendments<sup>9</sup> that replaced this dose with 1.5 mg. The trial was conducted from January 5, 2009 to January 25, 2010.

GBCZ: A multicenter, placebo-controlled, randomized, double-blind, parallel-arm trial to assess the safety and efficacy of dulaglutide administered SC once weekly in Japanese patients with T2DM who are OAM naïve or taking oral antidiabetic (OAD) monotherapy. Patients eligible for enrollment had to be at least 20 years but no older than 75 years, had BMI 18.5–40  $\text{kg/m}^2$ , and had  $7.0\% \leq \text{HbA1c} \leq 9.5\%$  for OAD naïve patients, or  $6.5\% \leq \text{HbA1c} \leq 8.5\%$  for patients on OAD therapy. The primary objective of the trial was to demonstrate a dose-dependent effect of once-weekly dulaglutide compared to placebo as measured by change in HbA1c from baseline to 12 weeks. The trial consisted of 4 periods: a 2-week screening period, a lead-in period (4 weeks for OAM naïve patients, at least 8 weeks for patients discontinuing OAD monotherapy except for thiazolidinediones, and at least 12 weeks for patients discontinuing thiazolidinedione monotherapy), a 12-week treatment period, and a 4-week safety follow-up. Patients who completed the lead-in period were randomized in a 1:1:1:1 ratio to placebo or 1 of 3 dulaglutide doses (0.25, 0.50, or 0.75 mg). There were 219 patients screened for this trial, of which 145 patients were randomized as follows: 37 patients to placebo, 36 patients to dulaglutide 0.25 mg,

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<sup>9</sup> Trial GBCK was originally designed with the highest dose of dulaglutide of (b) (4) dose. This dose was changed to 3.0 mg prior to patient enrollment and later to 1.5 mg; refer to protocol amendments (a) and (b), respectively. The 3 patients who were randomized to the 3.0 mg dose were discontinued from trial when the dose was changed to 1.5 mg.

37 patients to dulaglutide 0.50 mg, and 35 patients to dulaglutide 0.75 mg. The trial was conducted between December 11, 2009 and December 4, 2010.

GBDN: A multicenter, randomized, double-blind, parallel-arm, 26-week treatment, placebo-controlled trial to evaluate the effects dulaglutide on blood pressure and heart rate in patients with T2DM on 1 or more OAMs. Eligible patients were at least 18 years old, had  $7.0\% \leq \text{HbA1c} \leq 9.5\%$ , and BMI at least  $23 \text{ kg/m}^2$ . The primary objective of the trial is to demonstrate that the change from baseline in mean 24-hour systolic blood pressure of dulaglutide doses are noninferior to placebo at 16 weeks, as measured by ambulatory blood pressure monitoring. The trial comprised 3 periods: a 2-week screening and lead-in period, followed by a 26-week treatment period, and a 4-safety follow-up period. A total of 1497 patients were screened, of which 755 patients were randomized in a 1:1:1 ratio as follows: 250 patients to placebo, 254 patients to dulaglutide 0.75 mg, and 251 patients to dulaglutide 1.5 mg. The trial was conducted from July 8, 2010 to January 4, 2012.

### 3.2.1.2 Designs of Phase 3 Trials Included in Meta-analysis

GBCF: A multicenter, two-stage adaptive, randomized double-blind, controlled, efficacy and safety trial of once weekly dulaglutide compared to once daily sitagliptin (100 mg) and placebo in patients with T2DM on metformin. Eligible patients were between ages 18 and 75 inclusive, had  $7.0\% \leq \text{HbA1c} \leq 9.5\%$ , and had BMI  $25 - 40 \text{ kg/m}^2$ , inclusive. The trial comprised three periods: a screening and lead-in period of up to 11 weeks, a treatment period of 24 months, and a 30-day safety follow-up period. Two distinct randomization schemes were used in this trial: an adaptive scheme was used prior to dose selection and a fixed randomization scheme was used after dose selection. The randomization schemes divided the trial into two stages:

- Stage 1: This stage includes the time from start of trial until the Decision Point. During this stage, patients were randomized to 1 of 7 doses of dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, or 3.0mg), to a placebo/sitagliptin sequence, or sitagliptin using a ratio of 3:1:1 (60% to dulaglutide, 20% to placebo/sitagliptin<sup>10</sup>, and 20% to sitagliptin). Randomization to dulaglutide was done adaptively based on accumulating data and pre-specified safety and efficacy parameters. At the Decision Point, two doses of dulaglutide were selected. Dulaglutide 1.5 mg was selected as the maximum utility dose and dulaglutide 0.75 mg was selected as the lower dose to be continued in the remainder of the trial. Patients who were randomized to placebo/sitagliptin, placebo, or the selected dose of dulaglutide continued in the trial for 24 months. Patients who were originally randomized to the non-selected dulaglutide doses were discontinued from the trial.
- Stage 2: This stage includes the time from the Decision Point until the end of the 24-month treatment period. Patients enrolled after the Decision Point were randomized in a

<sup>10</sup> In trial GBCF, patients randomized to the placebo/sitagliptin arm were treated with placebo for 6 months, and then switched to sitagliptin for their remaining time in the trial.

fixed allocation ratio of 2:2:2:1 (dulaglutide 0.75 mg: dulaglutide 1.5 mg: sitagliptin: placebo/sitagliptin).

The primary objective was to show noninferiority of the higher dose of dulaglutide to sitagliptin with respect to change in HbA1c at 12 months. Key secondary endpoints were to be assessed after 6, 12, and 24 months. A total of 2195 patients were screened in the trial, of which 1202 were randomized during either Stage 1 or 2. There were 104 patients who were discontinued from trial when doses were not selected during Stage 1 leaving 1098 randomized patients in the primary treatment comparison arms: 302 patients to dulaglutide 0.75 mg, 304 patients to dulaglutide 1.5 mg, 315 patients to sitagliptin and 177 patients to placebo/sitagliptin. The trial was conducted between October 16, 2008 and July 6, 2012.

GBDA: A randomized, parallel-arm, controlled trial to compare the effects on glycemic control of two doses of dulaglutide, open-label exenatide, or placebo in patients with T2DM treated with maximum tolerated concomitant OAM, metformin, and pioglitazone. Patients on monotherapy with  $7.0\% \leq \text{HbA1c} \leq 11\%$  and patients on OAM therapy with  $7.0\% \leq \text{HbA1c} \leq 10\%$  at screening were eligible to enroll in the trial. Additionally, patients at least 18 years old and with BMI between 23 – 40 kg/m<sup>2</sup>, inclusive, were eligible to enroll in the trial. The primary objective of the trial was to demonstrate the superiority of once-weekly dulaglutide 1.5 mg injected SC versus placebo on HbA1c at 26 weeks. The trial consisted of 4 periods: a screening visit, a 12-week lead-in period, a 26-week double-blind treatment period followed by a 26-week safety treatment period, and a 4-week safety follow-up period. Eligible patients were randomly assigned in a 2:2:2:1 ratio to one of 4 treatment groups administered as SC injections: once weekly dulaglutide 1.5 mg for 52 weeks, once weekly dulaglutide 0.75 mg for 52 weeks, twice daily exenatide 5 mcg for 4 weeks followed by exenatide 10 mcg twice daily for 48 weeks, or once-weekly placebo for 26 weeks followed by switch to a 1:1 ratio of dulaglutide 1.5 mg or 0.75 mg for 26 weeks. A total of 2129 patients were screened, of which 978 were randomized as follows: 279 patients to dulaglutide 1.5 mg, 280 patients to dulaglutide 0.75 mg, 278 patients to open-label exenatide, and 141 patients to placebo. The trial was conducted between February 8, 2010 and May 11, 2012.

GBDB: A multicenter, randomized parallel-arm, open-label active controlled (double-blind with respect to dulaglutide) trial to evaluate the efficacy and safety of dulaglutide administered once weekly SC compared to daily basal insulin glargine in patients with inadequate glycemic control on metformin and glimepiride. Patients who were 18 years or older, had HbA1c at least 6.5%, and BMI 23 – 40 kg/m<sup>2</sup>, inclusive were eligible for enrollment. The primary objective of the trial was to compare the effect of dulaglutide to that of insulin glargine on HbA1c at 52 weeks. The trial consisted of 4 periods: a screening period, a 10 week lead-in period, a 52-week treatment period followed by an extended treatment period of 26 weeks, and a safety follow-up period 30 days after the patient's last visit. A total of 1300 patients were screened for the trial, of which 810 were randomized as follows: 273 patients to dulaglutide 1.5 mg, 272 patients to dulaglutide 0.75 mg, and 265 to insulin glargine. The trial was conducted between May 26, 2010 and November 23, 2012.

**GBDC:** A randomized, parallel-arm, active-controlled, double-blind, double-dummy trial to compare glycemic control achieved with dulaglutide to metformin in patients with T2DM. Eligible patients were at least 18 years old, with  $6.5\% \leq \text{HbA1c} \leq 9.5\%$ , and had BMI 23 – 45 kg/m<sup>2</sup> inclusive. The primary objective of the trial was to demonstrate the effect of once-weekly dulaglutide compared to metformin on HbA1c change from baseline to 26 weeks. The trial consisted of 4 periods: a screening period, a 2-week lead-in period, a 26-week treatment period followed by a 26-week extended treatment period, and a safety follow-up period of 4 weeks. Patients were randomized in a 1:1:1 ratio to 1 of 3 treatment arms: dulaglutide 0.75 mg SC once weekly + oral placebo tablets daily, dulaglutide 1.5 mg SC once weekly + oral placebo tablets daily, or metformin tablet daily + placebo injection weekly. A total of 1396 patients were screened, of which 807 patients were randomized as follows: 269 patients to dulaglutide 1.5 mg, 270 patients to dulaglutide 0.5 mg, and 268 patients to metformin. The trial was conducted between May 24, 2010 and June 19, 2012.

**GBDD:** A randomized, parallel-arm, open-label, active-controlled trial to evaluate the efficacy and safety of dulaglutide compared to basal insulin glargine, both in combination with prandial insulin lispro (with or without metformin) in patients with T2DM. Patients were at least 18 years of age, had BMI 23 – 45 kg/m<sup>2</sup> inclusive, and  $7.0\% \leq \text{HbA1c} \leq 11.0\%$ . The primary objective of the trial was to compare the effect of once-weekly dulaglutide to that of insulin glargine on HbA1c at 26 weeks. The trial consisted of three periods: a screening and lead-in period that lasted approximately 10 weeks, a treatment period lasting 52 weeks, and a safety follow-up period lasting 4 weeks. Eligible patients were randomized in a 1:1:1 ratio to 1 of 3 treatment arms: prandial insulin lispro (with or without metformin) in combination with dulaglutide 1.5mg, dulaglutide 0.75 mg, or insulin glargine. A total of 1256 patients were screened, of which 884 patients were randomized as follows: 295 patients to dulaglutide 1.5mg, 293 patients to dulaglutide 0.75 mg, and 296 patients to insulin glargine. The trial was conducted between October 27, 2010 and September 21, 2012.

**Reviewer's Comments:**

- 1. The dulaglutide CV meta-analysis comprises trials of various designs (with respect to randomization ratios, blinding strategies, parallel arm, adaptive design, trial durations, etc.). Therefore, while this CV meta-analysis is used to assess the 1.8 margin for approval, the recommendation is that findings from the dedicated cardiovascular outcomes trial (REWIND) be used to make definitive conclusions of whether dulaglutide is associated with an increased CV risk, that is, whether the 1.3 risk margin can be ruled out.***
- 2. Within some phase 3 trials, for example, in trial GDBD, there were differences in the blinding procedures for dulaglutide compared to active control arms. It is unclear why multiple blinding procedures were used within a single trial. This may introduce bias due to differential ascertainment of CV events that are recorded.***

### 3.2.2 Meta-Analysis Endpoints and Adjudication Methods

#### 3.2.2.1 Meta-Analysis Endpoints

The pre-specified agreed upon<sup>11</sup> primary endpoint for the CV meta-analysis is a composite endpoint consisting of CV death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke, or hospitalization due to unstable angina. This endpoint will be referred to as **MACE+** throughout this statistical review.

A pre-specified secondary endpoint for the CV meta-analysis is the composite endpoint of CV death (including fatal stroke and fatal MI), non-fatal MI, or non-fatal stroke. This secondary endpoint will be referred to as **MACE** in this statistical review.

Additional endpoints analyzed in this statistical review are the individual components of MACE+ and all-cause mortality.

***Reviewer's Comment: The Applicant pre-specified in the analysis plan additional CV related endpoints that are not described above. This review focuses on the evaluation of MACE+ and MACE because these are the typical endpoints used in the evaluation of CV safety for products intended to treat T2DM, as recommended in the FDA guidance<sup>12</sup>.***

#### 3.2.2.2 Endpoint Adjudication

All suspected CV endpoint events identified from the phase 2 and 3 trials were adjudicated by the (b) (4) Clinical Event Classification group (CEC). These suspected events included:

- CV events identified by the trial investigator: Site investigators completed the CV event-specific eCRF when the event occurred.
- CV events reported as serious adverse events (SAEs), AEs, or discovered during clinical data review: All AEs and SAEs reported from sites were reviewed by Lilly. Sites were to complete the eCRF for any potential CV event that was found during Lilly review, but not previously reported for adjudication
- CV events identified by database review: The clinical trial database was queried for specific events based on potential AE terms to identify potentially unreported events.

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<sup>11</sup> Refer to End of Phase 2 meeting minutes dated November 12, 2009.

<sup>12</sup> Refer to FDA Guidance for Industry *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (issued December 2008)

- Unreported CV events discovered at a monitoring visit: If the monitoring personnel identified a potential event that was not previously reported, the event was sent for adjudication.
- CV events identified by an adjudicator: If an adjudicator identified a potential event, either in addition to the event under adjudication or in lieu of the event under adjudication, the site was notified of the event so that documentation for adjudication could be submitted.

The CEC, governed under charter, adjudicated the events in a blinded manner using standardized definitions. The CV event definitions were adapted from the October 2010 draft document, “Standardized Definitions for Endpoint Events in Cardiovascular Trials”, DCARP, CDER, FDA. CEC members were not investigators in any of the dulaglutide clinical trials. If a CEC member worked with a designated investigative site, that member was not to adjudicate events from that particular site. Upon identification of an event requiring adjudication, the Applicant instructed the site investigator to prepare an adjudication packet, including event specific source documents and submit the complete packet to the CEC. All source documents were labeled with protocol identifier, site number, subject number and event number. All patient identifying information was removed from the source documents that were sent to the CEC. The CEC adjudicated each suspected event using pre-specified event criteria based on the clinical knowledge and experience.

The following information relates to the adjudication of MACE+ events that were included in the CV meta-analysis.

#### Adjudication of Deaths, MI, Hospitalization for Unstable Angina (UA)

A two-phase process was used to adjudicate deaths, MI, and UA.

Phase 1: Two cardiologists from a group of 5 CEC physician reviewers independently adjudicated the suspected events based on pre-specified criteria. If the two reviewers agreed, then the event adjudication was complete. If the two reviewers did not agree, then the suspected event was forwarded to Phase 2 review. If the reviewers agreed that an MI occurred but disagreed on the type of MI, the event was forwarded to a single (b) (4) CEC faculty cardiologist for classification.

Phase 2: During this phase, the suspected event was adjudicated by a committee of at least 3 experienced CEC physicians. Final adjudication results were obtained by consensus agreement.

#### Adjudication of Stroke

A committee of 3 experienced CEC physicians, consisting of at least one neurologist, reviewed all suspected strokes. A consensus agreement was needed for final adjudication of the event.

All final adjudication results were to be recorded on the CEC adjudication form and entered in the trial database by the CEC Coordinator or CEC Clinical Data Associate.

The CEC quality control (QC) plan was implemented based on a random sample of 20% of the first and second set of 20 adjudicated events followed by a random sample of 10% of every 40 adjudicated events. The selected events were reviewed by physicians blinded to the results of the original adjudication. The results of the QC review were summarized and reviewed by the CEC Chairperson and findings distributed to all CEC members. A recommendation to change the original adjudication result to that of the QC made based on the totality of the QC results.

According to the study report, the initial version of CEC charter was dated November 2008, with revisions in October 2010 (Version 2.0), February 2011 (Version 3.0) and August 2012 (Version 4.0, final version). The revisions in Version 2.0 and Version 3.0 included changes to the definitions for components of the CV endpoints assessed in the meta-analysis. The revisions in Version 4.0 were for non-CV related outcomes adjudicated for the ongoing CV outcomes trial and do not affect endpoints assessed in the CV meta-analysis.

**Reviewer's Comments:**

- 1. Given the trial dates provided in Section 3.2.1 and that the CEC charter was initialized in November 2008, it appears that the adjudication of CV events was retrospective for one small Phase 2 trial. This is not expected to affect the primary analysis results as few events are generally observed in such trials.*
- 2. According to the study report there were no events sent for adjudication under Version 1.0 of the CEC charter. There was one event sent for adjudication under Version 2.0; however, the Applicant notes that the revision in Version 3.0 did not change the result of the adjudication of this event. Therefore, it does not appear that the changes to endpoint definitions impact the CV meta-analysis.*
- 3. From a statistical perspective, the adjudication process appears adequate. Refer to review by Dr. Suchitra Balakrishnan for clinical interpretation of the appropriateness of the adjudication process.*

**3.2.3 Statistical Methodologies**

The main treatment effect measure discussed throughout this review is the hazard ratio (pooled dulaglutide doses relative to pooled comparators) for the outcomes defined in Section 3.2.2.1. An estimated hazard ratio of one is indicative of equivalent rates between the two treatment groups, a hazard ratio greater than one is indicative of higher rate in the dulaglutide treatment group compared to comparator, and vice versa for a hazard ratio less than one.

### 3.2.3.1 Analysis Populations

The safety population comprised all randomized patients. Patients were analyzed according to treatment assigned at randomization, regardless of actual treatment received. The primary and secondary analyses, also known as on-study analyses, included all CV events that occurred during the planned treatment period for each trial and up to the 30-day safety follow-up. Events with an onset date prior to first study medication date were not included in the analyses.

The on-treatment analysis population comprised all randomized patients and the analysis included events that occurred while patients were still on-treatment or within 30 days of treatment discontinuation. Note that this population was not defined by the Applicant, but are considered in analyses conducted by the reviewer, see Section 3.2.3.3 for description of reviewer's analyses.

***Reviewer's Comment: The Applicant defines several per protocol populations, which are subsets of the safety population, for sensitivity analyses of the primary endpoint. Because the evaluation of CV safety for diabetes products generally focuses on the on-study and on-treatment analyses, these sensitivity analyses based on per protocol populations are not included in this review.***

### 3.2.3.2 Type I Error Control

In accordance with the FDA Guidance, the Applicant designed the CV meta-analysis to rule out an unacceptable increase in risk based on a pre-market hazard ratio risk margin of 1.8. The Applicant planned to conduct two meta-analyses prior to submission of the BLA. The first meta-analysis was to include data from 9 phase 2 and 3 trials. If the first meta-analysis did not exclude 1.8, then a second meta-analysis was to be conducted. The second meta-analysis was to be performed after a minimum of 180 MACE+ had been observed and was to include interim data from REWIND; an ongoing dedicated CV outcomes trial. The Type I error for the multiple testing of the 1.8 risk margin was controlled using the Pocock spending function. The CV meta-analysis included in the BLA was based on data from the 9 phase 2 and 3 trials only, that is, the first meta-analysis. Therefore, using the Pocock spending function, tests of the 1.8 risk margin are based on if the upper bound of the 2-sided 98.02% confidence interval is less than 1.8.

***Reviewer's Comment: The Applicant used the alpha-adjusted 98.02% CI when assessing the 1.8 risk margin for the primary endpoint (MACE+) and MACE+ components; however, the analyses of MACE and all-cause mortality were based on the nominal 95% CI. All primary and secondary endpoint analyses results presented in this review are based on 98.02% CIs using the pre-specified alpha-spending function. Subgroup analyses results are presented using 95% CIs as they are for exploratory purposes only.***

### 3.2.3.3 Statistical Analyses

This section describes the pre-specified statistical analyses performed by the Applicant for the endpoints defined in Section 3.2.2.1 as well as additional post-hoc analyses conducted by the reviewer. Any changes to the Applicant's pre-specified analyses are also described in this section.

#### Pre-specified Analyses Performed by the Applicant

The primary meta-analysis to evaluate the 1.8 risk margin, as agreed upon with the FDA, estimates the time from randomization to first MACE+ in patients randomized to dulaglutide (pooling all doses) to patients randomized to all comparators (pooling active and placebo controls). The hazard ratio (dulaglutide versus comparator) for MACE+ is estimated using a stratified Cox proportional hazard (PH) model. Patients without an event were censored at the time the patient was last known to be event-free, but no later than the safety follow-up visit that occurred approximately 30 days after the end of the treatment period or after early trial discontinuation.

In trial GBDA, patients who were randomized to placebo were re-randomized to one of two dulaglutide doses after 6 months of placebo treatment. Events occurring after this re-randomization were not included in the primary analysis. In trial GBCF, patients randomized to the placebo/sitagliptin arm were treated with placebo for 6 months, and then switched to sitagliptin for their remaining time in the trial. Because the primary analysis was based on all comparators combined, events occurring after the patients switched to sitagliptin were included.

***Reviewer's Comment: Although not specifically stated in the meta-analysis plan, the censoring date for placebo patients in trial GBDA, who did not experience any events or discontinued the trial while on placebo, should be the date of switch to dulaglutide. In other words, these patients should contribute no more than approximately 180 days to the time at risk for comparator arm for the CV analyses. An investigation of whether the Applicant's analyses conformed to this is presented in Section 3.2.5 of this review.***

Kaplan Meier (KM) plots are provided for graphical comparison of the survival functions between treatment groups.

***Reviewer's Comment: The KM plots for meta-analysis of trials with imbalanced randomization ratios do not adequately account for trial-level differences and therefore, may be subject to Simpson's Paradox. These plots are provided in this review for descriptive purposes rather than for testing significant differences between curves for the treatment groups.***

The Applicant estimated the hazard ratio for the secondary endpoint of MACE as well as the individual components of MACE+ and all-cause mortality each using a stratified Cox PH model provided the number of events exceeds 10, also referred as the "rule of 10".

***Reviewer's Comment: For the analyses of MACE+ components, and all-cause mortality, when the number of events is less than 10, the Applicant presented the odds ratio rather than the hazards ratio. Note that the odds ratios do not account for time; as such, they are not directly comparable to the hazard ratios. The rule of 10 is generally implemented to prevent unreliable CI coverage and problems with Cox model convergence. Throughout this review, model stability checks are performed using the SAS statistical software used for Cox modelling. Therefore, unless issues with model convergence are observed, all analysis results presented in this review are based on hazard ratios.***

The analyses of MACE+ for patient subgroups of age, gender, race, geographical region, BMI, renal function, duration of diabetes, history of CV disease, and tobacco use are also presented in this review.

Exploratory analyses of MACE+ were performed for each dulaglutide dose (0.75 mg or 1.5 mg) compared to all comparators. These pairwise comparisons were performed in separate Cox models and included only those trials which included the treatment arms being compared.

#### Changes to Planned Analyses

According to the meta-analysis plan, the Cox models were to be stratified into 6 strata; stratum 1 comprising all phase 2 trials combined and stratum 2 through 6 comprising each of the five phase 3 trials. Because one phase 3 trial, GBDC, did not have any positively adjudicated CV events in the control arm, this trial was combined with trial GBCF to form a single stratum. Trial GBCF was chosen because it was most similar to GBDC in terms of background therapy or comparator. Therefore, all Cox analyses presented in the study report were based on 5 strata and not 6 as originally planned. The Applicant performed sensitivity analyses based on the original 6 defined strata; results of this sensitivity analysis are presented in this review.

#### Additional Analyses Conducted by Reviewer

The reviewer performed on-treatment analysis of MACE+ in which only the events occurring while the patients was still on treatment or within 30 days of last treatment were included. Patients without events were censored at the earliest of the lost to follow-up date, death date, end of trial date, or last treatment date+30 days. This on-treatment analysis was based on a stratified Cox proportional hazards model similar to that used in the on-study analysis.

### **3.2.4 Patient Disposition, Demographic and Baseline Characteristics**

There were a total of 6010 randomized patients (3885 dulaglutide and 2125 comparator) enrolled in the 9 trials included in the meta-analysis, thereby comprising the safety analysis population. This population contains patients who were originally randomized to discontinued doses of dulaglutide in trials GBCK and GBCF; see Section 3.2.1. The distributions of trial follow-up and treatment exposure were similar between the treatment groups, see Table 3. Table 4 shows that

the overall trial discontinuation rate (for all reasons combined) was slightly lower in the dulaglutide group (20.5%) compared to the comparator group (21.7%). This table also shows that the discontinuation rates by trial were generally similar between the treatment groups. Most of the discontinuations occurred in trial GBCF. In this trial, the majority of patients discontinued due to adverse events (19.3% dulaglutide compared to 21.1% comparator) or sponsor decision (12.3% dulaglutide compared to 0% comparator). Recall that this was a two-stage adaptive design trial in which patients initially randomized to non-selected dulaglutide doses were discontinued from the trial in the subsequent stage; hence, the high percentage of discontinuation in dulaglutide arm due to sponsor decision. The Applicant states that most notable adverse events leading to early trial discontinuations were due to gastrointestinal disorders and metabolism and nutrition disorders.

***Reviewer’s Comment: The discontinuation rates presented in Section 4.1 of the study report are based on the number of patients who discontinued rather than the number of patients randomized as presented in this review. Because the Applicant’s rates are based on smaller denominators they therefore appear much higher than they should be; for example, the study report suggests that the overall discontinuation rate due to adverse events is about 33% in each treatment group when in fact it is approximately 7%.***

Table 3 Summary of Trial Follow-up and Treatment Exposure

	Dulaglutide N=3885	Comparator N=2125
<u>Study follow-up, in months</u>		
Mean (SD)	12.4 (6.8)	12.7 (7.0)
Median	13.1	13.1
Range	0.17 – 29.8	0.03 – 27.1
<u>Treatment exposure, in months</u>		
Mean (SD)	10.9 (6.8)	11.8 (7.0)
Median	11.9	12.1
Range	0.03 – 27.8	0.03 – 25.4

SD=standard deviation

Source: Created by the reviewer using dataset “cv\_all.xpt”

Table 4 Trial Discontinuation Rates Overall and By Trial

Trial ID/ Treatment	N	Reason for Trial Discontinuation										Total number of patients discontinued n (%)
		Adverse Event n (%)	Death n (%)	Unmet entry criteria n (%)	Lack of Efficacy n (%)	Loss to follow-up n (%)	Physician Decision n (%)	Protocol violation n (%)	Sponsor Decision n (%)	Subject Decision n (%)	Treatment non- compliance n (%)	
<b>GBCF</b>												
Dulaglutide	710	137 (19.3)	1 (0.1)	9 (1.3)	4 (0.6)	26 (3.7)	16 (2.3)	7 (1.0)	87 (12.3)	47 (6.6)	0 (0.0)	334 (47.0)
Comparator	492	104 (21.1)	3 (0.6)	2 (0.4)	10 (2.0)	13 (2.6)	18 (3.7)	4 (0.8)	0 (0.0)	57 (11.6)	0 (0.0)	211 (42.9)
<b>GBCJ</b>												
Dulaglutide	196	11 (5.6)	0 (0.0)	3 (1.5)	0 (0.0)	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	6 (3.1)	0 (0.0)	24 (12.3)
Comparator	66	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.6)	0 (0.0)	6 (9.1)
<b>GBCK</b>												
Dulaglutide	135	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	4 (3.0)	3 (2.2)	1 (0.7)	0 (0.0)	12 (8.9)
Comparator	32	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	3 (9.4)
<b>GBCZ</b>												
Dulaglutide	108	4 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.6)
Comparator	37	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	3 (8.1)
<b>GBDA</b>												
Dulaglutide	559	13 (2.3)	2 (0.4)	3 (0.5)	1 (0.2)	17 (3.0)	4 (0.7)	2 (0.4)	0 (0.0)	16 (2.9)	2 (0.4)	60 (10.7)
Comparator	419	14 (3.3)	0 (0.0)	1 (0.2)	5 (1.2)	19 (4.5)	0 (0.0)	1 (0.2)	3 (0.7)	17 (4.1)	1 (0.2)	61 (14.6)
<b>GBDB</b>												
Dulaglutide	545	17 (3.1)	1 (0.2)	5 (0.9)	2 (0.4)	6 (1.1)	6 (1.1)	2 (0.4)	0 (0.0)	18 (3.3)	3 (0.6)	60 (11.0)
Comparator	265	5 (1.9)	2 (0.8)	1 (0.4)	0 (0.0)	3 (1.1)	3 (1.1)	1 (0.4)	0 (0.0)	10 (3.8)	2 (0.8)	27 (10.2)

N=number of patients randomized, n=number of patients who discontinued

Source: Created by the reviewer using dataset "subjinfo xpt"

Table 4 Trial Discontinuation Rates Overall and By Trial (continued)

Trial ID/ Treatment	N	Reason for Trial Discontinuation										Total number of patients discontinued n (%)
		Adverse Event n (%)	Death n (%)	Unmet entry criteria n (%)	Lack of Efficacy n (%)	Loss to follow-up n (%)	Physician Decision n (%)	Protocol violation n (%)	Sponsor Decision n (%)	Subject Decision n (%)	Treatment non- compliance n (%)	
<b><u>GBDC</u></b>												
Dulaglutide	539	22 (4.1)	0 (0.0)	2 (0.4)	5 (0.9)	28 (5.2)	2 (0.4)	1 (0.2)	9 (1.7)	30 (5.8)	2 (0.4)	101 (18.7)
Comparator	268	12 (4.5)	0 (0.0)	2 (0.8)	4 (1.5)	9 (3.4)	2 (0.8)	2 (0.8)	7 (2.6)	14 (5.2)	3 (1.1)	55 (20.5)
<b><u>GBDD</u></b>												
Dulaglutide	588	34 (5.8)	1 (0.2)	4 (0.7)	0 (0.0)	13 (2.2)	14 (2.4)	1 (0.2)	2 (0.3)	44 (7.5)	0 (0.0)	113 (19.2)
Comparator	296	8 (2.7)	3 (1.0)	1 (0.3)	0 (0.0)	9 (3.0)	9 (3.0)	1 (0.3)	0 (0.0)	21 (7.1)	0 (0.0)	52 (17.6)
<b><u>GBDN</u></b>												
Dulaglutide	505	28 (5.5)	0 (0.0)	2 (0.4)	0 (0.0)	6 (1.2)	8 (1.6)	4 (0.8)	1 (0.2)	32 (6.3)	0 (0.0)	81 (16.0)
Comparator	250	11 (4.4)	0 (0.0)	2 (0.8)	0 (0.0)	5 (2.0)	6 (2.4)	6 (2.4)	1 (0.4)	13 (5.2)	0 (0.0)	44 (17.6)
<b><u>Overall</u></b>												
Dulaglutide	3885	269 (6.9)	5 (0.1)	28 (0.7)	12 (0.3)	101 (2.6)	51 (1.3)	21 (0.5)	102 (2.6)	194 (5.0)	7 (0.2)	790 (20.3)
Comparator	2125	156 (7.3)	8 (0.4)	11 (0.5)	19 (0.9)	60 (2.8)	38 (1.8)	15 (0.7)	11 (0.5)	138 (6.5)	6 (0.3)	462 (21.7)

N=number of patients randomized, n=number of patients who discontinued

Source: Created by the reviewer using dataset "subjinfo xpt"

As shown in Table 5, the distributions for demographic characteristics were similar between the dulaglutide and comparator treatment groups. The majority of the patients were male (50.7% dulaglutide and 52.2% comparator), white (68.4% dulaglutide and 68.1% comparator) with a mean age of approximately 56 years and mean BMI approximately 32 kg/m<sup>2</sup>. Most of the patients were enrolled in sites in North America and Europe.

Table 5 Distribution of Baseline Demographic Characteristics across All Trials

Demographic Characteristic	Dulaglutide, N=3885 n (%)	Comparator, N=2125 n (%)
<u>Sex</u>		
Female	1916 (49.3)	1016 (47.8)
Male	1969 (50.7)	1109 (52.2)
<u>Race</u>		
White	2656 (68.4)	1446 (68.1)
Non-white <sup>1</sup>	1229 (31.7)	679 (32.0)
<u>Age group, in years,</u>		
≤65	3177 (81.8)	1724 (81.1)
>65	708 (18.2)	401 (18.9)
<u>Age, in years</u>		
Mean (SD)	56.2 (10.0)	56.0 (10.1)
Range	19.8 – 86.9	21.7 – 84.8
<u>BMI group, in kg/m<sup>2</sup>,</u>		
<30	1453 (37.4)	766 (36.1)
≥30	2432 (62.6)	1359 (63.9)
<u>BMI, in kg/m<sup>2</sup></u>		
Mean	32.3 (5.3)	32.4 (5.4)
Range	18.7 – 54.3	19.3 – 56.2
<u>Region</u>		
North America	2145 (55.2)	1202 (56.6)
Europe	856 (22.0)	457 (21.5)
South America	399 (10.3)	209 (9.8)
Asia Pacific	262 (6.7)	142 (6.7)
Other	223 (5.7)	115 (5.4)

N=number of patients randomized, n=number of patients in subgroup level, SD=standard deviation

<sup>1</sup>Non-white race includes 341 patients (208 dulaglutide, 133 comparator) that had race recorded as unknown.

Source: Created by the reviewer using dataset “subjinfo.xpt” and “cv\_all.xpt”

Table 6 shows similar distributions for baseline CV risk factors between the dulaglutide and comparator treatment groups. Renal function was measured using the Modification of Diet in Renal Disease scale: eGFR<30 (severe), 30≤eGFR<60 (moderate), 60≤eGFR (mild/normal). The majority of patients had duration of diabetes exceeding 5 years (61.5% dulaglutide and 64.0% comparator), had mild/normal renal impairment (94.0% dulaglutide and 94.0% comparator), had hypertension (63.1% dulaglutide and 63.9% comparator), or hyperlipidemia (54.5% dulaglutide and 55.3% comparator). There were few patients that had a history of CV disease (9.6% dulaglutide and 8.3% comparator).

Table 6 Distribution of Baseline Cardiovascular Risk Factors across All Trials

CV Risk Factor	Dulaglutide, N=3885 n (%)	Comparator, N=2125 n (%)
<u>Duration of Diabetes, in years</u>		
<5	1494 (38.5)	765 (36.0)
<=5, <10	1303 (33.5)	701 (33.0)
≥10	1088 (28.0)	659 (31.0)
<u>Current Tobacco Use*</u>		
Yes	551 (14.2)	335 (15.8)
No	3312 (85.3)	1779 (83.7)
<u>Renal Function, eGFR</u>		
<30	12 (0.1)	1 (0.1)
30-60	228 (5.9)	126 (5.9)
≥60	3654 (94.0)	1998 (94.0)
<u>History of CV Disease**</u>		
Yes	372 (9.6)	177 (8.3)
No	3513 (90.4)	1948 (91.7)
<u>Hypertension</u>		
Yes	2451 (63.1)	1357 (63.9)
No	1431 (36.8)	767 (36.1)
<u>Hyperlipidemia</u>		
Yes	2116 (54.5)	1176 (55.3)
No	1769 (45.5)	949 (44.7)

\*Tobacco use was missing for 33 patients (22 dulaglutide and 11 comparator)

\*\*History of at least one of the following: MI, UA, coronary revascularization, stroke or TIA, peripheral vascular disease, heart failure, lower extremity arterial revascularization, carotid revascularization, or coronary artery disease

Source: Created by the reviewer using dataset “cv\_all.xpt”

### 3.2.5 Results and Conclusions

#### 3.2.5.1 Descriptive Statistics for MACE+

For the primary MACE+ endpoint, the overall incidence was 0.7% in patients randomized to dulaglutide compared to 1.2% in patients randomized to comparator; see Table 7. Note that the overall incidences do not account for trial, see Section 3.2.5.2 for stratified analysis results. The incidences for MACE+ for each trial are also presented in this table. There were no MACE+ events observed in the small phase 2 trials (GBCK, GBCJ, and GBCZ).

Table 7 Incidence of MACE+ Overall and by Trial

Trial	Dulaglutide n/N (%)	Comparator n/N (%)
<u>Phase 2</u>		
GBCJ	0/196 (0.0)	0/66 (0.0)
GBCK	0/135 (0.0)	0/32 (0.0)
GBCZ	0/108 (0.0)	0/37 (0.0)
GBDN	1/505 (0.2)	2/250 (0.8)
<u>Phase 3</u>		
GBCF	7/710 (1.0)	8/492 (1.6)
GBDA	5/559 (0.9)	2/419 (0.5)
GBDB	5/545 (0.9)	5/265 (1.9)
GBDC	2/539 (0.4)	0/268 (0.0)
GBDD	6/588 (1.0)	8/296 (2.7)
<b>Overall*</b>	<b>26/3885 (0.7)</b>	<b>25/2125 (1.2)</b>

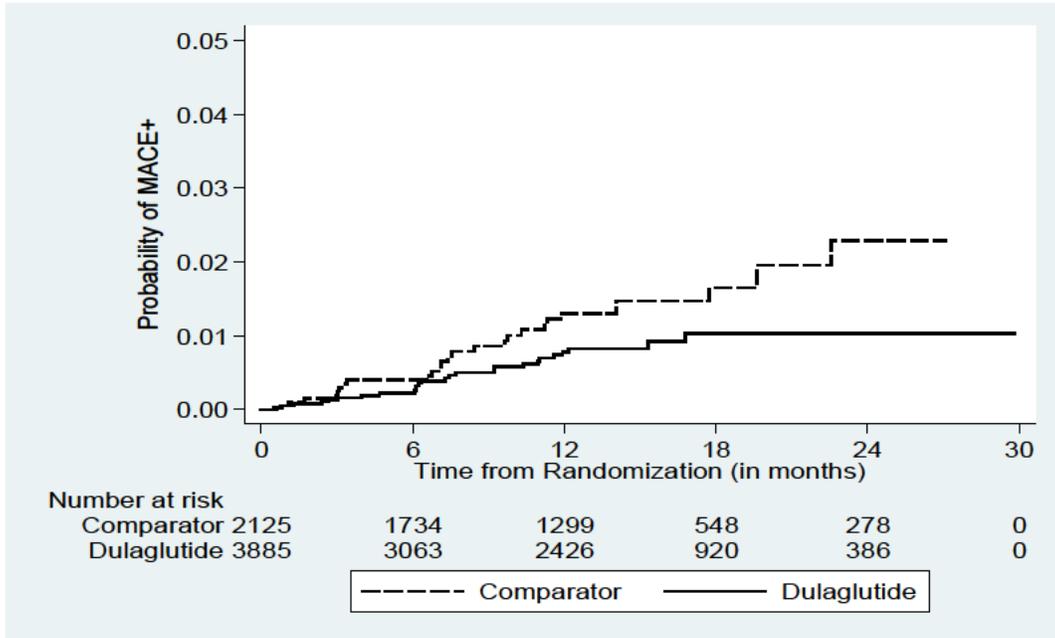
\*Overall (or crude) incidences do not account for trial.

Source: Created by the reviewer using dataset “cv\_all.xpt”

Note that all MACE+ observed in dulaglutide arm of trial GBCF (the two-stage adaptive design trial) were in doses 0.75mg and 1.5 mg, that is, there were no events reported in patients who were randomized to the doses that were discontinued.

Figure 1 shows the cumulative incidence of MACE+ for the dulaglutide and comparator groups across all trials included in the meta-analysis. As shown in the plot, the patients in the dulaglutide arm were less likely to experience MACE+ than the comparator patients over the duration of the trials. The divergence of the curves is most notable starting at month 6. There were 3 patients (2 dulaglutide and 1 comparator) with MACE+ occurring during the first 30 days after randomization. Because this plot is pooled across the trials included in the meta-analysis caution is advised when interpreting the difference in plots for the two treatment groups.

Figure 1 Estimated Probability of MACE+ by Time across All Trials



Source: Created by reviewer using dataset “cv\_all.xpt”

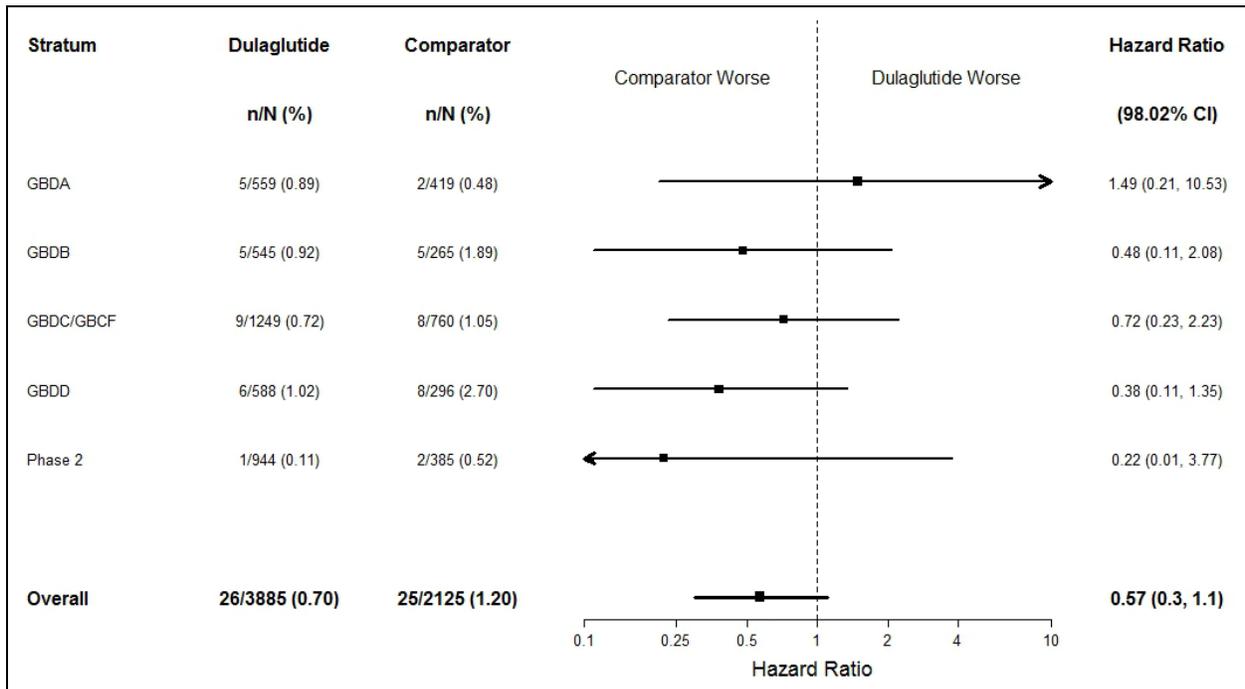
### 3.2.5.2 CV Meta-analysis Results

This section focuses on the meta-analysis results for MACE+ and MACE for assessing the 1.8 pre-market risk margin. The results for all-cause mortality are also presented in this section.

#### 3.2.5.2.1 Meta-analysis Results of MACE+

Figure 2 illustrates the stratum-level and overall hazard ratios, and corresponding 98.02% CIs for the primary analysis of MACE+. The overall estimated HR for MACE+ based on the Cox PH model was 0.57 with corresponding 98.02% CI (0.30, 1.10). There were no concerns about violation of the PH assumption; refer to Appendix I. The upper bound for the 98.02% CI was less than the pre-specified margin of 1.8. Recall that the Applicant changed the primary analysis of MACE+ from one based on six strata to one based on five strata in the study report; see Section 3.2.3.3. When MACE+ is analyzed as originally planned the resulting HR was 0.59 with 98.02% CI (0.30, 1.13); therefore, the change in the planned analysis does not affect the overall findings of the meta-analysis. Therefore, all results that follow in this review are based on the five strata used for the study report.

Figure 2 Forest Plot of Primary Analyses of MACE+



n=number of patients with MACE+, N=number of patients randomized, Phase 2=All phase 2 trials combined, GBDC/GBCF=trials GBDC and GBCF combined  
Source: Created by the reviewer using dataset “cv\_all.xpt”

***Reviewer’s Comment: In general for CV meta-analyses, the Cox model is stratified by trial. Because the incidence of events in the phase 2 trials was extremely low, stratification by each trial instead of pooling phase 2 trials into one stratum is not expected to alter the results.***

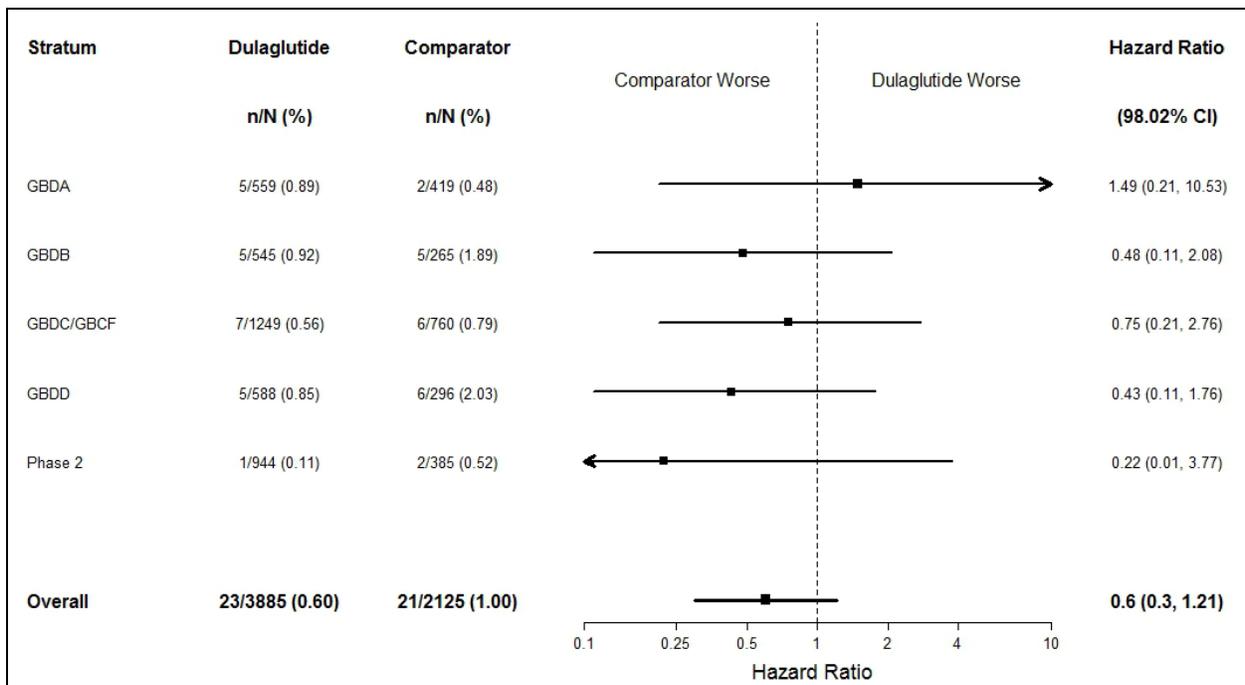
Recall that patients randomized to placebo in trial GDBA were re-randomized to dulaglutide after 6 months. According to the study report, there was one patient (GDBA-200-6024) who experienced a positively adjudicated MACE+ after the patient was switched from placebo to dulaglutide. In accordance with the pre-specified analysis plan, this event was not included in the analyses. Upon inspection of the submitted time to event dataset for this trial, there were 13 placebo patients who were considered at risk past 190 days when these patients should have been already switched to dulaglutide; and thus not contributing the comparator risk set. Censoring the time at risk to 190 days for these patients does not affect the overall findings of the primary analysis.

In the reviewer’s on-treatment analysis, there were 47 MACE+ (23 or 0.6% dulaglutide and 24 or 1.1% comparator) that occurred while the patients were still on treatment or within 30 days of treatment discontinuation. The resulting hazard ratio estimate was 0.53 with 98.02% CI (0.27, 1.05). The upper bounds for the reviewer’s on-treatment analysis results were consistent with the primary MACE+ analysis.

### 3.2.5.2.2 Meta-analysis Results for MACE

Figure 3 illustrates the stratum-level and overall hazard ratios and 98.02% CIs for MACE. There were 44 MACE, 23/3885 (0.6%) dulaglutide and 21/2125 (1.0%) comparator, observed across all trials included in the meta-analysis. The overall estimated HR was 0.60 with corresponding 98.02% CI (0.30, 1.21). The upper bound for the 98.02% CI was less than the pre-specified risk margin of 1.8.

Figure 3 Forest Plot of Secondary Analyses Results for MACE

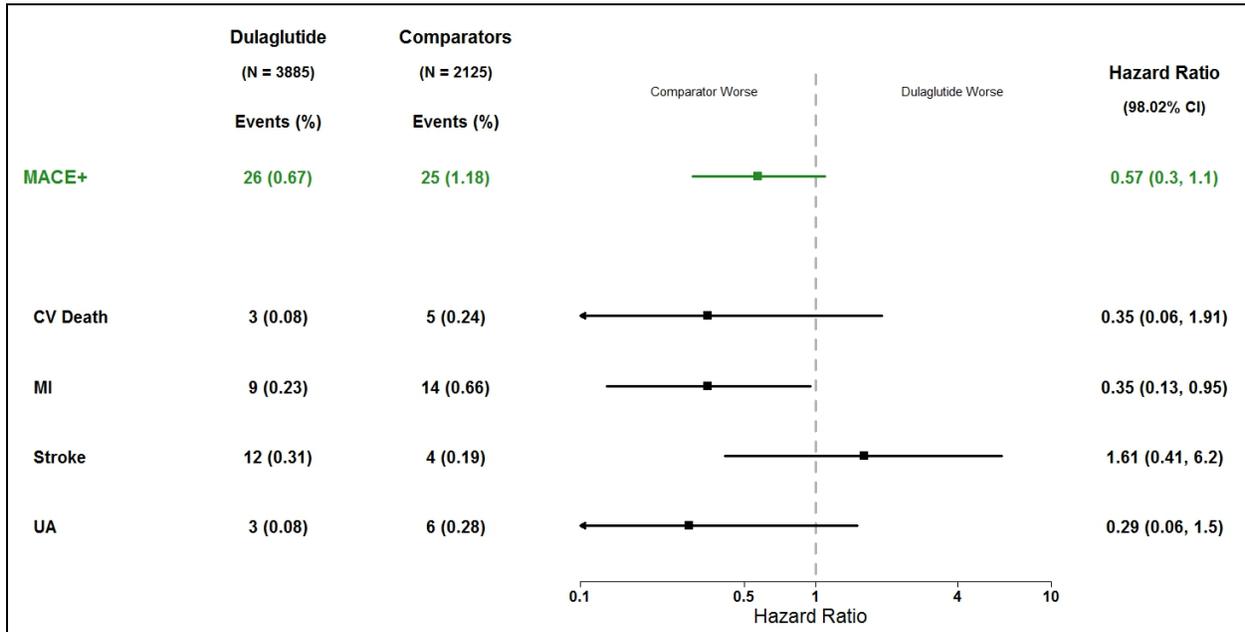


n=number of patients with MACE+, N=number of patients randomized, Phase 2=All phase 2 trials combined, GBDC/GBCF=trials GBDC and GBCF combined  
Source: Created by the reviewer using dataset "cv\_all.xpt"

### 3.2.5.2.3 Meta-analysis Results for Individual Components of MACE+

Figure 4 shows the results of analyses of the individual components of MACE+. For all components with the exception of nonfatal stroke, the point estimates for the HRs were less than one. According to the study report, the majority of patients who had a non-fatal stroke had a history of vascular disease or multiple CV risk factors. Note that these analyses are meant for descriptive purposes only, and thus upper bounds exceeding the 1.8 risk margin as well as upper bounds less than one should not be over-interpreted.

Figure 4 Forest Plot of MACE + Component Analysis



MI=myocardial infarction, UA=unstable angina, CV=cardiovascular  
Source: Created by the reviewer using dataset “cv\_all.xpt

#### 3.2.5.2.4 Meta-analyses Results for All-Cause Mortality

There were 15 deaths (7 dulaglutide or 0.2% and 8 or 0.4% comparator) due to all causes across all trials included in the CV meta-analysis. The estimated HR for all-cause mortality was 0.50 with corresponding 98.02% CI (0.15, 1.67).

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the results of analyses for MACE+ for patient subgroups that were determined pre-treatment to be of interest. Given the small number of events observed, all subgroups are classified into at most two levels. The analyses of MACE+ by dulaglutide dose (0.75 mg and 1.5 mg are also presented in this section). Note that these subgroup analyses are for exploratory purposes only; as such, results are presented at the nominal alpha level of 0.05 (two-sided) instead of the 0.0198 used in the primary and secondary analyses presented in Section 3.2.5.2. There were no adjustments for multiple comparisons; therefore, the results of these subgroup analyses should be interpreted as exploratory or hypothesis generating only.

#### 4.1 Gender, Race, Age, and Geographic Region

Table 8 shows the results of subgroup analyses by gender, race, age group and geographic region. Note that there were 341 patients (208 dulaglutide and 133 comparator) with race recorded as unknown that are not included in this table. No events were reported among these patients.

Table 8 Results of Subgroup Analyses for MACE+ by Gender, Race, Age, and Geographic Region

	Dulaglutide n/N (%)	Comparator n/N (%)	HR (95% CI)
<u>Gender</u>			
Male	14/1969 (0.71)	16/1109 (1.44)	0.48 (0.24, 0.99)
Female	12/1916 (0.63)	9/1016 (0.89)	0.72 (0.30, 1.72)
<u>Race</u>			
White	22/2656 (0.83)	19/1446 (1.31)	0.61 (0.33, 1.13)
Non-White	4/1021 (0.39)	6/546 (1.10)	0.38 (0.11, 1.34)
<u>Age, in years</u>			
<65	17/3177 (0.54)	15/1724 (0.87)	0.61 (0.30, 1.21)
≥65	9/708 (1.27)	10/401(2.49)	0.54 (0.22, 1.33)
<u>Geographic Region</u>			
US	10/2145 (0.47)	11/1202 (0.92)	0.50 (0.21, 1.18)
Non-US	16/1740 (0.92)	14/923 (1.52)	0.63 (0.31, 1.29)

n=number of MACE+, N=number of patients randomized in subgroup

Source: Created by the reviewer using dataset “cv\_all.xpt”

#### 4.2 Other Special/Subgroup Populations

Table 9 shows the results of subgroup analyses by BMI category, duration of diabetes, tobacco use, history of CV disease and renal function. Note that tobacco use was missing for 33 patients (22 dulaglutide and 11 comparator); no MACE+ were reported among these patients.

Table 9 Results of Analysis for MACE+ by CV Risk Factors

	Dulaglutide n/N (%)	Comparator n/N (%)	HR (95% CI)
<u>BMI, by kg/m<sup>2</sup></u>			
<30	8/1453 (0.55)	5/766 (0.65)	0.96 (0.31, 2.93)
≥30	18/2432 (0.74)	20/1359 (1.47)	0.48 (0.25, 0.91)
<u>Duration of Diabetes, in years</u>			
<5	7/1494 (0.47)	6/765 (0.78)	0.64 (0.21, 1.90)
≥5	19/2391 (0.79)	19/1360 (1.40)	0.56 (0.30, 1.07)
<u>Tobacco Use</u>			
Yes	8/551 (1.45)	4/335 (1.19)	1.38 (0.42, 4.58)
No	18/3312 (0.54)	21/1779 (1.18)	0.45 (0.24, 0.85)
<u>History of CV Disease</u>			
Yes	10/372 (2.69)	9/177 (5.08)	0.58 (0.23, 1.44)
No	16/3513 (0.46)	16/1948 (0.82)	0.56 (0.28, 1.12)
<u>Renal Function</u>			
<60	3/231 (1.30)	4/127 (3.15)	0.50 (0.11, 2.23)
≥60	23/3654 (0.63)	21/1998 (1.05)	0.59 (0.33, 1.07)
n=number of MACE+, N=number of patients randomized in subgroup			
Source: Created by the reviewer using dataset "cv_all.xpt"			

### 4.3 Dulaglutide Dose

Table 10 shows the analyses of MACE+ for each dulaglutide dose (0.75 mg or 1.5mg) compared to all comparators. Recall that the Applicant is seeking to commercialize the 1.5mg dose only. For the 0.75 mg dose, the HR estimate of MACE+ was 0.56 with 95% CI (0.29, 1.11). For the 1.5 mg dose, the HR estimate was 0.58 with 95% CI (0.30, 1.14).

Table 10 Results of Analysis for MACE+ by Dulaglutide Dose

	Dulaglutide n/N (%)	Comparator n/N (%)	HR (95% CI)
0.75 mg <sup>1</sup>	13/1706 (0.76)	25/2027 (1.23)	0.56 (0.29, 1.11)
1.5 mg <sup>2</sup>	13/1700 (0.76)	25/2022 (1.24)	0.58 (0.30, 1.14)
n=number of MACE+, N=number of patients randomized			
<sup>1</sup> 0.75 mg analysis based on data from trials GBCF, GBCZ, GBDA,GBDB, GBDC, GBDD, GBDN			
<sup>2</sup> 1.5 mg analysis based on data from trials GBCF, GBCK, GBDA,GBDB, GBDC, GBDD, GBDN			
Source: Created by the reviewer using dataset "cv_all.xpt"			

Note that data from trial GBCJ were excluded from all dose-level analyses because it did not study either the 0.75 mg or 1.5 mg dulaglutide dose. There were no MACE+ events reported in this trial.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Collective Evidence and Statistical Issues

The CV meta-analysis which is the subject of this review was conducted in accordance with the meta-analysis plan, but for a minor change in the primary analysis as described in Section 3.2.3.3. The plan was finalized July 2012 and agreed upon with the FDA<sup>13,14</sup>. The agreed upon population of interest for the meta-analysis comprised all randomized patients. Data from 9 completed phase 2 and 3 trials were included in the meta-analysis. The agreed upon primary safety endpoint of this meta-analysis was MACE+, a composite endpoint comprising cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. The key secondary endpoint was MACE, a composite endpoint comprising cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The analysis of all-cause mortality (including non-CV related deaths) is also presented in this review. All CV events included in the meta-analysis were based on positively adjudicated events determined by an independent blinded Clinical Event Committee and were based on standardized definitions of the components of the composite endpoint.

The primary objective of the meta-analysis was to demonstrate that the hazard ratio (pooled dulaglutide doses to pooled comparators) was smaller than the pre-market risk of 1.8 as stipulated in the 2008 FDA Diabetes Guidance for assessing CV safety. The pre-specified primary statistical analysis used a stratified Cox proportional hazards model. Because the meta-analysis included in the submission was one of two planned analyses to assess the 1.8 risk margin, tests of the primary and secondary endpoints are based on alpha-adjusted two sided 98.02% CIs (alpha adjustment determined using Pocock spending function).

There were a total of 26/3885 (0.7%) dulaglutide patients compared to 25/2125 (1.2%) comparator patients with positively adjudicated MACE+. The estimated hazard ratio for MACE+ across all trials included in the meta-analysis was **0.57** with 98.02% CI (**0.30, 1.10**). The upper bound of the 98.02% CI for MACE+ was less than the 1.8 pre-market risk margin. Analyses of MACE and the individual components of MACE+ were also conducted; see summary of findings below in Table 11. Note that the analyses of individual components are meant for descriptive purposes only, and thus upper bounds exceeding the 1.8 risk margin as well as upper bounds less than one should not be over-interpreted.

---

<sup>13</sup> Refer to Statistical Review by Dr. Lee Ping Pian dated August 19, 2011

<sup>14</sup> Refer to FDA Correspondence dated June 12, 2012

Subgroup analyses were conducted to compare the risk of MACE+ within each dulaglutide dose relative to all comparators. For the 0.75 mg dose, the HR estimate of MACE+ was 0.56 with 95% CI (0.29, 1.11). For the 1.5 mg dose, the HR estimate was 0.58 with 95% CI (0.30, 1.14).

Table 11 Summary of Meta-analysis Findings for MACE+, MACE, and MACE+ Individual Components

Outcome	Number of Patients with Events		HR (98.02% CI)
	Dulaglutide <sup>1</sup> , N=3885 n (%)	Comparator <sup>2</sup> , N=2125 n (%)	
MACE+	26 (0.67)	25 (1.18)	0.57 (0.30, 1.10)
MACE	23 (0.59)	21 (0.99)	0.60 (0.30, 1.21)
CV Death	3 (0.08)	4 (0.19)	0.35 (0.06, 1.91)
Non-fatal MI	9 (0.23)	14 (0.66)	0.35 (0.13, 0.95)
Non-fatal Stroke	12 (0.31)	4 (0.19)	1.61 (0.41, 6.20)
Hospitalization for UA	3 (0.08)	6 (0.28)	0.29 (0.06, 1.50)

<sup>1</sup>Pooled dulaglutide doses

<sup>2</sup>Pooled active and placebo comparators

CV=cardiovascular, MI=myocardial infarction, UA=unstable angina

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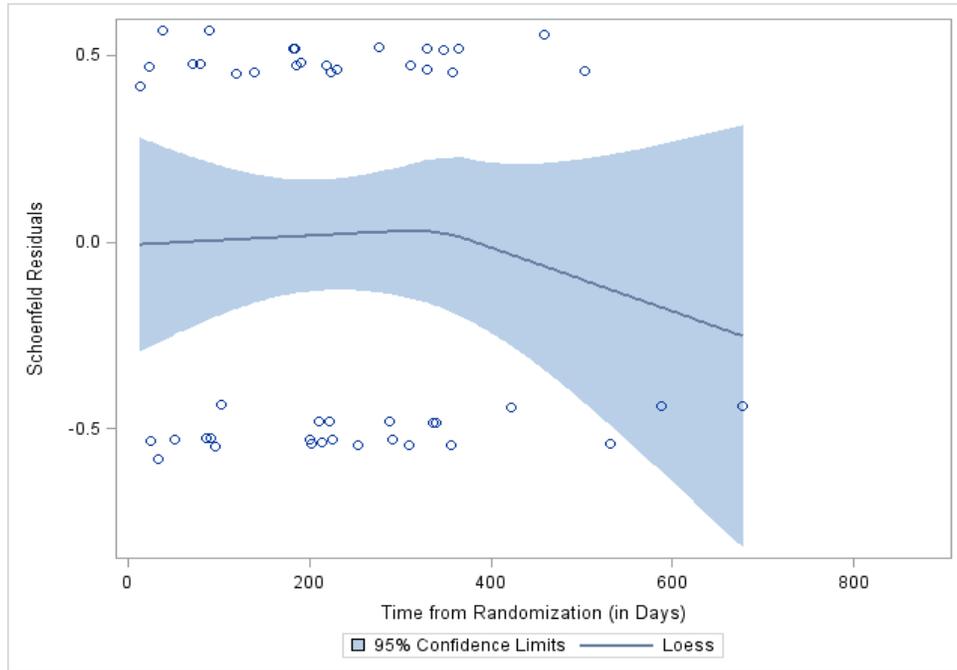
## 5.2 Conclusions and Recommendations

This is a statistical safety review of a CV meta-analysis report submitted by Eli Lilly, the Applicant for this BLA, to assess the CV safety of dulaglutide injection relative to all comparators. The meta-analysis included 9 phase 2 and 3 trials in the dulaglutide development program. The estimated HR for MACE+ (the primary endpoint) was **0.57** with corresponding 98.02% CI (**0.30, 1.10**). The upper bound of this confidence interval was less than 1.8 and therefore ruled out the unacceptable risk margin of 1.8 set forth in the FDA Guidance to establish CV safety of new antidiabetic products.

It is important to note that the dulaglutide meta-analysis comprises trials of various designs (with respect to randomization ratios, blinding strategies, parallel arm, adaptive design, trial durations, etc.), and was designed to test whether the premarket 1.8 risk margin only can be ruled out. As a result, the conclusion is that meta-analysis data was sufficient to show that dulaglutide is not associated with an 80% increase in CV risk. The recommendation is that further evaluation of the CV risk of dulaglutide be based on data from the REWIND trial, which is designed around the MACE endpoint and conducted in a high risk population with prolonged exposure.

## APPENDIX I ASSESSMENT OF PROPORTIONAL HAZARDS

The plot below shows the Schoenfeld residuals, based on all trials in the meta-analysis, and loess curve along with 95% confidence bands. A slope of zero is indicative that the PH assumption is not violated. Therefore, there is no apparent violation of this assumption for the stratified Cox model across all trials.



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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**BLA #:** BLA 125469

**Drug Name:** Trulicity (dulaglutide)

**Indication(s):** Improve glycemic control in adults with type two diabetes mellitus

**Applicant:** Eli Lilly and Company

**Date(s):** Stamp date: September 18, 2013  
PDUFA due date: May 18, 2014

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics II

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**Keywords:** Non-Inferiority, Missing data sensitivity analysis.

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## 1 EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

Eli Lilly proposes Trulicity (dulaglutide) for the improvement of glycemic control in adults with type two diabetes mellitus (T2DM). Based on the prespecified analysis of the primary study endpoint:

- Dulaglutide 1.5 mg and Dulaglutide 0.75 mg achieved statistically significantly better HbA1c reduction compared to sitagliptin and placebo when added to metformin, metformin when used as monotherapy, exenatide and placebo when added to metformin and pioglitazone, and insulin glargine when added to insulin lispro.
- Dulaglutide 1.5 mg achieved statistically significantly better HbA1c reduction than insulin glargine when added to metformin and sulfonylurea. Dulaglutide 0.75 mg was non-inferior to insulin glargine when added to metformin and sulfonylurea.

An investigation into the potential impact of missing data revealed (1) there is robust support for the non-inferiority of high and low dose dulaglutide to active-controls, and (2) uncertainty as to whether dulaglutide is superior to select active-controls: insulin glargine (0.75 mg dose) and metformin (both doses). My review of the statistical evidence found that two doses of dulaglutide investigated are both effective therapies for treatment for patients with T2DM. I recommend approval of this BLA for the proposed indication.

### 1.2 Brief Overview of Clinical Studies

Five trials were reviewed as part of this BLA submission. They were all randomized, multi-center and multi-national but had differing treatment durations, active comparators, background therapy, and blinding. All trials had a high dose (1.5 mg) and low dose (0.75 mg) dulaglutide arm. The experimental study drug was administered as subcutaneous injections once weekly. The primary study endpoint was change in HbA1c from baseline to either week 26 or to week 52. The primary study hypothesis was to either test for superiority relative to placebo or non-inferiority (NI) to active control. Key secondary hypotheses were prespecified for all trials and were incorporated into the formal testing sequence. Secondary hypotheses included tests for NI of low-dose dulaglutide, and superiority of high and low dose to active control. Hypotheses contrasting the high and low dulaglutide doses were not evaluated. The NI margin was prespecified as 0.4% for all trials except trial GBCF, where it was set at 0.25%.

Trial GBCF was a double-blind, adaptive, seamless Phase 2/3 dose-finding 104 week controlled study. In total, 972 subjects in the confirmatory phase were randomized in a 2:2:2:1 ratio to receive dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin, or placebo followed by sitagliptin 100 mg after 6 months. All study arms were investigated in combination with metformin.

Trial GBDC was double-blind, double-dummy, parallel-arm, metformin controlled 52 week study in patients with early T2DM. In total, 807 subjects were randomized in a 1:1:1 ratio to the three arms.

Trial GBDA investigated patients treated with maximally tolerated metformin and pioglitazone for 52 weeks. Exenatide was administered twice daily as the active control. In total, 978 subjects

were randomized in a 2:2:2:1 ratio to receive dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide, or placebo followed by a switch (1:1 ratio) to high dose or low dose dulaglutide after 26 weeks. The exenatide arm was not blinded to assigned therapy.

Trial GBDB investigated patients treated with maximally tolerated metformin and sulfonylurea for 78 weeks. Insulin glargine was administered twice daily (titrated to target) as the active control. In total, 810 subjects outside the US were randomized in a 1:1:1 ratio to the three treatment arms. Subjects were not blinded to randomized therapy.

Trial GBDD investigated patients treated in combination with insulin lispro with or without metformin for 52 weeks. Insulin glargine was administered once daily at night (titrated to target) as the active control. In total, 884 subjects were randomized in a 1:1:1 ratio to the three treatment arms. Subjects were not blinded to randomized therapy.

### 1.3 Statistical Issues and Findings

In all trials, both high and low dose dulaglutide improved glycemic control on the primary study endpoint (Table 1). The upper limit of the 95% confidence intervals (CI) for the difference in mean change between the experimental and control arms were all below the prespecified non-inferiority (NI) margin, and excluded zero for all but one comparison. The exception was the comparison of low dose dulaglutide with insulin glargine in trial GBDB.

The estimated excess reductions in HbA1c compared to active control varied from -0.1% to -0.5% for low dose dulaglutide and from -0.2% to -0.7% for high dose dulaglutide. The improvement in HbA1c for dulaglutide compared to active control tended not to be as dramatic when dulaglutide was administered as monotherapy (GBDC) compared to being administered in combination with background therapies.

Across all trials the high dose dulaglutide had greater estimated reductions in HbA1c than the low dose dulaglutide. The excess reduction ranged from 0.05% to 0.32%. Although comparisons between dulaglutide doses were exploratory, the high dose had statistically significantly greater HbA1c reduction at the nominal 5% level in three trials (GBDB, GBCF, and GBDA). The high dose was also associated with an excess number of study discontinuations due to an adverse event (AE); the most frequent event was associated with gastrointestinal disorders.

The extent of missing data varied across trials, treatment arms, and the timing of the primary endpoint landmark visit. In the two trials where the landmark for the primary endpoint was at week 52 the percent of missing data was 9% (GBDB) and 18% (GBDC). When the endpoint was at week 26 the percent of missing data ranged from 7% to 12%. In the two trials with a placebo the frequency of missing data was considerably greater in placebo group than either the experimental therapy or active control (GBDA: 16% vs. 3%; GBCF at week 26: 22% vs. 10%).

**Table 1. Summary of Study Findings on the Primary Endpoint**

Study	Comparator (endpoint visit)	Dula 0.75 - Comparator LS Mean (95% CI)	Dula 1.5 - Comparator LS Mean (95% CI)
<b>Metformin add-on</b>			
GBCF	Placebo (wk 26)	-1.04 (-1.22, -0.86)†	-1.23 (-1.41, -1.05)†
	Sitagliptin (wk 52)	-0.50 (-0.67, -0.33)‡‡	-0.71 (-0.87, -0.54)‡‡
<b>Monotherapy</b>			
GBDC	Metformin (wk 26)	-0.15 (-0.29, -0.01)‡‡	-0.22 (-0.36, -0.08)‡‡
<b>Metformin and Pioglitazone add-on</b>			
GBDA	Placebo (wk 26)	-0.84 (-1.01, -0.67)†	-1.05 (-1.22, -0.88)†
	Exenatide (wk 26)	-0.31 (-0.44, -0.18)‡‡	-0.52 (-0.66, -0.39)‡‡
<b>Metformin and Sulfonylurea add-on</b>			
GBDB	Insulin Glargine (wk 52)	-0.13 (-0.29, 0.02)‡	-0.45 (-0.60, -0.29)‡‡
<b>Insulin Lispro add-on</b>			
GBDD	Insulin Glargine (wk 26)	-0.17 (-0.33, -0.02)‡‡	-0.22 (-0.38, -0.07)‡‡

‡ - Prespecified test for non-inferiority statistically significant

† - Prespecified test for superiority statistically significant

For the primary analysis it is unclear whether it provides a reliable estimate of the intention-to-treat (ITT) effect. Two issues are:

- Subjects that had used rescue medication had their primary endpoint value represented by their last pre-rescue observation (LprOCF). While this approach was recommended by FDA, it is unclear whether it accurately represents the intended study endpoint.
- The analysis excluded a subset of the randomized population that did not have at least one post-baseline assessment. Excluding randomized subjects based on post-baseline considerations leads to the possibility that the statistical inferences do not preserve the integrity of randomization. The percentage of randomized patients excluded from the primary analysis ranged across trials from 1.1% to 6.8%.

The NI margins that were used were similar to margins used in other T2DM trials and consistent with the 2008 FDA draft guidance for diabetes mellitus. Given that the study findings supported superiority of experimental therapy to active control no formal assessment of the NI margins was performed.

A sensitivity analysis on the potential impact of missing data on the ITT effect for the primary study endpoints was performed. The impact of missing data on study conclusion was assessed by considering (i) what the mean response in the subgroup missing the primary endpoint would have to be to result in a different statistical conclusion (e.g., experimental therapy is inferior to active control), and (ii) whether the means from (i) are likely to characterize responses in subjects missing the primary endpoint. This investigation revealed (1) the NI findings across trials were not impacted by missing data, and (2) the superiority conclusion was impacted for select trials and dulaglutide doses. Superiority conclusions that are not considered robust to missing data are: low dose dulaglutide vs. insulin glargine, and both dulaglutide doses vs. metformin.

Across individual trials the average HbA1c reduction was fairly similar to the reduction in subgroups defined by gender, race (White, non-White), age ( $\leq 65$  years,  $> 65$  years), region (US, non-US), baseline HbA1c ( $\leq 8.5\%$ ,  $> 8.5\%$ ), and baseline BMI ( $\leq 30$ ,  $> 30$ ). No statistical interactions between the above factors and dulaglutide dose (high vs. low) were observed.

Across individual trials there was a consistent trend that the dulaglutide arms had a greater percentage of subjects having HbA1c  $< 7.0\%$  at the primary landmark visit and did not receive rescue medication prior to the landmark visit. For weight loss, there was a consistent trend across trials that high dose dulaglutide was associated with a reduction in average weight loss from baseline. There was no consistent trend between low dose dulaglutide and weight loss.

## **2 INTRODUCTION**

### **2.1 Overview**

#### **2.1.1 Class and Indication**

Trulicity (dulaglutide), a long acting human glucagon-like peptide-1 (GLP-1) receptor agonist, is being investigated for the improvement of glycemic control in adults with T2DM. The product is intended for once weekly subcutaneous injections. The proposed dosage is 1.5 mg that will be administered in a single-use pen that has auto-injection function.

A second dose of dulaglutide (0.75 mg) was also investigated during the clinical development program. The sponsor's intention is to label a single dose for both initiation of treatment and for maintenance. Findings from the low dose were not presented in the package insert included with the submission.

#### **2.1.2 History of Drug Development**

Eli Lilly submitted IND 70930 for dulaglutide on August 4, 2005. Dulaglutide is being developed as a Critical Path Initiative pilot project, using an adaptive randomization, seamless Phase 2/3 trial (GBCF) in clinical development.

The End-of-Phase 2 (EOP2) meeting was held on November 10, 2009. The Phase 2/3 trial was ongoing at the time of the EOP2 meeting. Advice on the handling of missing data was discussed at the EOP2 meeting. FDA recommended the primary analysis should use last observation carried forward (LOCF) to impute missing response data. For patients that received a rescue medication prior to the primary endpoint, the sponsor was further advised to use the last observation prior to rescue. Additional discussion of missing data is given in Section 3.2.1 below.

For the adaptive Phase 2/3 study there was a FDA-sponsor agreement on combination of data from the dose finding stage and the confirmatory stage. At the March 07, 2008 Type C meeting (IND 70930 – serial number: 0055) “FDA agreed that Lilly can conduct and analyze the trial as proposed, understanding that FDA may only consider data from patients enrolled in Stage 2 as confirmatory.” At issues is combining data from both Stages presents non-trivial statistical issues impacting the ability to strongly control type I error and reliably estimate the treatment effect. Due to these considerations this review considers subject that enrolled during the confirmatory phase. The sponsor's primary analysis combines data from both stages.

#### **2.1.3 Specific Studies Reviewed**

Five trials were reviewed as part of this BLA submission. The trials were all randomized, multi-center, and multi-national but had differing treatment durations, active comparators, background therapies, and blinding. The primary study endpoint was change in HbA1c from baseline to either week 26 or to week 52. The two dulaglutide doses investigated in the Phase 3 trials (0.75

mg and 1.5 mg) were identified in Trial GBCF. Two trials had a placebo arm and all had an active control. Insulin glargine was the active control in Trials GBDB and GBDD; the other studies had different active controls, as well as different background antidiabetic treatments. Details of the trial design are available in the Table below.

**Table 2. Summary of Trial Designs**

Study	Design	Controlled Data (wks)	Primary Endpoint (wk)	Number of Subjects Randomized
<b>Metformin add-on</b>				
H9X-MC-GBCF (Stage II)	R, PG, DB, PC, AC, ADF	104 weeks	Sitagliptin: week 52 Placebo: week 26	Dula 0.75 mg-281 Dula 1.5 mg-279 Sitagliptin-273 Pbo/sitagliptin*-139
<b>Monotherapy</b>				
H9X-MC-GBDC	R, PG, DB, DD, AC	52 weeks	week 26	Dula 0.75 mg-270 Dula 1.5 mg-269 Metformin-268
<b>Met and Pio add-on</b>				
H9X-MC-GBDA	R, PG, DB PC, DB Dula, OL AC,	52 weeks	week 26	Dula 0.75 mg-280 Dula 1.5 mg-279 Pbo/Dulaglutide*-141 Exenatide-278
<b>Met and SU add-on</b>				
H9X-MC-GBDB	R, PG, OL, AC	78 weeks	week 52	Dula 0.75 mg-272 Dula 1.5 mg-279 Insulin glargine-265
<b>Insulin Lispro add-on</b>				
H9X-MC-GBDD	R, PG, OL, DBDA Dula, AC	52 weeks	week 26	Dula 0.75 mg-293 Dula 1.5 mg-295 Insulin glargine-296

PC-placebo controlled; AC-Active Comparator; OL-Open Label; R-Randomized, DB-Double Blind; DD-Double dummy; ADF-Adaptive dose finding; DBDA- Double-blind dose assignment; PG-Parallel Group; Pbo-Placebo; Dula-Dulaglutide; Met-Metformin; Pio-Pioglitazone; SU-sulfonylurea

\*Placebo given for 26 weeks followed by experimental or active control thereafter.

## 2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission, organized as an .enx file, was archived at the following link:

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6812e0f42>

All tables and figures in this review were created by this reviewer unless noted otherwise.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

All required documents necessary for a statistical review were submitted. No software code was submitted.

The datasets for the five clinical trials were found to be in good organization. Across trials the variables for the primary analysis were not consistently named. Value labels were also not consistent across individual trials. I was able to reproduce the results on the primary endpoints presented in the individual Clinical Study Reports.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

This section provides an overview of the trials reviewed, focusing on design elements shared across trials. Issues that are common to all trials are also discussed here. Trial specific features including study specific hypotheses are described in the sub-sections below.

**Primary Efficacy Endpoint** was prespecified as the change in HbA1c from baseline to week 26 for trials GBDC, GBDA, and GBDD, and as the change in HbA1c from baseline to week 52 for trials GBDB and GBCF.

*Reviewer Comment: It is noted that the prespecified primary endpoint is not consistent with the endpoint analyzed. The endpoint analyzed is the change in HbA1c from baseline to earliest of the following: the landmark visit, or the initiation of rescue. While it's acknowledge FDA recommended handling rescue in this way at the EOP2 meeting, I do not agree with the recommendation. My issues are*

- *It violates the ITT principle; and*
- *The analyzed endpoint may not be meaningful for all subjects, particularly if rescue is used shortly after randomization*

*My impression is that using data up until rescue is an attempt to isolate the contribution of experimental therapy on HbA1c change. At issue is being able to disentangle the fraction of HbA1c change at the landmark visit that may be attributed to experimental therapy in the presence of rescue. Whether revising the endpoint definition in this way is appropriate to achieve this is unclear. It is likely that equally convincing and opposing arguments can be made on why this approach is either conservative or anti-conservative, thus making the approach problematic. Being concerned with the impact of rescue on HbA1c makes the problem multi-dimensional. It is therefore important to consider supportive analyses to provide some confidence that the change in HbA1c from baseline to landmark is not confounded by rescue. Supportive analyses used to support this are (1) the timing of rescue use relative landmark, (2) comparison of the rescue-free response rate, and (3) analyzing the HbA1c at landmark irrespective of rescue use. The second analysis is described below. These analyses were not investigated for trial GBCF since they handled patients that used rescue differently (See Rescue Medication below).*

**Secondary Endpoints** investigated in this review per consultation with Dr. Suchitra Balakrishnan are: change in body weight from baseline, change in fasting serum glucose from baseline, and hypoglycemic events (documented symptomatic and severe). Results and findings for hypoglycemic events are presented in the *Summary of Safety* (Section 3.3).

**Rescue Medication** was handled differently in trial GBCF than in the other Phase 3 trials. In GBCF a subject who developed persistent or worsening hyperglycemia was discontinued from the study. In such cases the event hyperglycemia was recorded as the AE associated with study discontinuation.

In the other Phase 3 trials rescue medication was permitted for subjects who met the criteria for persistent severe hyperglycemia. Subjects were also considered to be on rescue if they required new intervention for any reason which included subjects who discontinued study drug due to any reason such as AEs, patient decision, or any other reason. Unlike trial GBCF, subjects that used rescue for hyperglycemia did not discontinue from the trial.

**Primary and Secondary Hypotheses** are described for the respective trials in the sections below. Contrasts of the mean HbA1c reduction between dulaglutide doses were prespecified for all trials; the comparison was exploratory as there was no formal hypothesis and the test was not incorporated into the formal testing sequence.

*Reviewer Comment: The prespecified testing strategy used to evaluate primary and secondary endpoints does not control the study-wise type-I error at 5%. The problem is that testing of the secondary endpoints was not incorporated into the testing sequence/hierarchy used to test the primary and key secondary objectives. Secondary endpoints were instead tested irrespective of whether the primary and key secondary objectives were satisfied. Under a sequential testing procedure the testing of secondary endpoints cannot be done once there is no alpha to pass along. A realization of this problem occurred in trial GBDB. Formal hypothesis tests were performed on a secondary endpoint even though the last hypothesis test in the sequence for the primary endpoint was not statistically significant.*

*This problem will be addressed in this review as follows. Secondary endpoints will be tested if and only if the primary and key secondary objectives were satisfied. If not all primary and key secondary objectives were satisfied, secondary endpoints will be considered descriptive. This ad hoc strategy is far from optimal, but is in the same spirit as the prespecified testing strategy.*

**Analysis Populations** that were prespecified were the ITT population and the per-protocol (PP) population. The ITT population was defined by the sponsor as all randomized patients who have received at least one dose of study medication. The PP population was defined as all randomized patients who have completed the study, have overall compliance with study treatment across visits of at least 75%, and have no significant protocol violations. The prespecified primary analysis set was the subset of the ITT population that had at least one post-baseline measurement.

*Reviewer Comment: There is the possibility that the primary analysis set does not preserve the integrity of randomization due its reliance on post-randomization events, which is particularly concern for trials that had an open-label design. To avoid possible confusion this review will not refer to the analysis population as the ITT population since it violates the ITT principle.*

## Analysis Methods

An analysis of covariance (ANCOVA) model was prespecified as the primary analysis method. The model included the primary endpoint as the dependent variable and included treatment, country, and baseline HbA1c as independent variables; trial GBDC additionally included a covariate for prior medication group (previous oral antidiabetic medication (OAM) vs. no previous OAM) and GBDD additionally included a variable for baseline metformin use. Missing post-baseline values were imputed using LOCF in trial GBCF and LprOCF in the other trials. If there was no data after randomization, the endpoint was considered missing and the subject was excluded from the analysis.

*Reviewer Comment: LOCF was recommended at the EOP2 meeting and is described in the 2008 draft Guidance for Industry: Diabetes Mellitus: developing drugs and therapeutic biologics for treatment and prevention. However, the Division has reconsidered this approach to missing data following publication of the 2010 report on missing data by the National Academy of Sciences, The Prevention and Treatment of Missing Data in Clinical Trials. The report states “The panel believes that in nearly all cases, there are better alternatives to [LOCF] ...which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects.”*

A secondary analysis of the primary endpoint was prespecified using a mixed model with repeated-measures (MMRM) approach. This model included study visit, visit by treatment interaction in addition to the covariates for the primary analysis model listed above. For patients that used rescue only measurements obtained prior to taking rescue are included in the analysis.

*Reviewer Comment: The MMRM model assumes that the missing data are missing at random (MAR). This assumption means that, given the covariates in the model and observed responses, the statistical behavior of the missing data is the same as the observed data. For subjects that used rescue this implies the model assumes the counterfactual experience: what the response would have been if the subject did not use rescue. In the case of a subject discontinuing from the study early, the model estimates a “counterfactual outcome in that it estimates the effect that would have been observed had patient stayed in the trial, contrary to the fact that some patients dropped out” (Mallinckrod et al., Therapeutic Innovation and Regulatory Science 2007; 42: 303-319). In addition to the counterfactual experience not being considered clinically meaningful, no empirical data exists to evaluate whether the counterfactual experience implied by the model is valid.*

*Another important consideration is the MMRM model represents subjects with missing change in HbA1c at the landmark visit by subjects that have HbA1c measured at the landmark. An implication of this is that if the MMRM model is not correctly specified the results from the analysis may not be generalizable to the randomized population. To illustrate this point consider the covariate baseline insulin use. Suppose a study population had an equal number of subjects that did and did not use insulin at baseline and this variable was an effect modifier, where subjects that used insulin at baseline had more favorable HbA1c reductions. Also suppose at the landmark visit there were disproportionately more subjects with an HbA1c measurement that used baseline insulin. The problem is that if the MMRM model was not correctly specified the*

*treatment effect estimated at the landmark visit would be inflated since the estimated effect would be weighted towards the effect in the group that contributed data (i.e., those that used insulin at baseline). The task of prespecifying a statistical model where the MAR will be approximately true is non-trivial and relies on untestable assumption. No justification was provided on why the assumed MMRM model would support valid inferences of the treatment effect in the randomized sample.*

**Impact of Missing Data and Rescue Medication** was considered not to be fully evaluated by the sponsor.

Because of this I investigated the potential impact of missing data on study conclusions in the full randomized population by considering (i) what the mean response in the subgroup missing the primary endpoint would have to be to result in a different statistical conclusion, and (ii) whether the means from (i) are likely to characterize responses in subjects missing the primary endpoint. This was assessed using a multiple imputation (MI) framework. For each treatment arm the subjects that did not have a measurement on the primary endpoint had their endpoint value imputed, where the distribution of imputed responses across subjects was centered at a prespecified value. The value that the imputed responses were centered at is a sensitivity parameter, which was varied for the treatment groups. For a given pair of sensitivity parameters (one for the experimental arm and one for the control arm), multiple imputed datasets were created and CIs for the comparison of mean change between dulaglutide and control were constructed. The impact of missing data on the study conclusion was then assessed by evaluating the upper 95% CI limit (for the combined observed and imputed data) relative to zero and the prespecified NI margin. Missing data was not considered to impact study findings if the sensitivity parameters that resulted in a different statistical conclusion based on the primary analysis were unlikely to characterize responses in subjects missing the primary endpoint. Formal details on this sensitivity analysis are given in Appendix A.1

I also performed an exploratory analysis investigating the impact of rescue medication on HbA1c reduction in the full randomized sample by evaluating the frequency of rescue-free response. A subject was considered to have a rescue-free response if (1) no rescue medication was used prior to the primary landmark visit; and (2) HbA1c measured at the primary landmark visit was < 7.0%. Subjects without a primary endpoint assessment were coded as having a non-response. The frequency of treatment success was tabulated by treatment group and 95% CIs for the differences between groups were computed.

**Non-inferiority Margin** was prespecified as 0.25% for trial GBCF and 0.4% for the other four trials. These margins are similar to margins used in other T2DM trials and consistent with the 2008 FDA draft guidance for diabetes mellitus. However, given that the study findings consistently supported superiority of experimental therapy to active control across trials, I did not evaluate whether the NI margins are justified.

**Sample Size** for trials GBDC, GBDB, and GBDD was determined to have at least 90% power to show non-inferiority of dulaglutide 1.5 mg to active comparator, assuming no difference in mean change between groups at the primary endpoint visit 26 and a 0.4% margin of non-inferiority. Sample size for trial GBDA was determined to ensure at least 90% power to 1) detect a

difference of 0.54% in the mean change from baseline between dulaglutide and placebo, and 2) show non-inferiority of dulaglutide to extenatide, assuming no difference in mean change between groups and a 0.4% margin of non-inferiority. The calculations assume a 2-sided test with 0.05 alpha-level, SD of 1.3%, and 11% dropout by week 26 for trials GBDA and GBDC, and a 20% dropout by week 52 for trials GBDB and GBDD.

*Reviewer Comment: It is noted that the actual statistical power to show NI was nearly 1, as evident by the widths of the CI in Table 1. Under the sample size assumptions the expected CI width is about 0.44%; this calculation assumes 270 subjects in the experimental and control arm, which is reasonably representative of the number of randomized subjects per treatment arm (Table 2). The width of several CIs is about 0.3% or 68% narrower than expected, which coincides with 99.9% statistical power to show NI.*

### 3.2.1.1 Study H9X-MC-GBCF (Add-on to Metformin)

Study GBCF was a two-stage, randomized, adaptive, Phase 2/3, double-blind, parallel-arm trial comparing dulaglutide with sitagliptin and placebo in combination with metformin in patients with T2DM. The design for the study is shown below. In Stage I seven dulaglutide doses were investigated, with the 0.75 mg and 1.5 mg doses being identified for further investigation in Stage II. This review considers only data from Stage II for reasons given Section 2.1.2.

Figure 1. Trial GBCF Study Design

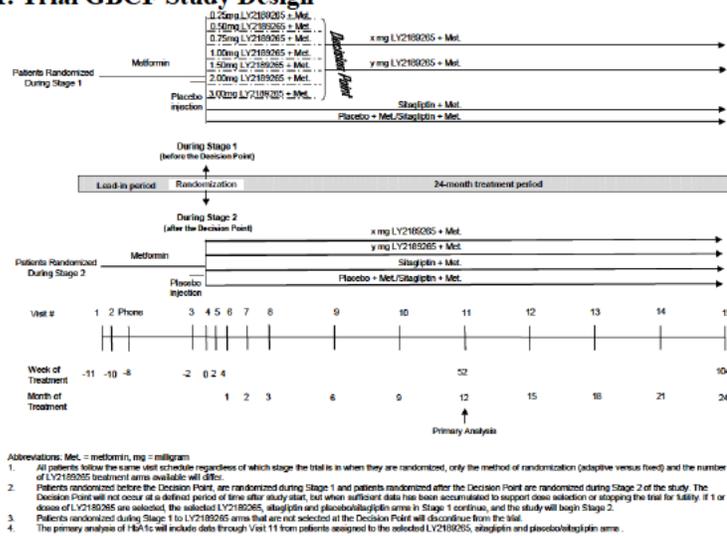


Figure GBCF.1. Illustration of study design for Protocol H9X-MC-GBCF.

In Stage II a total of 972 subjects in 111 centers in 12 countries were randomized in a 2:2:2:1 ratio to receive dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin, or placebo followed sitagliptin after 6 months. Randomization was stratified by country and baseline HbA1c (< 8.5%, ≥ 8.5%).

Subjects randomized to dulaglutide were to inject study drug subcutaneously once weekly and take placebo tablets orally once daily. Patients randomized to sitagliptin were to take 100 mg orally once daily and administer placebo subcutaneously once weekly. Patients randomized to the placebo/sitagliptin sequence were to administer placebo subcutaneously once weekly and take placebo tablets orally once daily. After 6 months the placebo tablets were replaced (blinded) with sitagliptin 100 mg tablets. All subjects were to take metformin ≥ 1500 mg per day, not to exceed the maximum daily dose allowed per local labeling.

The primary and key secondary endpoint was respectively prespecified as change in HbA1c from baseline to week 52 and week 26. Table 3 lists the prespecified hypotheses and the tree-gatekeeping strategy to control the family-wise error rate at the one-sided 2% level. The non-inferiority margin was prespecified at 0.25%.

**Table 3. Hypotheses for HbA1c for Trial GBCF**

Hypothesis	Rejection rule
H1: Dula 1.5 mg NI to SITA at mo. 12	p-value $\leq$ 0.02
H2: Dula 1.5 mg SUP to PLA at mo. 6	p-value $\leq$ 0.02 and H1 rejected
H3: Dula 1.5 mg SUP to SITA at mo. 12	p-value $\leq$ 0.012
H4: Dula 0.75 mg SUP to PLA at mo. 6	- p-value $\leq$ 0.012, and H3 rejected, or - p-value $\leq$ 0.004, H3 not rejected
H5: Dula 0.75 mg NI to SITA at mo. 12	- p-value $\leq$ 0.02, and H3 and H4 rejected, or - p-value $\leq$ 0.008, and H3 rejected and H4 not rejected
H6: Dula 0.75 mg SUP to SITA at mo. 12	- p-value $\leq$ 0.02, and H3 rejected, or - p-value $\leq$ 0.008, and H3 rejected,

### 3.2.1.1.1 Patient Disposition, Demographic and Baseline Characteristics

All 972 subjects randomized in Stage II received at least one dose of study drug. By week 26, a total of 16% of subjects discontinued from the study, with the frequency being greatest in the placebo/sitagliptin group compared to the other arms (30% vs. 14%). This trend was consistent over the 104 week treatment period (Appendix A.1, Figure 12). For the two dulaglutide groups, more subjects in the high dose group discontinued (15% vs. 12%), where the imbalance was driven by an excess number of discontinuations due to an AE. By week 52 there were more subjects in the high dose group compared to the low dose group discontinued for an AE classified under the gastrointestinal disorder MedDRA system organ class (SOC, 12 vs. 6). By week 52 fewer subjects in the dulaglutide arms discontinued due to hyperglycemia (dulaglutide 0.75 mg, 8; dulaglutide 1.5 mg, 8; placebo/sitagliptin, 15; sitagliptin, 14). Recall that subjects who developed persistent or worsening hyperglycemia were discontinued from the study, and the event hyperglycemia was recorded as the AE associated with study discontinuation. By week 52, 24% of randomized subjects discontinued from the study. The frequency of discontinuations was greater in US sites versus non-US sites at weeks 26 (24% vs. 14%) and 52 (34% vs. 21%).

Select baseline and diabetes characteristics are summarized in Table 5. Subject characteristics were reasonably comparable across treatment groups at baseline.

**Table 4. Patient Disposition (Trial GBCF, Stage II)**

	Dulaglutide		Placebo/ Sitagliptin	Sitagliptin
	0.75 mg	1.5 mg		
Randomized	281	279	139	273
Randomized and received one dose of study medication	281	279	139	273
Discontinued study by week 26 (52)	33 (54)	42 (61)	41 (52)	42 (66)
<i>Adverse Event</i>	12 (21)	20 (32)	16 (20)	14 (26)
<i>Death</i>	0 (0)	1 (1)	0 (0)	0 (1)
<i>Entry Criteria Not Met</i>	1 (2)	4 (5)	1 (1)	0 (0)
<i>Lack of Efficacy</i>	0 (0)	1 (1)	4 (4)	2 (3)
<i>Lost to Follow-Up</i>	3 (6)	4 (6)	3 (3)	6 (8)
<i>Physician Decision</i>	6 (7)	3 (3)	7 (8)	4 (5)
<i>Protocol Violation</i>	0 (2)	0 (2)	0 (1)	1 (2)
<i>Sponsor Decision</i>	0 (1)	(0)	(0)	(0)
<i>Subject Decision</i>	11 (15)	9 (11)	10 (15)	15 (21)

**Table 5. Patient Baseline and Demographic Characteristics (Trial GBCF, Stage II)**

	Dulaglutide		Placebo N=139	Sitagliptin N=273
	0.75 mg N=281	1.5 mg N=279		
<b>Age (years)</b>				
Mean (SD)	54 (10)	53 (10)	55 (9)	53 (10)
Min, Max	19, 73	20, 75	26, 74	24, 74
≥ 65	39 (14%)	35 (13%)	20 (14%)	37 (14%)
<b>Gender: Males</b>	124 (44%)	136 (49%)	78 (56%)	130 (48%)
<b>Race:</b>				
White	149 (53%)	147 (53%)	76 (55%)	138 (51%)
Black	12 (4%)	14 (5%)	7 (5%)	5 (2%)
<b>Country: U.S.</b>	72 (26%)	63 (23%)	33 (24%)	64 (23%)
<b>Baseline HbA1c (%):</b>				
Mean (SD)	8.2 (1.1)	8.1 (1.0)	8.1 (1.2)	8.0 (1.1)
Min, Max	6.3, 13.9	5.1, 12.2	4.9, 12.1	6.0, 12.8
> 8.0%	133 (47%)	123 (44%)	59 (42%)	117 (43%)
<b>Duration Diabetes (yrs): mean (SD)</b>	7.3 (4.9)	6.8 (5.3)	6.9 (5.1)	6.9 (4.8)
<b>Weight (kg): mean (SD)</b>	86 (17)	87 (17)	87 (17)	86 (17)
<b>Fasting Serum Glucose (UNITS) : mean (SD)</b>	9.7 (3.0)	9.6 (3.2)	9.9 (3.3)	9.5 (2.8)
<b>Baseline BMI: &lt; 30 kg/m<sup>2</sup></b>	134 (48%)	121 (43%)	57 (41%)	127 (47%)
<b>Baseline creatinine clearance (mL/min)</b>				
< 60	3 (1%)	4 (1%)	1 (1%)	0 (0%)
60 to < 90	48 (18%)	46 (17%)	27 (20%)	41 (16%)
≥ 90	221 (81%)	221 (82%)	107 (79%)	223 (84%)

### 3.2.1.1.2 Results and Conclusions

#### Change in HbA1c

Eleven randomized subjects that did not have a post-baseline assessment were not included in the sponsor's primary analysis. A sizable percentage of randomized subjects did not have an HbA1c assessment at the week 52 visit (20%). The degree of missing data was more favorable for the analysis of HbA1c at week 26 (12%). The majority of the missing data at weeks 26 and 52 occurred in the placebo/sitagliptin group. At week 104 HbA1c was assessed on only 60% of randomized subjects.

**Table 6. Last available HbA1c assessment (Trial GBCF, Stage II)**

	Dulaglutide		Placebo/Sitagliptin N=139	Sitagliptin N=273
	0.75 mg N=281	1.5 mg N=279		
Included in sponsor's analysis	276	277	138	270
Week 26: LAFV				
<i>Visit 6 – Week</i>	10	14	12	9
<i>Visit 7 – Week</i>	3	4	8	8
<i>Visit 8 – Week</i>	5	10	10	12
<i>Visit 9 – Week 26</i>	258	249	108	241
Week 52: LAFV				
<i>Visit 6 – Week</i>	10	14	12	9
<i>Visit 7 – Week</i>	3	4	8	8
<i>Visit 8 – Week</i>	5	10	10	10
<i>Visit 9 – Week 26</i>	15	15	11	14
<i>Visit 10 – Week</i>	5	9	4	10
<i>Visit 11 – Week 52</i>	238	225	93	219

LAFV-last available follow-up visit for primary endpoint

At week 52, both dulaglutide 1.5 mg and dulaglutide 0.75 mg resulted in a statistically significant reduction in mean HbA1c compared to sitagliptin; the excess reduction for dulaglutide 1.5 mg was 0.71% with 95% CI (-0.87, -0.54) and 0.50% with (95% CI = -0.73, -0.36) for dulaglutide 0.75 mg (Table 7). At week 26, both dulaglutide doses resulted in a statistically significant reduction in mean HbA1c compared to placebo; the excess reduction for dulaglutide 1.5 mg was 1.23% (95% CI = -1.41, -1.05) and 1.04% (95% CI = -1.22, -0.86) for dulaglutide 0.75 mg. Based on the prespecified testing strategy, both dulaglutide doses were superior in HbA1c reduction to placebo at week 26, and sitagliptin at week 52.

For the prespecified contrast between the two dulaglutide doses the estimated HbA1c reduction was greater in the high dose group; at week 26 the estimated excess reduction in the high dose group was 0.19% with 95% CI = (-0.33, -0.04) and 0.21% with 95% CI (-0.37, -0.04) at week 52.

The superiority findings were supported by (1) the MMRM analysis, and (2) the ANCOVA model fit to the subgroup with an HbA1c assessment at week 26 and at week 52. In the latter analysis the magnitude of the treatment effect is smaller than the estimate from the primary analysis. This observation suggests that in the subgroup with an HbA1c measurement prior to the landmark visit, the dulaglutide groups had more favorable reductions than what was observed at the primary landmark visits. As a consequence, the treatment effect estimates in the primary analysis may not accurately characterize the change in HbA1c at the landmark visits.

The upper limit of the 95% CIs from the missing data sensitivity analysis in all randomized subjects are displayed in the contour plots below (Figure 2); refer to Table 37 to Table 40 in Appendix A.3.1 for the actual numerical results. To aide in the interpretation of this plot, recall our objective is to see how the upper 95% CI limit for each pairwise comparison of interest (dulaglutide – control) is impacted by missing data. Missing responses were imputed for the subgroup that did not have measurement at the primary landmark visit. The value that the imputed responses were centered for the group defines the sensitivity parameter. An upper CI

limit is computed using both the observed and imputed data. In the plots the CI limit is displayed as function of the sensitivity parameters. In particular, for a given sensitivity parameter for the experimental (y-coordinate) and control (x-coordinate) group the corresponding upper 95% CI limit value is represented by a color in the plot. As an illustration consider panel (a) and consider the case where the sensitivity parameter for both groups is zero, i.e. the mean HbA1c change for both the high dose and the placebo group in the subset without an HbA1c value at the week 26 visit is 0. The corresponding upper 95% CI limit is -0.82 which is well below the zero. In this example, while this pair of sensitivity parameters could possibly represent the mean change in the subset with missing data, it did not result in a different statistical conclusion. If we consider all of the combinations of sensitivity parameters (i.e., the entire plot) we observe that upper CI limit is always below zero. From this observation it is therefore reasonable to conclude that the superiority of dulaglutide 1.5 mg to placebo in HbA1c reduction at week 26 is not sensitive to missing data. Following this rationale a similar conclusion can be made for low dose dulaglutide compared to placebo in panel (c).

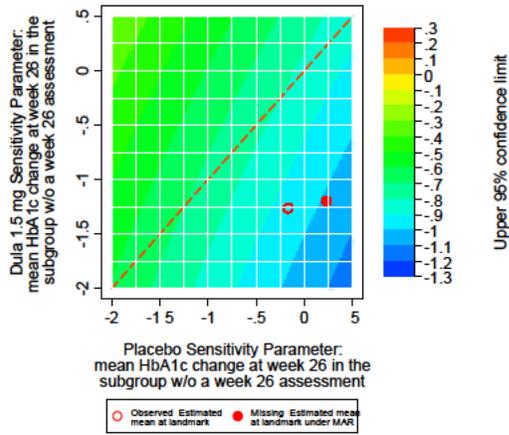
For the comparison of high dose dulaglutide to sitagliptin at week 52 in panel (b) we observe (1) for all combination of sensitivity parameters the upper CI limit is below the NI margin (0.25), and (2) for select sensitivity parameters the upper CI limit exceeds zero. The former observation provides support that the NI of dulaglutide 1.5 mg to sitagliptin in HbA1c reduction is not sensitive to missing data. Despite the latter observation I also consider that the superiority of dulaglutide to sitagliptin is not impacted by missing data. My reasoning for this is that the sensitivity parameters that resulted in the upper CI limit exceeding zero are unlikely to characterize the mean change in the group with missing data. In particular, considering the region of sensitivity parameters that resulted in the CI including zero would require that (i) the mean reduction in the sitagliptin group without a week 52 assessment would need exceed the HbA1c reduction in subjects with a value at week 52 by approximately 1.0%, and (ii) the sitagliptin group with missing data would have to have an excess HbA1c reduction of approximately 1.75% compared to dulaglutide. Following this rationale a similar conclusion can be made for low dose dulaglutide compared to sitagliptin.

**Table 7. Change in HbA1c at Weeks 26, 52 (Trial GBCF, Stage II)**

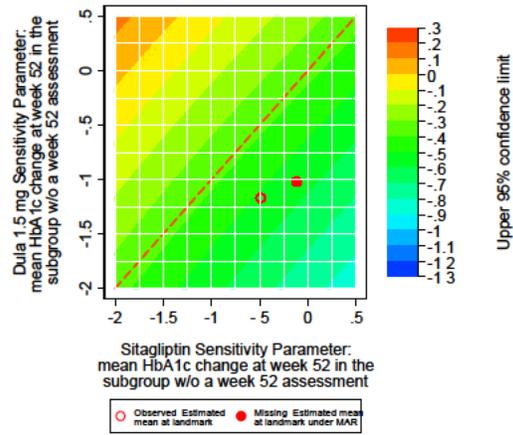
	Dulaglutide		Placebo	Sitagliptin
	0.75 mg	1.5 mg		
<b>Primary Analysis Model: ANCOVA w/LOCF</b>				
Adj. Mean Change (95% CI)				
Week 26	-0.99 (-1.11, -0.88)	-1.18 (-1.29, -1.07)	0.05 (-0.10, 0.20)	-0.58 (-0.70, -0.47)
Week 52	-0.86 (-0.99, -0.73)	-1.07 (-1.19, -0.94)	-	-0.36 (-0.49, -0.23)
Dulaglutide - Placebo (95% CI)				
Week 26	-1.04 (-1.22, -0.86)	-1.23 (-1.41, -1.05)		
p-value (1-sided): SUP	< 0.001	< 0.001		
Dulaglutide - Sitagliptin (95% CI)				
Week 26	-0.41 (-0.56, -0.26)	-0.60 (-0.74, -0.45)		
Week 52	-0.50 (-0.67, -0.33)	-0.71 (-0.87, -0.54)		
p-value (1-sided): NI	< 0.001	< 0.001		
p-value (1-sided): SUP	< 0.001	< 0.001		
<b>Supportive Analyses: Dulaglutide – Placebo (95% CI)</b>				
Week 26				
MMRM	-1.04 (-1.23, -0.84)	-1.22 (-1.41, -1.02)		
Week 26 assessment	-0.84 (-1.01, -0.65)	-1.05 (-1.23, -0.87)		
<b>Supportive Analyses: Dulaglutide – Sitagliptin (95% CI)</b>				
Week 26				
MMRM	-0.45 (-0.60, -0.29)	-0.63 (-0.78, -0.47)		
Week 26 assessment	-0.35 (-0.49, -0.21)	-0.56 (-0.71, -0.42)		
Week 52				
MMRM	-0.54 (-0.73, -0.36)	-0.74 (-0.93, -0.56)		
Week 52 assessment	-0.40 (-0.57, -0.23)	-0.66 (-0.83, -0.49)		

**Figure 2. Missing data sensitivity analysis: contour plots of upper 95% CI limits (GBCF)**

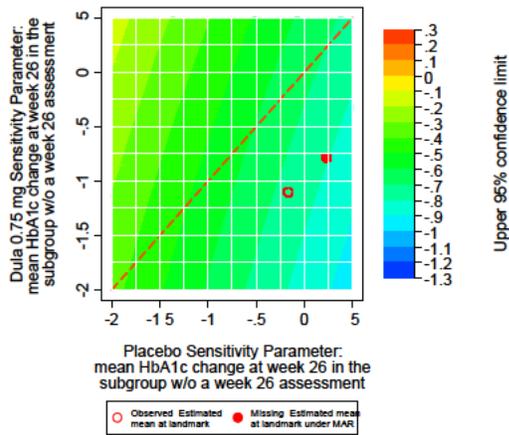
(a) High dose vs. Placebo at week 26



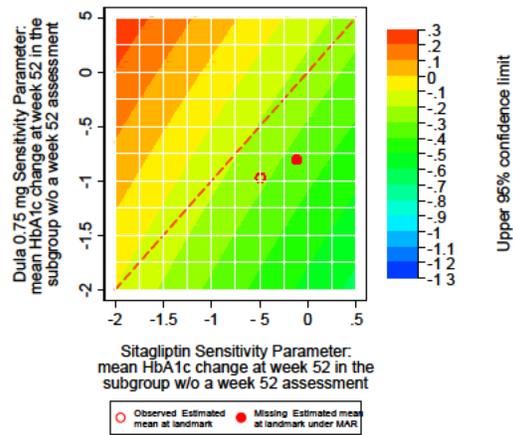
(b) High dose vs. Sitagliptin at week 52



(c) Low dose vs. Placebo at week 26



(d) Low dose vs. Sitagliptin at week 52



### **Secondary Endpoints**

**Weight:** At weeks 26 and 52, all treatments had a reduction in average weight compared to baseline (Table 8). At the nominal 5% alpha level, both dulaglutide groups had statistically significantly greater weight reduction relative to placebo at week 26, and relative to sitagliptin at weeks 26 and 52. The weight reduction had a slight dose dependency, with the high dose dulaglutide group having 0.3 kg greater reduction compared to the low dulaglutide dose.

**Fasting Serum Glucose:** At weeks 26 and 52, all treatments had a reduction in average fasting serum glucose compared to baseline (Table 8). At the nominal 5% alpha level, both dulaglutide groups had statistically significantly greater decrease in mean fasting serum glucose relative to placebo at week 26, and relative to sitagliptin at weeks 26 and 52.

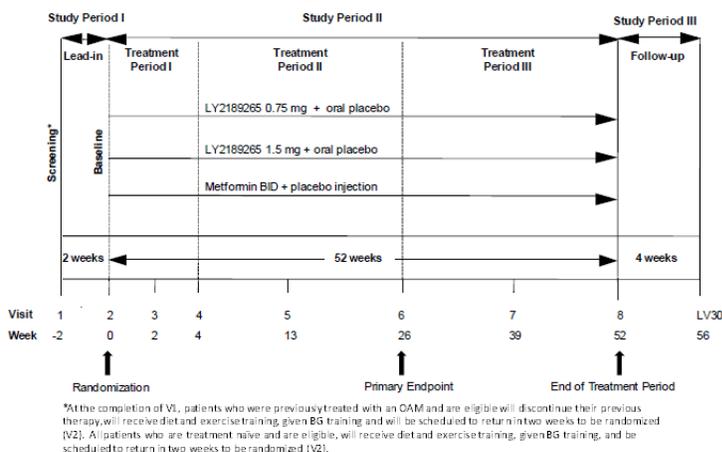
**Table 8. Analysis of Secondary Endpoints (GBCF, ANCOVA w/LOCF)**

	Dulaglutide		Placebo/ Sitagliptin	Sitagliptin
	0.75 mg	1.5 mg		
<b>Weight (kg)</b>				
Adj. Mean Change (95% CI)				
Week 26	-2.7 (-3.0, -2.3)	-3.0 (-3.4, -2.7)	-1.4 (-2.0, -0.9)	-1.4 (-1.8, -1.0)
Week 52	-2.7 (-3.2, -2.3)	-3.0 (-3.5, -2.6)	-	-1.5 (-2.0, -1.1)
Dulaglutide - Placebo (95% CI)				
Week 26	-1.2 (-1.9, -0.6)	-1.6 (-2.2, -1.0)		
Dulaglutide - Sitagliptin (95% CI)				
Week 26	-1.3 (-1.8, -0.8)	-1.7 (-2.2, -1.1)		
Week 52	-1.2 (-1.8, -0.6)	-1.5 (-2.1, -0.9)		
<b>Fasting Serum Glucose (mmol/L)</b>				
Adj. Mean Change (95% CI)				
Week 26	-2.0 (-2.3, -1.8)	-2.4 (-2.7, -2.2)	-0.5 (-0.8, -0.1)	-1.1 (-1.3, -0.8)
Week 52	-1.7 (-2.0, -1.4)	-2.3 (-2.6, -2.0)	-	-0.9 (-1.1, -0.6)
Dulaglutide - Placebo (95% CI)				
Week 26	-1.6 (-1.9, -1.2)	-1.9 (-2.3, -1.6)		
Dulaglutide - Sitagliptin (95% CI)				
Week 26	-0.9 (-1.2, -0.6)	-1.3 (-1.6, -1.0)		
Week 52	-0.8 (-1.2, -0.4)	-1.5 (-1.8, -1.1)		

### 3.2.1.2 Study H9X-MC-GBDC (Monotherapy)

Study GBDC was a 52 week, randomized, double-blind, double-dummy, parallel-arm, metformin controlled study in patients with early T2DM. Additional study design elements are shown below. Subjects randomized to dulaglutide were to inject study drug subcutaneously once weekly and take two placebo tablets twice daily by mouth. Subjects randomized to metformin were given two 500 mg tablets twice daily by mouth (total dose of 2000 mg/day) and were to inject placebo subcutaneously once weekly.

Figure 3. Trial GBDC Study Design



A total of 807 subjects in 101 centers in 19 countries were randomized in a 1:1:1 ratio to receive dulaglutide 1.5 mg, dulaglutide 0.75 mg, or metformin. Randomization was stratified by country and prior OAM medication (not on OAM, on one OAM).

The prespecified primary endpoint was change in HbA1c from baseline to week 26. The key secondary endpoint was change in HbA1c from baseline at 52 weeks. Table 9 lists the prespecified hypotheses and the tree-gatekeeping strategy to control the family-wise type-I error rate. The non-inferiority margin was prespecified as 0.4%.

Table 9. Hypotheses for HbA1c change from baseline (Trial GBDC)

Endpoint	Hypothesis	Rejection rule
Primary (week 26)	PH1: Dula 1.5 mg NI to MET PH2: Dula 0.75 mg NI to MET PH3: Dula 1.5 mg SUP to MET PH4: Dula 0.75 mg SUP to MET	p-value ≤ 0.025 p-value ≤ 0.0125 and PH1 rejected p-value ≤ 0.0125 and PH1 rejected - p-value ≤ 0.025, and PH2 and PH3 rejected, or - p-value ≤ 0.0125, PH2 rejected and PH3 not rejected
Secondary (week 52)	SH1: Dula 1.5 mg NI to MET SH2: Dula 0.75 mg NI to MET SH3: Dula 1.5 mg SUP to MET SH4: Dula 0.75 mg SUP to MET	p-value ≤ 0.025 p-value ≤ 0.0125 and SH1 rejected p-value ≤ 0.0125 and SH1 rejected - p-value ≤ 0.025, and SH2 and SH3 rejected, or - p-value ≤ 0.0125, SH2 rejected and SH3 not rejected

Dula-dulaglutide; MET-metformin; SUP-superior; NI-non-inferior

### 3.2.1.2.1 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition is summarized in Table 10. All 807 patients randomized received at least one dose of study medication. The discontinuation rate was similar across groups until approximately week 13 (Appendix A.2.2, Figure 13), after which discontinuations occurred more frequently in the metformin group. Among the dulaglutide arms, more subjects in the high dose group discontinued by week 26 due to an AE (13 vs. 6); the majority of AEs belonged to gastrointestinal disorder MedDRA SOC (1.5 mg, 9; 0.75 mg, 2). Subjects enrolled in US sites were approximately twice as likely to discontinue from the study as subjects in non-US sites (19% vs. 11).

Select baseline and diabetes characteristics are summarized in Table 11. Subject characteristics were reasonably comparable across treatment groups at baseline.

**Table 10. Patient Disposition (Trial GBDC)**

	Dulaglutide		Metformin
	0.75 mg	1.5 mg	
Randomized	270	269	268
Randomized and received one dose of study medication	270	269	268
Discontinued study prior to week 26	28	36	42
<i>Adverse Event</i>	6	13	10
<i>Entry Criteria Not Met</i>	1	1	2
<i>Lack of Efficacy</i>	2	1	4
<i>Lost to Follow-Up</i>	5	10	6
<i>Physician Decision</i>	1	1	2
<i>Protocol Violation</i>	1	0	1
<i>Sponsor Decision</i>	2	3	6
<i>Subject Decision</i>	10	7	9
<i>Treatment non-compliance</i>	0	0	2

**Table 11. Patient Baseline and Demographic Characteristics (Trial GBDC)**

	Dulaglutide		Metformin N=268
	0.75 mg N=270	1.5 mg N=269	
<b>Age (years)</b>			
Mean (SD)	55 (11)	55 (10)	55 (10)
Min, Max	29, 78	25, 83	27, 78
≥ 65	54 (20%)	45 (17%)	44 (16%)
<b>Gender: Males</b>	118 (44%)	114 (42%)	121 (45%)
<b>Race:</b>			
White	198 (73%)	201 (75%)	201 (75%)
Black	22 (8%)	17 (6%)	14 (5%)
<b>Country: U.S.</b>	80 (30%)	77 (29%)	74 (28%)
<b>Baseline HbA1c (%):</b>			
Mean (SD)	7.6 (0.9)	7.6 (0.9)	7.6 (0.8)
Min, Max	6.2, 10.1	6.0, 11.3	6.3, 10.5
> 8.0%	73 (27%)	77 (29%)	74 (28%)
<b>Baseline BMI: &lt; 30 kg/m<sup>2</sup></b>	87 (32%)	78 (29%)	80 (30%)
<b>Duration Diabetes (yrs): mean (SD)</b>	2.6 (2.2)	2.7 (1.5)	2.6 (1.8)
<b>Weight (kg): mean (SD)</b>	92 (19)	93 (19)	92 (19)
<b>Fasting Serum Glucose (mmol/L) : mean (SD)</b>	8.9 (2.6)	9.1 (2.8)	9.0 (2.4)
<b>Baseline creatinine clearance (mL/min)</b>			
< 60	0 (0%)	1 (0%)	0 (0%)
60 to < 90	47 (17%)	46 (17%)	41 (15%)
≥ 90	223 (83%)	222 (83%)	227 (85%)

### 3.2.1.2.2 Results and Conclusions

#### Change in HbA1c

Twelve subjects were excluded from the sponsor's primary analysis. Due to primary analysis using last available follow-up visit, Table 12 summarizes the last visit HbA1c was available. The majority of randomized subjects (90%) had HbA1c assessed at the week 26 visit. However, due to the handling of rescue medication the primary analysis had slightly fewer subjects (88%) with HbA1c assessed at the week 26 visit. Rescue use was similar across study arms and occurred uniformly throughout the 52 week treatment duration (Appendix A.2.2, Figure 14).

**Table 12. Last available HbA1c assessment (Trial GBDC, primary endpoint)**

	Dulaglutide		Metformin N=268
	0.75 mg N=270	1.5 mg N=269	
Included in sponsor's analysis	265	265	265
Received rescue medication at or before week 26	7	8	7
LAFV (LAprFV)			
<i>Visit 4 – Week 4</i>	6 (8)	14 (17)	15 (15)
<i>Visit 5 – Week 13</i>	9 (13)	9 (12)	14 (19)
<i>Visit 6 – Week 26</i>	251 (244)	243 (236)	238 (231)

LAFV-last available follow-up visit for primary endpoint

At week 26, both dulaglutide 1.5 mg and dulaglutide 0.75 mg resulted in a statistically significant reduction in mean HbA1c compared to metformin; the excess reduction for dulaglutide 1.5 mg was 0.22% with nominal 95% CI (-0.36, -0.08) and 0.15% with nominal 95% CI (-0.29, -0.01) for dulaglutide 0.75 mg (Table 13). Based on the prespecified testing strategy, both dulaglutide doses were superior to metformin in HbA1c reduction at week 26.

For the prespecified comparison between dulaglutide doses, the excess HbA1c reduction for the high dose group was only 0.07% greater with 95% CI (0.21, -0.07) that included zero.

The superiority of dulaglutide 0.75 mg to metformin in HbA1c reduction at week 26 was not supported by the prespecified MMRM analysis or the ANCOVA model using LOCF instead of LprOCF. The 95% CI from both of these analyses included zero. This observation was also observed in the subgroup with an HbA1c assessment at the week 26 visit. It is also noteworthy in this group that the estimated reduction for both dulaglutide groups compared to metformin was not as large as observed in the primary analysis. This attenuated difference may be explained by Figure 4. Specifically, notice that the within and between group mean change tended to be more favorable at the last available visit for dulaglutide in the subset with their last HbA1c *not* at the primary landmark visit. Given the mechanics of LOCF, it is of concern that the estimated treatment effect may be inflated due the exploitation of the early differences which could be attenuated by week 26.

For the supportive analysis of rescue-free response, the difference in response rates relative to metformin was 7% greater for dulaglutide 1.5 mg (0.56 vs. 0.49) and 8% greater for dulaglutide 0.75 mg (0.57 vs 0.49). The nominal 95% CI for both comparisons included zero.

At week 52, dulaglutide 1.5 mg resulted in a statistically significant reduction in mean HbA1c compared to metformin; the estimated increased reduction was 0.19% with 95% CI (-0.35, -0.02). For dulaglutide 0.75 mg the estimated excess reduction was 0.04% with 95% CI (-0.20, 0.12) that includes zero but rules out the NI margin. Based on the prespecified testing strategy for HbA1c reduction at week 52, the high dose was superior and the low dose was non-inferior to metformin. The supportive analyses did not support the superiority conclusion for high dose dulaglutide to metformin as the 95% CI from the different analyses included zero.

The upper limit of the 95% CI from the missing data sensitivity analysis in all randomized subjects are displayed in the contour plots below (Figure 5); refer to Table 41 and Table 42 in Appendix A.3.2 for numerical results. The investigation suggests:

- The non-inferiority conclusion for both dulaglutide doses is not sensitive to missing data. This assessment is based on the sensitivity parameters explored all resulted in the upper 95% CI limit being below the prespecified NI margin (0.4%).
- The superiority of dulaglutide 1.5 mg to metformin is considered sensitive to missing data. Of concern is that for the upper 95% CI limit to exclude zero occurs only when the sensitivity parameter for the dulaglutide group is similar to or less than the sensitivity parameter for the metformin group. This implies that for findings to be no longer statistical significant only requires the mean HbA1c reduction in the metformin group with missing data to be slightly more favorable than the mean HbA1c reduction in the dulaglutide group with missing data. Because such a scenario is not inconceivable, the superiority finding is not considered robust with respect to missing data.
- The superiority of dulaglutide 0.75 mg to metformin is considered sensitive to missing data. The region of sensitivity parameters that leads to the 95% CI excluding zero occurs when the sensitivity parameter for the dulaglutide group is at least 0.5 units smaller than the sensitivity parameter for the metformin group. This is not viewed to provide robust support since it suggests that for statistical significance to hold requires the excess mean reduction HbA1c in the dulaglutide subgroup with missing data be at least 0.5% greater than control. Following the reasoning for the high dose, the superiority for dulaglutide 0.75 mg to metformin at week 26 is not considered robust with respect to missing data.

**Table 13. Change in HbA1c at Weeks 26, 52 (Trial GBDC)**

	Dulaglutide		Metformin
	0.75 mg	1.5 mg	
<b>Primary Analysis: ANCOVA-LprOCF</b>			
Adj. Mean Change (95% CI)			
Week 26	-0.71 (-0.82, -0.59)	-0.78 (-0.90, -0.66)	-0.56 (-0.68, -0.44)
Week 52	-0.55 (-0.69, -0.42)	-0.70 (-0.83, -0.56)	-0.51 (-0.65, -0.37)
Dulaglutide-Metformin (95% CI)			
Primary: Week 26	-0.15 (-0.29, -0.01)	-0.22 (-0.36, -0.08)	
p-value (1-sided): non-inferiority	< 0.001	< 0.001	
p-value (1-sided): superiority	0.02	0.001	
Secondary: Week 52	-0.04 (-0.20, 0.12)	-0.19 (-0.35, -0.02)	
p-value (1-sided): non-inferiority	< 0.001	< 0.001	
p-value (1-sided): superiority	0.299	0.0121	
<b>Supportive Analyses: Dulaglutide – Metformin (95% CI)</b>			
Week 26			
MMRM	-0.10 (-0.25, 0.05)	-0.21 (-0.36, -0.05)	
Week 26 assessment	-0.06 (-0.21, 0.08)	-0.16 (-0.30, -0.01)	
ANCOVA-LOCF	-0.12 (-0.26, 0.02)	-0.19 (-0.33, -0.05)	
Week 52			
MMRM	0.03 (-0.16, 0.22)	-0.17 (-0.36, 0.01)	
Week 52 assessment	0.08 (-0.10, 0.25)	-0.13 (-0.30, 0.04)	
ANCOVA-LOCF	-0.00 (-0.16, 0.16)	-0.14 (-0.30, 0.02)	

LprOCF-last pre-rescue observation carried forward

**Figure 4. Unadjusted means and difference in means across visits by last available observation (Trial GBDC)**

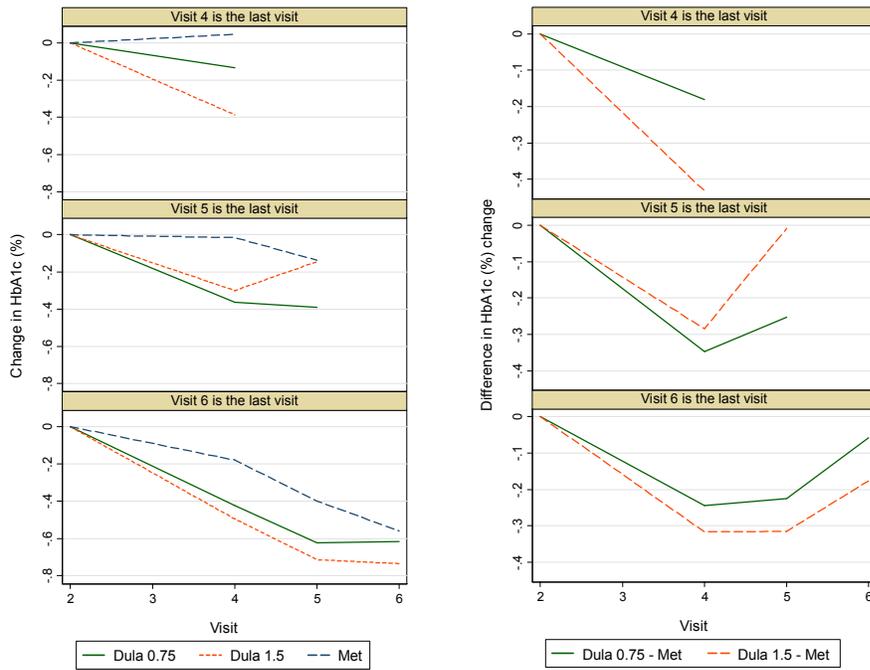
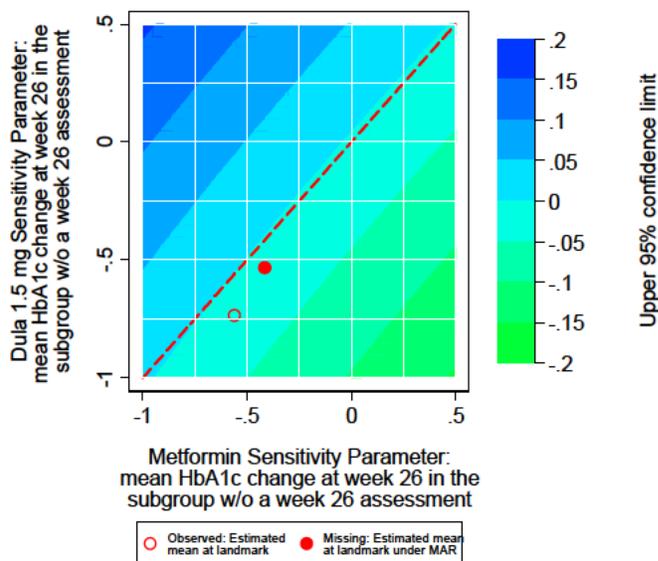
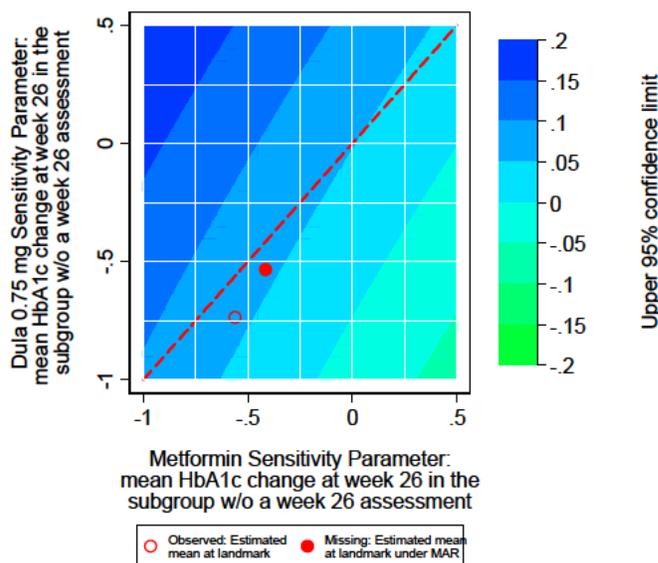


Figure 5. Missing data sensitivity analysis: contour plots of upper 95% CI limits (GBDC)

(a) High dose vs. Metformin at week 26



(b) Low dose vs. Metformin at week 26



### Secondary Endpoints

Weight: At weeks 26 and 52, all treatments groups had a reduction in average weight compared to baseline (Table 14). The difference in average weight loss was either similar or less favorable for the dulaglutide groups compared to metformin at weeks 26 and 52. For the two dulaglutide doses the high dose had a more favorable average reduction

**Fasting Serum Glucose:** At weeks 26 and 52, all treatments groups had a reduction in average fasting serum glucose compared to baseline (Table 14). Except for the comparison between dulaglutide 1.5 mg and metformin at week 52, there was no statistically significant difference between dulaglutides groups and metformin on this endpoint.

**Table 14. Analysis of Secondary Endpoints (GBDC, ANCOVA w/LOprCF)**

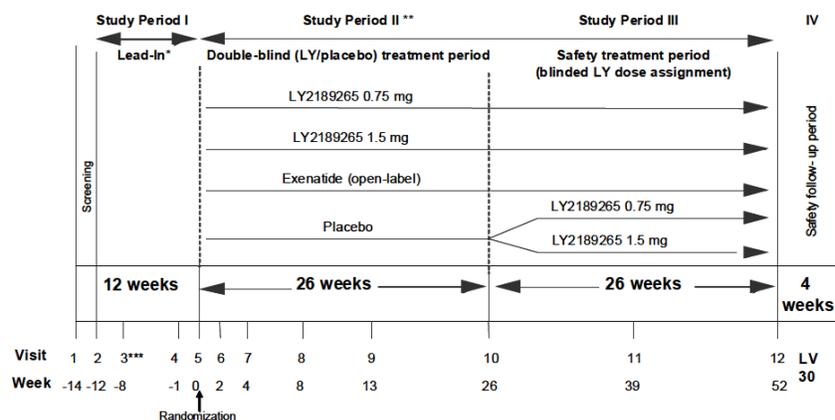
	Dulaglutide		Metformin
	0.75 mg	1.5 mg	
<b>Weight (kg)</b>			
Adj. Mean Change (95% CI)			
<b>Week 26</b>	-1.4 (-1.8, -0.9)	-2.3 (-2.8, -1.8)	-2.2 (-2.7, -1.7)
<b>Week 52</b>	-1.1 (-1.7, -0.5)	-1.9 (-2.5, -1.4)	-2.2 (-2.8, -1.6)
Dulaglutide - Metformin (95% CI)			
<b>Week 26</b>	0.9 (0.3, 1.4)	-0.1 (-0.6, 0.5)	
<b>Week 52</b>	1.1 (0.4, 1.8)	0.3 (-0.4, 0.9)	
<b>Fasting Serum Glucose (mmol/L)</b>			
Adj. Mean Change (95% CI)			
<b>Week 26</b>	-1.5 (-1.8, -1.2)	-1.6 (-1.9, -1.4)	-1.4 (-1.7, -1.1)
<b>Week 52</b>	-1.2 (-1.4, -0.9)	-1.6 (-1.9, -1.3)	-1.3 (-1.6, -1.0)
Dulaglutide - Metformin (95% CI)			
<b>Week 26</b>	-0.1 (-0.4, 0.2)	-0.2 (-0.5, 0.1)	
<b>Week 52</b>	0.1 (-0.2, 0.5)	-0.3 (-0.7, -0.0)	

### 3.2.1.3 Study H9X-MC-GBDA (Add-on to Metformin + Pioglitazone)

Study GBDA was a randomized, parallel-arm, partially blinded, placebo-controlled, active comparator study in patients treated with maximally tolerated concomitant OAM, metformin and pioglitazone. Additional study design elements are shown below. Subjects randomized to exenatide were (1) not blinded to therapy, and (2) to inject study drug subcutaneously starting at 5 mcg twice-daily for 4 weeks followed by 10 mcg twice daily. Subjects randomized to dulaglutide were to inject study drug subcutaneously once weekly. Subjects randomized to the placebo/dulaglutide sequence were to inject placebo subcutaneously once weekly for 26 weeks, followed by randomization (1:1 ratio) to either high or low dose dulaglutide.

**Figure 6. Trial GBDA Study Design**

Figure GBDA.1 illustrates the study design.



\*All patients start metformin and pioglitazone during the lead-in period and continue for the duration of the trial.  
 \*\* Study Period II for placebo patients will continue until the patient completes Visit 10; at that time, the patients on placebo will be randomized to either LY2189265 0.75 mg or 1.5 mg for the remainder of the trial.  
 \*\*\*The period between Visits 3 and 4 may be decreased to 1 week for patients already on stable, maximum doses of metformin and pioglitazone.

A total of 978 subjects in 99 centers in 3 countries were randomized in a 2:2:2:1 ratio to receive dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide, or the placebo/dulaglutide sequence. Randomization was stratified by country and baseline HbA1c ( $\leq 8.5\%$ ,  $> 8.5\%$ ).

The prespecified primary endpoint was change in HbA1c from baseline to week 26. The key secondary endpoint was change in HbA1c from baseline at 52 weeks. Table 15 lists the prespecified hypotheses and the tree-gatekeeping strategy to control the endpoint specific family-wise type-I error rate. The non-inferiority margin was prespecified as 0.4%.

**Table 15. Hypotheses for HbA1c change at week 26 (primary) and week 52 (secondary) for Trial GBDA**

Endpoint	Hypothesis	Prespecified rejection rule
Primary (wk 26)	PH1: Dula 1.5 mg SUP to PLA PH2: Dula 1.5 mg NI to EXEN PH3: Dula 0.75 mg SUP to PLA PH4: Dula 1.5 mg SUP to EXEN  PH5: Dula 0.75 mg NI to EXEN  PH6: Dula 0.75 mg SUP to EXEN	p-value $\leq$ 0.025 p-value $\leq$ 0.025 and H1 rejected p-value $\leq$ 0.02 and H2 rejected - p-value $\leq$ 0.0125, and H2 and H3 rejected, or - p-value $\leq$ 0.0051, H2 rejected and H3 not rejected - p-value $\leq$ 0.025, and H3 and H4 rejected, or - p-value $\leq$ 0.0065, H4 rejected and H3 not rejected - p-value $\leq$ 0.025, and H3, H4 and H5 rejected, or - p-value $\leq$ 0.0065, H4 and H5 rejected, and H3 is not rejected
Secondary (wk 52)	SH1: Dula 1.5 mg NI to EXEN SH2: Dula 0.75 mg NI to EXEN SH3: Dula 1.5 mg SUP to EXEN SH4: Dula 1.5 mg SUP to EXEN	p-value $\leq$ 0.025 p-value $\leq$ 0.0135 and SH1 rejected p-value $\leq$ 0.0135 and SH2 rejected - p-value $\leq$ 0.025, and SH2 and SH3 rejected, or - p-value $\leq$ 0.0135, SH2 rejected and SH3 not rejected

Dula-dulaglutide; EXEN-exenatide; PLA-placebo; SUP-superior; NI-non-inferior

### **3.2.1.3.1 Patient Disposition, Demographic and Baseline Characteristics**

Patient disposition is summarized in Table 16. All but two of the 978 randomized subjects received study drug; both patients were randomized to the open-label exenatide arm. By week 26, 8% of randomized subjects discontinued from the study. The discontinuation rate was reasonably similar for placebo, high dose dulaglutide and exenatide until about week 26 (Appendix A.2.3, Figure 15). Coinciding with transition from placebo to dulaglutide there was a notable jump in the rate of discontinuation, which was similar to the jump observed for the dulaglutide 1.5 mg arm at the beginning of the study. More subjects in the high dose dulaglutide group compared to the low dose group discontinued by week 26 due to an AE, with the majority of AEs belonging to gastrointestinal disorder MedDRA SOC (dulaglutide 1.5 mg, 6; dulaglutide 0.75 mg, 2). By week 26 all but four of the discontinuations occurred in subjects enrolled at US sites.

Select baseline and diabetes characteristics are summarized in Table 17. Subject characteristics were reasonably comparable across treatment groups at baseline.

**Table 16. Patient Disposition (Trial GBDA)**

	Dulaglutide		Placebo	Exenatide
	0.75 mg	1.5 mg		
Randomized	280	279	141	278
Randomized and received one dose of study medication	280	279	141	276
Discontinued study by week 26	17	19	17	24
<i>Adverse Event</i>	4	8	3	9
<i>Death</i>	1	1	0	0
<i>Entry Criteria Not Met</i>	0	3	0	0
<i>Lack of Efficacy</i>	0	1	3	1
<i>Lost to Follow-Up</i>	7	1	5	3
<i>Physician Decision</i>	1	1	0	0
<i>Protocol Violation</i>	1	0	1	0
<i>Sponsor Decision</i>	0	0	0	3
<i>Subject Decision</i>	3	3	5	8
<i>Treatment non-compliance</i>	0	1	0	0

**Table 17. Patient Baseline and Demographic Characteristics (Trial GBDA)**

	Dulaglutide		Placebo	Exenatide
	0.75 mg N=280	1.5 mg N=279		
<b>Age (years)</b>	56 (9)	56 (10)	54 (10)	55 (10)
Mean (SD)	20, 85	28, 81	21, 78	26, 79
Min, Max	44 (16%)	57 (20%)	23 (16%)	47 (17%)
≥ 65	56 (9)	56 (10)	54 (10)	55 (10)
<b>Gender: Males</b>	168 (60%)	163 (58%)	83 (59%)	156 (57%)
<b>Race:</b>				
White	207 (74%)	205 (73%)	103 (73%)	211 (76%)
Black	24 (9%)	24 (9%)	10 (7%)	18 (7%)
<b>Country: U.S.</b>	206 (74%)	211 (76%)	108 (77%)	212 (77%)
<b>Baseline HbA1c (%):</b>				
Mean (SD)	8.1 (1.2)	8.1 (1.3)	8.1 (1.3)	8.1 (1.3)
Min, Max	6.2, 13.0	6.3, 13.8	6.4, 11.9	6.3, 13.5
> 8.0%	116 (41%)	115 (41%)	58 (41%)	100 (36%)
<b>Baseline BMI: &lt; 30 kg/m<sup>2</sup></b>	87 (31%)	91 (33%)	45 (32%)	76 (28%)
<b>Duration Diabetes (yrs): mean (SD)</b>	8.8 (5.5)	8.8 (5.6)	8.9 (5.9)	8.6 (5.8)
<b>Weight (kg): mean (SD)</b>	96 (21)	96 (20)	98 (19)	94 (19)
<b>Fasting Serum Glucose (mmol/L): mean (SD)</b>	8.8 (2.8)	9.0 (3.1)	9.1 (3.1)	9.2 (3.0)
<b>Baseline creatinine clearance (mL/min)</b>				
< 30	0 (0%)	0 (0%)	1 (1%)	0 (0%)
30 to < 60	5 (2%)	3 (1%)	3 (2%)	1 (0%)
60 to < 90	49 (18%)	57 (20%)	33 (23%)	50 (18%)
≥ 90	226 (81%)	219 (78%)	104 (74%)	225 (82%)

### 3.2.1.3.2 Results and Conclusions

#### Change in HbA1c

Fifty-one subjects in the sponsor’s analysis population were excluded from the primary analysis (Table 18), with the majority excluded coming from the placebo arm. The majority of subjects (93%) had HbA1c assessed at the week 26 visit. However, due to the handling of rescue medication, the primary analysis had slightly fewer subjects (88%) with HbA1c assessed at the week 26 visit. Use of rescue across the study duration was similar for low dose dulaglutide and exenatide, both of which occurred more frequently than high dose dulaglutide (Appendix A.2.3, Figure 16).

**Table 18. Last available HbA1c assessment (Trial GBDA, primary endpoint)**

	Dulaglutide		Placebo N=141	Exenatide N=276
	0.75 mg N=280	1.5 mg N=279		
Included in sponsor’s analysis	269	271	119	266
Received rescue medication at or before week 26	14	4	22	13
LAFV (LAPrFV)				
Visit 6 – Week 2	0 (0)	1 (1)	2 (2)	2 (2)
Visit 7 – Week 4	0 (0)	0 (0)	2 (1)	1 (1)
Visit 8 – Week 8	0 (0)	1 (1)	0 (0)	2 (2)
Visit 9 – Week 13	13 (18)	9 (10)	8 (8)	12 (19)
Visit 10 – Week 26	264 (251)	263 (259)	127 (108)	255 (242)

LAFV-last available follow-up visit for primary endpoint

At week 26, both dulaglutide 1.5 mg and dulaglutide 0.75 mg resulted in a statistically significant reduction in mean HbA1c compared to both placebo and exenatide (Table 19). The estimated excess reduction compared to placebo was 1.05% (95% CI -1.22, -0.88) for dulaglutide 1.5 mg and 0.84% (95% CI = -1.01, -0.67) for dulaglutide 0.75 mg. Compared to exenatide, the excess reduction for dulaglutide 1.5 mg was 0.52% (95% CI = -0.66, -0.39) and 0.31% (95% CI = -0.44, -0.18) for dulaglutide 0.75 mg. Based on the prespecified testing strategy, both dulaglutide doses were superior to exenatide and placebo in HbA1c reduction at week 26.

For the prespecified comparison of dulaglutide doses, the high dose arm had an excess HbA1c reduction of 0.21% with 95% CI (-0.35, -0.08) that did not include zero.

The three supportive analyses supported the findings from the primary analysis. The comparison of rescue-free response rate also supported the above findings. The difference in rescue-free response rates relative to exenatide was 26% greater for dulaglutide 1.5 mg (73% vs. 47%) and 13% greater for dulaglutide 0.75 mg (60% vs. 47%). The difference in response rates relative to placebo was 39% greater for dulaglutide 1.5 mg (73% vs. 35%) and 26% greater for dulaglutide 0.75 mg (60% vs. 35%). Nominal 95% CI for these comparisons all excluded zero.

At week 52, both dulaglutide doses resulted in a statistically significant reduction in mean HbA1c compared to exenatide. The estimated excess reduction for dulaglutide 1.5 mg was

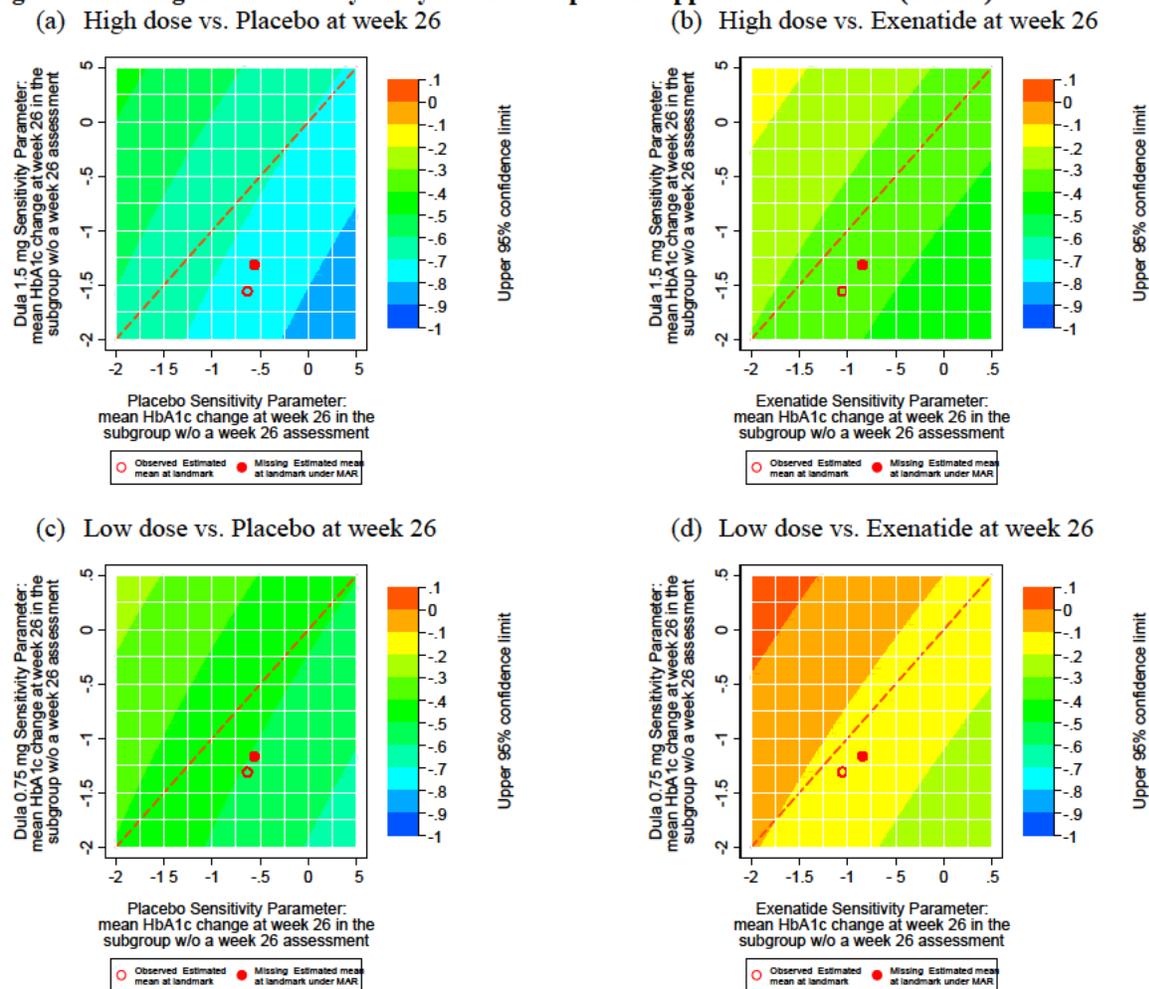
0.56% (95% CI = -0.73, -0.39) and 0.27% (95% CI = -0.44, -0.11) for dulaglutide 0.75 mg. Thus, based on the prespecified testing strategy the two dulaglutide doses were superior to exenatide in HbA1c reduction at week 52. The supportive analyses performed supported these findings.

Contour plots of the upper 95% CI limit from the missing data sensitivity analysis in all randomized subjects are displayed below (Figure 7); refer to Table 43 to Table 46 in Appendix A.3.3 for numerical results. In the plots the following was observed. In panels a, b, and c none of the sensitivity parameters resulted in the 95% CI including zero. In panel d, the comparison of low dose dulaglutide with exenatide, the 95% CI included zero when the sensitivity parameters imply that the exenatide group with missing data would have to have notably more favorable reductions in HbA1c than the dulaglutide group with missing data. From these observations I consider the superiority conclusions robust to missing data. In particular, the magnitude of the estimated treatment difference in the subgroup with week 26 data is substantial enough where the missing data scenarios that would lead to a different statistical conclusion are considered unlikely.

**Table 19. Change in HbA1c from Baseline at Weeks 26 and 52 (Trial GBDA)**

	Dulaglutide		Placebo	Exenatide
	0.75 mg	1.5 mg		
<b>Primary Analysis-ANCOVA w/LprOCF</b>				
Adj. Mean Change (95% CI)				
Week 26	-1.30 (-1.42, -1.18)	-1.51 (-1.63, -1.40)	-0.46 (-0.62, -0.30)	-0.99 (-1.11, -0.87)
Week 52	-1.07 (-1.22, -0.92)	-1.35 (-1.51, -1.21)	-	-0.80 (-0.94, -0.65)
Dulaglutide - Placebo (95% CI)				
Week 26	-0.84 (-1.01, -0.67)	-1.05 (-1.22, -0.88)		
p-value (1-sided): NI	< 0.001	< 0.001		
p-value (1-sided): SUP	< 0.001	< 0.001		
Dulaglutide - Exenatide (95% CI)				
Week 26	-0.31 (-0.44, -0.18)	-0.52 (-0.66, -0.39)		
p-value (1-sided): NI	< 0.001	< 0.001		
p-value (1-sided): SUP	< 0.001	< 0.001		
Week 52	-0.27 (-0.44, -0.11)	-0.56 (-0.73, -0.39)		
p-value (1-sided): NI	< 0.001	< 0.001		
p-value (1-sided): SUP	< 0.001	< 0.001		
<b>Supportive Analyses: Dulaglutide – Placebo (95% CI)</b>				
Week 26				
MMRM	-0.84 (-1.01, -0.66)	-1.06 (-1.23, -0.89)		
Week 26 assessment	-0.65 (-0.83, -0.48)	-0.88 (-1.06, -0.70)		
ANCOVA w/LOCF	-0.72 (-0.89, -0.55)	-0.92 (-1.09, -0.75)		
<b>Supportive Analyses: Dulaglutide – Exenatide (95% CI)</b>				
Week 26				
MMRM	-0.29 (-0.43, -0.16)	-0.52 (-0.65, -0.38)		
Week 26 assessment	-0.28 (-0.42, -0.14)	-0.51 (-0.65, -0.36)		
ANCOVA w/LOCF	-0.30 (-0.44, -0.16)	-0.50 (-0.64, -0.36)		
Week 52				
MMRM	-0.26 (-0.45, -0.07)	-0.58 (-0.76, -0.39)		
Week 52 assessment	-0.20 (-0.37, -0.02)	-0.45 (-0.63, -0.28)		
ANCOVA w/LOCF	-0.26 (-0.43, -0.09)	-0.50 (-0.68, -0.33)		

**Figure 7. Missing data sensitivity analysis: contour plots of upper 95% CI limits (GBDA)**



**Secondary Endpoints**

**Weight:** At weeks 26 and 52, dulaglutide 1.5 mg and exenatide treatment groups had a reduction in average weight compared to baseline (Table 20). At the nominal 5% alpha level, both dulaglutide groups had statistically significantly greater weight reduction relative to placebo at week 26. High dose dulaglutide had a slightly greater average weight reduction compared to exenatide at weeks 26 and 52.

**Fasting Serum Glucose:** At weeks 26 and 52, all treatments had a reduction in average fasting serum glucose compared to baseline (Table 20). At the nominal 5% alpha level, both dulaglutide groups had statistically significantly greater mean fasting serum glucose decrease relative to placebo at week 26, and to exenatide at weeks 26 and 52.

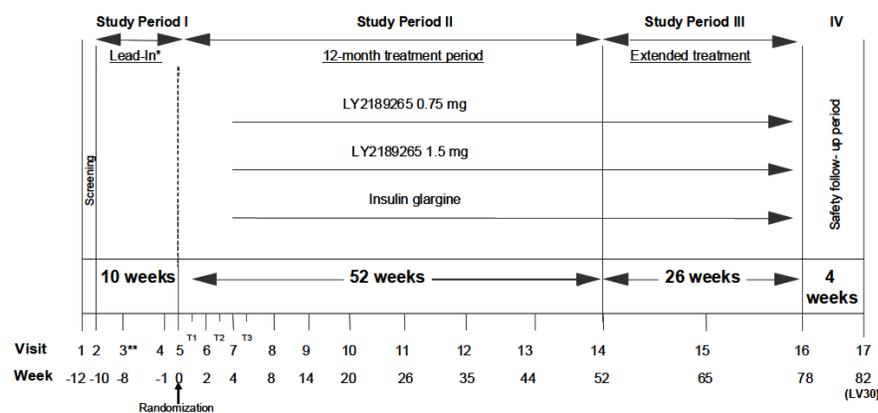
**Table 20. Analysis of Secondary Endpoints (GBDA, ANCOVA w/LOprCF)**

	Dulaglutide		Placebo	Exenatide
	0.75 mg	1.5 mg		
<b>Weight (kg)</b>				
Adj. Mean Change (95% CI)				
<b>Week 26</b>	0.2 (-0.4, 0.8)	-1.3 (-1.9, -0.7)	1.2 (0.5, 2.0)	-1.1 (-1.6, -0.5)
<b>Week 52</b>	0.5 (-0.2, 1.3)	-1.0 (-1.7, -0.3)		-0.7 (-1.4, 0.0)
Dulaglutide - Placebo (95% CI)				
<b>Week 26</b>	-1.0 (-1.8, -0.3)	-2.5 (-3.3, -1.8)		
Dulaglutide - Exenatide (95% CI)				
<b>Week 26</b>	1.3 (0.6, 1.9)	-0.2 (-0.9, 0.4)		
<b>Week 52</b>	1.3 (0.4, 2.1)	-0.3 (-1.1, 0.5)		
<b>Fasting Serum Glucose (mmol/L)</b>				
Adj. Mean Change (95% CI)				
<b>Week 26</b>	-1.9 (-2.2, -1.7)	-2.4 (-2.6, -2.1)	-0.7 (-1.0, -0.3)	-1.3 (-1.6, -1.0)
<b>Week 52</b>	-1.5 (-1.9, -1.2)	-1.9 (-2.3, -1.6)	-	-0.9 (-1.3, -0.6)
Dulaglutide - Placebo (95% CI)				
<b>Week 26</b>	-1.3 (-1.7, -0.9)	-1.7 (-2.1, -1.3)		
Dulaglutide - Exenatide (95% CI)				
<b>Week 26</b>	-0.7 (-1.0, -0.3)	-1.1 (-1.4, -0.8)		
<b>Week 52</b>	-0.6 (-1.0, -0.2)	-1.0 (-1.4, -0.6)		

### 3.2.1.4 Study H9X-MC-GBDB (Add-on to Metformin + Sulfonylurea)

Study GBDB was a randomized, open-label, parallel-arm, active comparator study performed outside the US in patients treated with maximally tolerated concomitant OAM, metformin and sulfonylurea. Additional study design elements are shown below. Subjects randomized to dulaglutide were to inject study drug subcutaneously once weekly. Subjects randomized to insulin glargine were to inject study drug subcutaneous once daily and titrate to target after week 4.

Figure 8. Trial GBDB Study Design



\*All patients start metformin and glimepiride during the lead-in period and continue for duration of trial.  
T1, T2, T3: On Weeks 1, 3, and 6, study sites will contact patients by phone per the Study Schedule of Events (Protocol Attachment GBDB.1).  
\*\*The period between Visits 3 and 4 may be decreased to 1 week for patients already on stable, maximum doses of metformin and glimepiride.

A total of 810 subjects in 87 centers in 20 countries outside the US were randomized in a 1:1:1 ratio to dulaglutide 1.5 mg, dulaglutide 0.75 mg or insulin glargine. Randomization was stratified by country and baseline HbA1c ( $\leq 8.5\%$ ,  $> 8.5\%$ ).

The primary endpoint was prespecified as HbA1c change from baseline at 52 weeks. Two key secondary endpoints were change in HbA1c from baseline to weeks 26 and 78. Table 21 lists the prespecified hypotheses for the primary endpoint and the tree-gatekeeping strategy to control the family-wise type-I error rate. Prespecified hypotheses for the secondary endpoints are not listed since the last hypothesis in the testing sequence was not statistically significant. Section 3.2.1 provides a discussion of the issues with the prespecified testing strategy. The NI margin was prespecified as 0.4%.

Table 21. Hypotheses for HbA1c change for Trial GBDB

Hypothesis	Rejection rule (one-sided p-value)
H1: Dula 1.5 mg NI to IGlar	p-value $\leq 0.025$
H2: Dula 0.75 mg NI to IGlar	p-value $\leq 0.0135$ and H1 rejected
H3: Dula 1.5 mg SUP to IGlar	p-value $\leq 0.0135$ and H1 rejected
H4: Dula 0.75 mg SUP to IGlar	- p-value $\leq 0.025$ , and H2 and H3 rejected, or - p-value $\leq 0.0135$ , H2 rejected and H3 not rejected

Dula-dulaglutide; IGlar-insulin glargine; SUP-superior; NI-non-inferior

### 3.2.1.4.1 Patient Disposition, Demographic and Baseline Characteristics

Prior to the study completion the sponsor found Site 504 (India) to have good clinical practice (GCP) non-compliance issues. The sponsor terminated the Site in May 2012 and notified FDA of this decision on July 12, 2012 (eCTD #304 submitted under IND 70390). The 27 individual enrolled in the Site are excluded from the sponsor's and this review.

All but three of the 810 subjects randomized received one dose of study medication; the three subjects that did not receive study drug were randomized to insulin glargine. By week 52, 9% randomized subjects discontinued from the study. While the frequency of discontinuation was relatively similar across treatment arms by week 52, discontinuations were more frequent shortly after randomization in the insulin glargine arm (Appendix A.2.4, Figure 17). For AEs associated with study discontinuation, there were numerically more in the high dose arm compared to the low dose arm belonging to the MedDRA SOC gastrointestinal disorders (4 vs. 2).

Select baseline and diabetes characteristics are summarized in Table 23. Subject characteristics were reasonably comparable across treatment groups at baseline.

**Table 22. Patient Disposition (Trial GBDB)**

	Dulaglutide		Insulin Glargine
	0.75 mg	1.5 mg	
Randomized	272	273	265
Randomized and received one dose of study medication	272	273	262
Discontinued study prior to week 52	20	25	25
<i>Adverse Event</i>	7	8	4
<i>Death</i>	0	0	2
<i>Entry Criteria Not Met</i>	2	3	1
<i>Lost to Follow-Up</i>	2	3	3
<i>Physician Decision</i>	1	1	3
<i>Protocol Violation</i>	2	0	1
<i>Subject Decision</i>	4	9	10
<i>Treatment non-compliance</i>	2	1	1

1- At or before week 52 (visit 14)

**Table 23. Patient Baseline and Demographic Characteristics (Trial GBDB)**

	Dulaglutide		Insulin Glargine N=262
	0.75 mg N=272	1.5 mg N=273	
<b>Age (years)</b>			
Mean (SD)	57 (9)	56 (10)	57 (9)
Min, Max	30, 77	27, 87	32, 79
≥ 65	51 (19%)	54 (20%)	56 (21%)
<b>Gender: Males</b>	136 (50%)	144 (53%)	134 (51%)
<b>Race:</b>			
White	193 (71%)	193 (71%)	184 (70%)
Black	1 (0%)	1 (0%)	2 (1%)
<b>Country: U.S.</b>	0 (0%)	0 (0%)	0 (0%)
<b>Baseline HbA1c (%):</b>			
Mean (SD)	8.1 (1.0)	8.2 (1.0)	8.1 (1.0)
Min, Max	6.6, 13.3	6.6, 12.5	6.6, 10.9
> 8.0%	129 (47%)	146 (53%)	126 (48%)
<b>Baseline BMI: &lt; 30 kg/m<sup>2</sup></b>	111 (41%)	121 (44%)	108 (41%)
<b>Duration Diabetes (yrs): mean (SD)</b>	9.3 (5.9)	9.1 (6.2)	8.9 (6.0)
<b>Weight (kg): mean (SD)</b>	86 (18)	85 (18)	88 (20)
<b>Fasting Serum Glucose (mmol/L): mean (SD)</b>	9.0 (2.7)	9.2 (2.7)	9.1 (2.7)
<b>Baseline creatinine clearance (mL/min)</b>			
< 30	0 (0%)	0 (0%)	1 (0%)
30 to < 60	4 (1%)	4 (1%)	2 (1%)
60 to < 90	55 (20%)	58 (21%)	48 (18%)
≥ 90	213 (78%)	211 (77%)	211 (81%)

### 3.2.1.4.2 Results and Conclusions

#### Change in HbA1c

Twenty-one randomized subjects were excluded from the sponsor's primary analysis. Due to the primary analysis using last available follow-up visit, Table 24 displays last the visit which HbA1c was available. The majority of randomized subjects (91%) had HbA1c assessed at week 52. However, due to the handling of rescue medication, the primary analysis included notably fewer subjects (86%) with HbA1c assessed at the week 52 visit. An imbalance in rescue medication use was observed across treatment groups, with the frequency being notably greater in the dulaglutide groups (**Appendix A.2.4**, Figure 18).

**Table 24. Last available HbA1c assessment (Trial GBDB, primary endpoint)**

	Dulaglutide		Insulin Glargine N=265
	0.75 mg N=272	1.5 mg N=273	
Included in sponsor's analysis	267	263	259
Received rescue medication at or before week 52	29	15	8
LAFV (LAPrFV before rescue)			
<i>Visit 9 – Week</i>	8 (12)	6 (7)	14 (14)
<i>Visit 11 – Week</i>	1 (9)	9 (11)	2 (6)
<i>Visit 12 – Week</i>	2 (8)	0 (3)	0 (3)
<i>Visit 13 – Week</i>	7 (12)	2 (4)	5 (6)
<i>Visit 14 – Week 52</i>	251 (226)	250 (238)	238 (230)

LAFV-last available follow-up visit for primary endpoint

At week 52, dulaglutide 1.5 mg resulted in a statistically significant reduction in mean HbA1c change compared to insulin glargine (diff = -0.45%; 95% CI = -0.60, -0.29). The excess reduction in HbA1c for dulaglutide 0.75 mg was not statistically significant but ruled-out the prespecified NI margin (diff = -0.13%; 95% CI = -0.29, 0.02). Based on the prespecified testing strategy high dose dulaglutide was superior and low dose dulaglutide was non-inferior to insulin glargine in HbA1c reduction at week 52.

For the prespecified comparison between the two dulaglutide doses, the high dose had an excess reduction of 0.32% with 95% CI (-0.47, -0.16) that did not include zero.

The week 52 findings were not categorically supported by the three supportive analyses. The ANCOVA model using LOCF (not LOprCF) showed the excess reduction for low dose dulaglutide was statistically significant while the two other analyses did not. The superiority finding for dulaglutide 1.5 mg is supported by differences in rescue-free response rate. The comparative response rate was 20% greater for dulaglutide 1.5 mg (0.49 vs. 0.28) with 95% CI (0.12, 0.28). For low dose dulaglutide the difference in the response rate was 6% greater for dulaglutide 0.75 mg (0.34 vs. 0.28) with 95% CI (-0.02, 0.14).

The findings from the week 52 analysis were generally supported by the exploratory analysis of HbA1c change at weeks 26 and 78. Statistical testing at these two time points was not performed since dulaglutide 0.75 mg was not superior to insulin glargine at week 52.

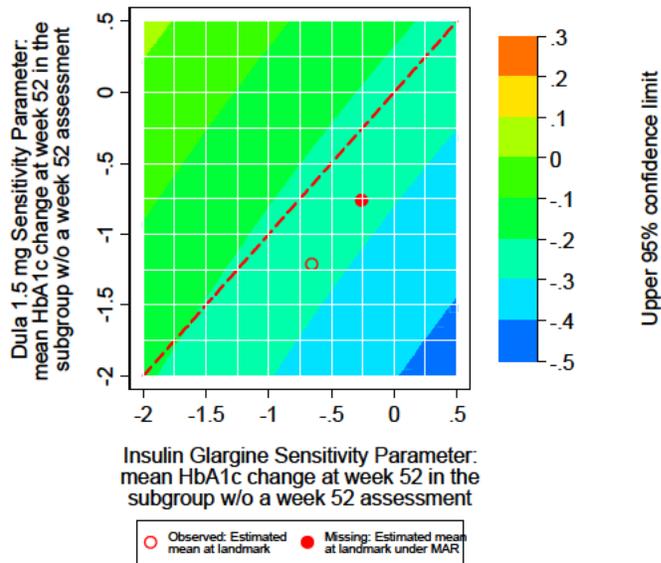
Contour plots of the upper 95% CI limit from the missing data sensitivity analysis in all randomized subjects are displayed below (Figure 9); refer to Table 47 and Table 48 in Appendix A.3.4 for numerical results. For low dose dulaglutide (panel b) none of the configurations of the sensitivity parameters investigated resulted in the 95% CI including the prespecified NI margin. For high dose dulaglutide the 95% CI included zero when the sensitivity parameters imply that the insulin glargine group with missing data would have to have notably more favorable reductions in HbA1c than the dulaglutide group with missing data. From these observations I consider the superiority conclusion for high dose and the NI conclusion for low dose are robust to missing data. In particular, the magnitude of the estimated treatment difference in subjects with week 52 data is substantial enough where the missing data scenarios that would lead to a different conclusion are considered unlikely.

**Table 25. Change in HbA1c at Weeks 26, 52, and 78 (Trial GBDB)**

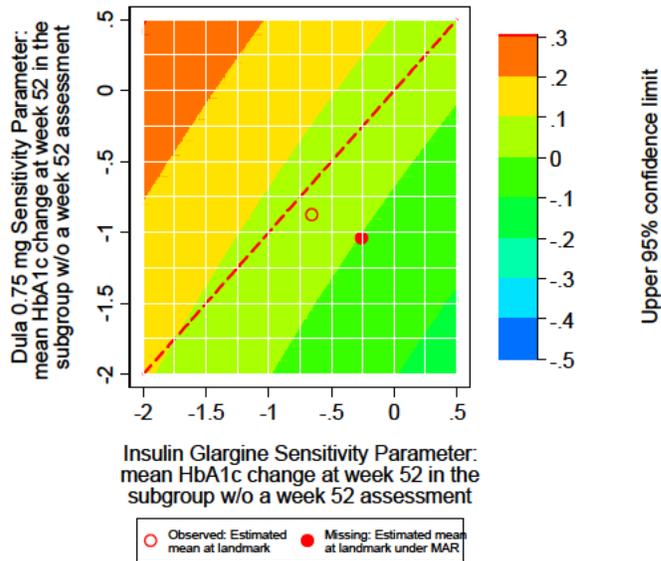
	Dulaglutide		Insulin Glargine
	0.75 mg	1.5 mg	
<b>Primary Analysis Model: ANCOVA w/LprOCF</b>			
Adj. Mean Change (95% CI)			
Week 26	-0.89 (-1.00, -0.78)	-1.16 (-1.27, -1.05)	-0.65 (-0.76, -0.54)
Week 52 (primary endpoint)	-0.76 (-0.88, -0.64)	-1.08 (-1.20, -0.96)	-0.63 (-0.75, -0.51)
Week 78	-0.62 (-0.76, -0.48)	-0.90 (-1.04, -0.76)	-0.59 (-0.73, -0.44)
Dulaglutide-Insulin Glargine (95% CI)			
Week 26	-0.24 (-0.38, -0.10)	-0.51 (-0.65, -0.37)	
Week 52 (primary endpoint)	-0.13 (-0.29, 0.02)	-0.45 (-0.60, -0.29)	
p-value (1-sided): non-inferiority	< 0.001	< 0.001	
p-value (1-sided): superiority	0.05	< 0.001	
Week 78	-0.03 (-0.21, 0.15)	-0.31 (-0.50, -0.13)	
<b>Supportive Analyses: Dulaglutide – Insulin Glargine (95% CI)</b>			
Week 26			
MMRM	-0.24 (-0.38, -0.10)	-0.51 (-0.65, -0.37)	
Week 26 assessment	-0.24 (-0.38, -0.10)	-0.19 (-0.63, -0.35)	
ANCOVA w/LOCF	-0.25 (-0.38, -0.11)	-0.50 (-0.64, -0.36)	
Week 52			
MMRM-LprO	-0.13 (-0.29, 0.03)	-0.46 (-0.62, -0.29)	
Week 52 assessment	-0.12 (-0.28, 0.04)	-0.42 (-0.58, -0.27)	
ANCOVA w/LOCF	-0.16 (-0.31, -0.01)	-0.43 (-0.59, -0.28)	
Week 78			
MMRM	-0.02 (-0.22, 0.18)	-0.33 (-0.53, -0.14)	
Week 78 assessment	-0.05 (-0.23, 0.14)	-0.32 (-0.51, -0.13)	
ANCOVA w/LOCF	-0.08 (-0.26, 0.10)	-0.31 (-0.49, -0.13)	

**Figure 9. Missing data sensitivity analysis: contour plots of upper 95% CI limits (GBDB)**

(a) High dose vs. Insulin Glargine at week 52



(b) Low dose vs. Insulin Glargine at week 52



### **Secondary Endpoints**

**Weight:** At weeks 26 and 52, only the dulaglutide treatment groups had a reduction in average weight compared to baseline (Table 26). The average weight reduction in the two dulaglutide groups was about 2.8 kg greater than for insulin glargine; this difference was statistically significant at the nominal 5% level.

**Fasting Serum Glucose:** At weeks 26 and 52, all treatments groups had a reduction in average fasting serum glucose compared to baseline (Table 26). The reduction was greater for insulin glargine compared dulaglutide 0.75 mg at the two follow-up visits, and similar to the reduction for the high dose dulaglutide.

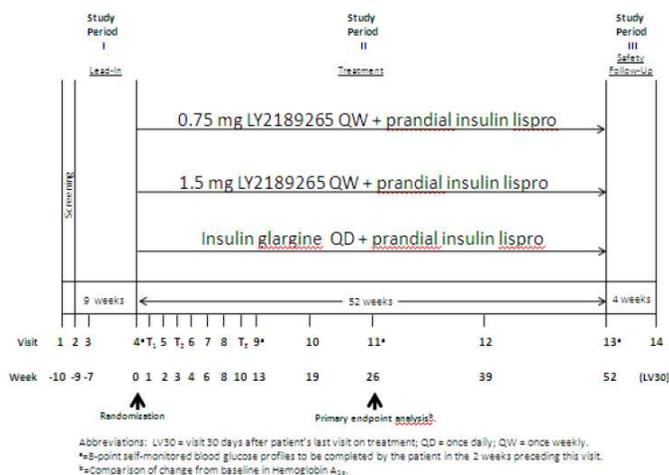
**Table 26. Analysis of Secondary Endpoints (GBDB, ANCOVA w/LOprCF)**

	Dulaglutide		Insulin Glargine
	0.75 mg	1.5 mg	
<b>Weight (kg)</b>			
Adj. Mean Change (95% CI)			
Week 26	-1.5 (-1.9, -1.1)	-1.8 (-2.2, -1.4)	1.0 (0.6, 1.4)
Week 52	-1.3 (-1.8, -0.9)	-1.9 (-2.3, -1.4)	1.4 (1.0, 1.9)
Dulaglutide – Insulin Glargine (95% CI)			
Week 26	-2.5 (-3.0, -2.0)	-2.8 (-3.3, -2.3)	
Week 52	-2.8 (-3.4, -2.2)	-3.3 (-3.9, -2.7)	
<b>Fasting Serum Glucose (mmol/L)</b>			
Adj. Mean Change (95% CI)			
Week 26	-1.1 (-1.4, -0.8)	-1.7 (-2.0, -1.4)	-1.6 (-1.9, -1.3)
Week 52	-0.9 (-1.2, -0.6)	-1.5 (-1.7, -1.2)	-1.7 (-2.0, -1.4)
Dulaglutide – Insulin Glargine (95% CI)			
Week 26	0.5 (0.1, 0.8)	-0.1 (-0.5, 0.3)	
Week 52	0.9 (0.5, 1.2)	0.3 (-0.1, 0.6)	

### 3.2.1.5 Study H9X-MC-GBDD (Add-on to Insulin Lispro)

Study GBDD was a 52 week, randomized, parallel-arm, open label with double-blind assignment to experimental drug dose, active comparator study in combination with insulin lispro with or without metformin. Additional study design elements are shown below. Subjects randomized to receive dulaglutide were (1) blinded to the dose, and (2) to inject the study drug subcutaneously once weekly. Subjects randomized to insulin glargine were to inject the study drug subcutaneously once daily at night, initiated at 50% of the pre-randomization total daily insulin dose and could be titrated. Insulin lispro doses could be adjusted based on a prespecified algorithm.

Figure 10. Trial GBDD Study Design



A total of 884 subjects in 105 centers in 16 countries were randomized in a 1:1:1 ratio to receive dulaglutide 1.5 mg, dulaglutide 0.75 mg, or insulin glargine. Randomization was stratified by country and metformin use at baseline.

The primary endpoint was prespecified as HbA<sub>1c</sub> change from baseline at 26 weeks. The key secondary endpoint was change in HbA<sub>1c</sub> from baseline to week 52. Table 27 lists the prespecified hypotheses and the tree-gatekeeping strategy to control the family-wise type-I error rate. The non-inferiority margin was prespecified as 0.4%.

**Table 27. Hypotheses for HbA1c change for Trial GBDD**

Endpoint	Hypothesis	Rejection rule (one-sided p-value)
Primary (Wk 26)	PH1: Dula 1.5 mg NI to IGlar PH2: Dula 0.75 mg NI to IGlar PH3: Dula 1.5 mg SUP to IGlar PH4: Dula 0.75 mg SUP to IGlar	p-value $\leq$ 0.025 p-value $\leq$ 0.0135 and PH1 rejected p-value $\leq$ 0.0135 and PH1 rejected - p-value $\leq$ 0.025, and PH2 and PH3 rejected, or - p-value $\leq$ 0.0135, PH2 rejected and PH3 not rejected
Secondary (Wk. 52)	SH1: Dula 1.5 mg NI to IGlar SH2: Dula 0.75 mg NI to IGlar SH3: Dula 1.5 mg SUP to IGlar SH4: Dula 0.75 mg SUP to IGlar	p-value $\leq$ 0.025 p-value $\leq$ 0.0135 and SH1 rejected p-value $\leq$ 0.0135 and SH1 rejected - p-value $\leq$ 0.025, and SH2 and SH3 rejected, or - p-value $\leq$ 0.0135, SH2 rejected and SH3 not rejected

Dula-dulaglutide; IGlar-insulin glargine; SUP-superior; NI-non-inferior

### 3.2.1.5.1 Patient Disposition, Demographic and Baseline Characteristics

Prior to the study completion the sponsor found Site 100 (Argentina) to have GCP non-compliance issues. The sponsor terminated the Site in February 2012 and notified FDA of this decision on September 17, 2012 (eCTD #314 submitted under IND 70390). The 19 individual enrolled in the Site are excluded from the sponsor's and this review.

Patient disposition is summarized in Table 28. All 884 subjects that were randomized received at least one dose of study medication. By week 26 the dulaglutide 1.5 mg group had the greatest frequency of discontinuations; this trend was relatively consistent throughout the 52 week treatment phase (**Appendix A.2.5**, Figure 19Error! Reference source not found.). The excess discontinuations by week 26 in the high dose versus low dose dulaglutide arm can be attributed the imbalance in AEs (21 vs. 11), where the majority were classified under the gastrointestinal disorder MedDRA SOC (11 vs. 7). The rate of discontinuation was almost twice as great in US sites (20% vs. 11%).

Select baseline and diabetes characteristics are summarized in Table 29. Subject characteristics were reasonably comparable across treatment groups at baseline.

**Table 28. Patient Disposition (Trial GBDD)**

	Dulaglutide		Insulin Glargine
	0.75 mg	1.5 mg	
Randomized	293	295	296
Randomized and received one dose of study medication	293	295	296
Discontinued study prior to week 26	38	47	40
<i>Adverse Event</i>	11	21	6
<i>Death</i>	1	0	0
<i>Entry Criteria Not Met</i>	1	3	1
<i>Lost to Follow-Up</i>	3	6	7
<i>Physician Decision</i>	5	3	9
<i>Protocol Violation</i>	0	1	1
<i>Sponsor Decision</i>	1	0	0
<i>Subject Decision</i>	16	13	16

**Table 29. Patient Baseline and Demographic Characteristics (Trial GBDD) excluding Site 100**

	Dulaglutide		
	0.75 mg N=293	1.5 mg N=295	Insulin Glargine N=296
<b>Age (years)</b>			
Mean (SD)	59 (9)	58 (10)	59 (9)
Min, Max	36, 82	28, 79	34, 83
≥ 65	78 (27%)	78 (26%)	90 (30%)
<b>Gender: Males</b>	148 (51%)	160 (54%)	165 (56%)
<b>Race:</b>			
White	235 (80%)	231 (78%)	231 (78%)
Black	27 (9%)	32 (11%)	26 (9%)
<b>Country: U.S.</b>	95 (32%)	103 (35%)	96 (32%)
<b>Baseline HbA1c (%):</b>	n=291	n=293	n=291
Mean (SD)	8.4 (1.0)	8.5 (1.1)	8.5 (1.0)
Min, Max	6.3, 13.0	6.0, 12.8	6.3, 12.0
> 8.0%	173 (59%)	182 (62%)	194 (66%)
<b>Baseline BMI: &lt; 30 kg/m<sup>2</sup></b>	89 (30%)	112 (38%)	104 (35%)
<b>Duration Diabetes (yrs): mean (SD)</b>	12.4 (6.9)	12.8 (7.2)	13.0 (6.8)
<b>Weight (kg): mean (SD)</b>	92 (18)	91 (18)	91 (19)
<b>Fasting Serum Glucose (mmol/L): mean (SD)</b>	8.4 (2.8)	8.7 (3.0)	8.5 (3.1)
<b>Baseline creatinine clearance (mL/min)</b>			
< 30	0 (0%)	2 (1%)	0 (0%)
30 to < 60	42 (14%)	34 (12%)	54 (18%)
60 to < 90	157 (54%)	163 (55%)	163 (55%)
≥ 90	94 (32%)	96 (33%)	79 (27%)

### 3.2.1.5.2 Results and Conclusions

#### Change in HbA1c

Sixty randomized subjects were excluded from the primary analysis; nine of these subjects had a missing baseline HbA1c measurement. Due to the primary analysis using last available follow-up visit, Table 30 displays the last visit which HbA1c was available. The majority of randomized subjects (88%) had HbA1c assessed at week 26. Subjects in US sites were less likely to have a week 26 HbA1c assessment (83% vs. 91%). Due to the handling of rescue medication, the primary analysis had fewer subjects (86%) with HbA1c assessed at the week 26 visit. While the frequency of rescue was relatively similar across treatment arms by week 52, rescue use occurred more frequently shortly after randomization in the high dose dulaglutide arm (**Appendix A.2.5**, Figure 20Error! Reference source not found.).

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**Table 30. Last Available HbA1c assessment (Trial GBDD, primary endpoint)**

	Dulaglutide		Insulin Glargine N=296
	0.75 mg N=293	1.5 mg N=295	
Included in sponsor's analysis	275	273	276
Received rescue medication at or before week 52	12	13	13
LAFV (LAFV before rescue)			
<i>Visit 5 – Week</i>	0 (0)	0 (1)	0 (0)
<i>Visit 9 – Week</i>	20 (24)	24 (20)	21 (22)
<i>Visit 11 – Week 26</i>	280 (251)	258 (252)	261 (254)

At week 26, both dulaglutide 1.5 mg and dulaglutide 0.75 mg resulted in a statistically significant reduction in mean HbA1c compared to insulin glargine (Table 31). The estimated excess reduction for dulaglutide 1.5 mg was 0.22% (95% CI = -0.38, -0.07) and 0.17% (95% CI = -0.33, -0.02) for dulaglutide 0.75 mg. Based on the prespecified testing strategy, both dulaglutide doses were superior to insulin glargine in HbA1c reduction at week 26.

The week 26 findings were not categorically supported by the three supportive analyses. The ANCOVA model with LOCF showed the excess reduction for low dose dulaglutide was not statistically significant while the two other analyses did. The superiority findings are supported by differences in the rescue-free response rate; compared to control, the response rate was 11% greater for dulaglutide 1.5 mg (0.61 vs. 0.50) with 95% CI (0.03, 0.19) and 13% greater for dulaglutide 0.75 mg (0.63 vs. 0.50) with 95% CI (0.05, 0.21).

For the comparison of the two dulaglutide doses the estimated HbA1c reduction was reasonably similar between treatment groups; the estimated excess HbA1c reduction was 0.05% greater for the high dose group with 95% CI (-0.21, 0.11).

At week 52, both dulaglutide 1.5 mg and dulaglutide 0.75 mg resulted in a statistically significant reduction in mean HbA1c compared to insulin glargine. The estimated excess reduction for dulaglutide 1.5 mg was 0.25% (95% CI = -0.42, -0.07) and 0.19% (95% CI = -0.37, -0.02) for dulaglutide 0.75 mg. Based on the prespecified testing strategy, both dulaglutide doses were superior to insulin glargine in HbA1c reduction at week 52. These conclusions were supported by the supportive analyses.

Contour plots of the upper 95% CI limit from the missing data sensitivity analysis in all randomized subjects with a baseline HbA1c value are displayed below (Figure 11); refer to Table 49 and Table 50 in Appendix A.3.5 for numerical results. The investigation suggest:

- The non-inferiority conclusion for both dulaglutide doses is not sensitive to missing data. This conclusion was based on the sensitivity parameters explored all resulted in the upper 95% confidence limit being below the NI margin (0.4%).
- The superiority finding for dulaglutide 0.75 mg is considered sensitive to missing data. Of concern is that for the 95% CI limit excludes when the sensitivity parameter for the dulaglutide group is similar to or less than the sensitivity parameter for the metformin group. This implies that for findings to be no longer statistical significant only requires the mean HbA1c reduction in the insulin glargine to be slightly more favorable than the mean HbA1c reduction in the dulaglutide group with missing data. Because such a

scenario is not inconceivable, the superiority finding is not considered robust with respect to missing data.

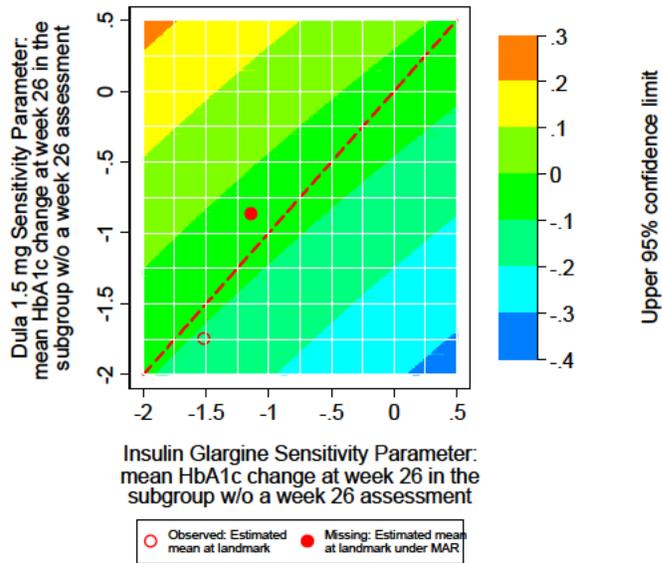
- While not considered robust, there is reasonable support that the superiority conclusion for high dose dulaglutide is not impacted by missing data. This assessment is supported by the 95% CI for would still exclude zero if the dulaglutide subgroup with missing data had moderately less favorable HbA1c reductions than the insulin glargine group with missing data.

**Table 31. Change in HbA1c at Weeks 26, 52 (Trial GBDD)**

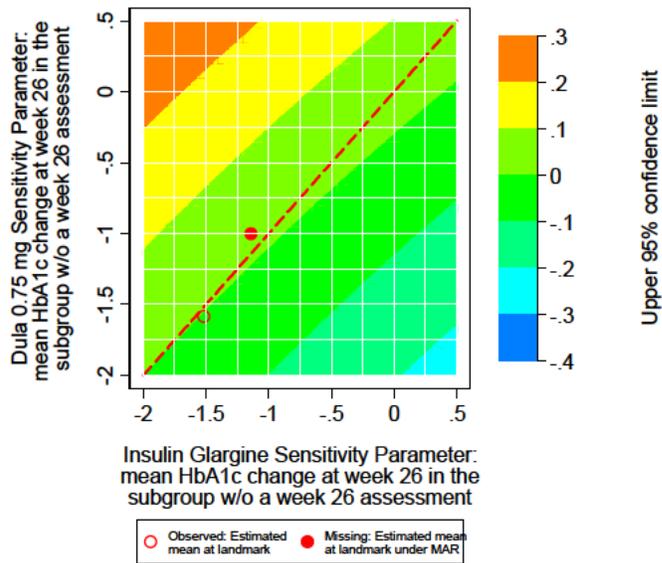
	Dulaglutide		Insulin Glargine
	0.75 mg	1.5 mg	
<b>Primary Analysis Model: ANCOVA w/LprOCF</b>			
Adj. Mean Change (95% CI)			
Week 26 (primary endpoint)	-1.59 (-1.72, -1.45)	-1.64 (-1.77, -1.50)	-1.41 (-1.55, -1.28)
Week 52	-1.42 (-1.57, -1.27)	-1.48 (-1.63, -1.33)	-1.23 (-1.38, -1.08)
Dulaglutide-Insulin Glargine (95% CI)			
Week 26 (primary endpoint)	-0.17 (-0.33, -0.02)	-0.22 (-0.38, -0.07)	
p-value (1-sided): non-inferiority	< 0.001	< 0.001	
p-value (1-sided): superiority	0.015	0.003	
Week 52	-0.19 (-0.37, -0.02)	-0.25 (-0.42, -0.07)	
p-value (1-sided): non-inferiority	< 0.001	< 0.001	
p-value (1-sided): superiority	0.014	0.003	
<b>Supportive Analyses: Dulaglutide – Insulin Glargine (95% CI)</b>			
Week 26			
MMRM	-0.17 (-0.33, -0.01)	-0.23 (-0.39, -0.07)	
Week 26 assessment	-0.18 (-0.34, -0.03)	-0.26 (-0.41, -0.10)	
ANCOVA w/LOCF	-0.13 (-0.29, 0.03)	-0.19 (-0.35, -0.03)	
Week 52			
MMRM	-0.21 (-0.39, -0.02)	-0.27 (-0.46, -0.08)	
Week 52 assessment	-0.22 (-0.40, -0.04)	-0.32 (-0.50, -0.13)	
ANCOVA w/LOCF	-0.18 (-0.36, -0.00)	-0.23 (-0.41, -0.06)	

**Figure 11. Missing data sensitivity analysis: contour plots of upper 95% CI limits (GBDD)**

(a) High dose vs. Insulin Glargine at week 26



(b) Low dose vs. Insulin Glargine at week 26



### **Secondary Endpoints**

**Weight:** At weeks 26 and 52, only the high dose dulaglutide treatment group had a reduction in average weight compared to baseline (Table 32). The weight loss reduction was respectively about 2kg and 3kg greater for the low dose and high dulaglutide groups compared to insulin glargine; these differences were statistically significant at the nominal 5% level.

**Fasting Serum Glucose:** At both weeks 26 and 52, only insulin glargine had a reduction in average fasting serum glucose compared to baseline (Table 32). The reduction was greater statistically significantly greater for insulin glargine compared to the two dulaglutide groups.

**Table 32. Analysis of Secondary Endpoints (GBDD, ANCOVA w/LOprCF)**

	Dulaglutide		Insulin Glargine
	0.75 mg	1.5 mg	
<b>Weight (kg)</b>			
Adj. Mean Change (95% CI)			
Week 26	0.2 (-0.3, 0.7)	-0.9 (-1.4, -0.3)	2.3 (1.8, 2.9)
Week 52	0.9 (0.2, 1.5)	-0.3 (-1.0, 0.3)	2.9 (2.2, 3.5)
Dulaglutide – Insulin Glargine (95% CI)			
Week 26	-2.1 (-2.8, -1.5)	-3.2 (-3.8, -2.6)	
Week 52	-2.0 (-2.8, -1.3)	-3.2 (-4.0, -2.5)	
<b>Fasting Serum Glucose (mmol/L)</b>			
Adj. Mean Change (95% CI)			
Week 26	0.2 (-0.2, 0.7)	-0.3 (-0.7, 0.2)	-1.7 (-2.1, -1.2)
Week 52	0.5 (0.1, 1.0)	0.2 (-0.3, 0.7)	-1.2 (-1.7, -0.7)
Dulaglutide – Insulin Glargine (95% CI)			
Week 26	1.9 (1.4, 2.4)	1.4 (0.9, 1.9)	
Week 52	1.7 (1.2, 2.3)	1.4 (0.9, 1.9)	

### 3.3 Evaluation of Safety

This section summarizes by trial the frequency of documented symptomatic and severe hypoglycemic events (Table 33).

The reader is referred to the following reviews for additional safety evaluations. The Meta-analyses on cardiovascular events was reviewed by Dr. Janelle Charles from the Division of Biometrics VII. Other safety events were reviewed by Dr. Suchitra Balakrishnan of the Division of Metabolism and Endocrinology Products.

Across trials there is no consistent trend between dulaglutide dose and hypoglycemic events. There was no consistent trend across trials in the frequency of events for dulaglutide relative to active control. Compared to exenatide in trial GBDA and to insulin glargine in trial GBDB, the frequency of hypoglycemic event was less in the dulaglutide arms. In the other trials the frequency was relatively similar in the experimental and control arms.

**Table 33. Documented symptomatic and severe hypoglycemic events**

	<b>Dula 0.75 mg N = 281</b>	<b>Dula 1.5 mg N=279</b>	<b>Sitagliptin N=273</b>	<b>Placebo N=139</b>
<b>GBCF: MET add-on</b>				
Documented Symptomatic: Week 26	7 (2.5%)	14 (5.0%)	7 (2.6%)	1 (0.7%)
Documented Symptomatic: Week 52	11 (3.9%)	23 (8.2%)	9 (3.3%)	4 (2.9%)
Severe: Week 26	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe: Week 52	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>GBDC: Monotherapy</b>	<b>Dula 0.75 mg N=270</b>	<b>Dula 1.5 mg N=269</b>	<b>Metformin N=268</b>	-
Documented Symptomatic: Week 26	13 (4.8%)	9 (3.3%)	10 (3.7%)	-
Documented Symptomatic: Week 52	16 (5.9%)	17 (6.3%)	13 (4.9%)	-
Severe: Week 26	0 (0%)	0 (0%)	0 (0%)	-
Severe: Week 52	0 (0%)	0 (0%)	0 (0%)	-
<b>GBDA: MET+PIO Add-on</b>	<b>Dula 0.75 mg N=280</b>	<b>Dula 1.5 mg N=279</b>	<b>Exenatide N=276</b>	<b>Placebo N=141</b>
Documented Symptomatic: Week 26	13 (4.6%)	14 (5.0%)	31 (11.2%)	2 (1.4%)
Documented Symptomatic: Week 52	17 (6.1%)	18 (6.5%)	37 (13.4%)	-
Severe: Week 26	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Severe: Week 52	0 (0%)	0 (0%)	2 (0.7%)	-
<b>GBDB: MET+SU Add-on</b>	<b>Dula 0.75 mg N=272</b>	<b>Dula 1.5 mg N=273</b>	<b>IGlar* N=265</b>	-
Documented Symptomatic: Week 26	89 (32.7%)	82 (30.0%)	101 (38.1%)	-
Documented Symptomatic: Week 52	102 (37.5%)	103 (37.7%)	123 (46.4%)	-
Severe: Week 26	0 (0%)	1 (0.4%)	1 (0.4%)	-
Severe: Week 52	0 (0%)	1 (0.4%)	2 (0.8%)	-
<b>GBDD: Insulin Lispro add-on</b>	<b>Dula 0.75 mg N=293</b>	<b>Dula 1.5 mg N=295</b>	<b>IGlar* N=296</b>	-
Documented Symptomatic: Week 26	242 (82.6%)	228 (77.3%)	243 (82.1%)	-
Documented Symptomatic: Week 52	250 (85.3%)	235 (79.7%)	247 (83.4%)	-
Severe: Week 26	5 (1.7%)	6 (2.0%)	11 (3.7%)	-
Severe: Week 52	7 (2.4%)	10 (3.4%)	15 (5.1%)	-

\*IGlar- Insulin Glargine

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### **Dulaglutide compared to control**

Comparison of the primary efficacy endpoint in subpopulations is summarized by individual trials in Table 34 and Table 35.

The factors considered for the subgroup analyses include intrinsic factors (age, sex, BMI, Race, and region) and disease-related factors (baseline HbA1c). A disease-related factor that is of interest, baseline renal function, was not investigated as the trials randomized studied a very small number of subjects with mild renal function.

Subgroup analysis on HbA1c was conducted using the ANCOVA model used for the primary analysis. Effect estimates were obtained from the model being fit to the individual levels that defined the subgroup. Tests for statistical interactions were performed using the primary ANCOVA model for each combination pair of experimental and control therapies; subjects in arms not being tested were excluded from the analysis. The analysis was performed separately for each trial.

In trials GBDC and GBDB no statistical treatment-by-subgroup interaction was observed at the nominal 5% level. In trial GBDD there was a statistical interaction between high dose dulaglutide and race, where the comparative decrease in HbA1c was greater in non-whites compared to whites (-0.6% vs. -0.1%). The importance of this interaction is unclear. In two other studies that also had a treatment by race interaction, GBCF (each dulaglutide dose with sitagliptin) and GBDA (high dulaglutide dose with exenatide; the low dose was borderline statistically significant, p-value = 0.07), the non-whites compared to the whites did not categorically have more favorable HbA1c reductions. In trial GBCF there was a statistical interaction between baseline HbA1c for both sitagliptin and placebo with the two dulaglutide doses, where comparative reduction in HbA1c was greater in subjects with higher baseline values. A statistical interaction for this factor was also observed in trial GBDA for the comparisons between both dulaglutide doses and placebo. However, the importance of this interaction is unclear since there was not a clear trend of more favorable HbA1c reduction in the group with high HbA1c levels across trials.

### **High dose dulaglutide compared to low dose dulaglutide**

Comparison of the primary efficacy endpoint in subgroups investigated about for the two dulaglutide doses is summarized in Table 36. Subgroup analysis on change in HbA1c at week 26 and week 52 were investigated for the two dulaglutide doses. Data from the five studies were pooled. Effect estimates were obtained from the ANCOVA model with study identifier, baseline HbA1c, and treatment as covariates fit to the individual levels that defined the subgroup. Tests for statistical interactions were performed using the ANCOVA model described above with terms for the factor and treatment-by-factor interactions.

No statistical interaction between the factors investigated and dulaglutide dose was found from the integrated analysis at the nominal 5% level.

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**Table 34. Subgroup analysis comparing dulaglutide to control (Trials GBDC, GBDB, and GBDD)**

	GBDC at Wk. 26		GBDB at Wk. 52		GBDD at Wk. 26	
	Low-Met	High-Met	Low-IGlar	High-IGlar	Low-IGlar	High-IGlar
<b>Factor: Level</b>						
Sex: Females	-0.2 (-0.4, 0.0)	-0.3 (-0.4, -0.1)	-0.3 (-0.5, -0.0)	-0.6 (-0.8, -0.3)	-0.3 (-0.5, -0.1)	-0.2 (-0.5, -0.0)
Sex: Males	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.0)	-0.0 (-0.3, 0.2)	-0.4 (-0.6, -0.1)	-0.1 (-0.3, 0.2)	-0.2 (-0.4, 0.0)
Age: ≤ 65 years	-0.2 (-0.3, 0.0)	-0.2 (-0.4, -0.1)	-0.1 (-0.3, 0.0)	-0.4 (-0.6, -0.2)	-0.2 (-0.4, 0.0)	-0.2 (-0.4, -0.0)
Age: > 65 years	-0.0 (-0.3, 0.3)	-0.1 (-0.4, 0.2)	-0.1 (-0.4, 0.2)	-0.6 (-0.9, -0.2)	-0.2 (-0.4, 0.1)	-0.3 (-0.5, 0.0)
Race: White	-0.2 (-0.3, -0.0)	-0.2 (-0.4, -0.1)	-0.0 (-0.2, 0.1)	-0.4 (-0.6, -0.2)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.0)
Race: non-White	-0.1 (-0.5, 0.3)	-0.2 (-0.6, 0.2)	-0.3 (-0.7, -0.0)	-0.6 (-0.9, -0.2)	-0.4 (-0.8, -0.0)	-0.6 (-1.0, -0.2)
Region: US	-0.1 (-0.3, 0.1)	-0.1 (-0.4, 0.1)	NA	NA	0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.2)
Region: non-US	-0.1 (-0.3, 0.0)	-0.2 (-0.4, -0.1)	NA	NA	-0.3 (-0.4, -0.1)	-0.3 (-0.5, -0.1)
HbA1c: ≤ 8.5%	-0.1 (-0.3, 0.0)	-0.2 (-0.4, -0.1)	-0.2 (-0.4, -0.0)	-0.5 (-0.7, -0.3)	-0.2 (-0.3, 0.0)	-0.2 (-0.4, -0.0)
HbA1c: > 8.5%	-0.1 (-0.6, 0.4)	0.0 (-0.5, 0.6)	-0.0 (-0.3, 0.3)	-0.4 (-0.7, -0.0)	-0.3 (-0.5, 0.0)	-0.2 (-0.5, 0.1)
BMI: ≤ 30	-0.1 (-0.4, 0.2)	-0.0 (-0.3, 0.3)	-0.3 (-0.6, -0.0)	-0.5 (-0.8, -0.3)	-0.3 (-0.6, -0.0)	-0.3 (-0.6, -0.0)
BMI: > 30	-0.2 (-0.3, 0.0)	-0.3 (-0.5, -0.1)	0.0 (-0.2, 0.2)	-0.3 (-0.5, -0.1)	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.0)

**Table 35. Subgroup analysis comparing dulaglutide to control (Trials GBCF and GBDA)**

	GBCF (Pla at Wk. 26, Sita at Wk. 52)				GBDA at Wk. 26			
	Low-Pla	High-Pla	Low-Sita	High-Sita	Low-Pla	High-Pla	Low-Exen	High-Exen
<b>Factor: Level</b>								
Sex: Females	-0.9 (-1.2, -0.6)	-1.1 (-1.4, -0.8)	-0.4 (-0.7, -0.2)	-0.7 (-0.9, -0.5)	-0.9 (-1.2, -0.7)	-1.2 (-1.4, -0.9)	-0.4 (-0.6, -0.2)	-0.7 (-0.9, -0.5)
Sex: Males	-1.1 (-1.4, -0.9)	-1.3 (-1.5, -1.1)	-0.6 (-0.8, -0.3)	-0.7 (-0.9, -0.5)	-0.8 (-1.0, -0.6)	-0.9 (-1.2, -0.7)	-0.3 (-0.4, -0.1)	-0.4 (-0.6, -0.2)
Age: ≤ 65 years	-1.1 (-1.3, -0.9)	-1.3 (-1.5, -1.1)	-0.5 (-0.7, -0.3)	-0.7 (-0.9, -0.6)	-0.9 (-1.0, -0.7)	-1.1 (-1.3, -0.9)	-0.3 (-0.5, -0.2)	-0.6 (-0.7, -0.4)
Age: > 65 years	-0.8 (-1.3, -0.4)	-0.9 (-1.3, -0.4)	-0.4 (-0.8, 0.0)	-0.5 (-0.9, -0.1)	-0.7 (-1.1, -0.3)	-0.8 (-1.2, -0.5)	-0.2 (-0.5, 0.1)	-0.4 (-0.6, -0.1)
Race: White	-1.0 (-1.2, -0.7)	-1.1 (-1.4, -0.9)	-0.6 (-0.9, -0.4)	-0.9 (-1.1, -0.7)	-0.9 (-1.1, -0.7)	-1.1 (-1.3, -0.9)	-0.2 (-0.4, -0.1)	-0.5 (-0.6, -0.3)
Race: non-White	-1.1 (-1.4, -0.9)	-1.3 (-1.6, -1.1)	-0.3 (-0.6, -0.1)	-0.5 (-0.8, -0.3)	-0.7 (-1.0, -0.3)	-0.9 (-1.2, -0.6)	-0.5 (-0.8, -0.2)	-0.7 (-1.0, -0.5)
Region: US	-1.4 (-1.7, -1.0)	-1.4 (-1.8, -1.1)	-0.6 (-1.0, -0.3)	-0.8 (-1.1, -0.4)	-0.9 (-1.1, -0.7)	-1.1 (-1.3, -0.9)	-0.3 (-0.5, -0.2)	-0.5 (-0.6, -0.3)
Region: non-US	-0.9 (-1.1, -0.7)	-1.2 (-1.4, -1.0)	-0.5 (-0.7, -0.3)	-0.7 (-0.9, -0.5)	-0.5 (-0.9, -0.2)	-1.0 (-1.4, -0.7)	-0.3 (-0.6, 0.0)	-0.8 (-1.1, -0.5)
HbA1c: ≤ 8.5%	-0.9 (-1.0, -0.7)	-1.0 (-1.2, -0.8)	-0.4 (-0.6, -0.2)	-0.5 (-0.7, -0.4)	-0.7 (-0.9, -0.6)	-0.9 (-1.1, -0.8)	-0.3 (-0.4, -0.2)	-0.5 (-0.6, -0.4)
HbA1c: > 8.5%	-1.5 (-1.9, -1.1)	-1.8 (-2.2, -1.4)	-0.8 (-1.2, -0.4)	-1.1 (-1.5, -0.7)	-1.2 (-1.7, -0.8)	-1.5 (-2.0, -1.0)	-0.3 (-0.7, -0.0)	-0.6 (-0.9, -0.3)
BMI: ≤ 30	-1.1 (-1.4, -0.8)	-1.3 (-1.6, -1.0)	-0.5 (-0.7, -0.3)	-0.7 (-0.9, -0.5)	-0.8 (-1.1, -0.5)	-1.0 (-1.3, -0.7)	-0.5 (-0.8, -0.3)	-0.6 (-0.9, -0.4)
BMI: > 30	-1.0 (-1.2, -0.7)	-1.2 (-1.4, -0.9)	-0.5 (-0.7, -0.2)	-0.7 (-0.9, -0.5)	-0.9 (-1.1, -0.6)	-1.1 (-1.3, -0.9)	-0.2 (-0.4, -0.1)	-0.5 (-0.6, -0.3)

**Table 36. Subgroup analysis comparing high dose and low dose dulaglutide**  
**High Dose – Low Dose**

	Week 26	Week 52
<b>Factor: Level</b>		
Sex: Females	-0.2 (-0.3, -0.1)	-0.2 (-0.3, -0.1)
Sex: Males	-0.2 (-0.3, -0.1)	-0.2 (-0.3, -0.1)
Age: ≤ 65 years	-0.2 (-0.3, -0.1)	-0.2 (-0.3, -0.1)
Age: > 65 years	-0.1 (-0.2, 0.1)	-0.2 (-0.3, -0.0)
Race: White	-0.1 (-0.2, -0.1)	-0.2 (-0.3, -0.1)
Race: non-White	-0.2 (-0.4, -0.1)	-0.2 (-0.4, -0.0)
Region: US	-0.1 (-0.2, 0.0)	-0.1 (-0.3, -0.0)
Region: non-US	-0.2 (-0.3, -0.1)	-0.3 (-0.3, -0.2)
HbA1c: ≤ 8.5%	-0.1 (-0.2, -0.1)	-0.2 (-0.3, -0.1)
HbA1c: > 8.5%	-0.2 (-0.4, -0.1)	-0.2 (-0.4, -0.1)
BMI: ≤ 30	-0.1 (-0.2, -0.0)	-0.1 (-0.3, -0.0)
BMI: > 30	-0.2 (-0.3, -0.1)	-0.3 (-0.3, -0.2)

## 5 SUMMARY AND CONCLUSIONS

The primary study endpoint was change in HbA1c from baseline to either week 26 (GBDC, GBDA, and GBDD) or week 52 (GBDB and GBCF). Two doses of dulaglutide were investigated. The high dose achieved statistically significantly better HbA1c change than placebo and to the active controls evaluated. The low dose achieved statistically significantly better HbA1c change than placebo and to the active-controls except insulin glargine in GBDB, where it was non-inferior.

A sensitivity analysis on the potential impact of missing data on the ITT effect for the primary study endpoints was performed. This investigation revealed (1) the NI findings across trials were not impacted by missing data, and (2) the superiority conclusion was impacted for select trials and dulaglutide doses. Trials and comparison that are not considered robust to missing data are: low dose dulaglutide vs. insulin glargine, and both dulaglutide doses vs. metformin.

High dose dulaglutide consistently had greater estimated reductions in HbA1c than the low dose dulaglutide. The excess reduction ranged from 0.05% to 0.32%, and the nominal 95% CI for the comparison excluded zero in three trials (GBDB, GBCF, and GBDA). The high dose was also associated with an excess number of study discontinuations due to an adverse event (AE), primarily related to gastrointestinal disorders.

The main statistical issues in this submission are:

- The primary endpoint that was analyzed is not consistent with the endpoint that was prespecified. The endpoint analyzed is the change in HbA1c from baseline to earliest of the following: the landmark visit, or the initiation of rescue. This endpoint may not be clinically meaningful for a subjects
- The primary analysis excluded a subset of the randomized population that did not have at least one post-baseline assessment, leading to the possibility that the comparisons do not preserve the integrity of randomization. The percentage of randomized patients excluded ranged across trials from 1.1% to 6.8%.
- The prespecified testing strategy does not control the study-wise type-I error at 5%. The problem is that testing of the secondary endpoints was not incorporated into the testing sequence/hierarchy used to test the primary and key secondary objectives. In trial GBDB the testing of the secondary endpoints could not be done since the last hypothesis test in the sequence for the primary endpoint was not statistically significant.

## **A. Appendices**

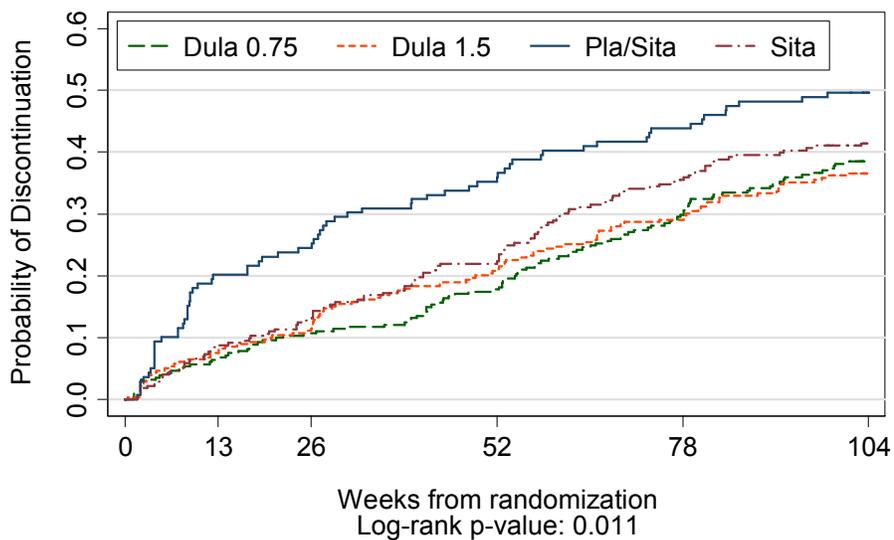
### **A.1 Missing data sensitivity analysis**

This section provides formal details of the missing data sensitivity analysis based on MI. Following Carpnter et al. (*Multiple Imputation and its Application* 2013. New York: Wiley), missing response data is imputed under MAR from multivariate normal regression model with using covariates included from the primary ANCOVA model. Imputed values were subsequently shifted so that the distribution of imputed values would be centered at the sensitivity parameter. The imputation was performed on all randomized subjects or a smaller subset that still preserved the integrity of randomization. A total of 50 imputed datasets were created. The regression estimates and standard errors from the primary ANCOVA model fit to the experimental and control pairing are combined based on Rubin's method. The analysis is repeated for the different experimental and control pairings. Findings for the different sensitivity parameters are presented as contour plots, which represents the upper 95% CI limit as a color. For reference the plots also include the estimated mean HbA1c change at the primary landmark visit for subjects with (observed) and without (missing) an HbA1c measurement at that visit; the mean at the landmark for those that did not have a landmark assessment is estimated from the MI datasets under the MAR assumption.

## A.2 Additional Plots

### A.2.1 Trial GBCF

Figure 12. Kaplan-Meier plot of time-to-study discontinuation (GBCF)



Number at risk		0	13	26	52	78	104
Dula 0.75	281	263	251	231	197	139	
Dula 1.5	279	258	248	221	198	127	
Pla/Sita	139	111	105	90	78	58	
Sita	273	250	238	213	176	122	

### A.2.2 Trial GBDC

Figure 13. Kaplan-Meier plot of time-to-study discontinuation (GBDC)

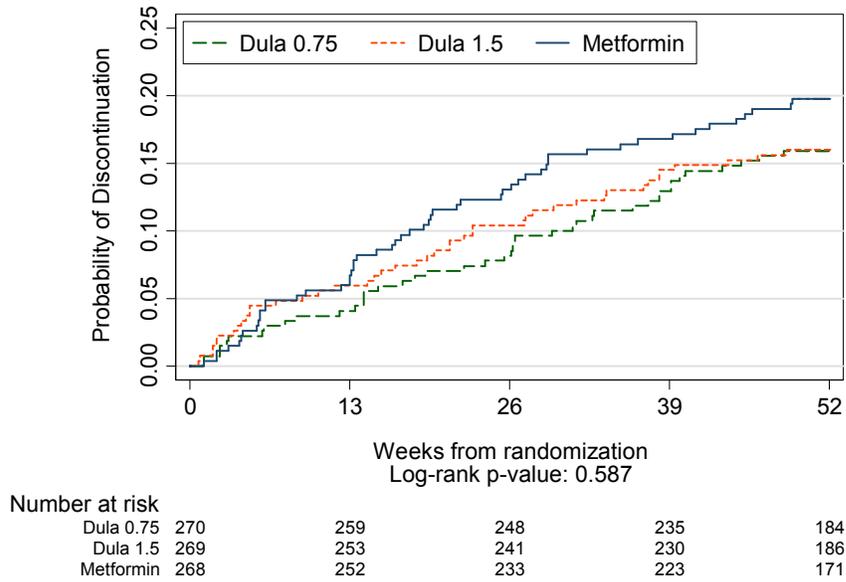
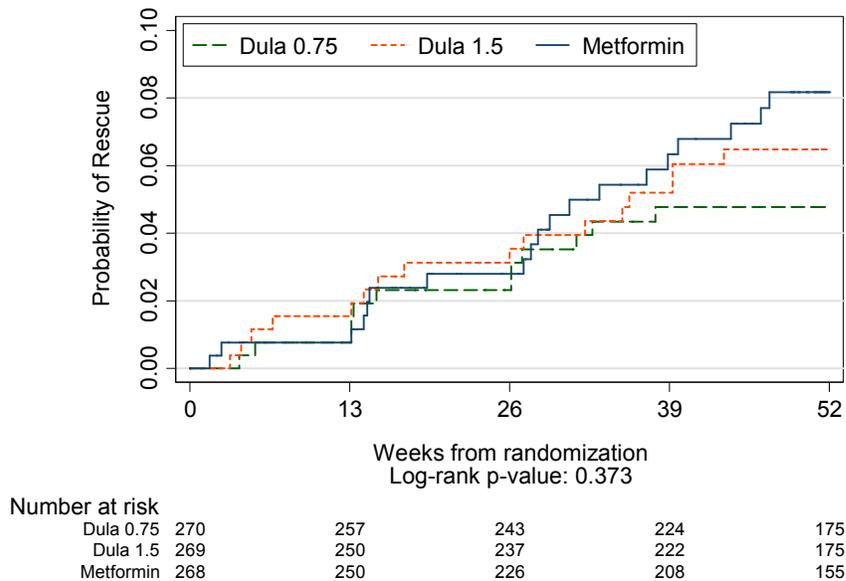
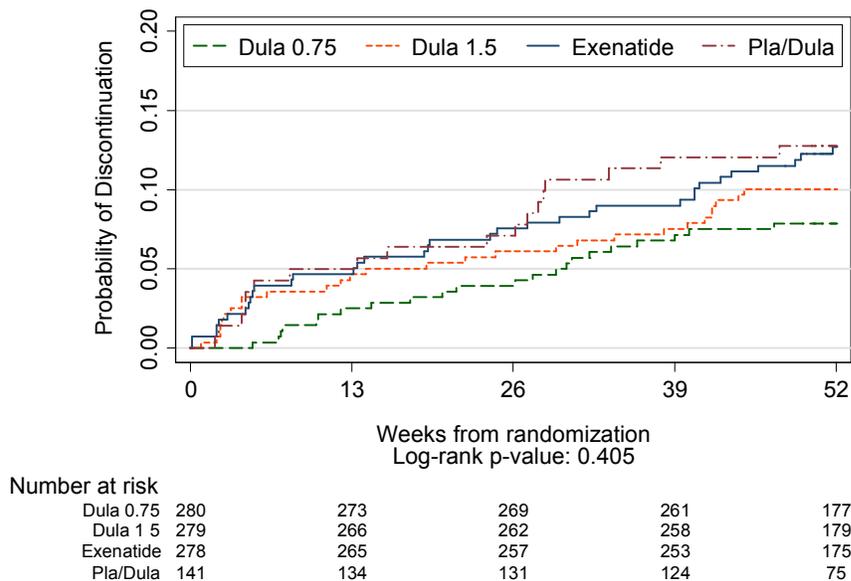


Figure 14. Kaplan-Meier plot of time-to-rescue (GBDC)

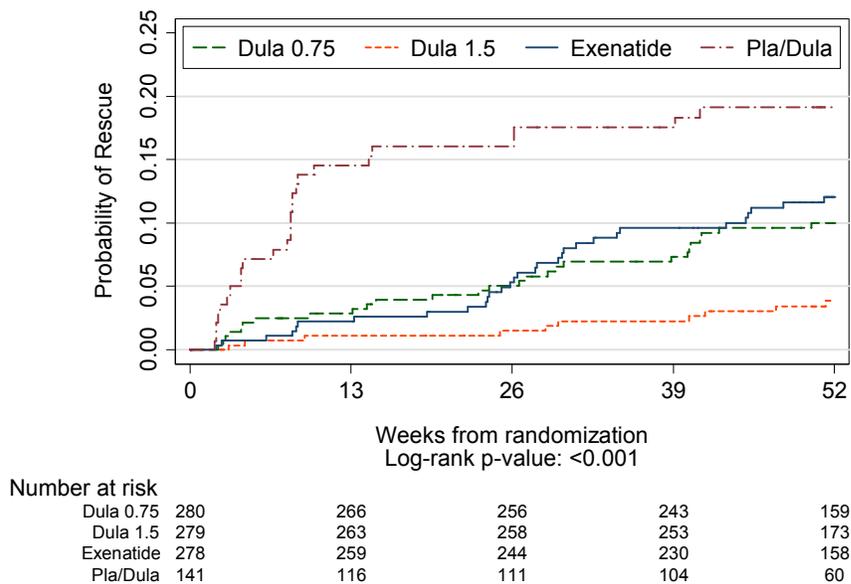


### A.2.3 Trial GBDA

**Figure 15. Kaplan-Meier plot of time-to-study discontinuation (GBDA)**



**Figure 16. Kaplan-Meier plot of time-to-rescue (GBDA)**



### A.2.4 Trial GBDB

Figure 17. Kaplan-Meier plot of time-to-study discontinuation (GBDB)

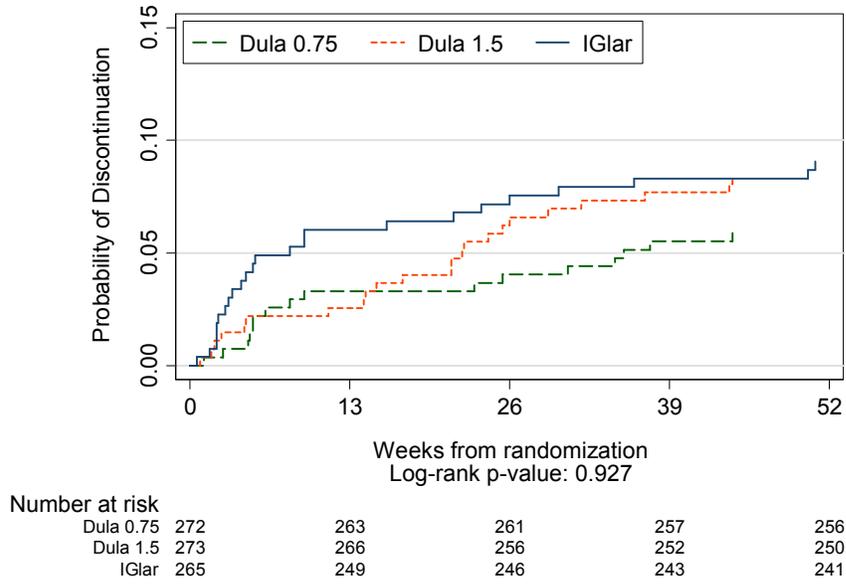
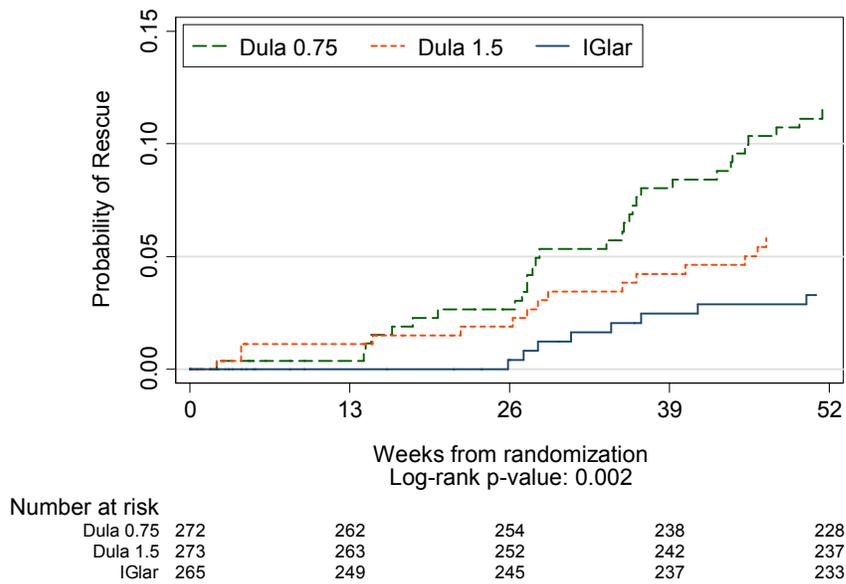


Figure 18. Kaplan-Meier plot of time-to-rescue (GBDB)



### A.2.5 Trial GBDD

Figure 19. Kaplan-Meier plot of time-to-study discontinuation (GBDD)

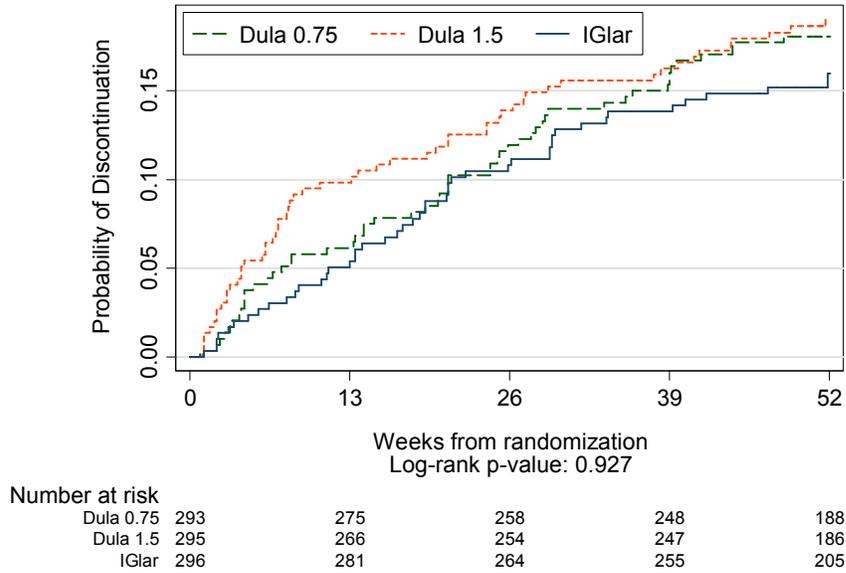
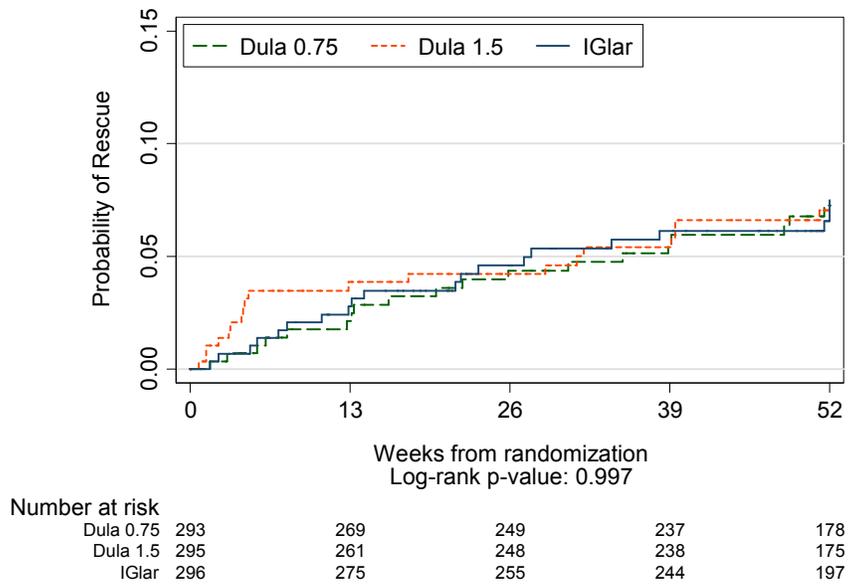


Figure 20. Kaplan-Meier plot of time-to-rescue (GBDD)



### A.3 Additional Tables

#### A.3.1 Trial GBCF

**Table 37. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 1.5 mg to placebo (GBCF)**

		Placebo Sensitivity Parameter:																									
		Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1.0	-0.9	-0.8	-0.7	-0.6	-0.5	-0.4	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.4	0.5
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	0.5	-0.31	-0.33	-0.36	-0.38	-0.4	-0.43	-0.45	-0.47	-0.49	-0.52	-0.54	-0.56	-0.58	-0.6	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.78	-0.8	-0.82	-0.84	-0.86
	0.4	-0.32	-0.35	-0.37	-0.39	-0.42	-0.44	-0.46	-0.48	-0.51	-0.53	-0.55	-0.57	-0.6	-0.62	-0.64	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.81	-0.83	-0.85	-0.87
	0.3	-0.34	-0.36	-0.38	-0.41	-0.43	-0.45	-0.47	-0.5	-0.52	-0.54	-0.56	-0.59	-0.61	-0.63	-0.65	-0.67	-0.7	-0.72	-0.74	-0.76	-0.78	-0.8	-0.82	-0.84	-0.87	-0.89
	0.2	-0.35	-0.37	-0.4	-0.42	-0.44	-0.46	-0.49	-0.51	-0.53	-0.56	-0.58	-0.6	-0.62	-0.64	-0.67	-0.69	-0.71	-0.73	-0.75	-0.77	-0.79	-0.82	-0.84	-0.86	-0.88	-0.9
	0.1	-0.36	-0.39	-0.41	-0.43	-0.45	-0.48	-0.5	-0.52	-0.55	-0.57	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.74	-0.76	-0.79	-0.81	-0.83	-0.85	-0.87	-0.89	-0.91
	0	-0.38	-0.4	-0.42	-0.44	-0.47	-0.49	-0.51	-0.54	-0.56	-0.58	-0.6	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8	-0.82	-0.84	-0.86	-0.88	-0.9	-0.92
	-0.1	-0.39	-0.41	-0.43	-0.46	-0.48	-0.5	-0.53	-0.55	-0.57	-0.59	-0.62	-0.64	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.81	-0.83	-0.85	-0.87	-0.9	-0.92	-0.94
	-0.2	-0.4	-0.42	-0.45	-0.47	-0.49	-0.52	-0.54	-0.56	-0.58	-0.61	-0.63	-0.65	-0.67	-0.69	-0.72	-0.74	-0.76	-0.78	-0.8	-0.82	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95
	-0.3	-0.41	-0.44	-0.46	-0.48	-0.51	-0.53	-0.55	-0.57	-0.6	-0.62	-0.64	-0.66	-0.69	-0.71	-0.73	-0.75	-0.77	-0.79	-0.82	-0.84	-0.86	-0.88	-0.9	-0.92	-0.94	-0.96
	-0.4	-0.43	-0.45	-0.47	-0.5	-0.52	-0.54	-0.56	-0.59	-0.61	-0.63	-0.65	-0.68	-0.7	-0.72	-0.74	-0.76	-0.78	-0.81	-0.83	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95	-0.97
	-0.5	-0.44	-0.46	-0.48	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.64	-0.67	-0.69	-0.71	-0.73	-0.75	-0.78	-0.8	-0.82	-0.84	-0.86	-0.88	-0.9	-0.92	-0.95	-0.97	-0.99
	-0.6	-0.45	-0.47	-0.5	-0.52	-0.54	-0.57	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.74	-0.77	-0.79	-0.81	-0.83	-0.85	-0.87	-0.89	-0.92	-0.94	-0.96	-0.98	-1
	-0.7	-0.46	-0.49	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8	-0.82	-0.84	-0.86	-0.89	-0.91	-0.93	-0.95	-0.97	-0.99	-1.01
	-0.8	-0.47	-0.5	-0.52	-0.54	-0.57	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79	-0.81	-0.83	-0.85	-0.88	-0.9	-0.92	-0.94	-0.96	-0.98	-1	-1.02
	-0.9	-0.49	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78	-0.8	-0.82	-0.84	-0.87	-0.89	-0.91	-0.93	-0.95	-0.97	-0.99	-1.01	-1.03
	-1	-0.5	-0.52	-0.54	-0.57	-0.59	-0.61	-0.64	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.81	-0.83	-0.86	-0.88	-0.9	-0.92	-0.94	-0.96	-0.98	-1	-1.02	-1.05
	-1.1	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78	-0.8	-0.82	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95	-0.97	-0.99	-1.02	-1.04	-1.06
	-1.2	-0.52	-0.54	-0.57	-0.59	-0.61	-0.64	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.81	-0.84	-0.86	-0.88	-0.9	-0.92	-0.94	-0.96	-0.99	-1.01	-1.03	-1.05	-1.07
	-1.3	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78	-0.8	-0.83	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95	-0.98	-1	-1.02	-1.04	-1.06	-1.08
	-1.4	-0.54	-0.57	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.81	-0.84	-0.86	-0.88	-0.9	-0.92	-0.94	-0.97	-0.99	-1.01	-1.03	-1.05	-1.07	-1.09
-1.5	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78	-0.8	-0.83	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95	-0.98	-1	-1.02	-1.04	-1.06	-1.08	-1.1	
-1.6	-0.56	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79	-0.81	-0.84	-0.86	-0.88	-0.9	-0.92	-0.94	-0.97	-0.99	-1.01	-1.03	-1.05	-1.07	-1.09	-1.11	
-1.7	-0.57	-0.6	-0.62	-0.64	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78	-0.8	-0.82	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95	-0.98	-1	-1.02	-1.04	-1.06	-1.08	-1.1	-1.12	
-1.8	-0.58	-0.61	-0.63	-0.65	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79	-0.81	-0.83	-0.86	-0.88	-0.9	-0.92	-0.94	-0.97	-0.99	-1.01	-1.03	-1.05	-1.07	-1.09	-1.11	-1.13	
-1.9	-0.6	-0.62	-0.64	-0.66	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8	-0.82	-0.85	-0.87	-0.89	-0.91	-0.93	-0.95	-0.98	-1	-1.02	-1.04	-1.06	-1.08	-1.1	-1.12	-1.14	
-2	-0.61	-0.63	-0.65	-0.67	-0.7	-0.72	-0.74	-0.77	-0.79	-0.81	-0.83	-0.86	-0.88	-0.9	-0.92	-0.94	-0.96	-0.99	-1.01	-1.03	-1.05	-1.07	-1.09	-1.11	-1.13	-1.15	

**Table 38. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 52 for dulaglutide 1.5 mg to sitagliptin (GBCF)**

		Sitagliptin Sensitivity Parameter:																									
		Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment	05	0.14	0.12	0.1	0.08	0.06	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36
	04	0.12	0.1	0.08	0.06	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.32	-0.34	-0.36	-0.38
	03	0.1	0.08	0.05	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.36	-0.38	-0.4
	02	0.08	0.05	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.4	-0.42
	01	0.06	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.44
	0	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.46
	-01	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49
	-02	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51
	-03	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53
	-04	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55
	-05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57
	-06	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59
	-07	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61
	-08	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63
	-09	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65
	-1	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67
	-11	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69
	-12	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54	-0.56	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71
	-13	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54	-0.56	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73
	-14	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.46	-0.48	-0.5	-0.52	-0.54	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.74
-15	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.76	
-16	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.76	-0.78	
-17	-0.3	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.76	-0.78	-0.8	
-18	-0.32	-0.34	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.76	-0.78	-0.8	-0.82	
-19	-0.34	-0.36	-0.38	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.76	-0.78	-0.8	-0.82	-0.84	
-2	-0.36	-0.38	-0.4	-0.42	-0.44	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	-0.65	-0.67	-0.69	-0.71	-0.73	-0.75	-0.76	-0.78	-0.8	-0.82	-0.84	-0.86	

**Table 39. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 0.75 mg to placebo (GBCF)**

		Placebo Sensitivity Parameter:																									
		Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1.0	-0.9	-0.8	-0.7	-0.6	-0.5	-0.4	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.4	0.5
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	0.5	-0.15	-0.18	-0.2	-0.22	-0.25	-0.27	-0.3	-0.32	-0.34	-0.37	-0.39	-0.42	-0.44	-0.46	-0.49	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.64	-0.67	-0.69	-0.71	-0.73
	0.4	-0.16	-0.19	-0.21	-0.23	-0.26	-0.28	-0.31	-0.33	-0.35	-0.38	-0.4	-0.43	-0.45	-0.47	-0.5	-0.52	-0.54	-0.56	-0.59	-0.61	-0.63	-0.65	-0.68	-0.7	-0.72	-0.74
	0.3	-0.17	-0.2	-0.22	-0.24	-0.27	-0.29	-0.32	-0.34	-0.36	-0.39	-0.41	-0.44	-0.46	-0.48	-0.5	-0.53	-0.55	-0.57	-0.6	-0.62	-0.64	-0.66	-0.69	-0.71	-0.73	-0.75
	0.2	-0.18	-0.21	-0.23	-0.25	-0.28	-0.3	-0.33	-0.35	-0.37	-0.4	-0.42	-0.44	-0.47	-0.49	-0.51	-0.54	-0.56	-0.58	-0.61	-0.63	-0.65	-0.67	-0.7	-0.72	-0.74	-0.76
	0.1	-0.19	-0.21	-0.24	-0.26	-0.29	-0.31	-0.34	-0.36	-0.38	-0.41	-0.43	-0.45	-0.48	-0.5	-0.52	-0.55	-0.57	-0.59	-0.62	-0.64	-0.66	-0.68	-0.71	-0.73	-0.75	-0.77
	0	-0.2	-0.22	-0.25	-0.27	-0.3	-0.32	-0.35	-0.37	-0.39	-0.42	-0.44	-0.46	-0.49	-0.51	-0.53	-0.56	-0.58	-0.6	-0.63	-0.65	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78
	-0.1	-0.21	-0.23	-0.26	-0.28	-0.31	-0.33	-0.35	-0.38	-0.4	-0.43	-0.45	-0.47	-0.5	-0.52	-0.54	-0.57	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79
	-0.2	-0.22	-0.24	-0.27	-0.29	-0.32	-0.34	-0.36	-0.39	-0.41	-0.44	-0.46	-0.48	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.64	-0.67	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8
	-0.3	-0.23	-0.25	-0.28	-0.3	-0.33	-0.35	-0.37	-0.4	-0.42	-0.44	-0.47	-0.49	-0.52	-0.54	-0.56	-0.58	-0.61	-0.63	-0.65	-0.68	-0.7	-0.72	-0.74	-0.76	-0.79	-0.81
	-0.4	-0.24	-0.26	-0.29	-0.31	-0.33	-0.36	-0.38	-0.41	-0.43	-0.45	-0.48	-0.5	-0.52	-0.55	-0.57	-0.59	-0.62	-0.64	-0.66	-0.68	-0.71	-0.73	-0.75	-0.77	-0.8	-0.82
	-0.5	-0.25	-0.27	-0.29	-0.32	-0.34	-0.37	-0.39	-0.42	-0.44	-0.46	-0.49	-0.51	-0.53	-0.56	-0.58	-0.6	-0.63	-0.65	-0.67	-0.69	-0.72	-0.74	-0.76	-0.78	-0.81	-0.83
	-0.6	-0.25	-0.28	-0.3	-0.33	-0.35	-0.38	-0.4	-0.42	-0.45	-0.47	-0.5	-0.52	-0.54	-0.57	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.81	-0.84
	-0.7	-0.26	-0.29	-0.31	-0.34	-0.36	-0.39	-0.41	-0.43	-0.46	-0.48	-0.5	-0.53	-0.55	-0.57	-0.6	-0.62	-0.64	-0.67	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8	-0.82	-0.84
	-0.8	-0.27	-0.3	-0.32	-0.35	-0.37	-0.39	-0.42	-0.44	-0.47	-0.49	-0.51	-0.54	-0.56	-0.58	-0.61	-0.63	-0.65	-0.68	-0.7	-0.72	-0.74	-0.77	-0.79	-0.81	-0.83	-0.85
	-0.9	-0.28	-0.31	-0.33	-0.35	-0.38	-0.4	-0.43	-0.45	-0.47	-0.5	-0.52	-0.55	-0.57	-0.59	-0.61	-0.64	-0.66	-0.68	-0.71	-0.73	-0.75	-0.77	-0.8	-0.82	-0.84	-0.86
	-1	-0.29	-0.31	-0.34	-0.36	-0.39	-0.41	-0.43	-0.46	-0.48	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.71	-0.74	-0.76	-0.78	-0.8	-0.83	-0.85	-0.87
	-1.1	-0.3	-0.32	-0.35	-0.37	-0.4	-0.42	-0.44	-0.47	-0.49	-0.51	-0.54	-0.56	-0.59	-0.61	-0.63	-0.65	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79	-0.81	-0.83	-0.86	-0.88
	-1.2	-0.31	-0.33	-0.35	-0.38	-0.4	-0.43	-0.45	-0.48	-0.5	-0.52	-0.55	-0.57	-0.59	-0.62	-0.64	-0.66	-0.69	-0.71	-0.73	-0.75	-0.78	-0.8	-0.82	-0.84	-0.86	-0.89
	-1.3	-0.31	-0.34	-0.36	-0.39	-0.41	-0.44	-0.46	-0.48	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.72	-0.74	-0.76	-0.78	-0.81	-0.83	-0.85	-0.87	-0.89
	-1.4	-0.32	-0.35	-0.37	-0.4	-0.42	-0.44	-0.47	-0.49	-0.52	-0.54	-0.56	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79	-0.81	-0.84	-0.86	-0.88	-0.9
	-1.5	-0.33	-0.35	-0.38	-0.4	-0.43	-0.45	-0.48	-0.5	-0.52	-0.55	-0.57	-0.59	-0.62	-0.64	-0.66	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8	-0.82	-0.84	-0.87	-0.89	-0.91
-1.6	-0.34	-0.36	-0.39	-0.41	-0.44	-0.46	-0.48	-0.51	-0.53	-0.55	-0.58	-0.6	-0.63	-0.65	-0.67	-0.69	-0.72	-0.74	-0.76	-0.79	-0.81	-0.83	-0.85	-0.87	-0.9	-0.92	
-1.7	-0.35	-0.37	-0.39	-0.42	-0.44	-0.47	-0.49	-0.51	-0.54	-0.56	-0.59	-0.61	-0.63	-0.66	-0.68	-0.7	-0.73	-0.75	-0.77	-0.79	-0.82	-0.84	-0.86	-0.88	-0.9	-0.93	
-1.8	-0.35	-0.38	-0.4	-0.43	-0.45	-0.47	-0.5	-0.52	-0.55	-0.57	-0.59	-0.62	-0.64	-0.66	-0.69	-0.71	-0.73	-0.76	-0.78	-0.8	-0.82	-0.85	-0.87	-0.89	-0.91	-0.93	
-1.9	-0.36	-0.38	-0.41	-0.43	-0.46	-0.48	-0.51	-0.53	-0.55	-0.58	-0.6	-0.62	-0.65	-0.67	-0.69	-0.72	-0.74	-0.76	-0.79	-0.81	-0.83	-0.85	-0.88	-0.9	-0.92	-0.94	
-2	-0.37	-0.39	-0.42	-0.44	-0.47	-0.49	-0.51	-0.54	-0.56	-0.58	-0.61	-0.63	-0.66	-0.68	-0.7	-0.72	-0.75	-0.77	-0.79	-0.82	-0.84	-0.86	-0.88	-0.9	-0.93	-0.95	

**Table 40. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 52 for dulaglutide 0.75 mg to placebo (GBCF)**

		Sitagliptin Sensitivity Parameter:																									
		Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment	05	0.28	0.26	0.24	0.21	0.19	0.17	0.15	0.13	0.1	0.08	0.06	0.04	0.02	0	-0.02	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25
	04	0.26	0.24	0.22	0.2	0.17	0.15	0.13	0.11	0.09	0.07	0.04	0.02	0	-0.02	-0.04	-0.06	-0.08	-0.1	-0.12	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.26
	03	0.25	0.23	0.2	0.18	0.16	0.14	0.11	0.09	0.07	0.05	0.03	0.01	-0.01	-0.04	-0.06	-0.08	-0.1	-0.12	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28
	02	0.23	0.21	0.19	0.16	0.14	0.12	0.1	0.08	0.05	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3
	01	0.22	0.19	0.17	0.15	0.13	0.1	0.08	0.06	0.04	0.02	0	-0.03	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31
	0	0.2	0.18	0.15	0.13	0.11	0.09	0.07	0.04	0.02	0	-0.02	-0.04	-0.06	-0.08	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33
	-01	0.18	0.16	0.14	0.12	0.09	0.07	0.05	0.03	0.01	-0.01	-0.04	-0.06	-0.08	-0.1	-0.12	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.26	-0.29	-0.31	-0.32	-0.34
	-02	0.17	0.15	0.12	0.1	0.08	0.06	0.03	0.01	-0.01	-0.03	-0.05	-0.07	-0.09	-0.12	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36
	-03	0.15	0.13	0.11	0.08	0.06	0.04	0.02	0	-0.02	-0.05	-0.07	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38
	-04	0.14	0.11	0.09	0.07	0.05	0.03	0	-0.02	-0.04	-0.06	-0.08	-0.1	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39
	-05	0.12	0.1	0.08	0.05	0.03	0.01	-0.01	-0.03	-0.06	-0.08	-0.1	-0.12	-0.14	-0.16	-0.18	-0.2	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41
	-06	0.11	0.08	0.06	0.04	0.02	-0.01	-0.03	-0.05	-0.07	-0.09	-0.11	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42
	-07	0.09	0.07	0.05	0.02	0	-0.02	-0.04	-0.06	-0.09	-0.11	-0.13	-0.15	-0.17	-0.19	-0.21	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44
	-08	0.07	0.05	0.03	0.01	-0.01	-0.04	-0.06	-0.08	-0.1	-0.12	-0.14	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45
	-09	0.06	0.04	0.01	-0.01	-0.03	-0.05	-0.07	-0.1	-0.12	-0.14	-0.16	-0.18	-0.2	-0.22	-0.24	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47
	-1	0.04	0.02	0	-0.02	-0.04	-0.07	-0.09	-0.11	-0.13	-0.15	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48
	-11	0.03	0.01	-0.02	-0.04	-0.06	-0.08	-0.1	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.25	-0.27	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5
	-12	0.01	-0.01	-0.03	-0.05	-0.07	-0.1	-0.12	-0.14	-0.16	-0.18	-0.2	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51
	-13	0	-0.02	-0.04	-0.07	-0.09	-0.11	-0.13	-0.15	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.3	-0.32	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53
	-14	-0.01	-0.04	-0.06	-0.08	-0.1	-0.13	-0.15	-0.17	-0.19	-0.21	-0.23	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54
-15	-0.03	-0.05	-0.07	-0.1	-0.12	-0.14	-0.16	-0.18	-0.21	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.37	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54	-0.56	
-16	-0.04	-0.07	-0.09	-0.11	-0.13	-0.15	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	
-17	-0.06	-0.08	-0.1	-0.12	-0.15	-0.17	-0.19	-0.21	-0.23	-0.26	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.51	-0.53	-0.54	-0.56	-0.58	
-18	-0.07	-0.09	-0.12	-0.14	-0.16	-0.18	-0.2	-0.23	-0.25	-0.27	-0.29	-0.31	-0.33	-0.35	-0.38	-0.4	-0.42	-0.44	-0.46	-0.48	-0.5	-0.52	-0.54	-0.56	-0.58	-0.6	
-19	-0.09	-0.11	-0.13	-0.15	-0.18	-0.2	-0.22	-0.24	-0.26	-0.28	-0.31	-0.33	-0.35	-0.37	-0.39	-0.41	-0.43	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	
-2	-0.1	-0.12	-0.14	-0.17	-0.19	-0.21	-0.23	-0.25	-0.28	-0.3	-0.32	-0.34	-0.36	-0.38	-0.4	-0.42	-0.45	-0.47	-0.49	-0.51	-0.53	-0.55	-0.57	-0.59	-0.61	-0.63	

**A.3.2 Trial GBDC**

**Table 41. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 1.5 mg to metformin (GBDC)**

		Metformin Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment															
		-10	-09	-08	-07	-06	-05	-04	-03	-02	-01	0	01	02	03	04	05
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	0.16	0.15	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0
	04	0.15	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01
	03	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02
	02	0.13	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03
	01	0.12	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04
	0	0.11	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.04	-0.05	-0.06
	-01	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.04	-0.05	-0.06	-0.07
	-02	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.05	-0.06	-0.07	-0.08
	-03	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.06	-0.07	-0.08	-0.09
	-04	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.07	-0.08	-0.09	-0.1
	-05	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.08	-0.09	-0.1	-0.11
	-06	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.1	-0.11	-0.12
	-07	0.04	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12
	-08	0.03	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13
	-09	0.02	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14
	-1	0.01	0	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15

**Table 42. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 0.75 mg to metformin (GBDC)**

		Metformin Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment															
		-10	-09	-08	-07	-06	-05	-04	-03	-02	-01	0	01	02	03	04	05
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	0.2	0.19	0.18	0.17	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04
	04	0.19	0.18	0.17	0.16	0.15	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03
	03	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.08	0.07	0.06	0.05	0.04	0.03	0.02
	02	0.18	0.17	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02
	01	0.17	0.16	0.15	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01
	0	0.16	0.15	0.14	0.13	0.12	0.11	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0
	-01	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.04	0.03	0.02	0.01	0	-0.01
	-02	0.15	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01
	-03	0.14	0.13	0.12	0.11	0.1	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02
	-04	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03
	-05	0.13	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03
	-06	0.12	0.11	0.1	0.09	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04
	-07	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05
	-08	0.11	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.04	-0.05	-0.06
	-09	0.1	0.09	0.08	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06
	-1	0.09	0.08	0.07	0.06	0.05	0.04	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07

A.3.3 Trial GBDA

Table 43. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 1.5 mg to placebo (GBDA)

		Placebo Sensitivity Parameter:																										
		Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																										
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05	
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	-0.46	-0.47	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.67	-0.68	-0.69	-0.7	-0.71	
	04	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73
	03	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74
	02	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.71	-0.72	-0.73	-0.74
	01	-0.49	-0.5	-0.51	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75
	0	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76
	-01	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77
	-02	-0.51	-0.52	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77
	-03	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.62	-0.63	-0.64	-0.65	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78
	-04	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79
	-05	-0.53	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8
	-06	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.64	-0.65	-0.66	-0.67	-0.68	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8
	-07	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81
	-08	-0.55	-0.56	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82
	-09	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82
	-1	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83
	-11	-0.57	-0.58	-0.59	-0.6	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84
	-12	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84
	-13	-0.58	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.8	-0.81	-0.82	-0.83	-0.84
	-14	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84	-0.85	-0.86
-15	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84	-0.85	-0.86	
-16	-0.6	-0.61	-0.62	-0.63	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84	-0.85	-0.86	
-17	-0.61	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84	-0.85	-0.86	-0.87	
-18	-0.61	-0.62	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.81	-0.82	-0.83	-0.84	-0.85	-0.86	-0.87	
-19	-0.62	-0.63	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.84	-0.85	-0.86	-0.87	-0.88	
-2	-0.62	-0.64	-0.65	-0.66	-0.67	-0.68	-0.69	-0.7	-0.71	-0.72	-0.73	-0.74	-0.75	-0.76	-0.77	-0.78	-0.79	-0.8	-0.81	-0.82	-0.83	-0.83	-0.84	-0.85	-0.86	-0.87	-0.88	

**Table 44. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 1.5 mg to exenatide (GBDA)**

		Exenatide Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-09	-08	-07	-06	-05	-04	-03	-02	-01	0	01	02	03	04	05
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.22	-0.23	-0.24	-0.25	-0.26	-0.26	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.34
	04	-0.16	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35
	03	-0.16	-0.17	-0.18	-0.19	-0.2	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	-0.28	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35	-0.36
	02	-0.17	-0.18	-0.19	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26	-0.27	-0.28	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35	-0.36	-0.36
	01	-0.18	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.23	-0.24	-0.25	-0.26	-0.27	-0.27	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37
	0	-0.18	-0.19	-0.2	-0.21	-0.22	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.27	-0.28	-0.29	-0.3	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37	-0.38
	-01	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.26	-0.27	-0.28	-0.29	-0.3	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.38
	-02	-0.2	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.38	-0.39
	-03	-0.2	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26	-0.27	-0.28	-0.28	-0.29	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.38	-0.39	-0.4
	-04	-0.21	-0.22	-0.23	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35	-0.36	-0.37	-0.37	-0.38	-0.39	-0.4	-0.4
	-05	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.27	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35	-0.36	-0.37	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41
	-06	-0.22	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.42
	-07	-0.23	-0.24	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.41	-0.42
	-08	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.28	-0.29	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.38	-0.39	-0.4	-0.41	-0.41	-0.42	-0.43
	-09	-0.24	-0.25	-0.26	-0.27	-0.27	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.38	-0.39	-0.4	-0.41	-0.41	-0.42	-0.43	-0.43
	-1	-0.25	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.3	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35	-0.36	-0.37	-0.37	-0.38	-0.39	-0.4	-0.4	-0.41	-0.42	-0.43	-0.43	-0.44
	-11	-0.25	-0.26	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36	-0.37	-0.37	-0.38	-0.39	-0.4	-0.4	-0.41	-0.42	-0.42	-0.43	-0.44	-0.45
	-12	-0.26	-0.27	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.42	-0.42	-0.43	-0.44	-0.44	-0.45
	-13	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.41	-0.42	-0.43	-0.44	-0.44	-0.45	-0.46
	-14	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.34	-0.35	-0.36	-0.37	-0.38	-0.38	-0.39	-0.4	-0.41	-0.41	-0.42	-0.43	-0.44	-0.44	-0.45	-0.46	-0.46
-15	-0.28	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36	-0.37	-0.37	-0.38	-0.39	-0.4	-0.4	-0.41	-0.42	-0.43	-0.43	-0.44	-0.45	-0.46	-0.46	-0.47	
-16	-0.28	-0.29	-0.3	-0.31	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.42	-0.42	-0.43	-0.44	-0.45	-0.45	-0.46	-0.47	-0.47	
-17	-0.29	-0.3	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.42	-0.42	-0.43	-0.44	-0.45	-0.45	-0.46	-0.47	-0.47	-0.48	
-18	-0.29	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.38	-0.39	-0.4	-0.41	-0.41	-0.42	-0.43	-0.44	-0.44	-0.45	-0.46	-0.47	-0.47	-0.48	-0.49	
-19	-0.3	-0.31	-0.32	-0.32	-0.33	-0.34	-0.35	-0.36	-0.36	-0.37	-0.38	-0.39	-0.4	-0.4	-0.41	-0.42	-0.43	-0.43	-0.44	-0.45	-0.46	-0.46	-0.47	-0.48	-0.48	-0.49	
-2	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.39	-0.39	-0.4	-0.41	-0.42	-0.43	-0.43	-0.44	-0.45	-0.45	-0.46	-0.47	-0.48	-0.48	-0.49	-0.5	

**Table 45. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 0.75 mg to placebo (GBDA)**

		Placebo Sensitivity Parameter:																									
		Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1.0	-0.9	-0.8	-0.7	-0.6	-0.5	-0.4	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.4	0.5
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	0.5	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5
	0.4	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.48	-0.49	-0.5
	0.3	-0.26	-0.27	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51
	0.2	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52
	0.1	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.51	-0.52
	0	-0.28	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53
	-0.1	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54
	-0.2	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.53	-0.54
	-0.3	-0.3	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.54	-0.55
	-0.4	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56
	-0.5	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.54	-0.55	-0.56
	-0.6	-0.32	-0.33	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57
	-0.7	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58
	-0.8	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.55	-0.56	-0.57	-0.58
	-0.9	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59
	-1	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.58	-0.59
	-1.1	-0.35	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6
	-1.2	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61
	-1.3	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.57	-0.58	-0.59	-0.6	-0.61
	-1.4	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62
-1.5	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.6	-0.61	-0.62	
-1.6	-0.38	-0.39	-0.4	-0.41	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	
-1.7	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.62	-0.63	
-1.8	-0.39	-0.4	-0.41	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	
-1.9	-0.4	-0.41	-0.42	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.64	
-2	-0.4	-0.41	-0.43	-0.44	-0.45	-0.46	-0.47	-0.48	-0.49	-0.5	-0.51	-0.52	-0.53	-0.54	-0.55	-0.56	-0.57	-0.58	-0.58	-0.59	-0.6	-0.61	-0.62	-0.63	-0.64	-0.65	

**Table 46. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 0.75 mg to exenatide (GBDA)**

		Exenatide Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	0.06	0.05	0.04	0.03	0.03	0.02	0.01	0	-0.01	-0.02	-0.02	-0.03	-0.04	-0.05	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.13
	04	0.05	0.04	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.13	-0.14
	03	0.05	0.04	0.03	0.02	0.01	0	0	-0.01	-0.02	-0.03	-0.04	-0.04	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15
	02	0.04	0.03	0.02	0.01	0.01	0	-0.01	-0.02	-0.03	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.15
	01	0.03	0.02	0.02	0.01	0	-0.01	-0.02	-0.03	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.15	-0.16
	0	0.03	0.02	0.01	0	-0.01	-0.02	-0.02	-0.03	-0.04	-0.05	-0.06	-0.06	-0.07	-0.08	-0.09	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17
	-01	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.05	-0.06	-0.07	-0.08	-0.09	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17	-0.17
	-02	0.01	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.04	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18
	-03	0.01	0	-0.01	-0.02	-0.03	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19
	-04	0	-0.01	-0.02	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.16	-0.17	-0.18	-0.19	-0.19
	-05	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.06	-0.07	-0.08	-0.09	-0.1	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2
	-06	-0.01	-0.02	-0.03	-0.04	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.2
	-07	-0.02	-0.03	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.2	-0.21
	-08	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.2	-0.2	-0.21	-0.22
	-09	-0.03	-0.04	-0.05	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.19	-0.2	-0.21	-0.22	-0.22
	-1	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.09	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.16	-0.17	-0.18	-0.19	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23
	-11	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.23
	-12	-0.05	-0.06	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.2	-0.21	-0.22	-0.23	-0.23	-0.24
	-13	-0.05	-0.06	-0.07	-0.08	-0.09	-0.09	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.2	-0.2	-0.21	-0.22	-0.23	-0.23	-0.24	-0.25
	-14	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	-0.15	-0.16	-0.16	-0.17	-0.18	-0.19	-0.19	-0.2	-0.21	-0.22	-0.22	-0.23	-0.24	-0.24	-0.25
	-15	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17	-0.18	-0.19	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26
-16	-0.07	-0.08	-0.09	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26	-0.26	
-17	-0.08	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.2	-0.2	-0.21	-0.22	-0.23	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	
-18	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.16	-0.17	-0.18	-0.19	-0.19	-0.2	-0.21	-0.22	-0.22	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	-0.27	
-19	-0.09	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26	-0.27	-0.27	-0.28	
-2	-0.09	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.2	-0.21	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26	-0.26	-0.27	-0.28	-0.29	

A.3.4 Trial GBDB

Table 47. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 52 for dulaglutide 1.5 mg to insulin glargine (GBDB)

		Insulin Glargine Sensitivity Parameter:																									
		Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment	05	0.03	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23
	04	0.02	0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24
	03	0.01	0	-0.01	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25
	02	0	-0.01	-0.02	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26
	01	-0.01	-0.02	-0.03	-0.04	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27
	0	-0.02	-0.03	-0.04	-0.05	-0.06	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28
	-01	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29
	-02	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.28	-0.29
	-03	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.27	-0.28	-0.29	-0.3
	-04	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.21	-0.22	-0.23	-0.24	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31
	-05	-0.06	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32
	-06	-0.07	-0.08	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33
	-07	-0.08	-0.09	-0.1	-0.11	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34
	-08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35
	-09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.35
	-1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.33	-0.34	-0.35	-0.36
	-11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37
	-12	-0.12	-0.13	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38
	-13	-0.13	-0.14	-0.15	-0.16	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39
	-14	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4
-15	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.4	
-16	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	
-17	-0.16	-0.17	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	
-18	-0.17	-0.18	-0.19	-0.2	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	
-19	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.42	-0.43	-0.44	
-2	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.3	-0.31	-0.32	-0.33	-0.34	-0.35	-0.36	-0.37	-0.38	-0.39	-0.4	-0.41	-0.41	-0.42	-0.43	-0.44	

**Table 48. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 52 for dulaglutide 0.75 mg to insulin glargine (GBDB)**

		Insulin Glargine Sensitivity Parameter: Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 52 in the subgroup w/o a week 52 assessment	05	0.31	0.29	0.28	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05
	04	0.3	0.29	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04
	03	0.29	0.28	0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03
	02	0.28	0.27	0.26	0.25	0.24	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.03
	01	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.04	0.03	0.02
	0	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.07	0.06	0.05	0.04	0.03	0.02	0.01
	-01	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0
	-02	0.25	0.24	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01
	-03	0.24	0.23	0.22	0.21	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02
	-04	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02
	-05	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.02	0.01	0	-0.01	-0.01	-0.03
	-06	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.04
	-07	0.21	0.2	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04
	-08	0.2	0.19	0.18	0.17	0.16	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04	-0.05
	-09	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.04	-0.05	-0.06
	-1	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07
	-11	0.18	0.17	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08
	-12	0.17	0.16	0.15	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09
	-13	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09
	-14	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1
-15	0.15	0.14	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	
-16	0.14	0.13	0.12	0.11	0.1	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	
-17	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.12	
-18	0.13	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	
-19	0.12	0.11	0.1	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	
-2	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.12	-0.13	-0.14	

A.3.5 Trial GBDD

Table 49. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 1.5 mg to insulin glargine (GBDD)

		Insulin Glargine Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05
Dula 1.5 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02
	04	0.22	0.21	0.2	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0.01	0	-0.01	-0.02	-0.03
	03	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05
	02	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06
	01	0.18	0.17	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.03	-0.04	-0.05	-0.06	-0.07
	0	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09
	-01	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1
	-02	0.14	0.13	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09	-0.1	-0.11
	-03	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.12
	-04	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14
	-05	0.1	0.09	0.08	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15
	-06	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16
	-07	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18
	-08	0.06	0.05	0.04	0.03	0.02	0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19
	-09	0.05	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	-0.19	-0.2
	-1	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.21
	-11	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23
	-12	0.01	0	-0.01	-0.02	-0.03	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.24
	-13	0	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.25
	-14	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.26
	-15	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28
-16	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.29	
-17	-0.05	-0.06	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	
-18	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.29	-0.3	-0.31	
-19	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.32	
-2	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	-0.25	-0.26	-0.27	-0.28	-0.29	-0.3	-0.31	-0.32	-0.33	-0.34	

**Table 50. Missing data sensitivity analysis: Upper 95% CI limit comparing mean HbA1c reduction at week 26 for dulaglutide 0.75 mg to insulin glargine (GBDD)**

		Insulin Glargine Sensitivity Parameter:																									
		Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment																									
		-2	-19	-18	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	01	02	03	04	05
Dula 0.75 mg Sensitivity Parameter: Mean HbA1c change at week 26 in the subgroup w/o a week 26 assessment	05	0.3	0.29	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05
	04	0.28	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03
	03	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02
	02	0.26	0.25	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01
	01	0.25	0.24	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0
	0	0.23	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01
	-01	0.22	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.02	0.01	0	-0.01	-0.02
	-02	0.21	0.2	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03
	-03	0.2	0.19	0.18	0.17	0.16	0.15	0.13	0.12	0.11	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.04
	-04	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06
	-05	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07
	-06	0.16	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.04	-0.05	-0.06	-0.07	-0.08
	-07	0.15	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.07	-0.08	-0.09
	-08	0.14	0.13	0.12	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1
	-09	0.13	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12
	-1	0.11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13
	-11	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14
	-12	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.15
	-13	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.13	-0.14	-0.15	-0.16
	-14	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.15	-0.16	-0.17
-15	0.06	0.05	0.04	0.03	0.02	0.01	-0.01	-0.02	-0.03	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.17	-0.18	
-16	0.05	0.04	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.19	
-17	0.03	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	
-18	0.02	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.14	-0.15	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	
-19	0.01	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.16	-0.17	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	
-2	0	-0.01	-0.02	-0.03	-0.04	-0.05	-0.06	-0.07	-0.08	-0.09	-0.1	-0.11	-0.12	-0.13	-0.14	-0.15	-0.16	-0.17	-0.18	-0.18	-0.19	-0.2	-0.21	-0.22	-0.23	-0.24	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BRADLEY W MCEVOY  
05/16/2014

MARK D ROTHMANN  
05/16/2014  
I conur

THOMAS J PERMUTT  
05/16/2014  
I concur.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**BLA Number:** 125469      **Applicant:** Eli Lilly and Company      **Stamp Date:** 09-18-13

**Drug Name:** Dulaglutide  
(proposed dose 1.5 mg)      **BLA Type:** Standard review  
Electronic submission,  
<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6812e0f42>>

This statistical safety filing review relates only to contents of the submission relevant to the cardiovascular (CV) meta-analysis. A separate statistical filing review by Dr. Bradley McEvoy covers the overall efficacy and safety data contained in the application.

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	See below*
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

\*The study protocols and reports for all trials included in the meta-analysis as well as the meta-analysis plan and report were included in the submission.

### IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			Cardiovascular outcomes trial was initiated in response to the guidance for type 2 diabetes drugs. Meta-analysis for CV safety contains data from Phase 2 and 3 trials.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			In the Phase 2 and 3 trials, cardiovascular events were defined and adjudicated in a consistent manner so that meta-analysis could be performed.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			See sections below for pre-specified alpha adjustments for meta-analysis. DSMB meetings not applicable.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

### Background

Dulaglutide is a novel glucagon-like peptide-1 (GLP-1) receptor agonist. The Applicant seeks the indication “indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus”. In accordance with the 2008 FDA diabetes guidance, the planned cardiovascular (CV) meta-analysis was conducted to rule out an excessive risk margin of 1.8 as measured by the hazard ratio (HR). The Applicant planned to conduct at most two meta-analyses with the objective to rule out the 1.8 risk margin prior to the BLA submission. The agreed upon<sup>1</sup> primary endpoint for the meta-analysis was a composite endpoint comprising CV death, nonfatal MI, nonfatal stroke, or hospitalization due to unstable angina, also known as **MACE+**. The first meta-analysis was to be based on data from nine Phase 2 and 3 trials. If the first meta-analysis did not meet the pre-specified 1.8 risk margin, a second (and final) meta-analysis was to be conducted when 180 primary events were accumulated. The second meta-analysis was to be based on all trials in the first meta-analysis and interim data from the ongoing CV outcomes trial (REWIND). The Type I error rate was controlled through a planned group sequential multiple testing procedure at an overall  $\alpha=0.025$  level (one-sided) using the Pocock spending function. According to the study report, the first meta-analysis met the FDA requirement by demonstrating that the upper bound of the alpha-adjusted confidence interval for the HR was less than 1.8 (study report results provided below); therefore, no data from REWIND were included in the meta-analysis to demonstrate CV safety at the time of BLA submission.

Post approval, the Applicant plans to use all the data from REWIND to determine whether the CV risk based on the 1.3 margin can be ruled out. The primary endpoint in REWIND is a composite endpoint comprising CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, also known as MACE.

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<sup>1</sup> Refer to FDA meeting minutes dated January 19, 2010.

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

## Brief summary of cardiovascular meta-analysis

The CV meta-analysis included data from 9 completed Phase 2 and 3 randomized controlled trials: 4 Phase 2 trials (study durations: 12-26 weeks) and 5 pivotal phase 3 glycemetic control trials (study durations: 52-102 weeks); see Table 1 for summary of trial designs. All CV events were prospectively adjudicated, in a blinded manner, by an independent Clinical Event Classification group (CEC), which was governed under a charter. The CEC charter was included in the application.

Table 1 Summary of Trials Included in CV Meta-analysis

	Phase 2 Studies				
	GBCJ	GBCK <sup>a</sup>	GBCZ	GBDN	
Dulaglutide doses (mg)	0.5→1.0, 1.0, 1.0→2.0	0.1, 0.5, 1.0, 1.5	0.25, 0.5, 0.75	0.75, 1.5	
Comparator	Placebo	Placebo	Placebo	Placebo	
Background therapy	2 OAMs	None	None	≥1 OAM(s)	
Number randomized	262	167	145	755	
Number receiving dulaglutide	196	135	108	505	
Treatment duration (weeks)	16	12	12	26	
Median Exposure (days)	107	85	78	183	
	Phase 3 Studies				
	GBCF <sup>b</sup>	GBDA	GBDB	GBDC	GBDD
Dulaglutide doses (mg)	Stage 1: 0.25 to 3.0 Stage 2: 0.75, 1.5	0.75, 1.5	0.75, 1.5	0.75, 1.5	0.75, 1.5
Comparator	Placebo, Sitagliptin	Placebo, Exenatide	Insulin Glargine	Metformin	Insulin Glargine
Background therapy	Metformin	Metformin + Pioglitazone	Metformin + Glimepiride	None	Insulin Lispro +/- Metformin
Number randomized (actual)	1202	978	810	807	892
Number receiving dulaglutide	710	683 <sup>c</sup>	545	539	596
Treatment duration (weeks)	104	52	78	52	52
Primary time point (weeks)	52	26	52	26	26
Median Exposure (days)	715	175	545	359	362

Abbreviation: OAM = oral anti-diabetic medications.

a GBCK includes 3 patients who were randomized to 3.0 mg but were discontinued when the dose was replaced with 1.5 mg

b GBCF is an adaptive dose-finding, inferentially seamless Phase 2/3, placebo-controlled study in patients with T2DM on metformin. Adaptive treatment allocation was used to randomize patients and a Bayesian theoretical approach utilizing predictive probabilities was used to assess 7 weekly doses of dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, and 3.0 mg) to identify a maximal utility dose to continue in the study. This dose selection was based on a clinical utility index, utilizing prespecified measures of efficacy (HbA1c and weight) and safety (diastolic blood pressure and heart rate). A lower dose was also selected to mitigate the potential risk that a safety signal would be subsequently observed with the maximum utility dose. The lower dose was required to have an acceptable clinical utility index and be ≤ 50% of the maximum utility dose, to ensure minimal overlap of dulaglutide exposure. Dulaglutide 1.5 mg was selected as the maximum utility dose and dulaglutide 0.75 mg was selected as the lower dose to be continued in the remainder of Study GBCF. Following dose-finding, evaluation of the efficacy and safety of these doses and comparator arms continued, using a fixed randomization scheme (all other unselected doses were discontinued).

c The 683 patients include 124 patients who were originally randomized to placebo. In this study, treatment duration in the placebo arm was 26 weeks (6 months). After this period, placebo patients were re-randomized to 1 of dulaglutide arms. For these 124 patients, CV events reported only during the first 6 months (while on placebo) were included in the primary analysis of this meta-analysis.

Source: Applicant's meta-analysis report Table 1.1 (page 17)

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

The pre-specified primary analysis population was all randomized patients. Patients were analyzed according to treatment assigned, regardless of treatment received. The pre-specified primary analysis of time to first MACE+ was based on a stratified Cox proportional hazard regression with treatment (dulaglutide or control) included as an independent predictor. For the primary analysis, all patients randomized to any dose of dulaglutide were to be included in the dulaglutide treatment group and all patients randomized to placebo or active comparator were to be included in the control group. According to the meta-analysis plan, six total strata were to be used in the Cox model:

- Stratum 1: All Phase 2 trials (GBCJ, GBCK, GBCZ, and GBDN)
- Stratum 2-6: Each of the Phase 3 trials (GBCF, GBDA, GBDB, GBDC, and GBDD) was to form a separate stratum.

### **Reviewer's Comments:**

- 1. Typically each trial included in the meta-analysis, regardless of phase in the development program, forms an independent stratum in the Cox model. The impact of combining all Phase 2 trials into a single stratum will be discussed in the statistical review of CV safety.***
- 2. The study report states that there was a change to the pre-specified number of strata for the primary analysis. Because there were no observed MACE+ in control arm of trial GBDC, the Applicant combined this trial with trial GBCF to form a single stratum for the primary analysis. Therefore, the primary analysis as reported in the study report was based on 5 strata instead of 6 strata as pre-specified in the meta-analysis plan. This issue of modifying the pre-specified primary analysis will be addressed in the statistical review of CV safety.***

According to the study report, there were 6010 randomized patients included in the meta-analysis, 3885 were randomized to dulaglutide and 2125 patients were randomized to comparator medication. A total of 51 MACE+ (26 in dulaglutide patients and 25 in the control patients) were observed. With this many events, the test of the 1.8 risk margin was based on alpha-adjusted significance level of 0.0198 (two-sided); pre-specified alpha adjustment based on the Pocock spending function. The estimated hazard ratio was 0.57 with corresponding alpha-adjusted two-sided 98.02% CI of (0.30, 1.10).

### **Reviewer's Comments:**

- 1. The reviewer was able to use the integrated safety dataset, "cv\_all.xpt", that was included in the BLA to verify the overall number of reported MACE+ in both treatment arms as well as the number of randomized patients in both treatment arms. This dataset was also used to replicate the Applicant's estimated HR for MACE+ and 98.02% CI for assessing the 1.8 risk margin. No other analyses were attempted at the time of this filing review, but will be addressed during the course of the statistical safety review of cardiovascular safety.***

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

2. *Note that there were 892 patients randomized in trial GBDD according to Table 1; however, according to the dataset “cv\_all.xpt” this trial randomized 884 patients. It appears that 892 was erroneously entered in the table by the Applicant as the number of randomized patients recorded in the dataset matches the number of randomized patients reported in the study report for this trial.*

### Comments to be Conveyed to the Applicant

#### Refuse-to-file Information Requests

No refuse-to-file issues were noted; as such no additional information is required at this time.

#### Information Requests/Review Issues

No additional information requests are noted at this time.

Janelle K. Charles	November 12, 2013
Reviewing Statistician	Date
Mat Soukup	November 12, 2013
Supervisor/Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANELLE K CHARLES  
11/12/2013

MATTHEW J SOUKUP  
11/12/2013  
Concur

**STATISTICS FILING CHECLIST FOR BLA 125469  
Dulaglutide (LY2189265)**

Filing Meeting: November 1, 2013  
Statistical Reviewer: Bradley W. McEvoy

**BLA Number: 125469      Applicant: Eli Lilly and Company      Stamp Date: 9/18/2013**  
**Drug Name: dulaglutide      BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	<b>X</b>			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<b>X</b>			No ISE submitted
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	<b>X</b>			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	<b>X</b>			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? \_\_ YES \_\_**

***Reviewer Comment: The submission does not include an ISE in module 5 of the eCTD. However, the "Summary of Clinical Efficacy" in section 2.7.3 in the eCTD appears to provide an adequate integrated evaluation studies and results. Because the content in 2.7.3 appears adequate to support a statistical review, the application is considered fillable.***

If the NDA/BLA is not fileable from the statistical 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.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	<b>X</b>			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<b>X</b>			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	<b>X</b>			DMC minutes not submitted

File name: 5\_Statistics Filing Checklist for a New NDA\_BLA



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BRADLEY W MCEVOY  
11/05/2013

MARK D ROTHMANN  
11/05/2013  
I concur