CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125469Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Application Number(s)	125469
Priority or Standard	Standard
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Division / Office	DMEP/ODE2
Reviewer Name(s)	Suchitra Balakrishnan, MD, PhD.
Review Completion Date	August 10, 2014
Established Name	Dulaglutide
(Proposed) Trade Name	Trulicity™
Therapeutic Class	Glucagon like peptide (GLP-1) receptor agonist
Applicant	Eli Lilly and Company
Formulation(s)	Sub-cutaneous injection by single-use pen or pre-filled syringe
Dosing Regimen	0.75 mg and 1.5 mg q-weekly
Indication(s)	Treatment of Type 2 DM
Intended Population(s)	Adults with Type 2 DM

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Dulaglutide is a glucagon-like peptide-1 (GLP-1) agonist that acts on pancreatic beta cells to augment glucose dependent insulin secretion. The Applicant is seeking an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The Applicant is seeking approval for dulaglutide 1.5 mg once weekly as the only approved dose, although dulaglutide 0.75 mg once weekly has also been evaluated in the clinical program.

Based on my review of the clinical data, there is substantial evidence of effectiveness from the five Phase 3 trials and an acceptable safety profile for both doses. I recommend approval of dulaglutide 0.75 mg qweekly as the initiating dose. For patients that require additional glycemic control, the dose can be increased to 1.5 mg qweekly.

I have summarized my rationale for this recommendation in section 1.2 below.

1.2 Risk Benefit Assessment

Based on the evidence for efficacy and the observed adverse event (AE) profile for dulaglutide, I favor approval. Both of the studied doses have demonstrated efficacy in improving glycemic control as measured by hemoglobin A1c (HbA1c). While there are imbalances in some adverse events with evidence of dose dependency, none of the safety concerns are new or substantially more worrisome than other members of the drug class. Labeling and a Risk Evaluation and Mitigation Strategy (REMS) should help to mitigate these risks, and additional data for some of the concerns can be collected in the ongoing studies. The evidence for efficacy and the general safety observations are summarized here. Detailed discussion is found later in this review.

Evidence for Efficacy:

The phase 3 program included five clinical studies, ranging from 26 to 104 weeks, that were designed to evaluate the efficacy and safety of two doses (0.75 mg and 1.5 mg) of dulaglutide administered as a once weekly subcutaneous (SC) injection. A variety of background therapies were used in these studied. The efficacy of dulaglutide was evaluated using change in HbA1c. Additional secondary endpoints included change in weight, and the percentage of patients able to achieve a target HbA1c. A summary of key efficacy findings follow:

- At 26 weeks, dulaglutide 1.5 mg and dulaglutide 0.75 mg achieved statistically significantly better HbA1c reduction than placebo.

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- Dulaglutide 1.5 mg and 0.75 mg achieved nominally statistically significantly better HbA1c reduction compared to sitagliptin on a background of metformin, metformin as monotherapy, exenatide on a background of pioglitazone and metformin, and insulin glargine on a background of insulin lispro.
- At 52 weeks, Dulaglutide 1.5 mg achieved nominally statistically significantly better HbA1c reduction than insulin glargine on a background of metformin and sulfonylurea. Dulaglutide 0.75 mg was non-inferior to insulin glargine on a background of metformin and sulfonylurea.
- Both doses showed evidence of sustained efficacy over time (52 to 104 weeks) with results similar to what was seen at the primary time points.
- Dulaglutide 1.5 mg was nominally statistically significantly better for HbA1c reduction than dulaglutide 0.75 mg for HbA1c reduction in three out of five studies, in patients on background therapies of metformin, metformin and sulfonylurea and insulin lispro with metformin. This was also apparent at the final study time points. This comparison was exploratory.
- Dulaglutide 1.5 mg was associated with greater weight reduction than all comparators except metformin. Dulaglutide 0.75 mg was associated with greater weight reduction than insulin glargine, but not greater than metformin or exenatide.
- A larger proportion of dulaglutide treated subjects had an HbA1c under 7% or 6.5% compared to active comparators in all but one study. In that study, the difference vs. insulin glargine was statistically significant only for subjects treated with dulaglutide 1.5 mg for an HbA1c under 7%.

Safety Observations:

The safety database for dulaglutide includes 6,005 patients with T2DM in the Phase 2/3 trials who have received dulaglutide once weekly from 1 week to 104 weeks: 4,006 received dulaglutide, 703 received placebo, and 1,541 received active comparator. Of the 4,006 patients treated with dulaglutide, 1,357 patients were exposed to dulaglutide 1.5 mg, while 1,404 patients were exposed to dulaglutide 0.75 mg.

Safety findings for dulaglutide are consistent with other approved products in the GLP-1 agonist class. As is seen with other members of the class, certain safety issues were seen more commonly with the higher dose leading to my recommendation for dulaglutide 0.75 mg as the dose for initiating therapy. A summary of the safety concerns for dulaglutide follow.

Deaths, Serious Adverse Events and Discontinuations:

Deaths and serious adverse events (SAEs) were comparable between dulaglutide, placebo and all comparator. The SAEs were generally balanced between dulaglutide and all-comparator and were events that might be expected in the study population.

Discontinuations were overall balanced, but there were more discontinuations due to gastrointestinal (GI) events with dulaglutide. Patients treated with the 1.5 mg dose were nearly twice as likely to discontinue due to a GI adverse event (AE) compared to patients treated with the 0.75 mg dose (3.5% vs. 1.3%, respectively). Both doses were substantially more likely to result in a discontinuation due to a gastroinestinal event than placebo (0.1%).

Thyroid C- cell proliferation:

Proliferation of thyroid C-cells in nonclinical studies have raised concern that treatment with GLP-1 agonists (particularly long-acting GLP-1 agonists) could lead to development of thyroid C-cell tumors. Serum calcitonin was measured as part of the development program since it is used as a marker in medullary thyroid cancer. While neither dose of dulaglutide increased mean serum calcitonin compared to placebo, there were numerically more dulaglutide patients (n=6, 0.15%) with a calcitonin > 35 pg/ml than comparator patients (n=1, 0.05%). Most of these cases, however, had elevated calcitonin at baseline. The significance of this observation is not known. There was one case of medullary thyroid cancer diagnosed in a patient after being treated with dulaglutide. This patient had elevated calcitonin at baseline and also was found to have a high risk germ line mutation. The diagnosis was made after approximately six months of dulaglutide exposure. Taking all of this into consideration, it is unlikely that the development of medullary thyroid cancer was due to dulaglutide exposure.

There does not appear to be an increased risk for thyroid C-cell proliferation. However due to the rarity of this event, the clinical program may be too small to detect an increased risk.

Pancreatitis:

Drugs in the GLP-1 agonist class carry labelling warning against pancreatitis. Though dulaglutide was associated with dose-dependent increases in pancreatic enzymes (i.e. lipase and pancreatic amylase), there was no clear imbalance seen between dulaglutide and placebo for pancreatitis. Similar changes in pancreatic enzymes were seen with exenatide twice daily and with sitagliptin, but the magnitude of the observed increases were greater with dulaglutide. Serial measurements of pancreatic enzymes in Phase 2 and 3 trials did not predict the onset of acute pancreatitis. The clinical significance of these findings is unclear.

Pancreatic Cancer:

Pancreatic cancer is another concern with the GLP-1 agonist class. In the dulaglutide development program, there did not appear to be an imbalance in the incidence of pancreatic cancer. There were four cases of pancreatic cancer in dulaglutide treated

patients vs. three in the all comparator group (two who had been treated with placebo, one who had been treated with liraglutide). Though the available patient exposure is too small to definitively assess the risk for pancreatic cancer with dulaglutide, it seems reasonable to conclude that there is no evident increased risk versus comparator.

Immunogenicity:

The incidence of treatment-emergent dulaglutide anti-drug antibodies (ADAs) in patients treated with dulaglutide across Phase 2 and 3 trials was low (1.6% in dulaglutide treated patients vs. 0.7% in patients treated with placebo or non-GLP-1 comparators). No dose dependency was observed with respect to the incidence of treatment-emergent dulaglutide ADA. Among patients treated with dulaglutide and having treatment-emergent dulaglutide ADAs (n=64) approximately half (n=34, 0.9% of the overall population) had dulaglutide neutralizing ADA, and approximately half (n=36, 0.9% of the overall population) developed native sequence GLP-1 (nsGLP-1) cross-reactive antibodies. There were four patients who developed neutralizing ADAs for nsGLP-1, and two patients with both nsGLP-1 cross-reactive and neutralizing ADAs.

The development of treatment-emergent dulaglutide ADAs was not associated with systemic hypersensitivity AEs. Injection site reactions were more common in patients with dulaglutide ADAs.

Hypersensitivity:

There do not appear to be any new or increased concerns about adverse reactions related to hypersensitivity and immunogenicity compared to the approved products in the drug-class. Across all placebo controlled-studies, five (0.7%) of placebo patients vs. seven (0.3%) of dulaglutide treated patients experienced a hypersensitivity reaction. While there was a case reported to be Steven Johnson syndrome and a case of anaphylactic shock reported in the phase 2/3 studies, the relationship to dulaglutide was not clearly established.

Injection site reactions:

Consistent with other drugs in the GLP-1 agonist class, there were numerically more injection site adverse events in the dulaglutide treatment group (n=38, 1.7%) when compared with the placebo-treated patients (n=6, 0.9%). There was no apparent dose dependence for injection site reactions. Consistent with other drugs in the GLP-1 agonist drug class, patients that developed treatment emergent ADAs were more likely to have injection site reactions than those patients that did not develop ADAs.

Renal Safety:

Renal impairment as a result of therapy with GLP-1 agonists has been reported. As a result, patients with moderate to severe renal impairment were in general excluded from study. In the dulaglutide development program there was no apparent decline in mean renal function as measured by estimated glomerular filtration rate (eGFR). Additionally, few patients had change in the stage of renal impairment. This observation needs to be caveated by the fact that there were few patients with advanced renal impairment, a population that may be at higher risk for this adverse event. Patients with more advanced renal impairment are being evaluated in an ongoing study, and renal safety can be better assessed after completion of this study.

Urinary albumin excretion was also measured during the development program. The patients treated with dulaglutide had a small, but statistically significant, decrease in urinary albumin to creatinine ratio (UACR). While UACR is considered to be a marker of diabetic nephropathy, this observation is of unknown clinical significance. Given the improvement in glycemic control with dulaglutide, it is inappropriate to consider this information as suggesting improvement in microvascular disease.

Hypoglycemia:

The risk for hypoglycemia with dulaglutide is consistent with the drug class. It is to be noted that unlike the clinical programs for some of the approved GLP-1 agonists, the add-on to insulin lispro and sulfonylurea studies used insulin glargine as an active comparator rather than placebo. This may increase the rate of hypoglycemia in the comparator arms, thus minimizing the apparent hypoglycemia risk with dulaglutide. Compared to placebo, patients on dulaglutide had an increased rate of documented symptomatic hypoglycemia[1]. Some studies showed a suggestion of dose dependency. There was more documented symptomatic hypoglycemia with dulaglutide 1.5 mg vs. 0.75 mg in studies GBCF, GBDC, and severe hypoglycemic episodes in studies GBDD and GBDB.

Hepatic Safety:

The potential of drug-induced hepatic injury is a concern with all new drugs. The proportion of patients with treatment-emergent abnormal hepatic enzymes was similar across treatment groups. Two patients on dulaglutide had hepatic enzyme elevations that satisfied Hy's Law criteria but had alternate etiologies (alcoholic liver disease and viral hepatitis) to explain the elevations.

Cholestasis is also a concern due to dulaglutide's mechanism of action. Seven patients on dulaglutide had total bilirubin elevations > 2X upper limit of normal (ULN). Of these, two satisfied Hy's law criteria[2] but had alternate etiologies as discussed earlier. The

1 Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).
2 The particular laboratory profile of ALT elevation >3x ULN seen concurrently with bilirubin >2 x ULN has been

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remaining five patients had baseline elevations or Gilbert's syndrome and did not meet criteria for Hy's law or concomitant elevations of alkaline phosphatase (AP) to suggest cholestasis.

Although the overall exposure with dulaglutide may not allow for definitive conclusions regarding drug-induced liver injury, there does not appear to be a significant hepatic safety signal based on the available data.

Cardiac Safety:

Cardiovascular (CV) risk is a concern with all anti-diabetic agents. As outlined in the "Guidance to Industry: Diabetes melliuts – Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes", a premarket risk margin of 1.8 must be excluded from the 95% confidence interval (CI) for major cardiovascular events[3] and hospitalization for unstable angina (MACE+).

In a meta-analysis of the completed studies, the estimated hazard ratio (HR) for MACE+ was 0.57 with 98.02% CI (0.30, 1.10). The upper bound of this confidence interval was less than 1.8 and therefore satisfied the requirement. Further evaluation of the CV risk of dulaglutide post-approval will be based on data from the cardiovascular outcomes study (Researching Cardiovascular Events with a Weekly Incretin in Diabetes [REWIND]). This trial is designed to exclude a 30% (i.e. a risk margin of 1.3) increase in CV risk based on major cardiovascular events (MACE), and is being conducted in a high risk population with prolonged exposure.

Additional non-MACE+ CV events were analyzed as part of the safety review. These included the occurrence of tachyarrhythmias, changes in heart rate (HR), and changes on electrocardiograms (ECGs).

Review of the broad and narrow Standardized Medical Dictionary of Regulatory Activities (MedDRA) Query (SMQ) for "any supraventricular arrhythmia" identified numerically more subjects on dulaglutide 1.5 mg with AEs compared to dulaglutide 0.75 mg. All the reported PT's were tachyarrhythmias. This was not observed for ventricular tachyarrhythmias.

There was an apparent dose-dependent increase in heart rate (Least significant [LS] mean change from placebo of 3.37 beats per minute (bpm) [dulaglutide 1.5 mg] and 2.15 bpm [dulaglutide 0.75 mg]). In addition, more treatment emergent abnormal outliers were noted on categorical analyses (i.e. sitting heart rate > 100 bpm; increase in heart rate > 15 bpm from baseline) with dulaglutide (placebo 0.7%, dulaglutide 0.75mg 1.3%, and dulaglutide 1.5 mg 2.2%).

referred to as Hy's Law. It has been used to identify a drug likely to cause severe drug-induced liver injury (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases
3 Cardiovascular death, non-fatal MI and non-fatal stroke (MACE).

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Small mean and categorical increases in PR interval (3-4 msec) were noted with dulaglutide in the placebo controlled studies, and more subjects on dulaglutide 1.5 mg developed first degree AV block (placebo: 0.9%, dulaglutide 0.75 mg: 1.8%, dulaglutide 1.5 mg: 2.3%). Clinically significant AEs under the conduction disorders High Level Term (HLT) were balanced. However, it should be noted that the clinical significance of this effect would be best seen in elderly patients with underlying ischemic heart disease or sick-sinus syndrome, patients with other pre-excitation syndromes, conduction disorders, or on underlying beta-blocker/calcium channel blocker therapy. This population will be better evaluated in the cardiovascular outcomes study.

Although the number of treatment emergent adverse events (TEAEs) reported under the supraventricular arrhythmias HLT was balanced compared to all comparator, review of individual patient narratives for SAEs and discontinuations due to AEs, taken together with the class effect on heart rate is suggestive of a dose dependent effect with dulaglutide. This can be further evaluated as an AE of special interest in the CV outcome trial.

Common Adverse Events:

Nausea and vomiting were the most common AEs, which is consistent with the drug class. They were clearly dose dependent and occurred roughly twice as often with dulaglutide 1.5 mg compared to dulaglutide 0.75 mg (21.1% vs. 12.4% for nausea, 12.6% vs. 6% for vomiting). The time course of nausea and vomiting with dulaglutide is consistent with approved products and peaked at 2 weeks. Prevalence over time was still higher with the dulaglutide 1.5 mg dose group. Thus, initiating therapy at the 0.75 mg dose may improve treatment adherence.

Dose dependency of adverse events:

Dose dependency was observed for the following adverse effects:

- Discontinuations due to adverse events (see 7.3.5 Dropouts and/or Discontinuations)
- Nausea and vomiting (see 7.4.1 Common Adverse Events)
- Pancreatic enzyme elevations (see 7.3.2.2 Pancreatitis)
- Heart rate effects (see 7.4.3 Vital Signs)

A suggestion of dose-dependency for adverse effects was observed for:

- Hypoglycemia (see 7.3.2.8 Hypoglycemia)
- Supraventricular arrhythmias (see 7.3.2.9 Cardiac Safety)
- PR interval prolongation (see 7.4.4 Electrocardiograms (ECGs))

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant has submitted a proposed Risk Evaluation Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh the potential risks of medullary thyroid carcinoma and pancreatitis. The REMS Elements include a "Dear Healthcare Professional" (DHCP) letter and a REMS-specific website as a communication plan to health care providers (HCPs) that are likely to prescribe dulaglutide. The intended audience for this DHCP letter will be all adult endocrinologists as well as other healthcare providers who have prescribed a glucagon-like peptide-1 (GLP-1) receptor agonist in the 12 months prior to dissemination of the letter. The Applicant has proposed that REMS assessments will be submitted to the FDA at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. This seems appropriate and is consistent with what has been done for other approved drugs in the class. The Division of Risk Management (DRISK) reviewer's final recommendations regarding the adequacy of the REMS Elements and the assessment plan are pending at the time this review was completed.

1.4 Recommendations for Postmarket Requirements and Commitments

I propose the following postmarketing requirements (PMRs) under section 505(o) of the Act (FDAAA Title IX):

1. A dedicated study to assess for increased cardiovascular risk (CV) in high risk patients per the FDA *Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The primary objective of this trial will be to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with albiglutide to that observed in the control group is less than 1.3.
    - Study GBDJ (Researching Cardiovascular Events with a Weekly INcretin in Diabetes [REWIND]) is ongoing. Only the 1.5 mg dose is being evaluated in this study, which is acceptable from a safety perspective. The following non-cardiac adverse events should be monitored as AEs of special interest: (1) pancreatitis, (2) pancreatic cancer, (3) hypersensitivity reactions, (4) acute renal failure, (5) hepatic events, (6) thyroid cancer, (7) severe hypoglycemia, (7) clinically significant supraventricular arrhythmias, and (8) clinically significant conduction disorders.
2. To better characterize the safety of dulaglutide in patients with Chronic Kidney disease (CKD) stage 3 and above, the sponsor will have to conduct a dedicated study in this population. There is an ongoing study (study GBDX), and I would require completion of that study.
3. To better characterize the safety signal for medullary thyroid cancer (MTC), the Applicant should be required to maintain an MTC case series registry of at least

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15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of dulaglutide into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of dulaglutide.

I propose the following PMRs under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c):

1. A study to evaluate the safety, efficacy, and pharmacokinetics of dulaglutide in pediatric patients ages 10-17 years (inclusive) with T2DM. This should be initiated after completion of the juvenile toxicology study recommended by the non-clinical reviewers.

2 Introduction and Regulatory Background

2.1 Product Information

Dulaglutide (LY2189265) is a long acting human GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, which is an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas. Non-pancreatic effects of GLP-1 include slowing of gastric emptying, reduction of food intake, and an increase in satiety, all of which contribute to improved glycemic control and decreased body weight[4].

The dulaglutide molecule consists of 2 identical, disulfide-linked chains, each containing a human GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small glycine-rich peptide linker (Figure 1).The Applicant states that the GLP-1 analog portion of dulaglutide is approximately 90% homologous to native human GLP-1 (b) (4)

(b) (4)

4 Drucker DJ. 2006. The biology of incretin hormones. Cell Metabolism 3, 153-165

Figure 1: Schematic diagram of dulaglutide

(b) (4)

(b) (4)

Source: Figure 2.2.1, Module 2.2

The proposed indication for dulaglutide is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The Applicant's rationale for this therapeutic intervention is that the GLP-1 receptor agonists are designed to mimic the effect of endogenous GLP-1. This should stimulate pancreatic insulin secretion in a glucose-dependent fashion, suppress pancreatic glucagon output, slow gastric emptying, and decrease appetite. This should result in improved glycemic control.

The proposed dose is 1.5 mg by subcutaneous (SC) injection administered once weekly.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently available therapies for Type 2 DM are listed in the table below:

Table 1: Available Therapeutic Options for the Management of T2DM

Pharmacologic Class	Antidiabetic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam

Pharmacologic Class	Antidiabetic Drug Products
DOPAMINE-2 AGONISTS	Bromocriptine
DIPEPTIDYL PEPTIDASE-4 (DPP4) INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Exenatide; Liraglutide, Exenatide LAR, albiglutide
INSULINS AND INSULIN ANALOGUES	Insulin Aspart: Insulin Detemir; Insulin Glargine; Insulin Glulisine; Insulin Isophane (NPH); Insulin Isophane and Regular; Insulin Lispro; Insulin Regular (human), Pre-mixed (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin, dapagliflozin, empagliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

Despite the number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, many of these drug classes may not be tolerated or have limited usefulness in certain populations. For example, thiazolidinediones (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors are contraindicated in patients with severe renal dysfunction. Additionally, progressive β-cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time requiring the addition of other agents. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies.

2.3 Availability of Proposed Active Ingredient in the United States

Dulaglutide is a new molecular entity (NME). It is not currently marketed in the United States or other countries.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety issues identified with all approved incretin based therapies (GLP-1 agonists and DPP4 inhibitors) include:

- Post-marketing reports of acute pancreatitis, including hemorrhagic or necrotizing pancreatitis. Excess events (of pancreatitis) versus comparator were noted in the clinical trials for linagliptin, liraglutide and albiglutide

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- Post-marketing reports of serious hypersensitivity reactions including anaphylaxis, angioedema and exfoliative skin conditions like Steven-Johnson Syndrome
- Hypoglycemia when used in combination with an insulin secretagogue (e.g. sulfonylurea) or insulin

In addition, the long-acting GLP-1 agonists (exenatide LAR, liraglutide and albiglutide) carry a box warning for the risk of thyroid C-cell tumors, contraindicating use in patients with personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2).

All of the approved GLP-1 agonists and sitagliptin carry a Warning and Precautions statement about post-marketing reports of acute renal failure, sometimes requiring dialysis.

Serious injection site nodules/abscesses requiring surgery have been reported with exenatide LAR.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Dulaglutide was developed as a Critical Path Initiative (CPI) pilot project, since the sponsor was using an adaptive randomization, seamless Phase 2/3 trial (trial GBCF) as part of its clinical development. There was extensive regulatory correspondence between the sponsor and the FDA related to this trial, which is discussed further in section 5.

The End-of-Phase 2 meeting between the Applicant and the FDA occurred on November 10, 2009. Key clinical safety and regulatory issues discussed included the toxicology plan, non-clinical evaluation of the exocrine pancreas and thyroid, pharmacokinetic studies in patients with hepatic impairment, plans for the CV safety meta-analysis, plans for the dedicated cardiovascular safety study, immunogenicity assessment including the threshold for treatment-emergent antibody response to trigger testing for neutralizing activity and cross-reactivity to endogenous GLP-1, safety monitoring and design/analyses of the Phase 3 pivotal efficacy studies, PK-PD analyses and adequate evaluation of subjects with chronic renal insufficiency.

The pre-BLA meeting was held in July 9, 2013. The Applicant had addressed clinical issues outlined in the meeting related to the submission content.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The organization of the submission, completeness and ease for finding information seem acceptable. For further details see clinical filing review dated November 5, 2013 completed by Dr. Karim Calis.

3.2 Compliance with Good Clinical Practices

The Applicant makes the following statement:

"All clinical trials in the dulaglutide clinical development program were conducted in accordance with i) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, ii) the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline [E6], and iii) applicable laws and regulations. Clinical trials conducted outside of the EU meet the ethical requirements of Directive 2001/20/EC."

Across the Phase 2 and 3 studies, several clinical sites were terminated due to noncompliance with GCP. In most instances data for all patients were included in safety analyses for the individual studies. For two sites (Site 504 in Study GBDB and Site 100 in Study GBDD), there were significant data integrity issues and thus patients enrolled at these sites were excluded from summaries and listings presented in the ISS document. The individual CSRs for Study GBDB and Study GBDD were reviewed for information on these sites and patient safety. There were no issues of significant concern that would affect the interpretation of results.

For additional discussion of compliance, refer to the OSI Clinical inspection summary review by Dr. Cynthia Kleppinger dated June 6, 2014.

3.3 Financial Disclosures

Financial disclosures were submitted for the nine phase 2/3 studies and comparative PK study GBDT (*see* 9.4 Financial disclosure reviews *for financial disclosure templates completed by Dr. William Chong*). Some investigators in the pivotal trials had disclosable financial interests. All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the trials (multi-center), size of the trials, and the small contribution from each of these investigators (each < 5% of the total number of subjects) for the individual trials.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the Chemistry Manufacturing and Controls (CMC) review by Dr. Joel Welch from the Office of BioTechnology Products (OBP) for full details. Key issues are summarized here.

The CMC reviewers state that "The data submitted in this Biologics License Application support the conclusion that the manufacture of Trulicity™ (dulaglutide) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that Trulicity™ (dulaglutide) be approved for human use (under conditions specified in the package insert). We recommend an expiration dating period of (b) (4) months for dulaglutide drug substance when stored at (b) (4) We recommend an expiration dating period of 24 months for dulaglutide drug product (both 1.5 mg/0.5 mL and 0.75 mg/0.5 mL dosage strengths) when stored at 2-8°C. We recommend approval of the proposed release and shelf-life specifications for dulaglutide drug substance and drug product"

(From OBP Review Summary dated May 30, 2014)

The commercial drug substance manufacturing facility was inspected and the following observations were noted:

- There was inadequate documentation of safety risk assessments of the raw materials and consumables, including (b) (4) used in the dulaglutide drug substance manufacturing process. The Applicant was required to perform additional assessments related to extractables and the reviewer has recommended post-marketing commitments (PMCs) to perform a reassessment of the (b) (4) used for drug substance and product manufacturing. This will include a product specific extractables and leachables study.
- Additional issues were identified related to the materials system, quality system and Facilites and Equipment, which are being addressed by the Applicant and reviewed by OBP.
- The OBP reviewers have also recommended additional studies as PMC's to evaluate drug-substance and drug-product lot release and stability specifications in future lots and to update the control strategy assessments.

None of these are issues that would affect approval.

Discussion of OBP's assessments for antibody assay validation and cut-points is found in section 7.3.2.4 Immunogenicity

Device issues:

Refer to the reviews by Drs. QuynhNhu Nguyen and Sarah K. Vee from Center for Devices and Radiological health (CDRH) and the Division of Medication Error Prevention and Management (DMEPA) respectively for detailed discussion.

The CDRH reviewers have not identified any approvability issues for the single-use pen (SUP) or pre-filled syringe (PFS). The Applicant was asked to submit a human factors differentiation study for the two strengths (0.75 mg and 1.5 mg) for both the PFS and SUP configurations and this has been conducted by the Applicant. The Applicant was also asked to submit a system level hazard analysis including information about specified hazardous situations for the single-use pen (SUP), including needle fracture hazards. This is was reviewed by the agency and found to be satisfactory.

4.2 Clinical Microbiology

Refer to the final product quality microbiology review by Dr. Colleen Thomas in DARRTs for full details and recommendations.

The drug product quality microbiology review of this BLA is not yet complete. There is uncertainty about the reliability of the endotoxin test release results for the drug substance and drug product due to the possible interferences by the citrate and polysorbate components in the formulation. The reviewers indicate that the endotoxin hold-time study should be conducted using (b) (4) instead of (b) (4). There is ongoing discussion related to this issue with the Applicant about the endotoxin control strategy for the drug product, which may result in a post-marketing commitments or requirements.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology/Toxicology review by Dr. Tim Hummer for full details. Effects on the exocrine pancreas and effects on thyroid C-cell proliferation are discussed in 7.3.2.2 Pancreatitis and 7.3.2.1 Potential thyroid C-cell proliferation

Several in vitro and in vivo studies showed that LY2189265 (i.e. dulaglutide) has high GLP-1 receptor binding potency and induces insulin secretion. LY2189265 was shown to have a similar potency to activate the human GLP-1 receptor in vitro as native GLP-1, with an EC_{50} value of 12.5 pM.

<u>Safety Pharmacology:</u>

In a cardiovascular safety pharmacology study, cynomolgus monkeys received a single SC dose of 1 or 10 mg/kg of LY2189265. Treatment resulted in dose-related increases in heart rate, with heart rate being approximately 22% higher than control values at 3 and 5 hours after dosing as well as at later time points. A dose-responsive increase in left ventricular inotropic state was also noted at both dose levels.

In a 9-month study in which monkeys received twice weekly subcutaneous injections of up to 8.15 mg/kg of LY2189265, no toxicologically meaningful effects on neurobehavior, heart rate, or ECG endpoints were noted. Although the primate findings (1-month and 3-month repeat dose toxicity studies) suggested a potential for dulaglutide to cause QT/QTc prolongation, QT/QTc prolongation has not been observed in the thorough QT study or the Phase 2/Phase 3 dulaglutide clinical program.

General Toxicology:

Standard toxicology studies were conducted in rats and monkeys for up to 6 and 9 months, respectively, with doses being administered by subcutaneous injection twice weekly. One-year studies were conducted in rats and monkeys as part of an enhanced analysis of potential drug-related effects on the thyroid and pancreas (monkey only).

Initial body weight effects were observed in mice, rats, and monkeys at ≥ 10, ≥ 1.6, and ≥ 0.41 mg/kg twice weekly, respectively. There were no consistent histologic changes attributed to dulaglutide in these studies to suggest direct toxicity. Mild histologic alterations considered secondary to body weight decrements noted in the 5-week rat study (atrophy of seminiferous tubules in testes, thymic atrophy) were not consistently observed in longer-duration studies and therefore, they were not considered toxicologically significant.

In the 1-month monkey toxicity study, assays for complement activation were included and there were no effects on C3a and Bb complement split products. An assessment of the ability to mount a humoral immune response was incorporated into the 9-month monkey toxicity study and the Applicant reports that there was no effect of dulaglutide treatment.

In the repeat-dose toxicity studies, local tolerance to dulaglutide was characterized by systematic histologic examination of the subcutaneous injection sites. Across the animal studies dulaglutide injections were well tolerated and not associated with a significant inflammatory reaction.

Reproductive and Developmental Toxicity:

Dr. Hummer recommends a designation of “Pregnancy category C due to the absence of adequate and well-controlled studies in pregnant women”.

In fertility and early embryonic development studies in male and female rats, no adverse effects of dulaglutide on sperm morphology, mating, fertility, conception, and embryonic survival were observed at up to 16.3 mg/kg (148-fold the maximum recommended human dose (MRHD) based on exposure-area under the curve (AUC). In female rats, an increase in the number of females with prolonged diestrus and a dose-related decrease in the mean number of corpora lutea, implantation sites, and viable embryos were observed at ≥4.9 mg/kg (≥32-fold the MRHD based on AUC).

In rats and rabbits, dulaglutide administered during the major period of organogenesis produced fetal growth reductions and/or skeletal ossification deficits in association with maternal effects at systemic exposures starting at ≥13-fold the MRHD based on AUC; dulaglutide was not teratogenic in rats at any systemic exposures.

In a prenatal-postnatal study in F0 maternal rats given subcutaneous doses of 0.2, 0.49, or 1.63 mg/kg every third day from implantation through lactation, F1 pups from F0 maternal rats given 1.63 mg/kg dulaglutide had statistically significantly lower mean body weight and F1 female offspring had a longer mean escape time and a higher mean number of errors relative to the concurrent control during 1 of 2 trials in the memory evaluation portion of the Biel water maze. The human relevance of these memory deficits in the F1 female rats is not known.

4.4 Clinical Pharmacology

A brief discussion of the information from the Applicant's Summary of Clinical Pharmacology (eCTD 2.7.2) is included here. Refer to the Clinical Pharmacology and Pharmacometrics reviews by Dr. Sang Chung and Dr. Lian Ma in DARRTS for full discussion.

4.4.1 Mechanism of Action

Dulaglutide is a GLP-1 agonist. The main physiological target tissues of GLP-1 action are pancreatic beta cells, the gastro-intestinal system, and peripheral sensory vagal afferent nerves. Physiologically, GLP-1 supports glucose homeostasis by enhancing glucose-dependent insulin secretion from β cells and suppressing inappropriately elevated postprandial glucagon secretion from α cells. In addition, GLP-1 has been demonstrated to reduce appetite and food intake, and inhibit gastric emptying. These mechanisms work in concert to reduce fasting and post-prandial plasma glucose, thereby leading to reduction in glycosylated hemoglobin (HbA1c) and yielding an overall glycemic benefit.

4.4.2 Pharmacodynamics

Dulaglutide improves glycemic control by lowering fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) concentrations. In patients with T2DM who received once weekly 1.5 mg doses for 6 weeks (Study GBCT), fasting glucose

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concentrations, 2-hour PPG concentrations, and post-prandial serum glucose AUC were significantly reduced compared to placebo (-25.6 mg/dL, -59.5 mg/dL, and - 197 mg•h/dL, respectively). These effects were sustained throughout the entire 6-week period.

In a 52 week phase 3 study, dulaglutide 1.5 mg once weekly was compared to 1500-2000 mg/day metformin (Study GBDC). In a subset of patients, PPG levels were measured following a standardized test meal. Following 26 weeks of treatment, the LS mean change from baseline in average PPG (average of values from 15 minutes through 180 minutes postmeal) was -51 mg/dL for dulaglutide 1.5 mg and -42 mg/dL for metformin (p=0.89), indicating similar reductions in PPG with dulaglutide and metformin.

Other pharmacodynamic effects include:

- Improved First and Second Phase Insulin Secretion in healthy subjects and patients with T2DM.
- Increased Glucose-Dependent Insulin Secretion.
- Reduced fasting glucagon levels.
- Delayed gastric emptying

4.4.3 Pharmacokinetics

The pharmacokinetic profile of dulaglutide supports once weekly dosing. Mean terminal half-life ($t_{1/2}$) after multiple 1.5 mg dosing was 4.7 days. Following single doses of dulaglutide 1 mg and higher, mean plasma concentrations were quantifiable up to 336 hours (14 days). Steady state was reached between the 2nd and 4th doses of dulaglutide. Accumulation after 1.5 mg multiple dose administration was approximately 1.56-fold, and was predictable from single dose data.

The average maximum plasma concentration (C_{max}) of dulaglutide at steady state after multiple 1.5 mg dosing in patients with T2DM was 114 ng/mL (35% coefficient of variation [CV]), and the median t_{max} was 48 hours (range 24 to 72 hours). The mean area under the concentration-time curve from zero to 168 hours ($AUC_{[0-168]}$) for patients with T2DM after multiple 1.5 mg dosing was 14000 ng•hr/mL (30% CV). Intra-subject variability estimates for dulaglutide $AUC_{[0-168]}$ and C_{max} after a single 1.5 mg dose were 11.9% and 16.1%, respectively.

The absolute bioavailability values for a 1.5 mg and a 0.75 mg SC dose of dulaglutide in healthy subjects were 47% and 65%, respectively. Mean apparent volume of distribution (Vz/F) after multiple 1.5 mg dosing was 17.4 L (range 9.3 to 33).

Dulaglutide is presumed to be degraded into component peptides and amino acids in lysosomes by general protein catabolism.

The Applicant indicates that the mean effects of intrinsic factors on PK parameters (AUC and C_{max}) were generally within the intersubject PK variability of dulaglutide. Based on exposure-response analyses and individual study data, these intrinsic factors did not affect the exposure (AUC and C_{max}) of dulaglutide to any clinically relevant degree.

The effect of hepatic impairment on dulaglutide PK was examined in Study H9X-MC-GBDO (GBDO), which compared the PK of dulaglutide in patients with stable hepatic impairment (classified as mild, moderate, or severe based on Child-Pugh classification) to that of healthy subjects. The Applicant reports that decreases in dulaglutide exposure of up to 30% and 33% (C_{max} and AUC, respectively) were observed across all groups with hepatic impairment compared with the control group. The time to C_{max} of dulaglutide generally increased with degree of hepatic impairment. There was, however, no trend in dulaglutide exposure relative to the degree of hepatic impairment. The Applicant concludes that the effect of hepatic impairment upon dulaglutide PK is not considered to be clinically relevant and does not require dose adjustments in patients with hepatic impairment.

In a clinical pharmacology study (Study H9X-MC-GBCM [GBCM]) that was conducted in healthy subjects and subjects with some degree of renal impairment, the PK profile of dulaglutide was characterized for 14 days following a single SC dose of dulaglutide 1.5 mg. The Applicant reports that there was no clinically relevant effect of renal impairment on the PK of dulaglutide.

The Applicant indicates that dulaglutide did not affect the exposure (AUC and C_{max}) of coadministered acetaminophen, lisinopril, metoprolol, digoxin, oral contraceptives, atorvastatin, sitagliptin, metformin, or warfarin to any clinically relevant degree. Since coadministration with sitagliptin, a dipeptidyl peptidase 4 (DPP4) inhibitor did not increase dulaglutide exposure, DPP4 does not play a role in dulaglutide metabolism.

Drug interactions are discussed further in the clinical pharmacology review and also in section 7.5.5 Drug-Drug Interactions

5 Sources of Clinical Data

At the time of filing the clinical program investigating dulaglutide for T2DM included 30 clinical studies. Theses consisted of:

- 21 Phase 1 studies
- 4 Phase 2 studies
- 5 Phase 3 studies

The pivotal efficacy and safety data in support of dulaglutide use in subjects with T2DM are derived from five Phase 3 studies conducted in a general population of patients with

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T2DM (studies GBCF, GBDA, GBDB, GBDC, and GBDD). Three of these studies had a 52-week treatment period (GBDA, GBDC, and GBDD), one had a 78-week treatment period (GBDB), and one had a 104-week treatment period (GBDF). At the time of the BLA submission, all five Phase 3 studies were complete.

Ten studies were ongoing at the time of submission (one clinical pharmacology study and nine phase 3 studies). This included the cardiovascular (CV) outcome study (GBDJ) and the dedicated study in patients with moderate to severe chronic kidney disease (GBDX).

At the time the 4-month safety update was submitted (data cut-off date: August 29, 2013), none of these studies were complete and only blinded safety information was available. Individual blinded cases in ongoing studies available in the Lilly Safety System (LSS) through October 3, 2013 were also presented in the 4-month safety update. However, since all the data was blinded, the information did not contribute significantly to the review. Selective unblinding of some cases was requested and is discussed further in the safety section.

5.1 Tables of Studies/Clinical Trials

Table 2 briefly describes the studies included in the completed dulaglutide clinical program.

Table 2: Completed Clinical Pharmacology/Biopharmaceutics, Phase 2 and 3 Clinical, and Device Studies (Data Cutoff Date-April 19, 2013)

Clinical Pharmacology and Biopharmaceutics Studies	Device Studies[a]
Healthy Subject PK, PD, and Tolerability	IQBA - safety/tolerability of single-use pen vs. prefilled syringe
GBCA – Single-dose safety, PK, and PD	IQBE – summative human factors study for the single-use pen
Studies Providing Patient PK and/or PD Information	**Phase 2 Studies**
GBCD – Multiple-dose safety, PK, and PD	GBCJ – 16-week, placebo-controlled, dulaglutide dose titration (background: 2 OAMs - MET, SU, TZD, or DPP-4 inhibitor)
GBCB – Single-dose safety, PK, and PD in Japanese patients with T2DM	GBCK – 12-week, placebo-controlled, dose-dependent effects on glycemic control (background: diet/exercise)
GBCL – Multiple-dose safety, PK, and PD in Japanese patients with T2DM	GBCZ – 12-week, placebo-controlled, dose-dependent effects on glycemic control, Japanese patients with T2DM (background: diet/exercise)
Effect of Intrinsic Factors	GBDN – 26-week, placebo-controlled, BP/HR with ABPM (background: OAM(s) - MET, SU, TZD, glinides, α-glucosidase inhibitors)
GBCM - Renal impairment (subjects with normal/impaired renal function)	
GBCT - Elderly (≥65 years of age) patients with T2DM	
GBDO - Hepatic impairment (subjects with normal/impaired hepatic function)	
GBCN - Effect of injection site on BA; effect of BMI (subjects with high/low BMI)	**Phase 3 Studies**
Effect of Dulaglutide on PK and/or PD of other Drugs	GBCF[c] – 104-week, placebo- and sitagliptin-controlled, HbA1c noninferiority vs. sitagliptin (background: MET)
GBCO - Lisinopril/metoprolol in subjects with hypertension (with/without T2DM) and healthy subjects	GBDA – 52-week, placebo- and exenatide BID-controlled, HbA1c superiority vs. placebo (background: MET+TZD)
GBCP - Atorvastatin in healthy subjects	GBDB – 78-week, insulin glargine-controlled, HbA1c noninferiority vs. comparator (background: MET+SU)
GBCQ - Oral contraceptives in healthy women taking OC	GBDC – 52-week, MET-controlled, HbA1c noninferiority vs. comparator (background: diet/exercise)
GBCR - Digoxin in healthy subjects	GBDD – 52-week, insulin glargine-controlled, HbA1c noninferiority vs. comparator (background: insulin lispro±MET)
GBCS - Warfarin in healthy subjects	
GBDM[b] – MET in patients with T2DM	
GBDW - Sitagliptin in patients with T2DM	
Special Studies	
GBCI - Restoration of first/second phase insulin (healthy subjects/T2DM)	
GBCH - Gastric emptying (healthy subjects)	
Thorough QT Interval Study	
GBCC - Thorough QT study	
Bioavailability (Healthy Subjects)	
GBDR - Absolute BA of SC; relative BA of IM vs. SC	
GBDT - Comparative PK of single-use pen vs. prefilled syringe	

Abbreviations: ABPM = ambulatory blood pressure monitoring; BA = bioavailability; BID = twice daily formulation; BMI = body mass index; BP = blood pressure; DPP4 = dipeptidyl peptidase 4; HbA1c = hemoglobin A1c; HR = heart rate; IM = intramuscular; MET = metformin; OAM = oral antihyperglycemic medication; OC = oral contraceptives; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; vs. = versus.

Source: Table ISS 4.1, eCTD 5.3.5.3

The clinical pharmacology and biopharmaceutics studies were designed primarily to assess pharmacokinetics (PK), pharmacodynamics (PD), the effect of extrinsic and intrinsic factors on dulaglutide PK and/or PD, the effects of dulaglutide on PK of other drugs, important drug-drug interactions, and safety and tolerability, including the effect of dulaglutide on corrected QT (QTc) interval. Single doses of dulaglutide were administered over a range of 0.1 mg to 12 mg, and multiple doses of 0.05 mg to 8 mg were administered once weekly for up to 6 weeks.

There were four Phase 2 (12-26 week) studies included with the initial dulaglutide submission. Of these, three Phase 2 placebo-controlled studies (GBCJ, GBCK, and GBCZ) were conducted in patients with T2DM with once weekly dulaglutide to evaluate dose titration, dose response as monotherapy, and dose response in Japanese patients, respectively. An additional 26-week Phase 2 study (GBDN) was conducted to evaluate the effects of dulaglutide (1.5 mg and 0.75 mg) versus placebo on blood

pressure (BP) and heart rate using ambulatory blood pressure monitoring (ABPM) in patients with T2DM.

The completed Phase 3 program includes five clinical studies, ranging from 52 weeks to 104 weeks in duration, designed to evaluate the efficacy and safety of two doses of once weekly subcutaneous injections of dulaglutide in a general T2DM population. The clinical program investigated dulaglutide as monotherapy, as add-on to single, dual, and triple oral antidiabetic agents, and in combination with insulin glargine. The program provided both placebo and active comparator data.

The following studies (Table 3) were reported as ongoing both in the BLA submission and 4-month safety update, which had a data cut-off date of August 29, 2013.

Table 3: Dulaglutide Clinical studies Ongoing as of August 29, 2013

Study	Protocol Title
	Phase 1
GBDL	Pharmacokinetics of a Single LY2189265 Dose in Healthy Chinese Subjects and of Multiple LY2189265 Doses in Chinese Patients with T2DM
	Phase 3
GBCG[a]	The Efficacy and Safety of Once-Weekly, Subcutaneous Dulaglutide Monotherapy Compared to Glimepiride in Patients with Type 2 Diabetes Mellitus
GBDE	A Randomized, Open-Label, Parallel-Arm Study Comparing the Effect of Once-Weekly Dulaglutide with Once-Daily Liraglutide in Patients with Type 2 Diabetes
GBDG	A Randomized, Parallel-Arm, Double-Blinded Study Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Patients with Type 2 Diabetes Mellitus on Sulfonylurea Therapy
GBDJ	The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly Incretin in Diabetes
GBDK[a]	The Efficacy and Safety of Once-Weekly, Subcutaneous Dulaglutide Compared to Once-Daily Insulin Glargine in Patients with Type 2 Diabetes Mellitus on Metformin and/or a Sulfonylurea
GBDP[b]	A Phase 3 Study of LY2189265 Monotherapy Compared to Placebo and Liraglutide in Patients with Type 2 Diabetes Mellitus
GBDQ[b]	A 52-Week, Open-Label, Long-Term Safety Study of LY2189265 in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus
GBDX	A Randomized, Open-Label, Parallel-Arm Study Comparing the Effect of Once-Weekly Dulaglutide With Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease
GBDY[b]	A Phase 3 Study of LY2189265 Compared to Insulin Glargine in Patients with Type 2 Diabetes Mellitus on a Sulfonylurea and/or Biguanide

Abbreviations: T2DM = Type 2 diabetes mellitus.
[a] Predominantly Asian subjects.
[b] Japanese subjects.

Source: Table ISS: 4.2, eCTD 5.3.5.3

5.2 Review Strategy

The data reviewed come from the original BLA submission and the 120-day safety update.

All phase 3 studies are discussed individually throughout section 6 Review of Efficacy. Individual study results are presented with respect to the primary and secondary endpoints of interest. When appropriate, studies were grouped together for subgroup analyses. The primary data source for my review of efficacy was the individual clinical study reports and the Integrated Summary of Efficacy (ISE).

To assess the safety of Dulaglutide, the data from nine controlled phase 2/3 studies were considered in integrated safety datasets discussed further in section 7.1.3. The primary document for the safety review was the Integrated Summary of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

The five Phase 3 studies were designed as follows:

- Monotherapy (GBDC)
- Add-on to metformin (GBCF)
- Add-on to metformin plus sulfonylurea (GBDB)
- Add-on to metformin plus thiazolidinedione (GBDA)
- Add-on to basal insulin with or without metformin (GBDD)

Comparators used included placebo and various active comparators (e.g. sitagliptin, exenatide, insulin).

In addition, a phase 2 study multicenter, randomized, double-blind, parallel-arm, 26-week treatment period, placebo-controlled study (study GBDN) evaluated the effects of dulaglutide 1.5 mg and dulaglutide 0.75 mg on blood pressure and heart rate using ambulatory blood pressure monitoring (ABPM) in patients with T2DM on at least 1 oral anti-diabetic medication (OAM). Although the primary end-points were BP and HR, HbA1C, fasting serum glucose (FSG) and weight were secondary end-points. This study is included in some of the integrated study-pools for safety (discussed further in section 7.1.3).

Table 4 provides key characteristics of study design, treatment allocation, and number of subjects enrolled in the 9 phase 2/3 studies

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Table 4: Completed Dulaglutide Clinical Program-Key Characteristics of Phase 2 and Phase 3 Studies

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Duration[a]
Phase 2 Studies						
H9X-MC-GBCJ	Evaluate dulaglutide compared to placebo on HbA1c change from baseline.	Phase 2, multi-center, multiple titrated and nontitrated doses, placebo-controlled, parallel-group, double-blind study	Dulaglutide: 0.5, 1.0, 2.0 mg; SC, once weekly Placebo: SC, once weekly Patients added assigned therapy to 2 OAMs (MET, SU, TZD, and DPP-4 inhibitor).	ITT = 262 (dulaglutide = 196; placebo = 66)	T2DM suboptimally controlled with 2 OAMs (MET, SU, TZD, DPP-4 inhibitor) (screening HbA1c >7.0% to ≤10.5%).	16 wks (final time point = 16 wks)
H9X-MC-GBCK	Demonstrate a dose-dependent effect of dulaglutide, as monotherapy, on HbA1c change from baseline.	Phase 2, parallel-arm, randomized, double-blind, placebo-controlled study	Dulaglutide: 0.1, 0.5, 1.0, 1.5 mg; SC, once weekly Placebo: SC, once weekly	ITT = 164 (dulaglutide = 132; placebo = 32)	T2DM suboptimally controlled with MET or antihyperglycemic medication-naïve (screening HbA1c ≥7.0% to ≤9.5% for patients on prestudy diet and exercise and >6.5% to ≤9.0% for patients who discontinued prestudy MET).	12 wks (final time point = 12 wks)

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Duration[a]
H9X-JE-GBCZ	Demonstrate the dose-dependent effect of dulaglutide, as monotherapy, on HbA1c change from baseline in Japanese patients.	Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-arm, comparative study	Dulaglutide: 0.25, 0.5, 0.75 mg; SC, once weekly Placebo: SC, once weekly	ITT = 145 (dulaglutide = 108; placebo = 37)	T2DM suboptimally controlled with monotherapy or antihyperglycemic medication-naïve (screening HbA1c ≥7.0% to ≤9.5% for patients on prestudy diet and exercise and ≥6.0% to ≤8.5% for patients who discontinued prestudy OAM).	12 wks (final time point = 12 wks)
H9X-MC-GBDN	Demonstrate change from baseline in mean, 24-hour systolic blood pressure (measured by ABPM) with dulaglutide was noninferior (3 mmHg margin) to placebo at 16 weeks.	Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study	Dulaglutide: 0.75, 1.5 mg; SC, once weekly Placebo: SC, once weekly Patients added assigned therapy to ≥1 OAM(s).	ITT = 755 (dulaglutide = 505; placebo = 250)	T2DM with ≥1 OAM(s) (screening HbA1c ≥7.0% and ≤9.5%), mean BP >90/60 mmHg and <140/90 mmHg at Visit 1; if treated for HTN, taking ≤3 antihypertensive medications.	26 wks (primary time point = 16 wks; final time point = 26 wks)

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Duration[a]
Phase 3 Studies - Comparative Efficacy						
H9X-MC-GBCF	Stage 1: Identify up to 2 doses of dulaglutide (referred to as high and low dose) for confirmatory studies. Stage 1 and Stage 2: Demonstrate dulaglutide was noninferior (0.25% margin) to sitagliptin on HbA1c change from baseline at 52 weeks.	Phase 2/3, adaptive, inferentially seamless, multicenter, randomized, placebo-controlled, double-blind, parallel-arm study	Stage 1: Dulaglutide: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0 mg; SC, once weekly Placebo: SC, once weekly Sitagliptin: 100 mg, PO, once daily placebo: PO, once daily Stage 2: Dulglutide: 1.5, 0.75 mg; SC, once weekly Placebo: PO, once daily; SC, once weekly up to 26 weeks Sitagliptin: 100 mg, PO, once daily Patients added assigned therapy to MET ≥1500 mg once daily.	Stage 1: ITT = 230 (dulaglutide = 150; placebo[b] = 38; comparator = 42) Stage 1 and 2, primary treatment groups: ITT = 1098 (dulaglutide 1.5 mg = 304; dulaglutide 0.75 mg = 302; placebo[b] = 177; sitagliptin = 315)	T2DM suboptimally controlled with MET, 1 other OAM, MET + 1 other OAM, or antihyperglycemic medication-naïve (screening HbA1c ≥7.0% to ≤9.5%).	104 wks (primary time point = 52 wks, final time point = 104 wks) Note: placebo-controlled = 26 wks[b]

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Duration[a]
H9X-MC-GBDC	Demonstrate dulaglutide 1.5 mg was noninferior (0.4% margin) to MET on HbA1c change from baseline at 26 weeks.	Phase 3, randomized, parallel-arm, active comparator, double-blind, double-dummy, noninferiority study	Dulaglutide: 0.75, 1.5 mg; SC, once weekly Placebo: PO, twice daily; SC, once weekly MET: 1000 mg, PO, twice daily (total dose of 2000 mg/day or 1500 mg/day as tolerated by the patient)	ITT = 807 (dulaglutide 1.5 mg = 269; dulaglutide 0.75 mg = 270; MET = 268)	T2DM for ≥3 months and ≤5 years, suboptimally controlled with 1 OAM or treatment-naïve (screening HbA1c ≥6.5% to ≤9.5%).	52 wks (primary time point = 26 wks; final time point = 52 wks)
H9X-MC-GBDA	Demonstrate dulaglutide 1.5 mg was superior to placebo on HbA1c change from baseline at 26 weeks.	Phase 3, multicenter, parallel-arm, double blind placebo-controlled, open-label to comparator, randomized, study	Dulaglutide: 0.75, 1.5 mg; SC, once weekly Placebo: SC, once weekly for 26 weeks Exenatide: 5 mcg, twice daily for 4 weeks followed by 10 mcg twice daily thereafter Patients added assigned therapy to MET up to 2550 mg/day or the highest tolerable local label dose, and pioglitazone up to 45 mg/day or the highest tolerable local label dose.	ITT = 976 (dulaglutide 1.5 mg = 279; dulaglutide 0.75 mg = 280; placebo[b] = 141; exenatide = 276)	T2DM suboptimally controlled with up to 3 OAM(s) (screening HbA1c ≥7.0% and ≤11.0% if on 1 OAM and ≥7.0% and ≤10.0% if on >1 OAM).	52 wks (primary time point = 26 wks; final time point = 52 wks)

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Duration[a]
H9X-MC-GBDB	Demonstrate dulaglutide 1.5 mg was noninferior (0.4% margin) to insulin glargine on HbA1c change from baseline at 52 weeks.	Phase 3, open-label to comparator, double-blind to dulaglutide dose, multicenter, parallel-arm, randomized study	Dulaglutide: 0.75, 1.5 mg; SC, once weekly Insulin glargine: starting dose 10 IU, SC; thereafter, adjusted based on treat-to-target algorithm of self-monitored FPG target <100 mg/dL Patients added assigned therapy to maximally tolerated doses of MET ≥1500 mg/day and glimepiride ≥4 mg/day.	ITT = 807 (dulaglutide 1.5 mg = 273; dulaglutide 0.75 mg = 272; insulin glargine = 262)	T2DM suboptimally controlled with up to 3 OAM(s), at least 1 of which must have been MET or SU (screening HbA1c ≥7.0% and ≤11.0% if on 1 OAM and ≥7.0% and ≤10.0% if on >1 OAM).	78 wks (primary time point = 52 wks; final time point = 78 wks)

Study	Primary Objective	Study Design	Study Drug	Number of Patients	Patient Population	Total Treatment Duration[a]
H9X-MC-GBDD	Demonstrate dulaglutide 1.5 mg was noninferior (0.4% margin) to insulin glargine on HbA1c change from baseline at 26 weeks.	Phase 3, parallel-arm, open-label, active comparator study	Dulaglutide: 0.75, 1.5 mg; SC, once weekly Insulin glargine: starting dose 50% of prerandomization total daily dose, SC, at bedtime; thereafter, adjusted based on treat-to-target algorithm of self-monitored FPG target >70 to <100 mg/dL All patients added assigned therapy to prandial insulin lispro (starting dose 50% of prerandomization total daily dose; thereafter adjusted to prespecified premeal FPG targets) ± MET.	ITT = 884 (dulaglutide 1.5 mg = 295; dulaglutide 0.75 mg = 293; insulin glargine = 296)	T2DM suboptimally controlled with ≥3 months of a conventional insulin regimen (≤2 doses of insulin per day), alone or in combination with OAMs (screening HbA1c ≥7.0% and ≤11.0%).	52 wks (primary time point = 26 wks; final time point = 52 wks)

Abbreviations: ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DPP-4 = dipeptidyl peptidase-IV; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin A1c; HTN = hypertension; ITT = intent-to-treat; IU = International Unit; MET = metformin; mmHg = millimeters of mercury; N = number of patients; OAM = oral antidiabetic medication; PO = orally; SC = subcutaneous; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones.

[a] An additional 4-week safety follow-up period was included in all studies with the exception of Study GBCJ; the follow-up period is not included in the treatment duration.

[b] Total duration of placebo-controlled period was 26 weeks; after 26 weeks, patients originally randomized to placebo were converted to active therapy (GBCF: sitagliptin; GBDA: dulaglutide 1.5 mg or dulaglutide 0.75 mg) in an effort to maintain study blind and collect long-term, controlled safety data across the treatment groups.

Source: Table 2.7.3.3, Summary of Clinical Efficacy, eCTD 2.7.3

5.3.1. Phase 3 Trial Characteristics:

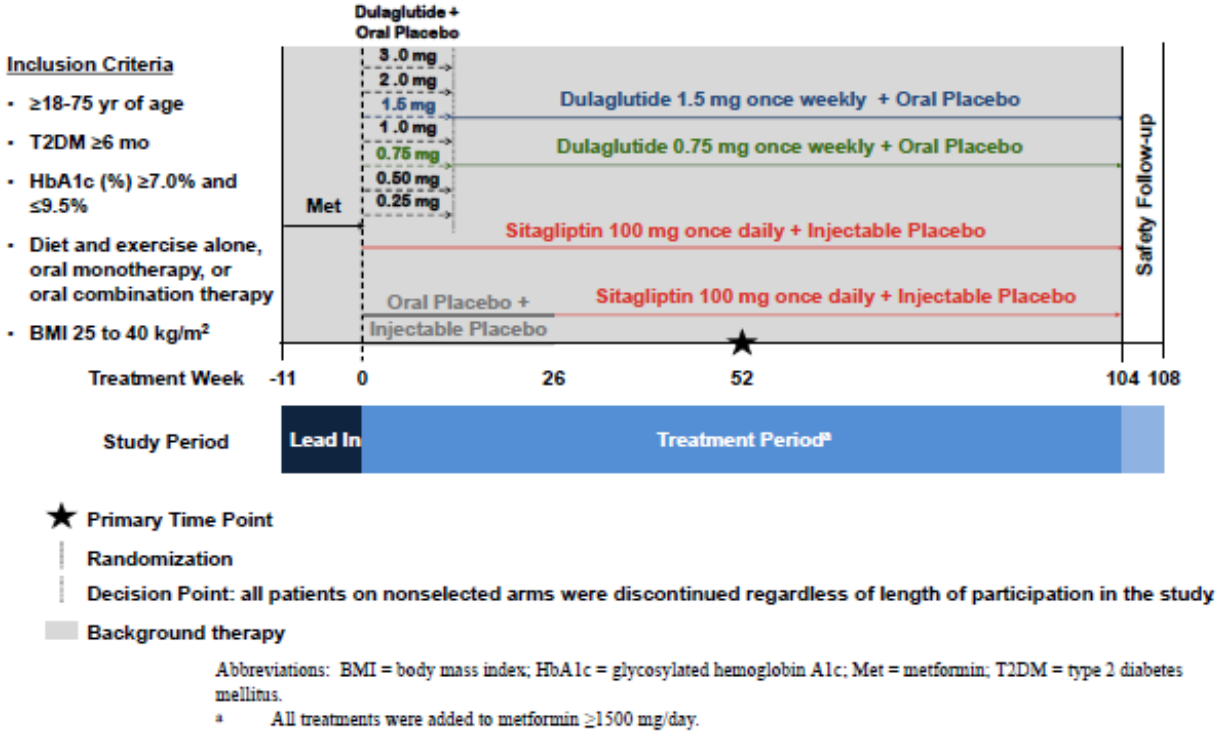
At the time of the BLA submission, five phase 3 studies were complete: GBDC, GBCF, GBDA, GBDB, and GBDD. Three of these studies had a 52 week treatment period (GBDA, GBDC and GBDD); one had a 78-week treatment period (GBDB), and one had a 104-week treatment period (GBDF). The primary endpoint analysis for the placebo comparison was at 26 weeks for studies GBCF and GBDA. The primary endpoint analysis against active comparator was at 52 weeks for studies GBCF and GBDB, and at 26 weeks for studies GBDC, GBDA and GBDD.

All of these long-term controlled clinical trials were conducted as randomized, parallel-arm trials. Placebo-controlled trials were double-blinded, consistent with standards of research and regulatory guidance. Two of the Phase 3 studies (GBCF and GBDA) had a 26-week placebo-controlled period, after which patients in the placebo arm were switched to an active comparator (sitagliptin 100 mg [Study GBCF]) or to dulaglutide (1.5 mg or 0.75 mg; [Study GBDA]) for the remainder of the study duration (≥52 weeks). The insulin-comparator studies (GBDB and GBDD) were conducted as open-label comparator studies due to the complexity of blinding and the need to titrate insulin doses. However, the two doses of dulaglutide were double-blinded. The exenatide twice daily comparator study (Study GBDA) was also open-label with respect to the active comparator due to the complexity of blinding the exenatide BID pen device. Again, the two doses of dulaglutide and placebo were double-blinded in this study.

As mentioned above, study GBCF was part of a Critical Path Initiative. The study was intended to be a "seamless" phase 2/3 study. Specific design features of study GBCF are discussed further below:

Study H9X-MC-GBCF (GBCF) was an adaptive, inferentially seamless, confirmatory, multicenter, randomized, 24-month, double-blind, double-dummy, parallel group clinical trial comparing once-weekly dulaglutide to once-daily sitagliptin (100 mg) and placebo in patients with type 2 diabetes mellitus (T2DM) treated with metformin (Figure 2). There was extensive regulatory correspondence between the sponsor and the FDA related to this trial. This study was designed to serve as the definitive dose-selection study for the dulaglutide program, and as a pivotal Phase 3 study. The primary objective was to show noninferiority of the higher dulaglutide dose (if 2 doses were selected) to sitagliptin with respect to change in glycosylated hemoglobin (HbA1c) at 12 months. The final endpoint was 24 months. Placebo comparisons were planned at 6 months (before switching patients from placebo to sitagliptin in a blinded manner as shown in figure below).

Figure 2: Study design for H9X-MC-GBCF:



Abbreviations: BMI = body mass index; HbA1c = glycosylated hemoglobin A1c; Met = metformin; T2DM = type 2 diabetes mellitus.

[a] All treatments were added to metformin ≥1500 mg/day.

Source: Figure 2.7.3.4, Summary of Clinical efficacy, eCTD 2.7.3.

Two randomization schemes were used during the trial:

- Stage 1: an adaptive randomization scheme to assign a patient to one of the 7 initial dulaglutide doses based on accumulating data analyzed every 2 weeks

was used prior to dose selection/Decision Point (i.e. patients were randomized to the placebo/sitagliptin sequence, sitagliptin, and dulaglutide arms in a fixed ratio of 1:1:3, but the randomization across the 7 dulaglutide treatment arms was to be done adaptively).

- Stage 2: a fixed randomization scheme (i.e., a 2:2:2:1 allocation ratio of dulaglutide low dose, dulaglutide high dose, sitagliptin, and placebo/sitgliptin) after dose selection.

Further details are discussed in page 29, section 7.1.1 of the protocol amendment for study GBCF (see h9x-mc-gbcf-05 protocol-a, eCTD 5.3.5.1).

A clinical utility index (CUI) was designed and used during Stage 1 to facilitate the adaptive randomization and to evaluate the dose decision rules for Stage 2. This was based on change from baseline in HbA1c, weight, diastolic blood pressure (DBP), and pulse rate. The Decision Point did not occur at a defined period of time after study start, but occurred when sufficient data had been accumulated to support dose selection or stopping the trial for futility. Patients randomized to the five non-selected dulaglutide doses (non-primary arms) were discontinued after the Decision Point. The final analyses were based on data from both stages from the primary treatment arms (dulaglutide 1.5 mg, dulaglutide 0.75 mg, placebo, and sitagliptin) in patients enrolled before and after dose selection.

The sponsor's rationale for this design was "efficient use of patient safety and efficacy data to characterize the dulaglutide dose-response relationship and to improve data-driven decisions to select doses that possessed the most acceptable efficacy and safety profile; permitted a single trial to combine objectives traditionally addressed in separate trials. This design was implemented to enable seamless transition between the 2 randomization schemes and inclusion of all randomized patients assigned to the selected dulaglutide doses and the comparator arms into the final analyses."

The sponsor was informed that FDA would only consider the stage 2 analyses for confirmatory inference and viewed stage 1 as exploratory with the potential for selection bias (see IND 070930, FDA correspondence dated January 17, 2008).

The overall design of the other phase 3 studies shared many similar components.

OBJECTIVES- Phase 3 Studies:

<u>Primary Objective</u>:

To demonstrate that dulaglutide (as mono or combination therapy) is safe and effective for the treatment of subjects with T2DM as determined by assessing the effect of dulaglutide relative to comparator (placebo or active) on the change in HbA1c from baseline to the primary assessment time point of 26 weeks for the individual studies

(except Study GBDB and comparison to sitagliptin in study GBCF, which used 52 weeks).

Secondary Objectives:

To determine the change from baseline in HbA1c over time, change from baseline in FPG, proportion of subjects who achieve an HbA1c treatment goal of <6.5% or <7.0%, and change from baseline in body weight.

STUDY PERIODS

- Pre-screening/Screening: 2 weeks.

- Run-in/Stabilization: 9-12 weeks (2 weeks in monotherapy study GBDC). During the Run-in/Stabilization Period, subjects received placebo injector pens and training on sterile techniques for self-administration at home during the treatment period.

- Treatment Period: evaluating efficacy and safety. Assessments performed during the Treatment Period include concomitant medications review, physical examinations, vital sign measurements, triplicate 12-lead ECGs, clinical laboratory assessments (including FPG, HbA1c, lipids, insulin, and immunogenicity samples), urinalysis, weight, pregnancy tests, monitor for hyperglycemia, exploratory biomarkers, and review of adverse events and hypoglycemia events as outlined in the Time and Events Table in individual clinical study reports .

- Post-treatment follow-up: 4 weeks- All Phase 3 studies and the Phase 2 studies, except Study GBCJ, included a 30-day safety follow-up period after the last week of scheduled dosing (or early study discontinuation visit during the dosing period) in the individual study protocol. Subjects attended a follow-up visit at the end of the 4-week post-treatment period. Assessments performed at the follow-up visit included concomitant medication review, vital sign measurements, safety laboratory assessments (hematology and clinical chemistry), HbA1c, immunogenicity samples, weight, urine pregnancy test, and review of adverse events and hypoglycemia events. In cases where a patient may have stopped study drug early, the period between last dose of study drug and the safety follow-up visit may have been longer than 30 days.

Randomization of eligible subjects was stratified by:
Study GBCF: by baseline HbA1c (<8.5%, >8.5%) in Stage 2
Studies GBDA, GBDB: by country and baseline HbA1c.
Study GBDC: country and prior oral antihyperglycemic medication (OAM) i.e. not on OAM and on one OAM.

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Study GBDD: by country and by metformin use at randomization.

Starting Dose:
In the Phase 3 studies the starting dose of dulaglutide was either 0.75 or 1.5 mg administered subcutaneously once weekly. There was no dose titration in any of the phase 3 studies.

Concomitant medications:

- GBCF: patients had to be able to tolerate metformin at a dose of ≥1500 mg daily for 6 weeks or more prior to randomization at Visit 4.
- GBDA: minimum dosage of metformin of 1500 mg/day and pioglitazone up to 30 mg/day, or the highest tolerable local label dose, established by 8 weeks prior to randomization and stable throughout the treatment period.
- GBDB: maximum tolerated/locally approved dose of metformin and SU, but not lower than minimal required dose of metformin 1500 mg and glimepiride 4 mg; for other sulfonylureas, the minimal required dose had to be 50% of the recommended maximum daily dose, established 8 weeks prior to randomization.
- GBDD: Treatment with metformin during the study was permitted if the patient was taking at least 1500 mg (minimal required dose), but no higher than the maximal locally approved dose of metformin by Visit 3 (8 weeks prior to randomization). The patients were instructed to administer their prandial insulin lispro with the 3 most significant (i.e. largest) meals of the day. The dose decision for insulin dose adjustment was to be based upon the median of the previous 3 SMBG values for each referenced time point
- Patients assigned to the insulin glargine treatment arm in studies GBDD and GBDB were to inject study drug according to the dosing method used in the Treat-to-Target algorithm described by Riddle, et al., 2003.

Rescue Treatment:

Patients who met pre-specified definitions for severe, persistent hyperglycemia qualified for rescue therapy (i.e. additional or alternative antihyperglycemic medication). The specific rescue therapy was determined by the investigator based on standards of care. Other GLP-1 receptor agonists were not allowed to be used as rescue therapy, but DPP4 inhibitors were not restricted.

- Rescue therapy was not employed in Study GBCF; patients who met prespecified thresholds for hyperglycemia were required to be discontinued from the study,
- In Studies GBDA, GBDB, and GBDC, rescue therapy was to be administered in combination with study drug.
- In Study GBDD, study drug was to be discontinued prior to initiation of additional or alternative antihyperglycemic medication. Due to the therapeutic requirements

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in this population that was already taking a regimen of multiple daily insulin injections, patient management was left to the discretion of the investigator.

Study Population: Dulaglutide was studied in men and women with established T2DM. Only adult subjects (i.e. > 18 years of age) were studied. No upper limit for age was imposed except in study GBCF (patients were to be < 75 years of age).

Key inclusion criteria:

1. Male or female (females of childbearing potential practicing adequate contraception) ≥18 years with type 2 diabetes mellitus experiencing inadequate glycemic control.
2. Duration of T2DM at least three months and less than five years (study GBDC); duration of T2DM at least six months in study GBCF
3. Body mass index (BMI) > 23 kg/m^2 and ≤ 45 kg/m^2.
4. HbA1c between:
    - 7-11% (GBDA, GBDB, and GBDD)
    - 7-9.5% (GBCF)
    - 6.5-9.5% (GBDC)
5. Patients treated with:
    - Diet and exercise alone, or 1 OAM that is ≤50% of recommended maximum daily dose (GBDC)
    - Diet and exercise alone, oral monotherapy, or oral combination therapy (GBCF, GBDA, and GBDB)
    - Study GBDD-A conventional insulin regimen of ≤2 doses/day including any combination of basal, basal with prandial, or premixed insulin, alone or in combination with OAMs. Total daily doses had to be within ±10% of most commonly administered total dose over three months.

Key exclusion criteria:

Patients were excluded from study if they met any of the following criteria:

1. Have known type 1 diabetes.
2. Have been treated with a GLP-1 analog (for example, exenatide, liraglutide) within 6 months prior to screening or being treated with insulin (except study GBDD, in studies GBCF, GBDA, GBDB, GBDC, only insulin for short-term management of acute conditions 3 months prior to the first visit was permitted)
3. Have had two or more episodes of ketoacidosis or hyperosmolar state/coma requiring hospitalization in the six months prior to screening
4. Have a known clinically significant gastric emptying abnormality (e.g. severe diabetic gastroparesis, gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery, or chronically take drugs that directly reduce gastrointestinal motility.
5. Are currently taking prescription or over-the-counter medications to promote weight loss.
6. Have had any of the following cardiovascular events within six months

prior to screening: unstable angina requiring hospitalization, myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention (diagnostic angiograms are permitted), heart failure, atrial or ventricular arrhythmia (for example, atrial fibrillation, ventricular tachycardia, long QT syndrome), pacemaker or defibrillator implantation, transient ischemic attack, or cerebrovascular accident.

a. Study GBDB, GBDC, and GBDD: Any of the following CV conditions within 2 months prior to screening- acute myocardial infarction, New York Heart Association (NYHA) class III or class IV heart failure, or cerebrovascular accident (stroke);
b. Study GBDA: Patients with a past history of edema or fluid retention, or any of the following CV conditions within 2 months of Visit 1: congestive heart failure, New York Heart Association (NYHA) Class II, III, or IV (or as excluded by local label)

7. Have poorly controlled hypertension (i.e., mean seated systolic blood pressure ≥160 mm Hg or mean seated diastolic blood pressure ≥95 mm Hg at screening or randomization), a change in antihypertensive medications between screening and randomization, evidence of renal artery stenosis, or evidence of labile blood pressure including symptomatic postural hypotension.
8. At screening, an ECG reading considered outside the normal limits by the investigator and relevant for interpretation or indicating cardiac disease (including QTc [Bazett] interval ≥450 ms for males or ≥470 ms for females); aberrant, blocked, or impaired propagation (PR interval ≥220 ms); and clinically significant signs of ischemic heart disease.
9. Have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, a history of chronic pancreatitis or idiopathic acute pancreatitis, or alanine transaminase (ALT) levels ≥ 3.0 times the upper limit of the reference range at screening, as determined by the central laboratory.
10. Have a serum creatinine ≥1.5 mg/dL, or a creatinine clearance ≤ 60 ml/minute, as determined by the central laboratory at screening, which would contraindicate the use of metformin per the label in the respective country.
    a. Study GBDD: Estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m^2 at screening
11. Have evidence of a significant active, uncontrolled endocrine or autoimmune abnormality, as judged by the screening investigator.
12. Have a history of a transplanted organ (corneal transplants [keratoplasty] allowed).
13. Are receiving chronic (≥2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have received such therapy within 4 weeks immediately prior to screening.
14. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years.

15. Have any other condition (such as, known drug or alcohol abuse or psychiatric disorder) that may preclude the patient from following and completing the protocol or taking CNS stimulants.
16. Have any contraindication, known allergy, or hypersensitivity to active ingredient or excipients contained in background study medications.
17. Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle-cell disease).
18. Studies GBDA, GBDB, GBDC and GBDD: Any personal or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial or part of MEN 2A or 2B syndrome) or a serum calcitonin ≥ 20 pcg/mL at screening.

Key withdrawal criteria:

1. The investigator decides that the patient should be withdrawn.
2. If the patient becomes pregnant during the study
3. The patient develops a marked prolongation (≥500 ms or ≥60 ms over baseline) of the QT/QTc interval.
4. For studies GBDA, GBCF and GBDC: The patient requires daily treatment with insulin for more than 14 consecutive days for management of diabetes.
5. The patient is unable to tolerate the study drug.
6. The patient is diagnosed with acute pancreatitis, and in the opinion of the investigator, should discontinue from the study.
7. Following randomization, a patient's mean diastolic blood pressure is observed to increase more than 15 mm Hg compared to baseline.
8. The patient develops persistent or worsening hyperglycemia beyond the thresholds for FPG or HbA1c as specified in the protocols
9. The patient requires chronic (≥14 consecutive days) systemic glucocorticoid therapy.
10. The patient develops acute hepatitis or ALT levels ≥3.0 times the upper limit of the reference range.
11. Studies GBCF, GBDA, GBDB and GBDC: The patient develops moderate (creatinine clearance [CC] ≥30 to ≤59 mL/minute), severe or end-stage renal disease (CC ≤30 mL/minute).
12. Studies GBDA, GBDB,GBDC and GBDD: The patient develops an increase in serum calcitonin by ≥50% of the mean of baseline and screening value AND an absolute value >35 pg/mL; patients with an increase in serum calcitonin by ≥50% of the mean of baseline and screening value AND an absolute value that is ≥20 pg/mL but ≤35 pg/ml were to discontinue the study drug only if the value increased after 1 month; those with stable or decreasing values on repeat testing were allowed to be monitored and assessed per protocol.

6 Review of Efficacy

Efficacy Summary

Based on the prespecified analyses of the primary study endpoints:

- Dulaglutide 1.5 mg and Dulaglutide 0.75 mg achieved statistically significantly better HbA1c reduction compared to sitagliptin and placebo when added to metformin. This was also true compared to 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 (multiplicity adjusted 1-sided p-value < 0.025),
- 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)
- Both doses showed evidence of sustained efficacy over time. Similar to the results at the primary time points, there was evidence for increased efficacy with dulaglutide 1.5 mg compared to 0.75 mg at the final study time points.
- In the individual Phase 3 studies, there were no significant issues noted with antihyperglycemic background, comparator or rescue therapy administration which would affect interpretability of the results for the primary efficacy endpoint.

At the final time point (52 to 104 weeks):

- Based on HbA1c change from baseline, dulaglutide 0.75 mg was statistically significantly superior to the active comparators sitagliptin, exenatide, and insulin glargine (GBDD) and noninferior to the active comparators metformin and insulin glargine (GBDB) in the remaining 2 studies.
- Based on HbA1c change from baseline, dulaglutide 1.5 mg was superior to active comparator in all 5 studies. This testing at the final time point was prespecified and multiplicity adjusted for all studies except GBCF and GBDB

Since it is useful to consider the efficacy results in the context of hypoglycemic episodes and rescue for hyperglycemia, my assessments from the individual studies are presented below:

- Dulaglutide 1.5 mg was more effective than dulaglutide 0.75 mg for reducing HbA1c in three out of five studies. However, dulaglutide 1.5 mg was associated with increased documented symptomatic hypoglycemia in GBCF, and increased severe hypoglycemia in Study GBDD.
- More subjects in study GBDB on dulaglutide 0.75 mg required rescue, however the pre-specified testing for the primary end-point was at pre-rescue and hence it should not affect interpretation of results.

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- In study GBDA, dulaglutide 0.75 mg was superior to exenatide for HbA1c reduction from baseline and there was less documented symptomatic and severe hypoglycemia.

A descriptive summary of relative results in each study is provided below:

Study GBCF (add on to metformin)

Endpoints	Placebo	Sitagliptin	Dula 0.75 mg	Dula 1.5 mg
HbA1c	-	+	++	+++
Rescue	NA	NA	NA	NA
Hypo-symp	-	+	+	++
Hypo-sev	None	None	None	None

- = least number of patients rescued, least number of hypoglycemic episodes, or least change in HbA1c compared to baseline; +, ++ or +++ = relative increase in number of patients rescued, number of hypoglycemic episodes, or increasing decline in HbA1c from compared to placebo or comparators; NA = not available; Hypo symp = documented symptomatic hypoglycemia; Hypo sev = severe hypoglycemia.

Study GBDA (add-on to metformin + TZD)

Endpoints	Placebo	Exenatide	Dula 0.75 mg	Dula 1.5 mg
HbA1c	-	+	++	+++
Rescue	++	+	+	-
Hypo-symp	-	++	+	+
Hypo-sev	None	+	None	None

- = least number of patients rescued, least number of hypoglycemic episodes, or least change in HbA1c compared to baseline; +, ++ or +++ = relative increase in number of patients rescued, number of hypoglycemic episodes, or increasing decline in HbA1c from compared to placebo or comparators; Hypo symp = documented symptomatic hypoglycemia; Hypo sev = severe hypoglycemia.

Study GBDC (monotherapy):

Endpoints	Metformin	Dula 0.75 mg	Dula 1.5 mg
HbA1c	-	+	+
Rescue	Similar	Similar	Similar
Hypo-symp	Similar	Similar	Similar
Hypo-sev	None	None	None

- = least number of patients rescued, least number of hypoglycemic episodes, or least change in HbA1c compared to baseline; + = relative increase in number of patients rescued, number of hypoglycemic episodes, or increasing decline in HbA1c from compared to placebo or comparators; Hypo symp = documented symptomatic hypoglycemia; Hypo sev = severe hypoglycemia.

Study GBDB (add on to metformin and sulfonylurea)

Endpoints	Insulin glargine	Dula 0.75 mg	Dula 1.5 mg
HbA1c	-	- (non-inferior)	+
Rescue	-	++	+
Hypo-symp	+	Less than insulin glargine	Less than insulin glargine
Hypo-sev	+	None	+

- = least number of patients rescued, least number of hypoglycemic episodes, or least change in HbA1c compared to baseline; +, or ++ = relative increase in number of patients rescued, number of hypoglycemic episodes, or increasing decline in HbA1c from compared to placebo or comparators; Hypo symp = documented symptomatic hypoglycemia; Hypo sev = severe hypoglycemia.

Study GBDD (add-on to insulin-lispro and metformin)

Endpoints	Insulin glargine	Dula 0.75 mg	Dula 1.5 mg
HbA1c	-	+	+
Rescue	Similar	Similar	Similar
Hypo-symp	Similar	Similar	Similar
Hypo-sev	+++	+	++

- = least number of patients rescued, least number of hypoglycemic episodes, or least change in HbA1c compared to baseline; +, ++ or +++ = relative increase in number of patients rescued, number of hypoglycemic episodes, or increasing decline in HbA1c from compared to placebo or comparators; Hypo symp = documented symptomatic hypoglycemia; Hypo sev = severe hypoglycemia.

Secondary Endpoints:

The Applicant did not adjust for multiplicity for secondary endpoint comparisons.

Weight loss with dulaglutide was dose-dependent. Dulaglutide 1.5 mg was associated with greater weight reduction than all comparators except metformin. Dulaglutide 0.75 mg was associated with less weight loss compared to metformin, dulaglutide 1.5 mg, and exenatide, but it was associated with more weight loss compared to insulin glargine. In all five Phase 3 studies, treatment with dulaglutide 1.5 mg resulted in weight reduction that was maintained through the final time point and and that was nominally statistically significantly superior to all comparators but metformin. In three of the Phase 3 studies, dulaglutide 0.75 mg was associated with weight reduction for the duration of the studies. Dulaglutide 0.75 mg was nominally statistically significantly inferior for weight loss to metformin at the final time point in study GBDC and exenatide in study GBDA.

The effect of dulaglutide on fasting serum glucose was dose-dependent. Both doses of dulaglutide was nominally statistically significantly superior to placebo, sitagliptin and exenatide for reduction of FPG, not significantly different from metformin, and inferior to insulin glargine.

A larger proportion of dulaglutide treated subjects achieved a target HbA1c (thresholds of under 7% and under 6.5%) compared to active comparators in all studies except GBDD. In study GBDD the difference vs. insulin glargine was statistically significant only for subjects treated with dulaglutide 1.5 mg for the HbA1c under 7% category. The difference between dulaglutide 1.5 mg versus 0.75 mg was statistically significant with a greater proportion of patients achieving a target HbA1c with dulaglutide 1.5 mg than dulaglutide 0.75 mg in studies GBCF, GBDA and GBDB. No gate-keeping strategy was followed for testing of this end-point.

Limitations:

There are certain therapeutic scenarios in which dulaglutide has not been studied. Dulaglutide has not been studied as an add-on therapy to a basal insulin. Compared to dulaglutide, the recently approved once-weekly GLP-1 agonist albiglutide had been studied as add-on therapy to insulin glargine in an active comparator (insulin lispro) study and liraglutide has been studied with insulin detemir. As such, it is appropriate it include a statement in the label describing the lack of information in this setting.

6.1 Indication

The Applicant is seeking an indication for dulaglutide as an adjunct to diet and exercise for improving glycemic control in patients with T2DM.

6.1.1 Methods

Refer to the statistical review by Dr. Bradley McEvoy for a complete discussion on the Applicant's analysis methods and additional sensitivity analyses conducted by the FDA reviewer.

Analysis populations are described in Table 5 below. The primary population analyzed was the intent to treat (ITT) population with missing data imputed by last observation carry forward (LOCF) in study GBCF and Last observation pre-rescue in the other four studies (LprOCF). This is further discussed in the Dr. McEvoy's statistical review for efficacy.

Table 5: Populations Presented within the Summary of Clinical Efficacy:

Population	Definition and Censoring
Intent-to-Treat (ITT; Without Post-Rescue Visits)	Applicable to the Phase 2 and Phase 3 studies. All randomized patients who received at least 1 dose of study treatment for all studies, with the exception of Study GBCF. In Study GBCF, the definition of ITT was all randomized patients. All randomized patients in Study GBCF received at least 1 dose of study treatment. For any particular analysis, only data from patients with at least 1 postbaseline measurement for the parameter of interest were included. In Studies GBDC, GBDA, GBDB, and GBDD, measurements obtained after the initiation of rescue therapy were censored for the purposes of the efficacy analyses.
Per-Protocol (Without Post-Rescue Visits)	Applicable to the Phase 3 studies. All ITT patients who completed the study to the time point of interest, had an overall compliance with study treatment across visits of at least 75%, and had no other significant protocol violations. In Studies GBDC, GBDA, GBDB, and GBDD, measurements obtained after the initiation of rescue therapy were censored for the purposes of the efficacy analyses.
Per-Protocol Without Rescued Patients	Applicable to Phase 3 Studies GBDC, GBDA, GBDB, and GBDD. A subset of the per-protocol population that excludes any patients who were rescued.
Completers (Without Post-Rescue Visits)	Applicable to the Phase 3 studies. All randomized patients with a valid HbA1c at the time point of interest. In Studies GBDC, GBDA, GBDB, and GBDD, measurements obtained after the initiation of rescue therapy were censored for the purposes of the efficacy analyses.
Completers Without Rescued Patients	Applicable to Phase 3 Studies GBDC, GBDA, GBDB, and GBDD. A subset of the completers population that excludes any patients who were rescued.

Abbreviation: HbA1c = glycosylated hemoglobin A1c.

Source: Table 2.7.3.4- SCE, eCTD 2.7.3

Efficacy time points

Efficacy was assessed at a primary efficacy time point, and at a final efficacy time point at the end of treatment. Study GBCF included a 26-week, placebo-controlled period in addition to the 52-week primary time point and 104-week final time point.

Primary and Final Time Points: Phase 3 Studies:

	GBDC	GBCF	GBDA	GBDB	GBDD
Primary Time Point (weeks)	26	52	26	52	26
Final Time Point (weeks)	52	104	52	78	52

Source: Table APP.2.7.3.2, SCE-app, eCTD 2.7.3

In the Phase 3 studies, analyses of the primary efficacy measure (change in HbA1c from baseline) examined the hypotheses (superiority of both dulaglutide doses [1.5 mg and 0.75 mg] to placebo and/or noninferiority/superiority of both dulaglutide doses [1.5 mg and 0.75 mg] to active comparator) at the primary and final time points using a tree-

gatekeeping strategy to control the family wise Type 1 error rate at each time point, except for the final time point in study GBCF.

The primary analysis method was analysis of covariance (ANCOVA) with imputation of missing data by the last observation carried forward method (LOCF) in study GBCF and prerescue observation for all other studies (LprOCF) as discussed earlier. In Studies GBDC, GBDA, GBDB, and GBDD, the pre-specified non-inferiority margin was 0.4%. In Study GBCF, the non-inferiority margin was pre-specified at 0.25%. If the 0.4% noninferiority margin was met but superiority was not achieved, then noninferiority at the 0.3% margin was also evaluated; this was not part of the formal tree-gatekeeping strategy.

Sensitivity Analyses:

Additional sensitivity analyses were performed by the Applicant. These included:

- Mixed-effects model for repeated measures (MMRM) analyses of HbA1c over time and change from baseline in weight in the ITT population
- Four different calculation methods were used to assess the robustness of the analyses of percentages of patients achieving HbA1c targets <7.0 or ≤6.5%
- Population sensitivity analyses (at the primary and final time points) evaluating the 5 differently defined populations described above (cross-reference to table) for change from baseline in HbA1c and percentages of patients achieving HbA1c targets.

Pooled Analyses:

Pooled analyses of the Phase 3 studies were performed post-hoc by the Applicant to compare the dulaglutide 1.5 mg and dulaglutide 0.75 mg doses and were conducted on the intent-to treat (ITT) and Per-Protocol (PP) patient populations for HbA1c, percentages of patients achieving HbA1c targets, and weight change from baseline.

The primary purpose of the integrated analysis was to compare the dulaglutide 1.5 mg and dulaglutide 0.75 mg doses over time; therefore, a MMRM was used to evaluate the treatment difference (dulaglutide 1.5 mg - dulaglutide 0.75 mg) at each time point for mean HbA1c and weight. Logistic regression (without imputation for missing data) was used to compare the dulaglutide 1.5 mg and dulaglutide 0.75 mg doses at each time point for percentages of patients who achieved HbA1c < 7% or ≤ 6.5%.

6.1.2 Demographics

Patient's baseline and demographic characteristics of the target populations in the individual phase 3 studies are discussed in Tables 5, 11, 17, 23 and 29 of the Dr. McEvoy's statistical review of efficacy. These characteristics (Age, Gender, Race,

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Country [%US], baseline BMI, Duration of diabetes, Weight, Fasting serum glucose and Baseline creatinine clearance) seemed reasonably balanced across treatment groups at baseline.

Patients in Study GBDD (insulin glargine comparator; concomitant insulin lispro with or without metformin) had a mean age of approximately 59 years which was approximately 3 to 5 years older than patients in the other studies. This may have been because this study recruited patients with a longer duration of diabetes. Diabetes duration varied across studies with a mean duration of 2.6 years in patients who were treated with diet and exercise or a single OAM prior to enrollment (Study GBDC) to a mean duration of 12.7 years in patients who were using prior insulin therapy (Study GBDD).

Baseline demographics in the major safety pools, (AS1-Placebo controlled studies comparing dulaglutide 0.75 mg and 1.5 mg to placebo, and AS3-Patients treated with dulaglutide 0.75 mg and 1.5mg in Phase 2/3 studies over 26 weeks in duration) are shown below (see Table 6 and Table 7). Demographics for patients included in the CV meta-analyses across all the phase 2/3 trials (dulaglutide vs. all comparators) are presented in Table 5 of the Dr. Janelle Charles' statistical review of cardiovascular safety. They are all comparable across treatment groups and consistent with the assessments by individual studies.

Table 6: Summary of Patient Characteristics at Baseline, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Studies GBCF, GBDA, GBDN) (AS1)

Variable	Placebo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)	Total (N=2238)
Age (yrs)					
Number of Patients	568	836	834	1670	2238
Mean	55.49	55.65	55.22	55.43	55.45
SD	9.97	9.85	10.02	9.94	9.94
Minimum	21.71	19.81	20.79	19.81	19.81
Median	56.00	56.10	55.73	55.97	55.98
Maximum	84.75	85.66	80.87	85.66	85.66
Age Group, n (%)					
< 65 (yrs)	473 (83.3)	708 (84.7)	699 (83.8)	1407 (84.3)	1880 (84.0)
>= 65 (yrs)	95 (16.7)	128 (15.3)	135 (16.2)	263 (15.7)	358 (16.0)
Age Group, n (%)					
< 75 (yrs)	560 (98.6)	825 (98.7)	824 (98.8)	1649 (98.7)	2209 (98.7)
>= 75 (yrs)	8 (1.4)	11 (1.3)	10 (1.2)	21 (1.3)	29 (1.3)
Age Group, n (%)					
< 65 (yrs)	473 (83.3)	708 (84.7)	699 (83.8)	1407 (84.3)	1880 (84.0)
>= 65 and < 75 (yrs)	87 (15.3)	117 (14.0)	125 (15.0)	242 (14.5)	329 (14.7)
>= 75 and < 85 (yrs)	8 (1.4)	10 (1.2)	10 (1.2)	20 (1.2)	28 (1.3)
>= 85 (yrs)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)

Variable	Placebo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)	Total (N=2238)
Gender, n (%)					
Female	264 (46.5)	403 (48.2)	395 (47.4)	798 (47.8)	1062 (47.5)
Male	304 (53.5)	433 (51.8)	439 (52.6)	872 (52.2)	1176 (52.5)
Ethnicity, n (%)					
Hispanic or Latino	174 (30.6)	254 (30.4)	242 (29.0)	496 (29.7)	670 (29.9)
Not Hispanic or Latino	394 (69.4)	582 (69.6)	592 (71.0)	1174 (70.3)	1568 (70.1)
Race, n (%)					
American Indian or Alaska Native	20 (3.5)	37 (4.4)	42 (5.0)	79 (4.7)	99 (4.4)
Asian	68 (12.0)	109 (13.0)	105 (12.6)	214 (12.8)	282 (12.6)
Black or African American	41 (7.2)	57 (6.8)	63 (7.6)	120 (7.2)	161 (7.2)
Multiple or Unknown*a	41 (7.2)	59 (7.1)	60 (7.2)	119 (7.1)	160 (7.1)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
White	397 (69.9)	573 (68.5)	563 (67.5)	1136 (68.0)	1533 (68.5)

Variable	Placebo (N=568)	Dula_0.75 (N=836)	Dula_1.5 (N=834)	All_Dula (N=1670)	Total (N=2238)
BMI Group, n (%)					
< 25 (kg/m2)	39 (6.9)	47 (5.6)	46 (5.5)	93 (5.6)	132 (5.9)
>= 25 and < 30 (kg/m2)	164 (28.9)	280 (33.5)	262 (31.4)	542 (32.5)	706 (31.5)
>= 30 and < 35 (kg/m2)	183 (32.2)	255 (30.5)	265 (31.8)	520 (31.1)	703 (31.4)
>= 35 (kg/m2)	182 (32.0)	254 (30.4)	261 (31.3)	515 (30.8)	697 (31.1)
Duration of Diabetes (yrs)					
Number of Patients	568	836	834	1670	2238
Mean	8.00	8.32	7.75	8.04	8.03
SD	5.70	5.63	5.52	5.58	5.61
Minimum	0.25	0.17	0.25	0.17	0.17
Median	7.00	7.00	7.00	7.00	7.00
Maximum	50.00	45.00	34.00	45.00	50.00
Duration of Diabetes Group, n (%)					
< 10 (yrs)	380 (66.9)	527 (63.0)	561 (67.3)	1088 (65.1)	1468 (65.6)
>= 10 (yrs)	188 (33.1)	309 (37.0)	273 (32.7)	582 (34.9)	770 (34.4)

Abbreviations: BMI = body mass index; kg = kilogram; kg/m2 = kilogram/square meter; N = total number of patients in specified treatment arm; CKD= chronic kidney disease; n = number of patients in specified category; SD = standard deviation; yrs = years.

*a - Multiple or Unknown includes patients self-declared as Hispanic race in study GBCF.

Source: Table ISS.APP.12- Page 700-703

Table 7: Summary of Patient Characteristics at Baseline, All Observations During the Planned Treatment Period – Phase 2 and 3 Studies with 0.75 mg and 1.5 mg Dulaglutide (Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS3)

Variable	Dula_0.75 (N=1671)	Dula_1.5 (N=1671)	All_Dula (N=3342)
Age (yrs)			
Number of Patients	1671	1671	3342
Mean	56.48	56.08	56.28
SD	9.84	10.04	9.94
Minimum	19.81	20.79	19.81
Median	56.85	56.54	56.70
Maximum	85.66	86.55	86.55
Age Group, n (%)			
< 65 (yrs)	1362 (81.5)	1360 (81.4)	2722 (81.4)
>= 65 (yrs)	309 (18.5)	311 (18.6)	620 (18.6)
Age Group, n (%)			
< 75 (yrs)	1638 (98.0)	1639 (98.1)	3277 (98.1)
>= 75 (yrs)	33 (2.0)	32 (1.9)	65 (1.9)
Age Group, n (%)			
< 65 (yrs)	1362 (81.5)	1360 (81.4)	2722 (81.4)
>= 65 and < 75 (yrs)	276 (16.5)	279 (16.7)	555 (16.6)
>= 75 and < 85 (yrs)	32 (1.9)	31 (1.9)	63 (1.9)
>= 85 (yrs)	1 (<0.1)	1 (<0.1)	2 (<0.1)

Variable	Dula_0.75 (N=1671)	Dula_1.5 (N=1671)	All_Dula (N=3342)
Gender, n (%)			
Female	836 (50.0)	814 (48.7)	1650 (49.4)
Male	835 (50.0)	857 (51.3)	1692 (50.6)
Ethnicity, n (%)			
Hispanic or Latino	538 (32.2)	532 (31.8)	1070 (32.0)
Not Hispanic or Latino	1133 (67.8)	1139 (68.2)	2272 (68.0)
Race, n (%)			
American Indian or Alaska Native	109 (6.5)	116 (6.9)	225 (6.7)
Asian	187 (11.2)	183 (11.0)	370 (11.1)
Black or African American	107 (6.4)	113 (6.8)	220 (6.6)
Multiple or Unknown*a	68 (4.1)	70 (4.2)	138 (4.1)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	1 (<0.1)	2 (<0.1)
White	1199 (71.8)	1188 (71.1)	2387 (71.4)

Variable	Dula_0.75 (N=1671)	Dula_1.5 (N=1671)	All_Dula (N=3342)
Body Weight (kg)			
Number of Patients	1671	1671	3342
Mean	90.27	90.31	90.29
SD	18.96	18.76	18.86
Minimum	51.00	46.00	46.00
Median	88.00	88.60	88.30
Maximum	157.30	156.20	157.30
Body Weight Group, n (%)			
< 90 (kg)	892 (53.4)	875 (52.4)	1767 (52.9)
>= 90 (kg)	779 (46.6)	796 (47.6)	1575 (47.1)
BMI (kg/m2)			
Number of Patients	1671	1671	3342
Mean	32.38	32.33	32.36
SD	5.41	5.31	5.36
Minimum	20.96	19.80	19.80
Median	31.87	31.80	31.83
Maximum	54.30	51.95	54.30

Abbreviations: BMI = body mass index; kg = kilogram; kg/m2 = kilogram/square meter; N = total number of patients in specified treatment arm; CKD= chronic kidney disease; n = number of patients in specified category; SD = standard deviation; yrs = years.

*a - Multiple or Unknown includes patients self-declared as Hispanic race in study GBCF.

Source: Table ISS. APP.14- Page 708-710

Pre-existing Conditions:

In general pre-existing conditions reported in the Integrated Summary of Safety (ISS) were comparable between treatment groups. Conditions in the MedDRA SOC GI disorders ranged from 23-26% at baseline. This is relevant for review of common adverse events (AEs) and AEs of interest. Baseline renal status is discussed in 7.3.2.7 Renal Safety.

The most frequently reported MedDRA Preferred Terms (PTs) at baseline were hypertension (65% to 67%) and hyperlipidemia (21% to 26%). Baseline CV risk factors were balanced between dulaglutide to all comparators and are shown below in Table 8.

Table 8: Baseline CV Risk Factors-Dulaglutide vs. All Comparators, CV Metaanalyses

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

Source: Table 6 of Dr. Janelle Charles' statistical review of cardiovascular safety

Concomitant medications:

The Applicant summarized antihyperglycemic, antihypertensive, lipid-lowering, anticoagulant, and anti-inflammatory agents in addition to cardiac therapies (inotropic agents, anti-arrhythmics, cardiac stimulants and vasodilators) (Table 9). In general, these seem balanced between treatments (AS1) and across the dulaglutide doses (AS3) (Table 10). Rescue therapy and background antihyperglycemic medications in individual studies will be discussed in section 6.1.4.

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Table 9: Summary of Baseline Concomitant Medication Use by Category – Placebo-Controlled Studieswith Dulaglutide 0.75 mg and 1.5 mg (AS1)

Concomitant Medication Category	Placebo (N=568) n (%)		Dula_0.75 (N=836) n (%)		Dula_1.5 (N=834) n (%)		All_Dula (N=1670) n (%)		p-value*a
Antihyperglycemic Medications									
Antihyperglycemic Agents	567	(99.8)	836	(100.)	834	(100.)	1670	(100.)	.254
Alpha-glucosidase Inhibitors	2	(0.4)	4	(0.5)	4	(0.5)	8	(0.5)	
Biguanides	547	(96.3)	816	(97.6)	804	(96.4)	1620	(97.0)	
DPP-IV Inhibitors	1	(0.2)	1	(0.1)	3	(0.4)	4	(0.2)	
Glinides	1	(0.2)	3	(0.4)	1	(0.1)	4	(0.2)	
Sulfonylureas	151	(26.6)	144	(17.2)	151	(18.1)	295	(17.7)	
Thiazolidinediones	172	(30.3)	318	(38.0)	304	(36.5)	622	(37.2)	
Insulin	0	(0.0)	0	(0.0)	2	(0.2)	2	(0.1)	
GLP-1 Analogs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Other	1	(0.2)	4	(0.5)	4	(0.5)	8	(0.5)	
Oral Antihyperglycemic Medication Use									.254
No	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	
Yes	567	(99.8)	836	(100.)	834	(100.)	1670	(100.)	
1 medication class	283	(49.8)	412	(49.3)	416	(49.9)	828	(49.6)	
2 medication classes	265	(46.7)	402	(48.1)	403	(48.3)	805	(48.2)	
>2 medication classes	19	(3.3)	22	(2.6)	15	(1.8)	37	(2.2)	

Abbreviations: ACE = angiotensin-converting enzyme; COX-2 = cyclooxygenase-2; DPP-IV= dipeptidyl peptidase-IV inhibitor; GLP-1 = glucagon like peptide 1; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; N = total number of patients in specified treatment arm; n = number of patients in specified category.

Concomitant Medication Category	Placebo (N=568) n (%)		Dula_0.75 (N=836) n (%)		Dula_1.5 (N=834) n (%)		All_Dula (N=1670) n (%)		p-value*a
Other Medications									
Antihypertensives	387	(68.1)	550	(65.8)	553	(66.3)	1103	(66.0)	.363
ACE Inhibitors	235	(41.4)	340	(40.7)	336	(40.3)	676	(40.5)	
Angiotensin Receptor Blockers	110	(19.4)	162	(19.4)	153	(18.3)	315	(18.9)	
Antiadrenergic Agents	12	(2.1)	10	(1.2)	16	(1.9)	26	(1.6)	
Beta Blockers	95	(16.7)	144	(17.2)	144	(17.3)	288	(17.2)	
Calcium Channel Blockers	77	(13.6)	104	(12.4)	123	(14.7)	227	(13.6)	
Diuretics	134	(23.6)	210	(25.1)	191	(22.9)	401	(24.0)	
Renin Inhibitors	3	(0.5)	4	(0.5)	5	(0.6)	9	(0.5)	
Other	5	(0.9)	5	(0.6)	2	(0.2)	7	(0.4)	
Lipid Lowering Agents	304	(53.5)	433	(51.8)	392	(47.0)	825	(49.4)	.090
HMG-CoA reductase inhibitors	274	(48.2)	389	(46.5)	364	(43.6)	753	(45.1)	
Niacin	11	(1.9)	19	(2.3)	8	(1.0)	27	(1.6)	
Fibrates	38	(6.7)	60	(7.2)	52	(6.2)	112	(6.7)	
Bile acid sequestrants	2	(0.4)	2	(0.2)	2	(0.2)	4	(0.2)	
Cholesterol absorption inhibitors	14	(2.5)	24	(2.9)	19	(2.3)	43	(2.6)	

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Concomitant Medication Category	Placebo (N=568) n (%)		Dula_0.75 (N=836) n (%)		Dula_1.5 (N=834) n (%)		All_Dula (N=1670) n (%)		p-value*a
Other Medications									
Anticoagulant Agents	204	(35.9)	301	(36.0)	273	(32.7)	574	(34.4)	.504
Aspirin	189	(33.3)	289	(34.6)	260	(31.2)	549	(32.9)	
Antiplatelet agents	19	(3.3)	19	(2.3)	22	(2.6)	41	(2.5)	
Vitamin K antagonists	6	(1.1)	8	(1.0)	6	(0.7)	14	(0.8)	
Antithrombotic agents	1	(0.2)	2	(0.2)	1	(0.1)	3	(0.2)	
Other	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	
Anti-Inflammatory Agents	91	(16.0)	123	(14.7)	132	(15.8)	255	(15.3)	.669
Non-steroidal anti-inflammatory	75	(13.2)	100	(12.0)	110	(13.2)	210	(12.6)	
COX-2 inhibitors	10	(1.8)	4	(0.5)	9	(1.1)	13	(0.8)	
Other	12	(2.1)	29	(3.5)	22	(2.6)	51	(3.1)	
Cardiac Therapy	64	(11.3)	120	(14.4)	118	(14.1)	238	(14.3)	.072
Inotropes	2	(0.4)	1	(0.1)	4	(0.5)	5	(0.3)	
Antiarrhythmics	2	(0.4)	3	(0.4)	2	(0.2)	5	(0.3)	
Stimulants	12	(2.1)	27	(3.2)	20	(2.4)	47	(2.8)	
Vasodilators (nitrates & other)	21	(3.7)	39	(4.7)	29	(3.5)	68	(4.1)	
Other	33	(5.8)	63	(7.5)	69	(8.3)	132	(7.9)	

Abbreviations: ACE = angiotensin-converting enzyme; COX-2 = cyclooxygenase-2; DPP-IV= dipeptidyl peptidase-IV inhibitor; GLP-1 = glucagon like peptide 1; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; N = total number of patients in specified treatment arm; n = number of patients in specified category.

Source: Table ISS. APP.22, page 1021-1023

Table 10: Summary of Baseline Concomitant Medication Use by Category – Placebo-Controlled Studies with 0Dulaglutide 0.75 mg vs. Dulaglutide 1.5 mg in Studies over 26 Weeks (AS3)

Concomitant Medication Category	Dula_0.75 (N=1671) n (%)		Dula_1.5 (N=1671) n (%)		All_Dula (N=3342) n (%)		p-value*a
Antihyperglycemic Medications							
Antihyperglycemic Agents	1430	(85.6)	1425	(85.3)	2855	(85.4)	.806
Alpha-glucosidase Inhibitors	4	(0.2)	4	(0.2)	8	(0.2)	
Biguanides	1336	(80.0)	1319	(78.9)	2655	(79.4)	
DPP-IV Inhibitors	1	(<0.1)	3	(0.2)	4	(0.1)	
Glinides	3	(0.2)	1	(<0.1)	4	(0.1)	
Sulfonylureas	418	(25.0)	426	(25.5)	844	(25.3)	
Thiazolidinediones	318	(19.0)	304	(18.2)	622	(18.6)	
Insulin	293	(17.5)	298	(17.8)	591	(17.7)	
GLP-1 Analogs	0	(0.0)	0	(0.0)	0	(0.0)	
Other	4	(0.2)	4	(0.2)	8	(0.2)	
Oral Antihyperglycemic Medication Use							.757
No	311	(18.6)	318	(19.0)	629	(18.8)	
Yes	1360	(81.4)	1353	(81.0)	2713	(81.2)	
1 medication class	666	(39.9)	664	(39.7)	1330	(39.8)	
2 medication classes	671	(40.2)	674	(40.3)	1345	(40.2)	
>2 medication classes	23	(1.4)	15	(0.9)	38	(1.1)	

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Concomitant Medication Category	Dula_0.75 (N=1671) n (%)		Dula_1.5 (N=1671) n (%)		All_Dula (N=3342) n (%)		p-value*a
Other Medications							
Antihypertensives	1128	(67.5)	1130	(67.6)	2258	(67.6)	.941
ACE Inhibitors	667	(39.9)	651	(39.0)	1318	(39.4)	
Angiotensin Receptor Blockers	351	(21.0)	335	(20.0)	686	(20.5)	
Antiadrenergic Agents	30	(1.8)	49	(2.9)	79	(2.4)	
Beta Blockers	337	(20.2)	351	(21.0)	688	(20.6)	
Calcium Channel Blockers	258	(15.4)	279	(16.7)	537	(16.1)	
Diuretics	466	(27.9)	456	(27.3)	922	(27.6)	
Renin Inhibitors	6	(0.4)	10	(0.6)	16	(0.5)	
Other	8	(0.5)	6	(0.4)	14	(0.4)	
Lipid Lowering Agents	856	(51.2)	805	(48.2)	1661	(49.7)	.078
HMG-CoA reductase inhibitors	769	(46.0)	731	(43.7)	1500	(44.9)	
Niacin	28	(1.7)	16	(1.0)	44	(1.3)	
Fibrates	126	(7.5)	118	(7.1)	244	(7.3)	
Bile acid sequestrants	3	(0.2)	2	(0.1)	5	(0.1)	
Cholesterol absorption inhibitors	37	(2.2)	28	(1.7)	65	(1.9)	

Concomitant Medication Category	Dula_0.75 (N=1671) n (%)		Dula_1.5 (N=1671) n (%)		All_Dula (N=3342) n (%)		p-value*a
Other Medications							
Anticoagulant Agents	625	(37.4)	575	(34.4)	1200	(35.9)	.071
Aspirin	593	(35.5)	542	(32.4)	1135	(34.0)	
Antiplatelet agents	39	(2.3)	41	(2.5)	80	(2.4)	
Vitamin K antagonists	24	(1.4)	16	(1.0)	40	(1.2)	
Antithrombotic agents	2	(0.1)	2	(0.1)	4	(0.1)	
Other	0	(0.0)	3	(0.2)	3	(<0.1)	
Anti-Inflammatory Agents	222	(13.3)	220	(13.2)	442	(13.2)	.919
Non-steroidal anti-inflammatory	186	(11.1)	180	(10.8)	366	(11.0)	
COX-2 inhibitors	10	(0.6)	11	(0.7)	21	(0.6)	
Other	43	(2.6)	42	(2.5)	85	(2.5)	
Cardiac Therapy	229	(13.7)	215	(12.9)	444	(13.3)	.476
Inotropes	9	(0.5)	13	(0.8)	22	(0.7)	
Antiarrhythmics	12	(0.7)	8	(0.5)	20	(0.6)	
Stimulants	37	(2.2)	28	(1.7)	65	(1.9)	
Vasodilators (nitrates & other)	79	(4.7)	58	(3.5)	137	(4.1)	
Other	116	(6.9)	120	(7.2)	236	(7.1)	

Abbreviations: ACE = angiotensin-converting enzyme; COX-2 = cyclooxygenase-2; DPP-IV= dipeptidyl peptidase-IV inhibitor; GLP-1 = glucagon like peptide 1; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; N = total number of patients in specified treatment arm; n = number of patients in specified category.

Source: Table ISS.APP.26-page 1039-1041.

Nearly all patients (approximately 99%) in AS1 and most patients (approximately 85%) in AS3 were receiving an antihyperglycemic agent at baseline. AS3 includes Study GBDC which was conducted in patients whose T2DM was not optimally controlled with diet and exercise alone or with 1 OAM at screening. Approximately 18% of patients in AS3 were taking insulin at baseline which is consistent with the protocol-defined use of prior conventional insulin therapy of ≤ 2 injections/day in Study GBDD.

6.1.3 Subject Disposition

Disposition in the individual phase 3 studies by treatments are discussed in Dr. McEvoy's statistical review of efficacy and shown below.

Some features common to the studies were that among the dulaglutide arms, more subjects in the high dose group discontinued by week 26 due to an AE (the majority of

AEs belonged to the MedDRA gastrointestinal disorder SOC), and that patients enrolled in U.S. sites were approximately twice as likely to discontinue from the study as patients in non-U.S. sites. Discontinuations from US sites seemed balanced between treatment arms. Discontinuations for reasons other than adverse events were comparable between treatment groups. The disposition of patients for each of the phase 3 studies will be discussed in more detail below.

Study GBCF (stage 2):

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%, Table 11). This trend was consistent over the 104 week treatment period. In this study, subjects who developed persistent or worsening hyperglycemia were discontinued from the study. By week 52, 24% of randomized subjects discontinued from the study. The frequency of discontinuations was greater in U.S. sites versus non-U.S. sites at weeks 26 (24% vs. 14%) and 52 (34% vs. 21%).

Table 11:Disposition in GBCF Stage 2 (add on to metformin)

	Dulaglutide			
	0.75 mg	1.5 mg	Placebo/ Sitagliptin	Sitagliptin
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)
Adverse Event	12 (21)	20 (32)	16 (20)	14 (26)
Death	0 (0)	1 (1)	0 (0)	0 (1)
Entry Criteria Not Met	1 (2)	4 (5)	1 (1)	0 (0)
Lack of Efficacy	0 (0)	1 (1)	4 (4)	2 (3)
Lost to Follow-Up	3 (6)	4 (6)	3 (3)	6 (8)
Physician Decision	6 (7)	3 (3)	7 (8)	4 (5)
Protocol Violation	0 (2)	0 (2)	0 (1)	1 (2)
Sponsor Decision	0 (1)	(0)	(0)	(0)
Subject Decision	11 (15)	9 (11)	10 (15)	15 (21)

Source: Table 4 from Dr. McEvoy's statistical review of efficacy

Study GBDC:

The discontinuation rate was similar across groups until approximately week 13, after which discontinuations occurred more frequently in the metformin group (Table 12Table 12).

Table 12: Disposition in Study GBDC (monotherapy):

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

Source Table 10 from Dr. McEvoy's statistical review of efficacy

Study GBDA:

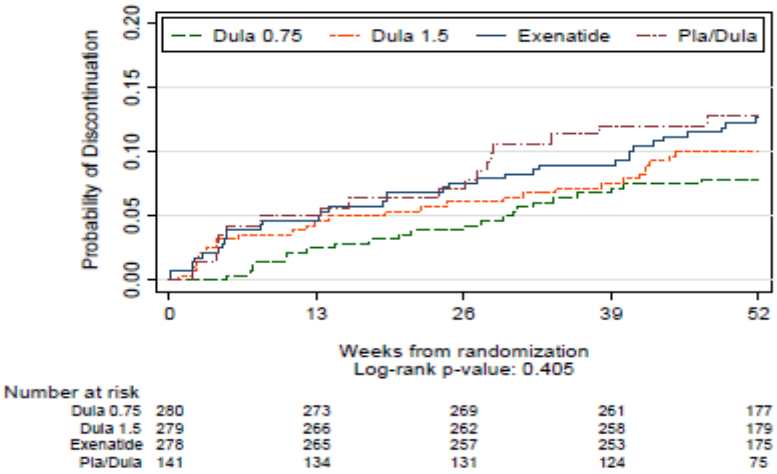
By week 26, 8% of randomized subjects discontinued from the study (Table 13). The discontinuation rate was reasonably similar for placebo, high dose dulaglutide and exenatide until about week 26. Coinciding with transition from placebo to dulaglutide there was a notable increase in the rate of discontinuation, which was similar to that observed for the dulaglutide arms at the beginning of the study (Figure 3). This is consistent with the time-course for GI side effects as discussed in 7.4.1 Common Adverse Events.

Table 13: Disposition in Study GBDA (add-on to metformin and TZD):

	Dulaglutide			
	0.75 mg	1.5 mg	Placebo	Exenatide
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
Adverse Event	4	8	3	9
Death	1	1	0	0
Entry Criteria Not Met	0	3	0	0
Lack of Efficacy	0	1	3	1
Lost to Follow-Up	7	1	5	3
Physician Decision	1	1	0	0
Protocol Violation	1	0	1	0
Sponsor Decision	0	0	0	3
Subject Decision	3	3	5	8
Treatment non-compliance	0	1	0	0

Source Table 16 from Dr. McEvoy's statistical review of efficacy

Figure 3: Kaplan-Meier plot of Time- to Study Discontinuation (study GBDA)



Source Figure 15 from Dr. McEvoy's statistical review of efficacy

Study GBDB:

By week 52, 9% randomized subjects discontinued from the study (Table 14). 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.

Table 14: Disposition in Study GBDB (add-on to metformin + SU):

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

1- At or before week 52 (visit 14)

Source Table 22 from Dr. McEvoy's statistical review for efficacy

Study GBDD:

In this study, by week 26 the dulaglutide 1.5 mg group had the greatest frequency of discontinuations (Table 15); this trend was relatively consistent throughout the 52 week treatment phase (Figure 19 in statistical review).

Table 15: Subject Disposition in Study GBDD

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

Source: Table 28 from Dr. McEvoy's statistical review for efficacy

6.1.4 Analysis of Primary Endpoint(s)

As discussed, the primary endpoint was change in HbA1c from baseline to either week 26 or week 52 in the five phase 3 studies. The primary study hypothesis was to either test for superiority relative to placebo or noninferiority (NI) to active control. The NI margin was pre-specified as 0.4% for all trials except trial GBCF, where it was set at 0.25%. Dulaglutide was able to demonstrate superiority relative to placebo and NI to active comparator for all five studies (Table 16).

Table 16: Summary of Study Findings on the Primary Endpoint at Primary Time point.

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

Model: Analyses of Covariance (ANCOVA); Missing Post-baseline values were imputed using LOCF for study GBCF and last pre-rescue observation carry forward-"LprOCF" for all other studies (refer to statistical review)
Source: Table 1 from Dr. McEvoy's statistical review for efficacy

In all five Phase 3 studies, at the primary time point, dulaglutide 1.5 mg was superior to placebo and the active comparators evaluated: metformin, sitagliptin, exenatide, and insulin glargine based on change in HbA1c from baseline. This effect was sustained in all studies through the final time points, for up to 104 weeks.

In four of the Phase 3 studies, dulaglutide 0.75 mg was superior to placebo and the active comparators of metformin, sitagliptin, exenatide, and insulin glargine at the primary time point based on change in HbA1c. Dulaglutide 0.75 mg was noninferior to insulin glargine in a fifth study (GBDB) at the primary time point. At the final time point, dulaglutide 0.75 mg was superior to the active comparators sitagliptin, exenatide, and insulin glargine (GBDD) and noninferior to the active comparators metformin and insulin glargine (GBDB) in the remaining 2 studies based on change in HbA1c.

Comparisons between dulaglutide doses were exploratory, but the high dose had a statistically significantly greater HbA1c reduction at the nominal 5% level in three studies (studies GBDB, GBCF, and GBDA).

The secondary analysis of the primary endpoint by the Applicant was prespecified using a mixed model with repeated-measures (MMRM) approach. The results were all consistent with the primary analyses except in study GBDC. For study GBDC, the MMRM analysis using the intent to treat population found that dulaglutide 0.75 mg was

noninferior to metformin ($p < 0.001$) but that it was not superior to metformin (adjusted 1-sided p-value = 0.098), with an LS mean difference of -0.10% and a nominal 95% CI of -0.25% to 0.05%.

In addition, the Applicant conducted population sensitivity analyses in the per-protocol population (without post-rescue visits [i.e. measurements obtained after initiation of rescue therapy were censored], and without rescued patients [i.e. any patients who were rescued were excluded]) and the completer population (without post-rescue visits and without rescued patients). These results were all consistent with the primary analyses.

The statistical reviewer conducted additional *post-hoc* analyses (details are discussed in Dr. McEvoy's review) to investigate the potential impact of missing data and rescue medication:

- 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. Superiority conclusions that are not considered robust to missing data are: low dose dulaglutide vs. insulin glargine (GBDD), and both dulaglutide doses vs. metformin (GBDC).
- 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, LOCF analyses for studies GBDC, GBDA, GBDB and GBDD and analyses for subjects who had HbA1c assessments at the primary time points were also performed:
    - In study GBDC 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.
    - In study GBDB, the ANCOVA model using LOCF (not LOprCF) showed the excess reduction in HbA1cfor low dose dulaglutide was statistically significant while the two other analyses did not
    - In study GBDD, the ANCOVA model with LOCF showed the excess reduction for low dose dulaglutide was not statistically significant while the two other analyses did.

Reviewer's Assessment of change in HbA1c:

Efficacy has been established in all the phase 3 studies for both the 0.75 mg and 1.5 mg dose based on the pre-specified assessments.

The exploratory analyses should be interpreted cautiously keeping in mind that the difference versus comparator was relatively small for dulaglutide 0.75 mg in studies GBDC, GBDB and GBDD (see Table 16*).*

An issue to be considered is the role of dulaglutide as monotherapy. All other long-acting GLP-1 agonists are not recommended as first-line therapy due to the risk for medullary thyroid cancer. The difference in HbA1c versus metformin (the most commonly used first line agent) was statistically significant but small (LS mean was 0.13 for dulaglutide 0.75 mg and 0.45 for dulaglutide 1.5 mg). The efficacy findings in study GBDC in combination with the nonclinical safety data are consistent with other drugs in class and support limitations of use in labelling similar to other agents in class.

Rescue Therapy and Concomitant therapies:

(Also refer to Figures 14, 16, 18 and 20 for Kaplan Meier plots of time-to-rescue comparing treatments for time-to-rescue in Dr. McEvoy's statistical review for efficacy).

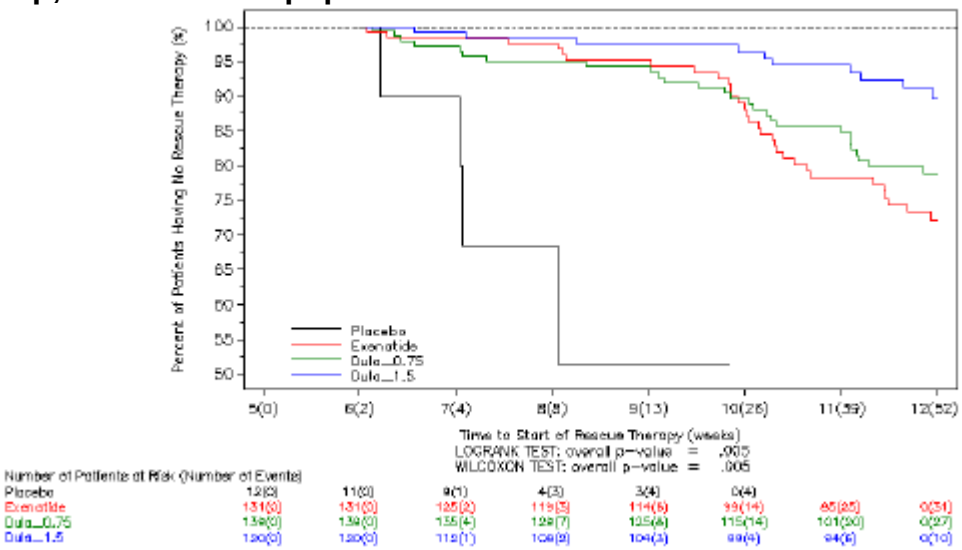
The individual CSRs for the studies were reviewed to compare frequencies of rescue therapy for severe persistent hyperglycemia between dulaglutide doses and to comparators. Background therapies over the course of the studies were also compared between treatment groups to ensure balance in protocol specified background antihyperglycemic therapies both for dose and duration. Comparator therapy was also reviewed to determine if patients were on adequate doses of metformin and exenatide, and to ensure that insulin glargine was adequately titrated as per protocols for glycemic target. Findings from each of the individual phase 3 studies are discussed below.

Study GBDA:

Rescue Therapy:

Time to rescue therapy was analyzed using a proportional hazard model (Figure 4) by Dr. McEvoy. At 26 weeks, a total of 53 patients (5.4%) had received rescue therapy (dulaglutide 1.5 mg, 4 patients [1.4%]; dulaglutide 0.75 mg, 14 patients [5.0%]; exenatide, 13 patient s [4.7%]; placebo, 22 patients [15.6%]; p<0.001). At 52 weeks, a total of 69 patients (8.3%) in the 3 primary treatment arms (and placebo up to 26 weeks) had received rescue therapy (dulaglutide 1.5 mg, 11 patients [3.9%]; dulaglutide 0.75 mg, 27 patients [9.6%]; exenatide, 31 patients [11.2%]; p=0.005). Most patients were rescued with a sulfonylurea, by long-acting insulin, sitagliptin. A few required prandial insulin.

Figure 4: Survival curve of time to rescue therapy; Kaplan-Meier by treatment group; intent to treat population.



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Source: Figure 12.5, CSR for study GBDA, page 330

Concomitant medications:

Patients were required to be on maximally tolerated doses of pioglitazone and metformin throughout the study. At baseline and Week 52, a majority of patients were receiving pioglitazone 45 mg (baseline, 95.9%; Week 52, 92.4%) or metformin ≥ 2500 mg (baseline, 88.7%; Week 52, 85.5%). The majority of patients (86.2% of patients at baseline and 82.9% of patients at Week 52) were receiving both pioglitazone 45 mg and metformin ≥ 2500 mg. The number of patients in each treatment group with the same doses of background medication was comparable.

Study GBDC:

Rescue therapy:

At 26 weeks, a total of 19 (2.4%) patients (dulaglutide 1.5 mg, 6 [2.2%]; dulaglutide 0.75 mg, 6 [2.2%]; metformin, 7 [2.6%]) received rescue therapy for severe, persistent hyperglycemia. At 52 weeks, a total of 34 (4.2%) patients (dulaglutide 1.5 mg, 12 [4.5%]; dulaglutide 0.75 mg, 8 [3.0%], and metformin, 14 [5.2%]) received rescue therapy. No significant differences between treatment groups were observed in the time to initiation of rescue therapy using log-rank and Wilcoxon tests in analyses conducted by the Applicant.

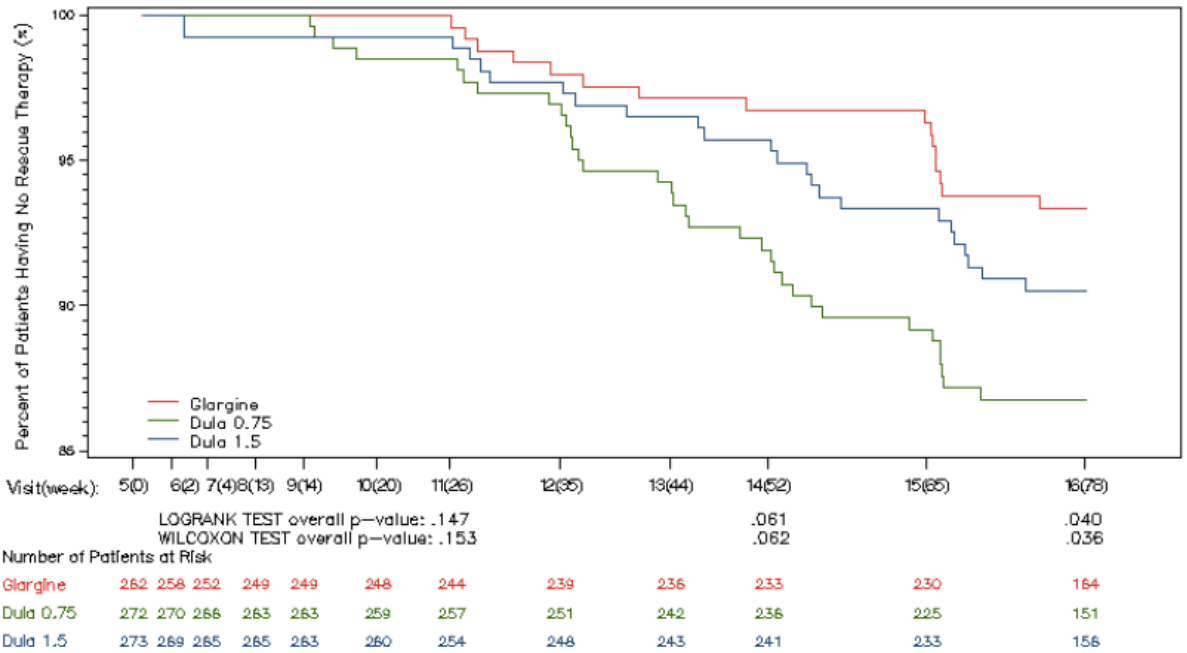
Concomitant medications:

The majority of patients assigned to metformin received a 2000 mg dose (191/225 [84.9%] patients and 178/212 [84.0%] patients at 26 and 52 weeks, respectively). Four patients received a dose less than 1500 mg at 26 weeks and five patients at 52 weeks.

Study GBDB:

Results of the Kaplan-Meier estimates of the survival curves of time to rescue therapy for severe, persistent hyperglycemia are displayed in Figure 5. An imbalance in rescue medication was observed across treatment groups. Rescue medication was needed most commonly in the dulaglutide 0.75 mg group, next most commonly in the dulaglutide 1.5 mg group, and least commonly in the insulin glargine group. Between baseline and Week 52, 11 patients (4.0%) in the dulaglutide 1.5 mg group, 20 patients (7.4%) in the dulaglutide 0.75 mg group, and 8 patients (3.1%) in the insulin glargine group received rescue therapy for severe, persistent hyperglycemia. Between baseline and Week 78, 24 patients (8.8%) in the dulaglutide 1.5 mg group, 34 patients (12.5%) in the dulaglutide 0.75 mg group, and 16 patients (6.1%) in the insulin glargine group received rescue therapy.

Figure 5: Plot of Kaplan-Meier Curve for time to start of rescue therapy by treatment group at 78 weeks; intent-to- treat population.



Source: Figure GBDB.10.2, CSR, page 105

Reviewer's Comment: These results should not affect the interpretability of the primary end-point results comparing dulaglutide 0.75 mg to insulin glargine, since pre-rescue observations were used for missing data imputation.

Concomitant medications:

During the stabilization period, most patients (>99%) were taking the appropriate background medications, metformin and glimepiride. Table 17 shows the patients who increased dose, decreased dose, or discontinued.

Table 17: Summary of Background Antihyperglycemic Concomitant Medications during Treatment Period; Excluding Concomitant Medications Used After Censoring of Efficacy Data; Intent-to-Treat Population

Background Anti-Hyperglycemic Concomitant Medication Visit (Weeks) Change Category	Glargine (N=262) n (%)	Dula_0.75 (N=272) n (%)	Dula_1.5 (N=273) n (%)	Total (N=807) n (%)	Overall p-value*a
Patients with Metformin at Baseline	262(100.0%)	271(99.6%)	273(100.0%)	806(99.9%)	.662
Background Anti-Hyperglycemic Concomitant Medication Visit (Weeks) Change Category	**Glargine (N=262) n (%)**	**Dula_0.75 (N=272) n (%)**	**Dula_1.5 (N=273) n (%)**	**Total (N=807) n (%)**	**Overall p-value*a**
Overall (52 weeks)					
Number of Patients	262	272	273	807	
Continuing with Dose Increased	3(1.1%)	4(1.5%)	6(2.2%)	13(1.6%)	.691
Continuing with Dose Decreased	8(3.1%)	9(3.3%)	14(5.1%)	31(3.8%)	.392
Discontinued	8(3.1%)	12(4.4%)	9(3.3%)	29(3.6%)	.665
Overall (78 weeks)					
Number of Patients	262	272	273	807	
Continuing with Dose Increased	4(1.5%)	5(1.8%)	10(3.7%)	19(2.4%)	.209
Continuing with Dose Decreased	8(3.1%)	10(3.7%)	15(5.5%)	33(4.1%)	.331
Discontinued	12(4.6%)	16(5.9%)	17(6.2%)	45(5.6%)	.683
Background Anti-Hyperglycemic Concomitant Medication Visit (Weeks) Change Category	**Glargine (N=262) n (%)**	**Dula_0.75 (N=272) n (%)**	**Dula_1.5 (N=273) n (%)**	**Total (N=807) n (%)**	**Overall p-value*a**
Patients with Glimepiride at Baseline	261(99.6%)	271(99.6%)	270(98.9%)	802(99.4%)	.628
Background Anti-Hyperglycemic Concomitant Medication Visit (Weeks) Change Category	**Glargine (N=262) n (%)**	**Dula_0.75 (N=272) n (%)**	**Dula_1.5 (N=273) n (%)**	**Total (N=807) n (%)**	**Overall p-value*a**
Overall (52 weeks)					
Number of Patients	261	271	272	804	
Continuing with Dose Increased	7(2.7%)	16(5.9%)	19(7.0%)	42(5.2%)	.068
Continuing with Dose Decreased	51(19.5%)	52(19.2%)	63(23.2%)	166(20.6%)	.450
Discontinued	24(9.2%)	25(9.2%)	23(8.5%)	72(9.0%)	.939
Overall (78 weeks)					
Number of Patients	261	271	272	804	
Continuing with Dose Increased	9(3.4%)	18(6.6%)	27(9.9%)	54(6.7%)	.012
Continuing with Dose Decreased	56(21.5%)	58(21.4%)	63(23.2%)	177(22.0%)	.854
Discontinued	31(11.9%)	38(14.0%)	30(11.0%)	99(12.3%)	.551

Censoring-point at which patients took additional/alternative medication for severe, persistent hyperglycemia or following study drug discontinuation
Source Table GBDB.14.13, CSR page 359

Insulin glargine dosing:

Per the study protocol, patients randomized to insulin glargine were to start therapy with a single subcutaneous injection of 10 units per day; subsequent doses were to be adjusted according to a titration algorithm targeting a FPG of <5.6 mmol/L (100 mg/dl). Insulin glargine doses increased progressively throughout the study up to Week 78. At Week 26, the mean (SD) daily dose (LOCF) of insulin glargine was 26.21 units (23.88) or 0.29 units/kg (0.21). At Week 52, the mean (SD) daily dose (LOCF) of insulin glargine was 29.40 units (25.85) or 0.33 units/kg (0.24). At Week 78, the mean (SD) daily dose (LOCF) of insulin glargine was 31.44 units (24.94) or 0.35 units/kg (0.24). The proportion of patients who met the fasting targets of <5.6 mmol/L (101 mg/dl) and <6.7 mmol/L (121 mg/dl) is shown in Table 18. The dulaglutide arms are included.

Table 18: Summary of Patients at Fasting Glucose Targets; Intent-to-Treat Population

Visit (week)	Self Monitoring Fasting Plasma Glucose (mmol/L)	Glargine (N=262) n	(%)	Dula 0.75 (N=272) n	(%)	Dula 1.5 (N=273) n	(%)	Total (N=807) n	(%)
Baseline	Number of Patients	254		264		262		780	
	< 5.6	10	(3.9)	16	(6.1)	12	(4.6)	38	(4.9)
	< 6.7	44	(17.3)	55	(20.8)	43	(16.4)	142	(18.2)
9 (14)	Number of Patients	230		255		249		734	
	< 5.6	56	(24.3)	34	(13.3)	36	(14.5)	126	(17.2)
	< 6.7	137	(59.6)	108	(42.4)	116	(46.6)	361	(49.2)
11 (26)	Number of Patients	235		240		243		718	
	< 5.6	51	(21.7)	36	(15.0)	41	(16.9)	128	(17.8)
	< 6.7	134	(57.0)	106	(44.2)	104	(42.8)	344	(47.9)
14 (52)	Number of Patients	226		239		231		696	
	< 5.6	53	(23.5)	30	(12.6)	37	(16.0)	120	(17.2)
	< 6.7	131	(58.0)	97	(40.6)	106	(45.9)	334	(48.0)
16 (78)	Number of Patients	226		226		234		686	
	< 5.6	61	(27.0)	31	(13.7)	26	(11.1)	118	(17.2)
	< 6.7	139	(61.5)	97	(42.9)	106	(45.3)	342	(49.9)

Source: Table GBDB.11.4, CSR page 136

Reviewer Assessment: Based on information available, it appears that titration of insulin glargine was acceptable. More patients on insulin glargine met fasting glucose targets.

Study GBDD:

Rescue therapy:

A total of 10 patients (dulaglutide 1.5 mg: 1; dulaglutide 0.75 mg: 7; insulin glargine: 2) discontinued the study drug due to inadequate response. Seven (1%) of these 10 patients (dulaglutide 1.5 mg: 1; dulaglutide 0.75 mg: 4; insulin glargine: 2) received rescue therapy for severe, persistent hyperglycemia and continued in the trial. The mean time to rescue therapy for these patients was 28.9, 38.9, and 27.6 weeks, respectively. The other three patients discontinued from the study early without receiving rescue therapy.

Concomitant Medications:

The following table summarizes concomitant medication use at baseline (until randomization) and treatment period (Table 19):

Table 19: Summary and Analysis of Antihyperglycemic Concomitant Medication Use By Treatment Group-All Randomized Patients

Concomitant Medication Category	Glargine (N=296) n (%)	Dula_0.75 (N=293) n (%)	Dula_1.5 (N=295) n (%)	Total (N=884) n (%)	Overall p-value*a
Stabilization Period and Baseline (visit 3 - 4)					
Insulin regimen - Per protocol					
Basal only	180 (60.8)	181 (61.8)	181 (61.4)	542 (61.3)	.971
Basal and prandial	116 (39.2)	112 (38.2)	114 (38.6)	342 (38.7)	
Antihyperglycemic Agent - Per protocol					
Biguanides	228 (77.0)	225 (76.8)	223 (75.6)	676 (76.5)	.908
Antihyperglycemic Agents - Protocol violation	6 (2.0)	6 (2.0)	5 (1.7)	17 (1.9)	.941
Alpha-glucosidase Inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Biguanides	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
DPP-IV Inhibitors	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.2)	
Glinides	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.2)	
Sulfonylureas	4 (1.4)	6 (2.0)	3 (1.0)	13 (1.5)	
Thiazolidinediones	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.2)	
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
GLP-1 analogs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Concomitant Medication Category	Glargine (N=296) n (%)	Dula_0.75 (N=293) n (%)	Dula_1.5 (N=295) n (%)	Total (N=884) n (%)	Overall p-value*a
Treatment Period					
Antihyperglycemic Agents - Per protocol pre-censoring*b	234 (79.1)	224 (76.5)	223 (75.6)	681 (77.0)	.581
Biguanides	232 (78.4)	224 (76.5)	222 (75.3)	678 (76.7)	
Insulin	11 (3.7)	10 (3.4)	1 (0.3)	22 (2.5)	
Antihyperglycemic Agents - Per protocol overall*c	267 (90.2)	259 (88.4)	266 (90.2)	792 (89.6)	.714
Alpha-glucosidase Inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Biguanides	227 (76.7)	212 (72.4)	218 (73.9)	657 (74.3)	
DPP-IV Inhibitors	4 (1.4)	4 (1.4)	3 (1.0)	11 (1.2)	
Glinides	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	
Sulfonylureas and related	5 (1.7)	13 (4.4)	7 (2.4)	25 (2.8)	
Thiazolidinediones	1 (0.3)	0 (0.0)	4 (1.4)	5 (0.6)	
Insulin	21 (7.1)	18 (6.1)	11 (3.7)	50 (5.7)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Antihyperglycemic Agents - Protocol violation	7 (2.4)	9 (3.1)	11 (3.7)	27 (3.1)	.629
Alpha-glucosidase Inhibitors	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	
Biguanides	4 (1.4)	4 (1.4)	2 (0.7)	10 (1.1)	

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Treatment Period									
DPP-IV Inhibitors	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)	
Glinides	1	(0.3)	0	(0.0)	1	(0.3)	2	(0.2)	
Sulfonylureas and related	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)	
Thiazolidinediones	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Insulin	3	(1.0)	5	(1.7)	7	(2.4)	15	(1.7)	
GLP-1 analogs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Other	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Antihyperglycemic Agents - rescue therapy*d	2	(0.7)	4	(1.4)	1	(0.3)	7	(0.8)	.324
Alpha-glucosidase Inhibitors	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Biguanides	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
DPP-IV Inhibitors	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)	
Glinides	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Sulfonylureas and related	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Thiazolidinediones	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Insulin	2	(0.7)	3	(1.0)	1	(0.3)	6	(0.7)	
Other	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	

Abbreviations: DPP-IV= dipeptidyl peptidase-IV inhibitor; N = total number of patients in specified treatment arm; n = number of patients in specified category.

Note: Dula_x.x refers to x.x milligrams dulaglutide once weekly.
*a - p-values are from Chi-squared test if at least 80% of cells have an expected value >=5, otherwise Fisher's exact test will be used.
*b - censoring = point at which patients took additional/alternative medication for severe, persistent hyperglycemia or following study drug discontinuation.
*c - all antihyperglycemic agents except for rescue therapies and those that are protocol violations.
*d - additional/alternative medication taken for severe, persistent hyperglycemia.

Source: Table GBDD.11.4- Page 132-134

Reviewer's Assessment: Overall the concomitant medications used in the treatment period in each category- per-protocol pre-censoring, per-protocol overall, protocol violation and recue therapy were comparable between groups and should not affect study interpretation.

Background and Comparator medication*:*

Metformin:

During the treatment period, 12 patients (dulaglutide 1.5 mg: 4; dulaglutide 0.75 mg: 2; insulin glargine: 6) required metformin dose adjustments. Metformin discontinuation was reported by 24 (2.7%) patients (dulaglutide 1.5 mg: 6; dulaglutide 0.75 mg: 12; insulin glargine: 6). Investigator decision was the most frequent reason for metformin discontinuation.

Reviewer Comment: Numerically more patients on dulaglutide 0.75 mg had their metformin discontinued, but this should not impact the interpretation of the efficacy results.

Insulin:

The table below (Table 20) shows the total daily dose of insulin glargine, insulin lispro and total daily insulin (TDI) dose in the treatment groups. At baseline the Applicant reports that the mean (SD) TDI dose was 56.07 (33.82) U and similar across treatment groups.

Table 20: Summary of Total Daily Insulin Dose by Components Post-baseline to 52 Weeks, by Visit Intent-to-Treat Population, Study GBDD

Visit (Week)	Treatment	N	Glargine Mean (± SD) (%)	Lispro Mean (± SD) (%)	TDI Mean (± SD)
Units					
5 (2)	Glargine	295	42.25 (± 21.67) (54.8)	35.89 (± 20.63) (45.2)	78.14 (± 39.43)
	Dula_0.75	289		45.66 (± 26.86) (100.0)	45.66 (± 26.86)
	Dula_1.5	290		41.26 (± 28.13) (100.0)	41.26 (± 28.13)
6 (4)	Glargine	289	51.74 (± 25.19) (53.9)	47.38 (± 43.48) (46.5)	98.78 (± 60.27)
	Dula_0.75	283		62.50 (± 34.79) (100.0)	62.50 (± 34.79)
	Dula_1.5	274		57.02 (± 35.40) (100.0)	57.02 (± 35.40)
7 (6)	Glargine	283	57.08 (± 29.31) (52.0)	53.80 (± 29.93) (48.3)	110.47 (± 54.44)
	Dula_0.75	276		75.24 (± 39.97) (100.0)	75.24 (± 39.97)
	Dula_1.5	265		67.14 (± 42.58) (100.0)	67.14 (± 42.58)
Units					
8 (8)	Glargine	281	59.90 (± 32.22) (50.9)	59.62 (± 34.60) (49.1)	119.51 (± 61.79)
	Dula_0.75	274		82.92 (± 45.77) (100.0)	82.92 (± 45.77)
	Dula_1.5	259		74.72 (± 45.07) (100.0)	74.72 (± 45.07)
9 (13)	Glargine	276	61.83 (± 34.23) (50.2)	63.56 (± 38.32) (49.9)	125.17 (± 66.82)
	Dula_0.75	266		91.10 (± 54.67) (100.0)	91.10 (± 54.67)
	Dula_1.5	254		83.19 (± 54.35) (100.0)	83.19 (± 54.35)
10 (19)	Glargine	266	62.70 (± 36.48) (50.0)	65.40 (± 40.50) (50.4)	127.62 (± 71.30)
	Dula_0.75	259		94.43 (± 59.57) (100.0)	94.43 (± 59.57)
	Dula_1.5	249		90.81 (± 70.03) (100.0)	90.81 (± 70.03)
Units					
11 (26)	Glargine	254	64.48 (± 40.23) (49.8)	67.79 (± 44.59) (50.4)	132.00 (± 79.01)
	Dula_0.75	251		96.69 (± 62.13) (100.0)	96.69 (± 62.13)
	Dula_1.5	244		93.24 (± 78.02) (100.0)	93.24 (± 78.02)
12 (39)	Glargine	246	64.69 (± 38.39) (50.2)	68.61 (± 47.62) (50.0)	133.04 (± 79.74)
	Dula_0.75	242		99.47 (± 73.24) (100.0)	99.47 (± 73.24)
	Dula_1.5	232		90.01 (± 70.02) (100.0)	90.01 (± 70.02)
13 (52)	Glargine	238	64.07 (± 38.60) (50.0)	69.12 (± 49.07) (50.0)	133.19 (± 80.75)
	Dula_0.75	227		95.00 (± 67.62) (100.0)	95.00 (± 67.62)
	Dula_1.5	224		88.15 (± 62.95) (100.0)	88.15 (± 62.95)

Source: Table GBDD.11.19, CSR page 168-170

Fasting plasma glucose was a target for patients in the insulin glargine group only, a summary of patients in the insulin glargine group with target FPG levels <100 mg/dL and <120 mg/dL is presented in the table below (Table 21).

Table 21: Summary and Analysis of Patients with FPG < 100 mg/dL and < 120 mg/dL-Baseline to 52 Weeks, By Treatment Group and Visit Intent-to-Treat Population, Study GBDD

Visit (Week)	FPG Target	Glargine (N=296) n (%)	Dula_0.75 (N=293) n (%)	Dula_1.5 (N=295) n (%)	Total (N=884) n (%)	Overall p-value*a	Pairwise p-value*a		
								vs Glargine	vs Dula_0.75
Baseline	Number of Patients	286	281	284	851				
	Patients with FPG < 120 mg/dL	72 (25.2)	75 (26.7)	71 (25.0)	218 (25.6)	.880			
	Patients with FPG < 100 mg/dL	31 (10.8)	29 (10.3)	27 (9.5)	87 (10.2)	.869			
9 (13)	Number of Patients	248	243	237	728				
	Patients with FPG < 120 mg/dL	169 (68.1)	33 (13.6)	46 (19.4)	248 (34.1)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.085
	Patients with FPG < 100 mg/dL	86 (34.7)	5 (2.1)	9 (3.8)	100 (13.7)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.254
11 (26)	Number of Patients	232	231	228	691				
	Patients with FPG < 120 mg/dL	135 (58.2)	34 (14.7)	48 (21.1)	217 (31.4)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.076
	Patients with FPG < 100 mg/dL	84 (36.2)	6 (2.6)	8 (3.5)	98 (14.2)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.570
LOCF at 11 (26)	Number of Patients	260	259	249	768				
	Patients with FPG < 120 mg/dL	148 (56.9)	38 (14.7)	50 (20.1)	236 (30.7)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.107
	Patients with FPG < 100 mg/dL	93 (35.8)	7 (2.7)	8 (3.2)	108 (14.1)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.734
13 (52)	Number of Patients	218	213	207	638				
	Patients with FPG < 120 mg/dL	131 (60.1)	39 (18.3)	31 (15.0)	201 (31.5)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.359
	Patients with FPG < 100 mg/dL	77 (35.3)	7 (3.3)	3 (1.4)	87 (13.6)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.210
LOCF at 13 (52)	Number of Patients	262	262	252	776				
	Patients with FPG < 120 mg/dL	152 (58.0)	45 (17.2)	40 (15.9)	237 (30.5)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.691
	Patients with FPG < 100 mg/dL	92 (35.1)	8 (3.1)	3 (1.2)	103 (13.3)	<.001	Dula_0.75	<.001	
							Dula_1.5	<.001	.137

Source: Table GBDD.14.42, CSR page 608-609

Reviewer's assessments:

- *Insulin lispro dose increased over the course of the study, with a larger increase in the dulaglutide 0.75 mg group. Mean insulin glargine dose increased from 42-62 U/day (0.46 [±0.19] to 0.67 [± 0.35] U/kg) in this population of patients on prior insulin therapy. The insulin glargine group used smaller doses of insulin lispro compared to dulaglutide 1.5 mg and dulaglutide 0.75 mg. At 26 weeks, the mean daily insulin lispro dose in the dulaglutide 1.5 mg and dulaglutide 0.75 mg groups were 93.2 (±78.0) and 96.7 (±62.1) units (0.99 [±0.70] and 1.03 [±0.57] units/kg), respectively. The mean daily dose of insulin lispro received by patients in the insulin glargine group was 67.8 (±44.59) units (0.72 [±0.43] units/kg). The mean total daily insulin (TDI) in the insulin glargine group was 132 (±79.0) units.*
- *Consistent with the effect of insulin glargine, the number of patients on insulin glargine with fasting plasma glucose under 120 or 100 mg/dl, improved*

compared to baseline at week 26 and 52. Insulin glargine was better at achieving this compared to dulaglutide. For unclear reasons percent of patients with FPG < 120 mg/dl was better at week 9 with insulin glargine compared to later time points. There were no appreciable differences between the dulaglutide doses.

- *Overall insulin lispro or insulin glargine titrations should not affect interpretability of the primary endpoint results.*

Study GBCF:

Subjects rescued for hyperglycemia in this study had to be discontinued. Balance in background therapy (metformin) was reviewed. The summary of reasons for metformin change post-baseline to 6, 12 and 24 months is shown below. As shown in Table 22, the majority of the subjects had no changes and so this would not affect interpretation of efficacy results.

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Table 22: Summary of Reasons for Metformin Dose Change – Post-Baseline to 6, 12, and 24 Months – Intent-to-Treat Patients in Primary Treatment Arms Randomized During Stage 1 or Stage 2, Study GBCF

Visit (Month)	Reason for Metformin Dose Adjustment	PL/Sit (N=177) n (%)	Sit (N=315) n (%)	Dula_0.75 (N=302) n (%)	Dula_1.5 (N=304) n (%)
Overall		N1 = 177	N1 = 315	N1 = 302	N1 = 304
	No Change	173(97.7)	305(96.8)	296(98.0)	294(96.7)
	Adverse Event	3(1.7)	2(0.6)	0(0.0)	2(0.7)
	Inadequate Response	0(0.0)	3(1.0)	2(0.7)	1(0.3)
	Investigator Decision	1(0.6)	5(1.6)	3(1.0)	6(2.0)
	Hypoglycemia	0(0.0)	0(0.0)	1(0.3)	1(0.3)
9 (6)		N1 = 140	N1 = 287	N1 = 280	N1 = 277
	No Change	138(98.6)	281(97.9)	279(99.6)	272(98.2)
	Adverse Event	1(0.7)	1(0.3)	0(0.0)	0(0.0)
	Inadequate Response	0(0.0)	2(0.7)	0(0.0)	1(0.4)
	Investigator Decision	1(0.7)	3(1.0)	1(0.4)	3(1.1)
	Hypoglycemia	0(0.0)	0(0.0)	0(0.0)	1(0.4)
11 (12)		N1 = 121	N1 = 254	N1 = 256	N1 = 247
	No Change	119(98.3)	253(99.6)	254(99.2)	246(99.6)
	Adverse Event	2(1.7)	1(0.4)	0(0.0)	0(0.0)
	Inadequate Response	0(0.0)	0(0.0)	1(0.4)	0(0.0)
	Investigator Decision	0(0.0)	0(0.0)	0(0.0)	1(0.4)
	Hypoglycemia	0(0.0)	0(0.0)	1(0.4)	0(0.0)
15 (24)		N1 = 96	N1 = 192	N1 = 196	N1 = 200
	No Change	96(100.0)	189(98.4)	193(98.5)	196(98.0)
	Adverse Event	0(0.0)	0(0.0)	0(0.0)	2(1.0)
	Inadequate Response	0(0.0)	1(0.5)	1(0.5)	0(0.0)
	Investigator Decision	0(0.0)	2(1.0)	2(1.0)	2(1.0)
	Hypoglycemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Abbreviations: N = total number of patients in specified treatment group; n = number of patients in specified category; N1 = number of patients evaluable at specified visit.

Source: GBCF. 14.15- page 507.

Reviewer's Overall Assessment for Rescue, Background and Comparator therapies:

In the individual Phase 3 studies, there were no significant issues noted with antihyperglycemic background, comparator or rescue therapy administration which would affect interpretability of the results for the primary efficacy endpoint. More subjects on placebo were rescued compared to dulaglutide or active comparator. Except for the monotherapy study, more subjects on dulaglutide 0.75 mg required

rescue compared to dulaglutide 1.5 mg, which is consistent with the exploratory efficacy comparison between doses. Rescue rates for dulaglutide 0.75 mg were comparable to exenatide and increased compared to insulin glargine.

6.1.5 Analysis of Secondary Endpoints(s)

Testing of the secondary endpoints was not incorporated into the testing sequence hierarchy used to test the primary and key secondary objectives. Hence these analyses can be considered as hypothesis-generating. Secondary endpoints were instead tested irrespective of whether the primary and key secondary objectives were satisfied. The statistical reviewer indicates that the testing of the secondary endpoints could not be done in study GBDB since the last hypothesis test in the sequence for the primary endpoint was not statistically significant.

Only the secondary endpoints of fasting serum glucose (studies GBDC, GBDA, GBDB, and GBDD), fasting plasma glucose (study GBCF), weight and categorical analyses of HbA1c are reviewed here (Table 23),.

Weight and Fasting serum glucose are presented from Dr. McEvoy's statistical review while categorical changes in HbA1c are presented from the Applicant's analyses.

Table 23: Analysis of Secondary Endpoints:
(GBCF, ANCOVA w/LOCF)

	Dulaglutide			
	0.75 mg	1.5 mg	Placebo/ Sitaglitpin	Sitagliptin
Weight (kg)				
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)		
Fasting Serum Glucose (mmol/L)				
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)		

Study GBDC, ANCOVA w/LOprCF

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

GBDA (ANCOVA w/LOprCF)

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

Study GBDD-ANCOVA with LOprCF:

	Dulaglutide		
	0.75 mg	**1.5 mg**	**Insulin Glargine**
Weight (kg)			
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)	
Fasting Serum Glucose (mmol/L)			
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)	

GBDB-ANCOVA w/LOprCF

	Dulaglutide		
	0.75 mg	1.5 mg	Insulin Glargine
Weight (kg)			
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)	
Fasting Serum Glucose (mmol/L)			
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)	

Source: Tables 8, 14, 20, 26 and 32 Efficacy Statistical Review

Weight:

- GBCF-At weeks 26 and 52, all treatments had a reduction in average weight compared to baseline. 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 suggestion of dose dependency.
- GBDC-At weeks 26 and 52, all treatments groups had a reduction in average weight compared to baseline. The difference in average weight loss was either similar or less favorable for the dulaglutide groups compared to metformin at weeks 26 and 52. Dulaglutide 1.5 mg had a more favorable average reduction compared to dulaglutide 0.75 mg.
- GBDA- At weeks 26 and 52, dulaglutide 1.5 mg and exenatide treatment groups had a reduction in average weight compared to baseline. Patient on dulaglutide 0.75 mg had less weight gain compared to placebo at week 26 but had no weight loss at week 26 and week 52. Dulaglutide 1.5 mg had a slightly greater average weight reduction compared to exenatide at weeks 26 and 52.
- GBDD: At weeks 26 and 52, only the high dose dulaglutide treatment group had a reduction in average weight compared to baseline. The weight loss was respectively about 2kg and 3kg greater for dulaglutide 0.75 mg and dulaglutide 1.5 mg groups compared to insulin glargine.
- GBDB: At weeks 26 and 52, only the dulaglutide treatment groups had a reduction in average weight compared to baseline. The average weight

reduction in the two dulaglutide groups was about 2.8 kg greater than for insulin glargine.

Fasting Serum Glucose (FSG):

- GBCF- At weeks 26 and 52, all treatments had a reduction in average fasting plasma glucose compared to baseline, both dulaglutide groups had statistically significantly greater decrease in mean fasting plasma glucose relative to placebo at week 26, and relative to sitagliptin at weeks 26 and 52.
- GBDC-At weeks 26 and 52, all treatments groups had a reduction in average fasting serum glucose compared to baseline. Except for the comparison between dulaglutide 1.5 mg and metformin at week 52, there was no statistically significant difference between dulaglutide groups and metformin on this endpoint.
- GBDA-At weeks 26 and 52, all treatments had a reduction in average fasting serum glucose compared to baseline 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.
- GBDD At both weeks 26 and 52, only insulin glargine had a reduction in average fasting serum glucose compared to baseline. The reduction was statistically significantly greater for insulin glargine compared to the two dulaglutide groups.
- GBDB: At weeks 26 and 52, all treatments groups had a reduction in average fasting serum glucose compared to baseline. 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.

Reviewer's assessment for weight and FSG:

- Weight loss with dulaglutide was dose-dependent; dulaglutide 1.5 mg was associated with greater weight reduction than all comparators except metformin. Dulaglutide 0.75 mg was associated with less weight loss compared to metformin and exenatide and more weight loss compared to insulin glargine.
- The effect of dulaglutide on fasting serum glucose was dose-dependent, superior to placebo, sitagliptin and exenatide, not significantly different from metformin and less than insulin glargine.

Table 24: Proportion of Patients with HbA1c under target at Primary Time Point:

Outcome	Dula 1.5	Dula 0.75	Comparator	Placebo
GBCF (Add on to metformin; placebo/sitagliptin control)				
HbA1c <7.0%, n (%)[a]	184 (60.9)[**,##]	164 (55.2)[**,##]	118 (37.8)**	37 (21.0)
HbA1c ≤ 6.5%, n (%)[a]	141 (46.7)[**,##,++]	92 (31.0)[**,##]	68 (21.8)*	22 (12.5)

Outcome	Dula 1.5	Dula 0.75	Comparator	Placebo
GBDA (add on to metformin/TZD, placebo and exenatide control)				
HbA1c <7.0%, n (%)[a]	212 (78.2)[**,##,++]	177 (65.8)[**,##]	139 (52.3)*	51 (42.9)
HbA1c ≤ 6.5%, n (%)[a]	170 (62.7)[**,##,+]	143 (53.2)[**,##]	101 (38.0)**	29 (24.4)
GBDB (add on to metformin +SU, insulin glargine control)				
HbA1c <7%, n (%)[a]	140 (53.2)[##,++]	99 (37.1)	80 (30.9)	-
HbA1c ≤ 6.5%, n (%)[a]	71 (27.0)[##]	60 (22.5)[#]	35 (13.5)	-
GBDD (add on to insulin lispro+ metformin, insulin glargine control)				
HbA1c <7.0%, n (%)[a]	161 (58.5)[#]	156 (56.3)	138 (49.3)	-
HbA1c ≤ 6.5%, n (%)[a]	101 (36.7)	96 (34.7)	85 (30.4)	-
GBDC (monotherapy vs metformin)				
HbA1c <7.0%, n (%)[a]	163 (61.5)[#]	166 (62.6)[#]	142 (53.6)	-
HbA1c ≤ 6.5%, n (%)[a]	122 (46.0)[##]	106 (40.0)[#]	79 (29.8)	-

a. Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator for percent to target analyses of HbA1c.
*p<.05, **p<.001 dulaglutide or comparator treatment group compared to placebo.
#p<.05, ##p<.001 dulaglutide treatment group compared to active comparator.
+p<.05, ++p<.001 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.
Source: Summary of Clinical Efficacy, Tables 2.7.3.13, 2.7.3.16, 2.7.3.20, 2.7.3.23 and 2.7.3.20

Reviewer's Assessment for proportion of patients with HbA1c under target:

There was no prespecified testing for this secondary end-point. However, a larger proportion of dulaglutide treated subjects had a HbA1c under 7% or 6.5% compared to active comparators in all studies except GBDD. In study GBDD the difference vs. insulin glargine was statistically significant only for subjects treated with dulaglutide 1.5 mg with a HbA1c under 7%. The difference between dulaglutide 1.5 mg and 0.75 mg was statistically significant for patients under HbA1c target in studies GBCF, GBDA and GBDB.

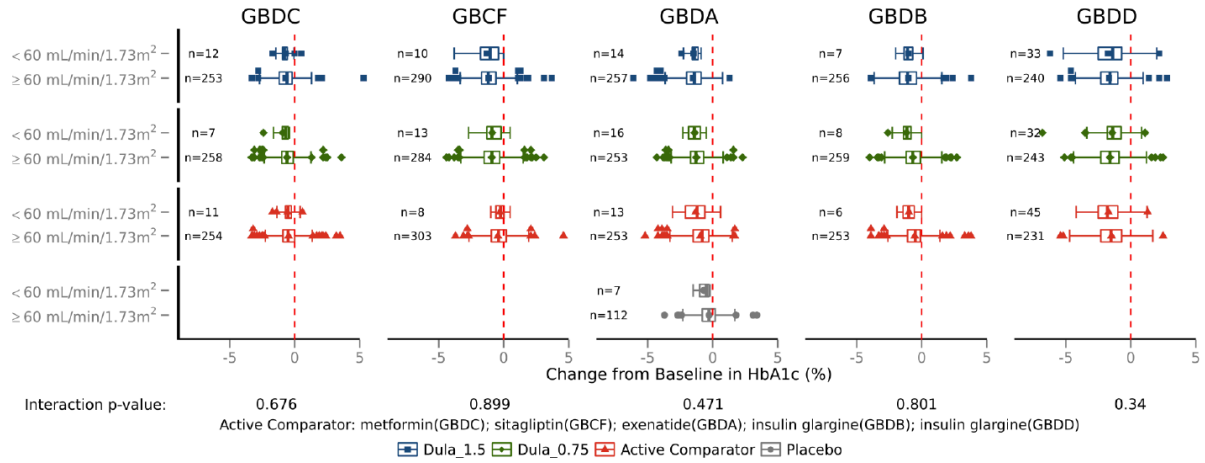
6.1.6 Subpopulations

Analyses of sub-populations are discussed in Dr.McEvoy's statistical review for efficacy. Across individual trials the average HbA1c reduction was fairly similar to the reduction in subgroups defined by gender, race (White, non-White), age (≤ 65 years, > 65 years), region (U.S., non-U.S.), baseline HbA1c (≤ 8.5%, > 8.5%), and baseline BMI (≤ 30

kg/m^2, > 30 kg/m^2). No statistical interactions between the above factors and dulaglutide dose (1.5 mg or 0.75 mg) were observed in the statistical reviewer's pooled analyses (see Tables 34-36 in Dr. McEvoy's statistical review for efficacy).

In addition the Applicant conducted subgroup analyses for subjects with mean baseline eGFR (CKD-EPI[5]) (<60 and ≥ 60 mL/min/1.73 m^2) and albuminuria (UACR[6] ≤ 300 and > 300 mg/g). The sub-populations defined by renal function are discussed in further detail below due to concerns regarding renal safety with the drug class (Figure 6).

Figure 6: Box-and-whisker plots of change from baseline in HbA1c (%) by renal status, at primary time points (using LOCF), ITT, without post-rescue visits, H9X-MC-GBDC, GBCF, GBDA, GBDB, and GBDD.



Source: Figure App.2.7.3.23, ISE- page 306

There was no significant treatment-by-eGFR (CKD-EPI) interaction effect on the change in HbA1c from baseline in any of the 5 studies but sample sizes in the renal impairment sub-groups are small.

In Study GBDA, a significant treatment-by-renal status interaction effect as measured by albuminuria on change in HbA1c from baseline was observed, based on a nominal alpha level of 0.1 (p=.039). There were very few patients with macroalbuminuria (UACR >300 mg/g; n=27 overall across all 4 treatment groups), and hence the findings are inconclusive.

5 Estimated glomerular filtration rate (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.- GFR = 141 X min(Scr/κ,1)$^{\alpha}$ X max(Scr/κ,1)$^{-1.209}$ X 0.993Age X 1.018 [if female] X 1.159 [if black]
Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.
6 Urine albumin-creatinine ratio.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Also refer to clinical pharmacology and pharmacometric reviews by Dr. Sang Chung and Dr. Lian Ma.

The dose finding portion of Phase 3 dulaglutide trial (Study GBCF- stage 1) enabled exploration of 7 dulaglutide doses (0.25, 0.5, 0.75, 1, 1.5, 2, and 3 mg). Stage 1 randomization was conducted in an adaptive manner based on four response measures that were included in the clinical utility index (CUI) developed for purposes of adaptive randomization and dose selection: change from baseline in HbA1c, weight, pulse rate, and diastolic blood pressure (DBP). Individual predictions were used to make inferences from these response measures for the parameters of interest: 12-month change from baseline in HbA1c relative to sitagliptin and 6-month change from baseline in weight, pulse rate, and DBP relative to placebo. The algorithm was designed to adaptively allocate patients to 7 dulaglutide doses until a dose decision could be made and the study progressed into Stage 2.

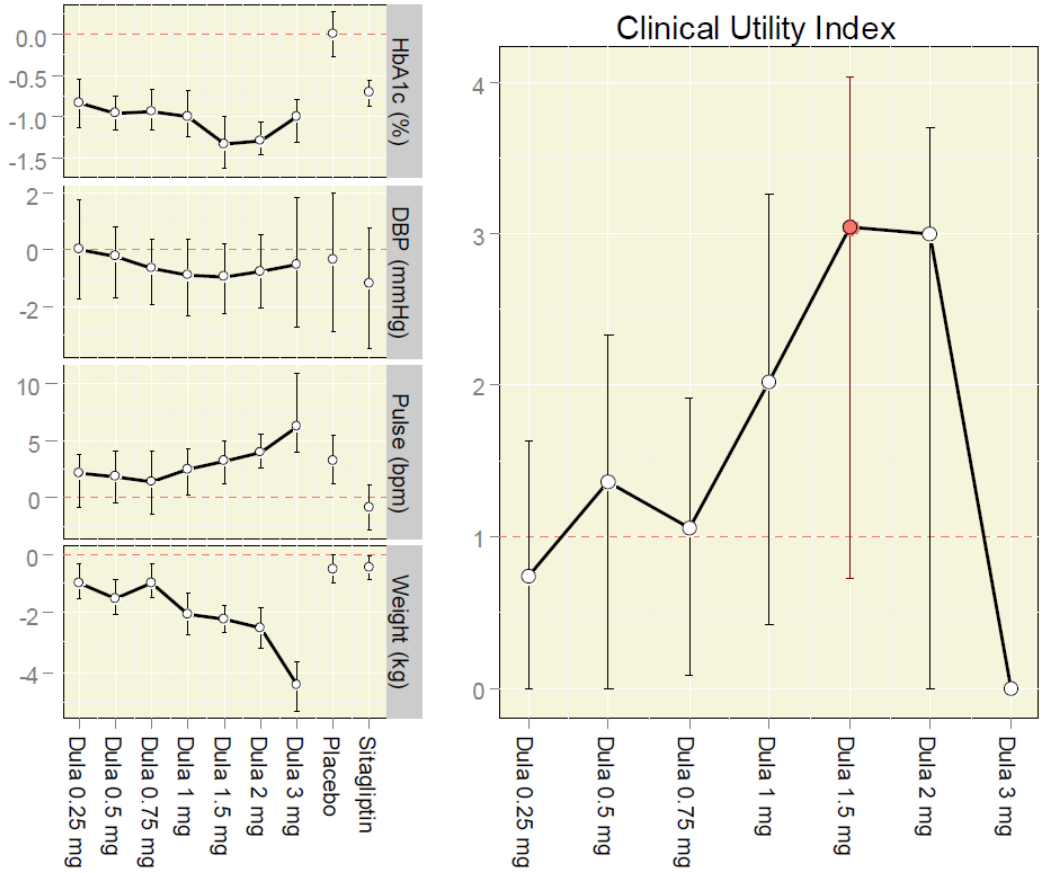
On 17 January 2008, the agency issued the Applicant a recommendation regarding the design of Study GBCF, to bring forward a second dose into Phase 3 development in case an unexpected safety signal was subsequently observed with the selected maximum utility dose.

The GBCF Data Monitoring Committee (DMC) discontinued dulaglutide 3.0 mg before dose selection due to concerns about increased incidence of gastrointestinal adverse events and elevated heart rate. It is to be noted that several subjects also discontinued from the TQT study where doses of 4 mg and 7 mg were evaluated due to GI tolerability issues.

Data from 199 patients were included in the analysis to determine the maximum utility dose (MUD) (Figure 7). The Applicant states that the 1.5 mg dose met the prespecified criteria for dose selection as the maximum utility dose, with the posterior probability that the CUI was $\geq$ 0.6 being 0.982 and the posterior predictive probability that the 1.5 mg dose was noninferior to sitagliptin at 12 months being > 0.99. Following the criteria for selecting a second dose, the algorithm indicated the 0.75 mg dose met prespecified requirements for efficacy and safety.

In addition, pharmacokinetic/pharmacodynamic modeling of available data from multiple Phase 1 studies in healthy subjects (Studies GBCA and GBCC) and in T2DM (Studies GBCD, GBCB, GBCL), and available phase 2/3 studies were also used for dose selection. The population exposure-response models estimated decreases from baseline of -35 mg/dL for FPG; -1.1% for HbA1c; and -1.7 kg for body weight at 1 year following the 1.5 mg dulaglutide dose in patients with T2DM. The model estimated an increase of 2.6 bpm in HR and no clinically relevant changes in BP, amylase (pancreatic and total), lipase, and calcitonin at the 1.5 mg dose level.

Figure 7: Clinical utility index (CUI) and change from baseline in CUI components, Bayesian posterior predicted means and 95% credible intervals at 6 Months (DBP, pulse, and weight) and 12 Months (HbA1c) – intent-to-treat population (data available up to Decision Point).



Abbreviations: bpm = beats per minute; DBP = diastolic blood pressure; Dula = dulaglutide dose delivered once weekly; HbA1c = glycosylated hemoglobin A1c; Pulse = pulse rate, Weight = body weight.

Source: Figure GBCF 11.1, CSR page 163.

Based on the completed phase 2/3 studies, the Applicant believes that dulaglutide 1.5 mg should be the only approved dose based on superior efficacy to dulaglutide 0.75 mg and comparable safety profile

Reviewer's Assessment:

From a clinical perspective, the dose-selection process seems acceptable. My assessments and conclusions regarding dose-related issues for efficacy are discussed in 6.1.4 Analysis of Primary Endpoint(s) and 6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects.

Benefits for dose titration are also discussed in the Clinical pharmacology review.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Applicant's table (Table 25) for the final time points in the five phase 3 studies is presented below and supports persistence of efficacy.

Table 25: Summary of Efficacy Results at Final Time Point for Dulaglutide Long-Term Active Comparator- Controlled Studies, ITT

Study	N	HbA1c (%)[a]	ΔHbA1c (%)[a]	ΔFBG (mg/dL)[a,b]	ΔFBG (mmol/L)[a,b]	Patients at Target <7.0% n (%)[c]	Patients at Target ≤6.5% n (%)[c]	ΔBody Weight (kg)[a]
H9X-MC-GBDC (Monotherapy) - [final time point=52 weeks]								
Dula_1.5 mg	269	6.89 (0.07)††	-0.70 (0.07)††	-28.08 (2.52)#,+	-1.56 (0.14)#,+	159 (60.0)#,+	112 (42.3)##,+	-1.93 (0.29)+
Dula_0.75 mg	270	7.03 (0.07)†	-0.55 (0.07)†	-18.00 (2.52)	-1.00 (0.14)	141 (53.2)	92 (34.7)	-1.09 (0.29)#
Metformin[d]	268	7.08 (0.07)	-0.51 (0.07)	-20.70 (2.52)	-1.15 (0.14)	128 (48.3)	75 (28.3)	-2.20 (0.29)
H9X-MC-GBCF (Metformin) - [final time point=104 weeks]								
Dula_1.5 mg	304	7.13 (0.06)††,+	-0.99 (0.06)††,+	-35.82 (2.70)##,+	-1.99 (0.15)##,+	164 (54.3)##,+	118 (39.1)##,++	-2.88 (0.25)##
Dula_0.75 mg	302	7.41 (0.07)††	-0.71 (0.07)††	-25.02 (2.70)##	-1.39 (0.15)##	133 (44.8)##	72 (24.2)##	-2.39 (0.26)
Sitagliptin[e]	315	7.80 (0.06)	-0.32 (0.06)	-8.46 (2.70)	-0.47 (0.15)	97 (31.1)	44 (14.1)	-1.75 (0.25)
H9X-MC-GBDA (Metformin + TZD) - [final time point=52 weeks]								
Dula_1.5 mg	279	6.66 (0.08)††,++	-1.36 (0.08)††,++	-36.72 (2.52)##,+	-2.04 (0.14)##,+	192 (70.8)##,++	155 (57.2)##,+	-1.10 (0.39)++
Dula_0.75 mg	280	6.95 (0.08)††	-1.07 (0.08)††	-28.44 (2.70)#	-1.58 (0.15)#	159 (59.1)#	130 (48.3)##	0.44 (0.39)#
Exenatide[f]	276	7.23 (0.08)	-0.80 (0.08)	-18.54 (2.70)	-1.03 (0.15)	131 (49.2)	92 (34.6)	-0.80 (0.39)
H9X-MC-GBDB (Metformin + SU) - [final time point=78 weeks]								
Dula_1.5 mg	273	7.23 (0.07)††,+	-0.90 (0.07)††,+	-19.80 (2.70)#,+	-1.10 (0.15)#,+	129 (49.0)##,++	74 (28.1)##	-1.96 (0.26)##
Dula_0.75 mg	272	7.51 (0.07)†	-0.62 (0.07)†	-10.44 (2.88)##	-0.58 (0.16)##	91 (34.1)	59 (22.1)	-1.54 (0.26)##
Glargine[g]	262	7.54 (0.07)	-0.59 (0.07)	-28.44 (2.70)	-1.58 (0.15)	79 (30.5)	43 (16.6)	1.28 (0.26)
H9X-MC-GBDD (Lispro ± Metformin) - [final time point=52 weeks]								
Dula_1.5 mg	295	6.99 (0.08)††	-1.48 (0.08)††	1.44 (3.96)##	0.08 (0.22)##	161 (58.5)#	101 (36.7)	-0.35 (0.34)##,+
Dula_0.75 mg	293	7.04 (0.08)††	-1.42 (0.08)††	7.38 (3.96)##	0.41 (0.22)##	156 (56.3)	96 (34.7)	0.86 (0.33)##
Glargine[g]	296	7.23 (0.08)	-1.23 (0.08)	-18.18 (3.96)	-1.01 (0.22)	138 (49.3)	85 (30.4)	2.89 (0.33)

Abbreviations: Δ = change from baseline; ANCOVA = analysis of covariance; FBG = fasting blood glucose; HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model for repeated measures; N = number of patients; SU = sulfonylurea; TZD = thiazolidinedione.
Note: Dula_x.x refers to dulaglutide x.x mg once weekly.
Note: Total, controlled duration for studies: GBDC = 52 weeks, GBCF = 104 weeks, GBDA = 52 weeks, GBDB = 78 weeks, and GBDD = 52 weeks.

Summary of Efficacy Results at Final Time Point for Dulaglutide Long-Term Active Comparator-Controlled Studies, ITT
Note: Analyses methods: change in HbA1c and weight ANCOVA (LOCF), percentages of patients achieving HbA1c targets logistic regression (LOCF), and change in FBG (MMRM).
a Data presented are LS mean (SE).
b Fasting blood glucose includes fasting serum glucose (GBDC, GBDA, GBDB, and GBDD) and fasting plasma glucose (GBCF), as measured by central laboratory.
c Number of evaluable patients (that is, patients with LOCF data for the time point) was used as denominator for percent to target analyses of HbA1c.
d Metformin dose was 1500 to 2000 mg QD.
e Sitagliptin dose was 100 mg QD.
f Exenatide dose was 10 mcg BID.
g Insulin glargine dose was adjusted based on treat-to-target algorithm to maintain fasting plasma glucose <100 mg/dl (<5.6 mmol/L).
†multiplicity adjusted 1-sided p-value <.025, for noninferiority, ††multiplicity adjusted 1-sided p-value <.025, for superiority of dulaglutide compared to active comparator, assessed only for HbA1c.
#p<.05, ##p<.001 dulaglutide treatment group compared to active comparator.
+p<.05, ++p<.001 dulaglutide 1.5 mg compared to dulaglutide 0.75 mg.

Source: Table 2.7.3.2 Summary of Clinical Efficacy, eCTD 2.7.3

- At the final time point, based on HbA1c change from baseline, dulaglutide 0.75 mg was superior to the active comparators sitagliptin, exenatide, and insulin glargine (GBDD) in 3 studies and noninferior to the active comparators metformin

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and insulin glargine (GBDB) in the remaining 2 studies. Dulaglutide 1.5 mg was superior to active comparator in all 5 studies.

- In all 5 Phase 3 studies, treatment with dulaglutide 1.5 mg resulted in weight reduction from baseline at the primary time point that was maintained through the final time and superior to all comparators but metformin. In 3 of the 5 Phase 3 studies, dulaglutide 0.75 mg was associated with weight reduction over the duration of the studies. Dulaglutide 0.75 mg was statistically inferior to metformin at the final time point in study GBDC and exenatide in study GBDA.
- More subjects were at HbA1c targets with dulaglutide compared to comparators in all 5 phase 3 studies at the final time point. More subjects on dulaglutide 1.5 mg compared 0.75 mg were at target in studies GBDC, GBCF, GBDA and GBDB

Reviewer's Assessment:
Both doses showed evidence of sustained efficacy over time. Similar to the results at the primary time points, there was evidence for greater efficacy with dulaglutide 1.5 mg compared to 0.75 mg.

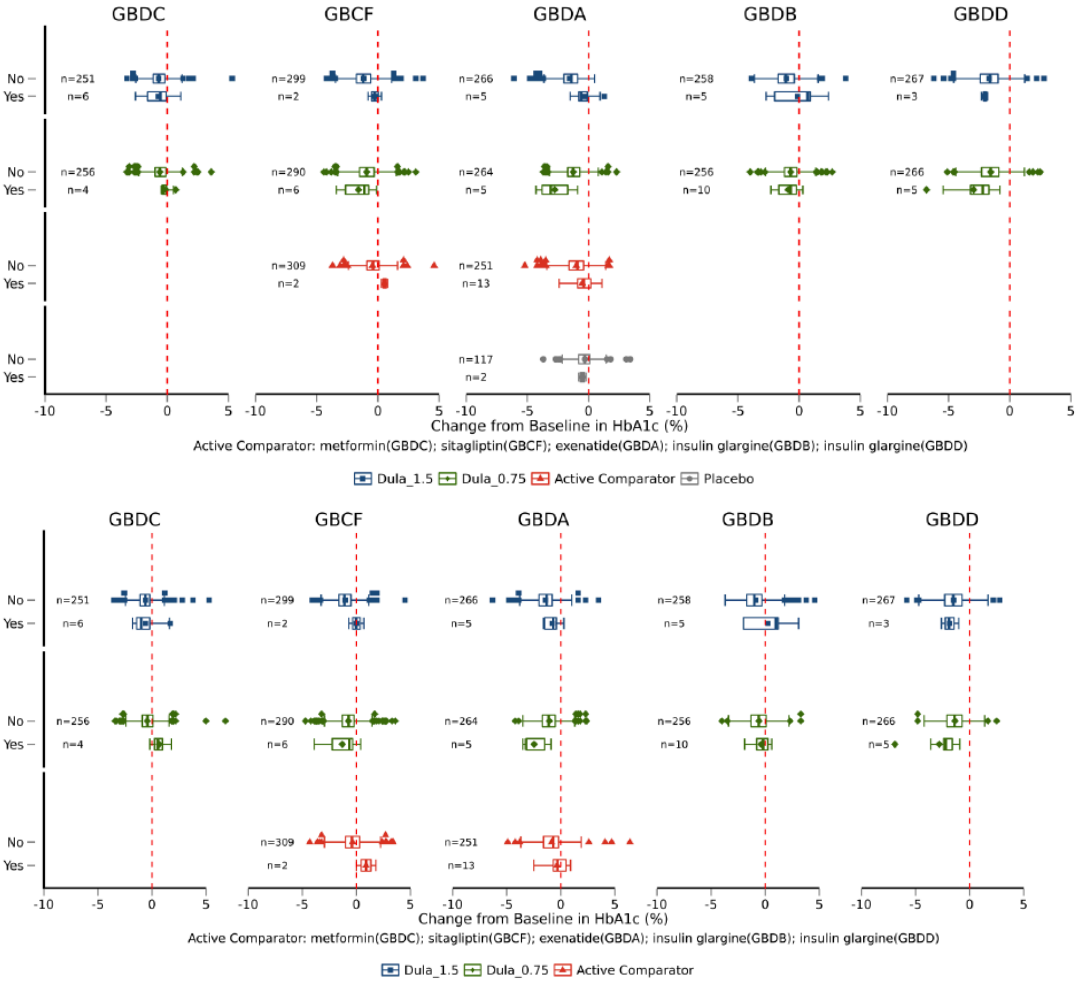
6.1.9 Additional Efficacy Issues/Analyses

Effect of dulaglutide ADAs on efficacy:

As will be discussed in 7.3.2.4 Immunogenicity, the development of antibodies with neutralizing activity could result in loss of efficacy.

The Applicant's box and whisker plots for change in HbA1c from baseline by ADA status are shown below (Figure 8). There is no evidence of the results being influenced by ADA status. Given the small number of subjects who were ADA positive, it is difficult to draw meaningful conclusions from the results.

Figure 8: Box-and-whisker plots of change from baseline in HbA1c (%) by treatment-emergent dulaglutide antidrug antibody status at primary and final time points (using LOCF), ITT, without post-rescue visits, H9X-MCGBDC, GBCF, GBDA, GBDB, and GBDD.



Abbreviations: HbA1c = glycosylated hemoglobin A1c; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of patients in specified category.

Notes: Dula_x.xx refers to x.xx mg dulaglutide once weekly. The boxes are based on the 1st quartile (Q1), median (Q2), and the 3rd quartile (Q3). The whiskers to the left and right of the boxes extend to the smallest and largest data points ≤1.5 x interquartile range (Q3-Q1) from Q1 and Q3, respectively. Individual points beyond the whiskers are plotted.

Final time point is 52 weeks for Studies GBDA, GBDC, and GBDD and 78 weeks for Studies GBDB; and 104 weeks for GBCF.

Source: Figures APP 2.7.3.26 and 27- Page 395-396, Summary of clinical efficacy-Appendix

7 Review of Safety

Safety Summary

Safety concerns for with dulaglutide are consistent with other approved products in the GLP-1 agonist class. Conclusions about the individual safety issues were as follows:

Deaths, Serious Adverse Events and Discontinuations:

Overall, deaths were comparable between dulaglutide (n=9, 0.22%) and comparator (n=8, 0.4%). Serious adverse events were generally balanced between dulaglutide and all-comparator and were events that might be expected in this population. The major reason for dulaglutide discontinuations compared to placebo was gastrointestinal side effects. Discontinuations due to PTs in the GI disorders SOC were dose-dependent (placebo 1 [0.2%], dulaglutide 0.75 mg- 11 [1.3%], dulaglutide 1.5 mg- 29 [3.5%]). The majority of the events were due to nausea.

Thyroid C- cell proliferation:

Based on preclinical data, there is concern for thyroid C-cell proliferation and medullary thyroid cancer with long-acting GLP-1 agonists.

Three thyroid cancers (all in dulaglutide-treated patients) were reported in the Phase 2 and 3 studies, and one event of medullary thyroid cancer was identified in a patient who received dulaglutide 2 mg for approximately six months and diagnosed three months after discontinuing treatment. Given this patient's baseline value for calcitonin being nearly 8x ULN and finding of a RET proto-oncogene germ line mutation this is unlikely to be due to dulaglutide.

Serum calcitonin was followed in the development program due to its utility as a marker of thyroid C-cell tumors. Dulaglutide 0.75 mg and 1.5 mg did not increase mean serum calcitonin values compared with placebo. Numerically more dulaglutide patients had lab values for calcitonin exceeding the threshold level of 35 pg/ml compared to all comparator. These cases were characterized by elevated baseline calcitonin (5/7 patients), pre-existing thyroid disorders or neoplasia, or single instances of an elevated calcitonin after a normal baseline value (one patient).The value of routine monitoring of serum calcitonin or thyroid ultrasound is uncertain in patients treated with dulaglutide.

Pancreatitis:

There were nine patients with events adjudicated to be pancreatitis. Four of these were treated with placebo or active comparator (all acute pancreatitis) and five were treated with dulaglutide (acute pancreatitis: 2; chronic pancreatitis: 2; type unknown: 1).There was one case of hemorrhagic pancreatitis which was reported in a placebo patient.

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There were an additional four patients with events deemed as “unknown if pancreatitis” (insulin glargine: 1; dulaglutide: 3).

Of the nine patients with pancreatitis determined by adjudication, eight had investigator reported pancreatitis. The last case was in a patient that was adjudicated because of repeated increases in pancreatic enzyme concentrations and non-specific GI symptoms.

Overall the Applicant’s process for capture of pancreatitis events seems acceptable. There do not appear to be any safety signals for pancreatitis with dulaglutide that are inconsistent with drug class.

Dulaglutide was also associated with increases in lipase, pancreatic amylase and, to a lesser degree, total amylase. The maximum increase in enzymes occurred between four and eight weeks of exposure, and remained relatively stable while on treatment. This increase demonstrated reversibility following drug-withdrawal. These effects were dose dependent with a greater effect observed with the dulaglutide 1.5 mg dose. There were also categorical increases in pancreatic enzymes, with more dulaglutide patients reporting a ≥ 3x upper limit of the reference range. The categorical increases do not appear to be significantly dose-dependent.

Similar changes in pancreatic enzymes observed with dulaglutide were seen with exenatide BID and sitagliptin, but the observed increases were greater with dulaglutide. The clinical significance of these findings is unknown. Serial measurements of pancreatic enzymes in Phase 2 and 3 trials did not predict the onset of acute pancreatitis.

Pancreatic Cancer:

Though there has been concern with regard to the development of pancreatic cancer with GLP-1 based therapies, no imbalance in the incidence of pancreatic cancer was seen in the dulaglutide development program (dulaglutide: 4, all comparators: 3). Though the available patient exposure is too small to definitively assess the risk for pancreatic cancer with dulaglutide, it seems reasonable to conclude that the incidence in clinical programs to date is comparable to comparator. Similar to approved agents in the GLP-1 agonist class, pancreatic cancer should continue to be followed as an AE of special interest in the CV outcome study.

Immunogenicity:

The overall incidence of treatment-emergent dulaglutide ADAs in patients treated with dulaglutide across Phase 2 and 3 trials was low (1.6% in dulaglutide treated patients vs. 0.7% in patients treated with placebo or non-GLP-1 comparators). Four patients had higher (≥1:128) treatment-emergent dulaglutide ADA titer and one patient had

progressive increases in antibody titer over time. No dose dependency (0.75 mg vs. 1.5 mg) was observed with respect to the incidence of treatment-emergent dulaglutide ADA.

Among patients treated with dulaglutide that had treatment-emergent dulaglutide ADAs (n=64), approximately half (34 patients) had dulaglutide neutralizing ADA (0.9% of the overall population). Among 64 patients treated with dulaglutide who developed treatment-emergent ADA, approximately half (36 patients) developed native sequence GLP-1 cross-reactive antibodies (0.9% of the overall population). Four of these patients developed neutralizing ADAs for nsGLP-1, and two patients had both nsGLP-1 cross-reactive and neutralizing ADA.

There were no systemic hypersensitivity adverse events reported in any of the 64 dulaglutide-treated patients with treatment-emergent dulaglutide ADAs.

Hypersensitivity:

There were 19 (0.5%) dulaglutide treated patients in the phase 2/3 program with hypersensitivity-related events versus 12 events in comparator treated patients (0.6%). Urticaria was the most frequently reported TEAE. None of these patients had dulaglutide ADAs detected.

There was one case each of Steven-Johnson syndrome and anaphylactic shock. Association between exposure to dulaglutide and these hypersensitivity events does not appear likely, but cannot be excluded.

Injection site reactions:

There were numerically more injection site adverse events in the dulaglutide treatment group (38, 1.7%) when compared with the placebo-treated patients (6, 0.9%). This is consistent with the drug class.

This AE was not dose-dependent-the same percentage (1.9%) of patients reporting injection site adverse events in the dulaglutide 1.5 mg treatment group and the 0.75 mg treatment group. Injection site hematoma was the most frequently reported injection site reaction for both the placebo (3, 0.4%) and all dulaglutide (17, 0.8%) treatment groups.

In the phase 2 and 3 studies, two dulaglutide-treated patients discontinued study drug due to injection site reactions versus none with placebo. Neither of these patients had treatment emergent dulaglutide ADAs.

Patients with treatment-emergent dulaglutide ADA had significantly higher incidence of injection site adverse event (3.1%; 2 of 64 patients) compared to patients who did not develop treatment-emergent dulaglutide ADA (0.5%; 18 of 3843) patients. Two of the

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five dulaglutide-treated patients who had high or progressive antibody titers had injection site reactions.

Renal Safety:

There was no apparent decline in renal function compared to baseline as measured by eGFR or UACR over the course of the clinical studies with dulaglutide 1.5 mg or dulaglutide 0.75 mg. Comparison of the long-term effects of treatment with dulaglutide 1.5 mg and 0.75 mg (up to 104 weeks) on renal function did not indicate any difference between the two doses. There were two patients treated with dulaglutide 0.75 mg who shifted from normal renal function (eGFR> 90ml/min/m^2) to CKD stage 3b and Stage 4 (eGFR ≤ 45 and 30 ml/min/m^2 respectively). Neither of these patients reported other AEs. The significance of this is unclear. The majority of patients did not change their CKD stage. Acute renal failure incidence with dulaglutide was comparable to all comparators.

There were limited numbers of dulaglutide treated patients with CKD stage 3 or worse (n=171). Safety in patients with more advanced CKD may be better assessed after review of the dedicated ongoing study in patients with renal impairment (study GBDX).

Given the increased risk for further renal failure in patients that already have baseline renal impairment, it may be prudent to initiate therapy with the 0.75 mg dose and titrate up to the 1.5 mg dose based on tolerability and need for additional glycemic control.

Hypoglycemia:

The risk for hypoglycemia with dulaglutide is consistent with the drug class. Compared to placebo, patients treated with dulaglutide on a background of metformin therapy had increased episodes of documented symptomatic hypoglycemia. There was a trend for dose dependency for hypoglycemia. There were numerically more documented symptomatic hypoglycemic episodes with dulaglutide 1.5 mg compared to 0.75 mg in patients on monotherapy and patients on background therapies of metformin or sulfonylurea ±metformin. In the add-on to sulfonylurea study, two patients had severe hypoglycemic events on dulaglutide 1.5 mg versus none on dulaglutide 0.75 mg.

Sixty-two events of severe hypoglycemia were reported for 41 patients in the Phase 2 and 3 program (insulin glargine: 18; exenatide BID: 2; dulaglutide 0.75 mg: 9; dulaglutide 1.5 mg: 12). The majority of patients (34 of 41 [82.9%]) who reported severe hypoglycemia received insulin lispro with or without metformin as background therapy. Of the 27 severe hypoglycemic events that required treatment with either IV glucose or glucagon injection (which may be considered as more objective evidence for requiring third-party assistance), 12 occurred in patients on dulaglutide 1.5 mg , 9 events in patients on insulin glargine, and 5 events in patient’s treated with dulaglutide 0.75 mg.

Hepatic Safety:

Although the overall exposure with dulaglutide does not allow any definitive conclusions regarding drug-induced liver injury, there does not appear to be a significant hepatic safety signal based on available data.

Drug induced liver injury:

Two patients on dulaglutide had hepatic enzyme elevations that satisfied Hy's Law criteria[7] versus none on comparator. Both had alternate etiologies (i.e. alcoholic liver disease and viral hepatitis) to explain the elevations. The proportion of patients with treatment-emergent abnormal hepatic enzymes was similar across treatment groups.

Cholestasis:

Cholestasis is another hepatic safety concern with GLP-1 agonists. Seven patients on dulaglutide versus one patient on placebo had total bilirubin elevations > 2X ULN. Two of these satisfied Hy's law criteria and were evaluated for potential drug-induced liver injury. Both had other etiologies. The remaining five patients had baseline elevations or Gilbert's syndrome. Concomitant elevations in alkaline phosphatase to suggest cholestasis were not seen.

Cardiac Safety:

Dulaglutide satisfied the pre-market criterion to exclude the 1.8 risk margin from the 95% confidence interval for MACE+, a composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina. This was achieved using a meta-analysis of completed trials. Further evaluation of the CV risk of dulaglutide post-approval will be based on data from the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial. This study will be conducted in a high risk population with and is designed to exclude the 1.3 risk margin for a composite endpoint of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (MACE).

In addition to assessing cardiovascular risk, other cardiac events were evaluated. Compared to placebo, tachycardia was more frequent with dulaglutide, consistent with the drug class. Other AEs in the Cardiac disorder SOC were balanced. The broad and narrow SMQ search "any supraventricular arrhythmias" revealed numerically more subjects on dulaglutide 1.5 mg (18, 1.1%) with these AEs compared to dulaglutide 0.75 mg (7, 0.4%), but comparable to all comparators (20, 1.1%). As expected, all the

7 The particular laboratory profile of ALT elevation >3x ULN seen concurrently with bilirubin >2 x ULN has been referred to as Hy's Law. It has been used to identify a drug likely to cause severe drug-induced liver injury (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases

reported PT's were tachyarrhythmias. No difference was observed for ventricular arrhythmias.

Consistent with other GLP-1 agonists, there was a dose dependent increase in heart rate (HR) (LS mean [95% CI] difference from placebo with dulaglutide 1.5 mg: 3.37 bpm [2.48, 4.25]; dulaglutide 0.75 mg: 2.15 bpm [1.30, 3.01]). In addition, more treatment-emergent outliers were noted with categorical analyses using the criteria of sitting heart rate > 100 bpm and increase of over 15 bpm from baseline (placebo-0.7%, dulaglutide 0.75mg-1.3%, dulaglutide 1.5 mg-2.2%).

There was also a dose dependent decrease in systolic BP with dulaglutide. Statistically significant decreases in systolic BP were observed for each dose of dulaglutide versus placebo (LS mean [95% CI] difference from placebo at 26 weeks for dulaglutide 1.5 mg: -2.58 [-3.88, -1.28] mm Hg; for dulaglutide 0.75 mg: -2.14 [-3.45, -0.83] mm Hg). Blood pressure changes from baseline peaked early in treatment and diminished to less than 1mm Hg compared to baseline after 26 weeks. There were no differences between dulaglutide and placebo treated groups for treatment–emergent abnormal values for systolic or diastolic BP.

There were small mean increases in PR interval (3-4 msec) with dulaglutide in the placebo controlled studies. There were three treatment emergent categorical outliers (increase over 220 msec with over 25% change from baseline) on dulaglutide 1.5 mg versus none on placebo or dulaglutide 0.75 mg. In the sponsor's analyses of qualitative ECG findings, more subjects on dulaglutide 1.5 mg developed first degree AV block (AS1: placebo 0.9%, dulaglutide 0.75 mg-1.8%, dulaglutide 1.5 mg-2.3%; AS3:dulaglutide 0.75 mg 1.5%, dulaglutide 1.5 mg- 2.4%). Adverse events reported under the conduction disorders HLT were balanced.

The clinical significance of this effect should be best assessed in elderly, patients with underlying ischemic heart disease, sick-sinus or other pre-excitation syndromes, conduction disorders or on underlying beta-blocker/calcium channel blocker therapy. Conduction disorders should be studied as an AE of special interest in the ongoing CV outcome study (GBDJ-REWIND).

Common Adverse Events:

Consistent with drug class, nausea and vomiting were the most common adverse events with dulaglutide compared to placebo. Nausea and vomiting were clearly dose dependent and occurred about twice as frequently with dulaglutide 1.5 mg compared to dulaglutide 0.75 mg (21.1% vs. 12.4%; 12.6% vs. 6% respectively). The time course of nausea and vomiting with dulaglutide is consistent with other approved GLP-1 agonists, and peaked at 2 weeks. Discontinuation due to gastrointestinal intolerance was more frequent with the 1.5 mg dose, thus initiating therapy at 0.75 mg may be considered for improved treatment adherence.

7.1 Methods

Key Safety and Tolerability Assessments conducted by the Applicant:

- Routine subject safety assessments included adverse events (AEs), serious adverse events (SAEs), dropouts, hypoglycemic events, and physical examinations.
- Routine monitoring included evaluation of clinical laboratory evaluations (hematology, chemistry [including renal function], amylase, lipase, liver enzymes and calcitonin values) 12-lead electrocardiograms (ECGs), and vital signs (blood pressure and pulse rate) measurements.
- The effects of dulaglutide on SBP, DBP, and HR were characterized over a 26-week period in study GBDN by 24-hour ambulatory BP monitoring (ABPM). The safety assessment also includes an analysis of ECG data from the thorough QT study (GBCC). In addition, treatment-emergent anti-dulaglutide antibodies (ADA), including cross-reactivity of the antibodies with endogenous GLP-1 and neutralizing activity was assessed in the phase2/3 program.
- Safety assessments of special interest in the dulaglutide program include: CV events, thyroid cancer events, pancreatitis, hypersensitivity reactions and immunogenicity, renal events, and hepatic events. Details on how these events of special interest were defined, captured and adjudicated can be found in the safety section dedicated to each particular event

The integrated summary and analyses of AEs were mostly descriptive. Categorical variables were summarized using frequency and percentage. Continuous variables were summarized with distributional information. No multiplicity adjustment was made for inferential safety analyses. A meta-analysis for major CV events positively adjudicated by a Clinical Events Committee (CEC) was also conducted to exclude an unacceptable increase in CV risk prior to marketing as recommended in 2008 FDA "Guidance to Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes".

Reviewer's Assessments:
The sponsor's methods for safety monitoring, capture and assessment of events seems adequate.

My strategy was to primarily review the integrated summary of safety provided by the Applicant followed by review of the individual study and patient data as appropriate. All of the individual patient narratives for SAEs and the Adverse events of Special Interest listed in the Table of Significant and Notable Persons (TOSNPs) were reviewed. Selected narratives are summarized in appropriate sections of the review. Additional summary analyses or individual patient data was requested from the Applicant as deemed necessary over the course of the review. The Applicant's summary analyses for treatment-emergent adverse events were verified using Empirica Study, JMP and/or

Reference ID: 3609106

MedDRA based Adverse Events Diagnostics (MAED) software. Additional analyses were conducted using the same software if needed.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.3.1. Phase 3 Trial Characteristics: for discussion of the clinical studies.

7.1.2 Categorization of Adverse Events

Adverse events in the ISS were coded based on Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. Standardized MedDRA queries (SMQs) and customized adverse event searches were performed to address special safety topics. The Medical Dictionary for Regulatory Activities Version 15.0 was also used for coding in the individual CSRs for the phase 3 studies. Adverse events were coded using MedDRA 14.1 for study GBDN.

A treatment emergent adverse event (TEAE) was defined as an event that first occurred or worsened in severity after baseline. TEAEs were analyzed based on MedDRA PT. Some Adverse Events of Special Interest (AESI) were also analyzed using SMQ searches.

A serious adverse event (SAE) was defined as any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolongation of inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Any AE considered significant by the investigator for any other reason.

Important medical events that did not result in death, were not life-threatening, or did not require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring after a patient had taken the last dose of study drug were collected for 30 days after the last dose, regardless of the investigators opinion of causation. Thereafter, SAEs were not required to be reported unless the investigator felt the events were related to either study drug, drug delivery system, or a protocol procedure.

Adverse events of Interest were:

- Thyroid Neoplasms (particularly medullary thyroid cancer)
- Acute Pancreatitis
- Hypersensitivity and/or Immunogenicity
- Renal events
- Hypoglycemia
- Hepatic events
- Cardiovascular Events
- Gastrointestinal events

The Applicant's definitions and assessments for AEs of special interest will be described in more detail in the relevant sections. Overall the process for categorization of adverse events appeared acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data in the ISS were primarily reported for the Safety Population. This population was defined as all patients who were randomly assigned to study treatment and received at least one dose of assigned study treatment.

Analysis of rare adverse events of special interest, including serious hypersensitivity reactions, pancreatitis, hepatotoxicity, acute renal failure, medullary thyroid cancer and all other malignancies, was based on the safety population from all phase 2/3 studies.

The Applicant had several analysis sets for safety. These were composed of specific sub-groups from the Safety Population and were created to facilitate different comparisons. The two primary analysis sets were Analysis Set 1 (AS1) and Analysis Set 3 (AS3). Analysis Set 1 was further divided by dose into AS1a and AS1b. The rationale for use of these analysis sets follows:

Analysis Set 1 (AS1): Integrated comparisons of both dulaglutide 0.75 mg and 1.5 mg doses (combined) versus placebo for all studies had a treatment duration ≥ 26 weeks. Analysis of this set was limited to events that occurred during the first 26 weeks of exposure. Two subsets of AS1 allowed for comparison of each dulaglutide dose versus placebo:

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

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

Analysis Set 3 (AS3): Integrated comparisons of dose effects for dulaglutide 0.75 mg versus 1.5 mg for all clinical studies (placebo- or comparator-controlled) that included both doses and had a treatment duration ≥ 26 weeks, covering the full treatment period (range based on protocols: 26 to 104 weeks). This analysis set provides long-term exposure data for the dulaglutide 0.75 mg and 1.5 mg doses individually and combined (that is, all dulaglutide) but no comparator data.

The AS1 dataset was reviewed for comparison to placebo. This included comparison for common AEs, discontinuations due to AEs, relevant laboratory values and vital signs compared to baseline, to get a better understanding of treatment effects compared to placebo.

The AS3 dataset was reviewed to assess the long-term safety of dulaglutide 1.5 mg vs. dulaglutide 0.75 mg.

Several secondary analysis datasets used by the Applicant. Of these, I examined the following:

- Analysis Set 2 (AS2) - a supportive integrated comparison of all dulaglutide doses combined [0.1 mg to 3.0 mg] versus placebo, up to the 26-week time point, for all Phase 2 and 3 studies that included a placebo comparator. This set was reviewed to provide additional information on injection site reactions.
- Analysis Set 7 (AS7) – a supportive integrated comparison of TEAEs and SAEs for dulaglutide 0.75 mg and 1.5 mg combined versus any comparator in studies of treatment duration ≥26 weeks, covering the full treatment period (range based on protocols: 26 to 104 weeks). Patients initially randomized to placebo in Study GBDA (n=141) were excluded from analyses in AS7, as the plan for these patients called for them to switch from placebo to dulaglutide at 26 weeks.

For both Study GBDA and Study GBCF, patients initially assigned to placebo were included in summaries and analyses for the first 26 weeks of the study as placebo patients, and were not included in summaries for any period beyond that time point. For line listings and narratives provided by the Applicant, these patients are included for their full treatment period even after switching from placebo to active treatment unless otherwise stated. For the patients in GBDA who were initially randomized to placebo and then switched to dulaglutide and the placebo patients switched to sitagliptin in GBCF, this may have lead to some underestimation of AEs in the respective groups, but since rare AEs of special interest were presented for all patients in phase 2/3 studies over the entire treatment period, this should not affect interpretation of the safety results.

It is to be noted that comparator information is provided only in the AS1, AS2 and AS7 integrated datasets and for the rare events analyzed using the entire phase 2/3 safety population. I requested additional analyses of all TEAEs and SAEs utilizing the AS7

dataset so that the placebo-controlled and all comparator data could be reviewed for dulaglutide and to assist in identifying dose-dependent effects.

The Applicant used the entire Safety Population in phase 2/3 studies to analyze rare events (e.g. pancreatitis, medullary thyroid cancer, hypersensitivity reactions, hepatic adverse events, neoplasms, and acute renal failure events).

I additionally reviewed safety information from clinical pharmacology studies for deaths and rare events like hepatitis, serious hypersensitivity reactions and pancreatitis. These were not integrated into the Safety population comprised of all phase 2/3 studies, since several of the studies were Phase 1 trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Two doses of dulaglutide were evaluated in the phase 3 clinical program: dulaglutide 0.75 mg once weekly and dulaglutide1.5 mg once weekly. Additional doses were studied in the phase 2 studies prior to selection of the doses for study in the phase 3 studies. A total of 6,005 patients received study drug in the nine completed Phase 2 and 3 studies (Table 26). Of these 4,006 received dulaglutide. There were a total of 1,724 patient-years of exposure to dulaglutide 0.75 mg and 1689 patient years of exposure to dulaglutide 1.5 mg.

A total of 3,045 patients received dulaglutide for at least 24 weeks in Phase 2 and 3 studies, and 2,279 patients were treated with dulaglutide for at least 50 weeks. There were a total of 369 patients treated with dulaglutide for approximately 2 years. In the placebo controlled pool (AS1) the total exposure for dulaglutide 1.5 mg (n=834), dulaglutide 0.75 mg (n=836) and placebo (n=568) were 380, 390 and 251 patient-years respectively. This dataset only analyzed data up to 26 weeks of exposure. In the AS3 dataset which collected data for the full treatment exposure, the exposures for dulaglutide 1.5 mg (n=1,671) vs. dulaglutide 0.75 mg (n=1,671) were 1,688 and 1,655 patient years respectively.

Table 26: Exposure Summary for the Safety Population in the Dulaglutide Clinical Program:

Summary of Treatment Exposure 07MAY2013 11:19
Safety Population
Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN

	Exposure to Study Drug *a		Time on Observation	
	N	Patient-Years	N	Patient-Years
Safety Population	6005	5536.6	6005	6194.0
Dulaglutide	4006	3531.2	4006	3983.7
Dula<0.75	191	42.9	191	60.3
Dula_0.75	1765	1724.2	1765	1932.8
Dula_0.75 only	1706	1695.1	1706	1898.1
Dula_0.75 after Placebo *b,c	59	29.1	59	34.6
Dula~1.0	175	47.2	175	55.2
Dula_1.5	1762	1689.1	1762	1900.6
Dula_1.5 only	1700	1661.0	1700	1865.3
Dula_1.5 after Placebo *b,c	62	28.1	62	35.3
Dula>1.5	113	27.7	113	34.9
Placebo *d	703	283.9	703	324.3
Active Comparator				
Metformin	268	226.7	268	254.8
Sitagliptin	439	637.3	439	680.6
Sitagliptin only	315	475.5	315	507.2
Sitagliptin after Placebo *c	124	161.8	124	173.5
Exenatide	276	236.3	276	274.8
Insuline Glargine	558	621.2	558	675.7

Abbreviation: N = Number of patients in the specified treatment group.
*a - For some studies (GBDA, GBDB, GBDC, GBDD), if a patient ceased study drug during the study, the patient was requested to remain in the study. "Treatment exposure" does not include any time after cessation of study drug.

*b - This group excludes patients in GBDA Placebo/Dula who discontinued study treatment while on Placebo, yet continued in study into the Dula portion of the study (n=3 Dula_0.75, n=0 Dula_1.5).

*c - This group includes patients who received Placebo prior to receiving Dulaglutide or Sitagliptin.

*d - This group includes patients who received Placebo only, and those who subsequently received Dulaglutide or Sitagliptin.

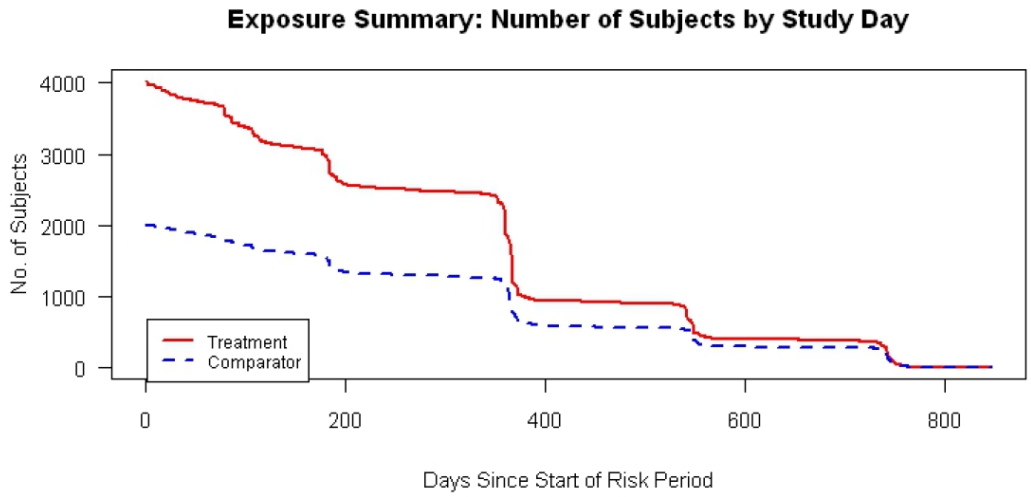
Source: Table ISS.6.1, page 178

To verify the Applicant's data regarding patient exposures in the clinical program, a Kaplan-Meier plot for patient exposure over time in the phase 2/3 studies comparing treatment to comparator was generated using the Empirica Signal program (Figure 9).

Figure 9: Kaplan-Meier Plot for Exposure over Time in the Dulaglutide Phase2/3 Studies, Safety Population.

Treatment includes: 'TR1_LY2189265-0.25mg+PLACEBO+METFORMIN', 'TR1_LY2189265-0.75mg', 'TR1_LY2189265 0.75mg+PLACEBO-ORAL', 'TR2_LY2189265-0.1mg', 'TR2_LY2189265-0.25mg', 'TR2_LY2189265-0.5mg+PLACEBO+METFORMIN', 'TR2_LY2189265-0.5mg_LY2189265-1.0mg', 'TR2_LY2189265-0.75mg', 'TR2_LY2189265-0.75mg+OAM', 'TR3_LY2189265-0.5mg', 'TR3_LY2189265-0.75mg', 'TR3_LY2189265-0.75mg+PLACEBO+METFORMIN', 'TR3_LY2189265-1.0mg_LY2189265-1.0mg', 'TR3_LY2189265-1.5mg', 'TR3_LY2189265-1.5mg+OAM', 'TR4_LY2189265-0.75mg', 'TR4_LY2189265-1.0mg', 'TR4_LY2189265-1.0mg_LY2189265-2.0mg', 'TR4_LY2189265-1.5mg', 'TR4_LY2189265-1mg+PLACEBO+METFORMIN', 'TR5_LY2189265-1.5mg', 'TR5_LY2189265-1.5mg+PLACEBO+METFORMIN', 'TR6_LY2189265-2mg+PLACEBO+METFORMIN', 'TR6_LY2189265-3.0mg', 'TR7_LY2189265-3mg+PLACEBO+METFORMIN', 'TR2_LY2189265-1.5mg', 'TR2_LY2189265-1.5mg+PLACEBO-ORAL', 'TR1_TS1_PLACEBO_LY2189265-0.75mg', 'TR1_TS2_PLACEBO_LY2189265-1.5mg'
Comparator includes: 'TR3_INSULIN-GLARGINE', 'TR3_METFORMIN+PLACEBO-INJECTION', 'TR1_INSULIN-GLARGINE', 'TR8_SITAGLIPTIN+PLACEBO+METFORMIN', 'TR9_PLACEBO+PLACEBO+METFORMIN_PLACEBO+SITAGLIPTIN+METFORMIN', 'TR1_PLACEBO', 'TR1_PLACEBO+OAM', 'TR1_PLACEBO_PLACEBO', 'TR2_EXENATIDE'
Time Frame: From 0 days after the study reference start date to 0 days after the study reference end date

Application: dulaglutide-125469, Study/Pool: Pool of 9 Phase 2 and Phase 3 Studies



No. of Subjects					
Treatment:	4026	2573	943	403	2
Comparator:	2006	1344	595	296	0

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Source: Generated by Reviewer, Empirica Study software, pooled SDTM datasets.

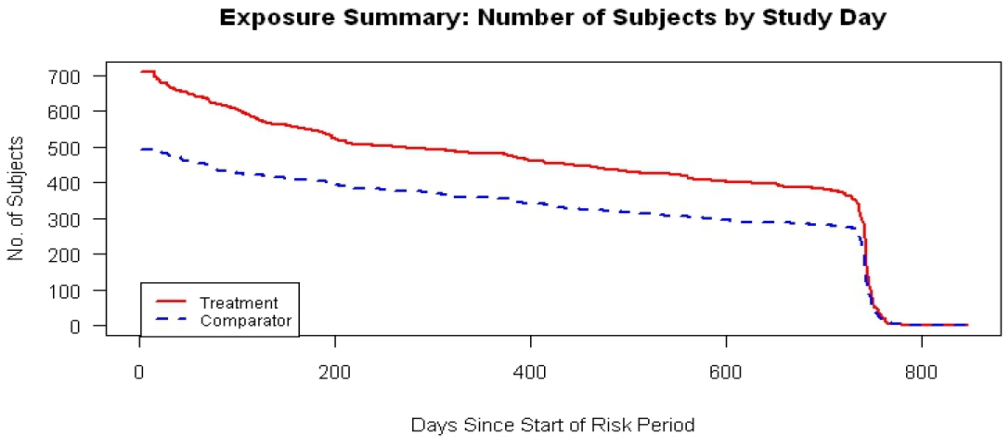
Minor discrepancies between the Applicant's data and numbers generated above (e.g. 4,026 dulaglutide exposed patients vs. 4,006 patients in Table 26) are due to the study pool for Empirica Signal being generated from the SDTM datasets containing data from individual studies, rather than coming from the Applicant's analyses datasets, which contain pooled data (i.e. the ADS datasets).

The apparent large drop in exposures just before 400 days was likely due to the design of the studies. Evaluation of the exposures using a similar Kaplan-Meier plot for those studies with exposure beyond 52 weeks Figure 10 and Figure 11), demonstrated that the exposure between dulaglutide and comparators was constant over the duration of these studies.

Figure 10 : Kaplan-Meier Plot of Exposure over Time in Study GBCF

Treatment includes: 'TR1_LY2189265-0.25mg+PLACEBO+METFORMIN', 'TR2_LY2189265-0.5mg+PLACEBO+METFORMIN', 'TR3_LY2189265-0.75mg+PLACEBO+METFORMIN', 'TR4_LY2189265-1mg+PLACEBO+METFORMIN', 'TR5_LY2189265-1.5mg+PLACEBO+METFORMIN', 'TR6_LY2189265-2mg+PLACEBO+METFORMIN', 'TR7_LY2189265-3mg+PLACEBO+METFORMIN'
Comparator includes: 'TR8_SITAGLIPTIN+PLACEBO+METFORMIN', 'TR9_PLACEBO+PLACEBO+METFORMIN_PLACEBO+SITAGLIPTIN+METFORMIN'
Time Frame: From 0 days after the study reference start date to 0 days after the study reference end date

Application: dulaglutide-125469, Study/Pool: h9x-mc-gbcf - Phase 3 study

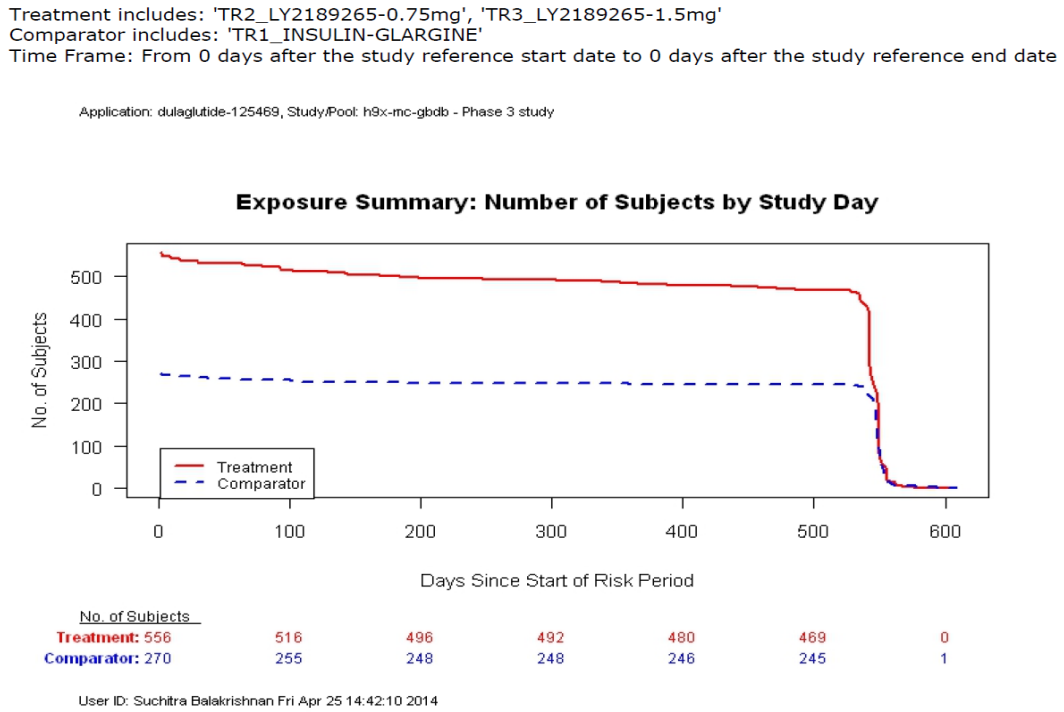


No. of Subjects					
Treatment:	710	523	462	403	2
Comparator:	492	395	343	295	0

User ID: Suchitra Balakrishnan Fri Apr 25 14:45:16 2014

Source: Generated by Reviewer, Empirica Study software, SDTM dataset for Study GBCF.

Figure 11: Kaplan-Meier Plot of Exposure over Time in Study GBDB



Source: Generated by Reviewer, Empirica Study software, SDTM dataset for Study GBDB.

The demographics of the study population are discussed in 6.1.2 Demographics. Overall the treatment arms were balanced.

7.2.2 Explorations for Dose Response

Study GBCF was designed for a “seamless” transition such that an optimal dose could be selected for further evaluation in Phase 3 studies. The Applicant was also advised to study a second lower dose in case study of the selected dose yielded an unforeseen safety concern.

Based on their dose-finding algorithm from Study GBCF, the 1.5 mg dose was selected as the dose which demonstrated optimal clinical utility. The 0.75 mg dose was selected as a lower dose to study in the Phase 3 studies.

The Applicant has proposed that the dulaglutide 1.5 mg dose be the only approved dose. The rationale for this is that it is optimally efficacious and has an acceptable tolerability profile (see the Applicant’s response to Information request received in DARRTS on April 22, 2014).

For additional discussion of dose dependency, see sections 5.3, 6.1.7 and 7.5.1. My assessment for dose–dependency of adverse events is discussed in Section 7.5.1, and

conclusions/recommendations for regulatory actions related to dose are discussed in the safety summary and Section 1.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Dr. Hummer's Pharmacology/Toxicology review for additional details.

Studies to evaluate potential thyroid-C cell proliferation and potential effects on the pancreas in a diabetic rat model are discussed in the relevant sections. No other special non-clinical testing was conducted other than the standard pharmacology and toxicology evaluations for an NME.

7.2.4 Routine Clinical Testing

Overall, clinical assessments including prospective evaluations for adverse events of special interest seemed adequate. Details are discussed in section 7.3.2 Submission Specific Primary Safety Concerns

7.2.5 Metabolic, Clearance, and Interaction Workup.

The non-clinical pharmacokinetics/toxicokinetics, the clinical pharmacokinetics and drug- interaction workup seem adequate, and are discussed in the Pharmacology-Toxicology and Clinical Pharmacology reviews.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The GLP-1 agonists are labeled with the following adverse events:

- The long-acting GLP-1 agonists (exenatide LAR, liraglutide and albiglutide) carry a box warning for risk of thyroid C-cell tumors, contraindicating use in patients with personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
- Post-marketing reports of acute pancreatitis, including hemorrhagic or necrotizing pancreatitis.
- Post-marketing reports of serious hypersensitivity reactions including anaphylaxis, angioedema and exfoliative skin conditions like Steven-Johnson Syndrome
- When used in combination with an insulin secretagogue (e.g. sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required
- All approved GLP-1 agonists carry a Warning and Precautions statement about post-marketing reports of acute renal failure, sometimes requiring dialysis.
- Gastrointestinal adverse events (nausea/vomiting) related to delayed gastric empting

7.3 Major Safety Results

7.3.1 Deaths

A total of 15 deaths occurred after patients received study drug in the Phase 2 and Phase 3 studies (sitagliptin: n=3 [0.68%]; insulin glargine: n=5 [0.90%]; dulaglutide 0.75 mg: n=3 [0.17%]; dulaglutide 1.5 mg: n=4 [0.23%]). The individual cases along with the associated PT and days of exposure are summarized in the table below (Table 27).

Table 27: Deaths in completed phase 2/3 program- Safety Population

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of Death	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBCF	46	2373	Placebo/Sitagliptin*	72	M	Cardio-respiratory arrest /cardiopulmonary arrest	(b) (6)	400	400	ongoing
	401	5003	Dula 1.5	65	M	Cerebrovascular accident /Stroke		176	182	6
	504	6157	Sitagliptin	61	M	Sudden death /sudden death		210	210	ongoing
	924	9700	Sitagliptin	58	F	Uterine cancer /uterine cancer		196	213	17
GBDA	12	555	Dula 1.5	56	F	Pancreatic carcinoma /Pancreatic cancer		162	166	4
	64	3151	Dula 1.5	61	M	Myocardial infarction /Myocardial Infarction		56	90	34
	75	3716	Dula 0.75	63	M	Death /Death- Natural Causes		89	102	13
GBDB	302	3106	Dula 0.75	53	M	Cardiac failure /Heart failure		456	504	48
	501	5052	Insulin Glargine	44	F	Respiratory failure /Respiratory Failure		309	356	47
	856	8628	Insulin Glargine	74	F	Sudden death /suddent death		318	352	34
GBDD	7	408	Dula 0.75	61	M	Pneumonia /pneumonia		78	81	3

Abbreviations: AE = adverse event; F = female; Inv = investigator identification number; M = male; Pat = patient identification number.

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of Death	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDD	251	4045	Dula 1.5	66	M	Staphylococcal sepsis /Septicemia Staphylococcus aureus	(b) (6)	190	213	23
	455	5392	Insulin Glargine	63	F	Cardiogenic shock /Cardiogen shock		291	292	1
	552	6104	Insulin Glargine	62	M	Death /Death		244	245	1
	602	6451	Insulin Glargine	51	M	Ventricular fibrillation /Ventricular fibrilation		189	312	123

Abbreviations: AE = adverse event; F = female; Inv = investigator identification number; M = male; Pat = patient identification number.

Source: Table ISS.6.18, page 223

An additional four deaths were identified during my review of the BLA submission. These additional patients along with a summary of the events follow:

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- Patient GBCZ-117-1712 died of pancreatic carcinoma after discontinuing from the study. The patient received only one dose of study drug (dulaglutide 0.75 mg).
- Patient GBDO-401-1301 died while participating in the hepatic impairment study. The patient had a history of severe hepatic impairment from alcoholic cirrhosis and died of acute hepatic failure after receiving a single dose of dulaglutide 1.5 mg. Thirteen days after the dose, the subject was diagnosed with bacterial peritonitis. Approximately 18 days after the dose, the subject suffered a grand-mal seizure which was reported as an SAE of status epilepticus. Aphasia and hemiparesis were observed. The subject subsequently developed acute renal failure approximately 44 days after the dose followed by acute hepatic failure the next day. Approximately 12 days after the development of acute hepatic failure, the patient died of acute renal and hepatic failure, which was attributed to worsening of the underlying alcoholic cirrhosis.
- Patient GBDD-803-8075 died as a result of cardiovascular disease. This death occurred after screening but before randomization. There was no exposure to study drug.
- Patient GBDD-252-4052 died as a result of an infected skin ulcer. This death occurred after screening but before randomization. There was no exposure to study drug.

These four additional cases seem reasonably excluded from the Applicant's comparison of deaths in the development program. Inclusion of the two cases with exposure to dulaglutide does not substantially affect the comparison.

No obvious imbalance in deaths was noted between dulaglutide and all comparators (dulaglutide-7 [0.18%], active comparator-8 [0.4%], placebo-0 [0.0%]). No deaths occurred on placebo, but placebo exposure was limited to 26 weeks.

All of the narratives for deaths were reviewed. I did not discover any narratives where I disagreed with the assessment. Most causes of death were cardiac or respiratory, with no imbalance in preferred terms between treatment groups.

7.3.2 Submission Specific Primary Safety Concerns

In the following sections, safety concerns related to this specific submission will be discussed. Much of the discussion will be based on drug class related safety concerns.

- 7.3.2.1 Potential thyroid C-cell proliferation

All the approved long-acting GLP-1 agonists have a box warning in the package insert and a Risk Evaluation and Mitigation Strategy (REMS) with a communication plan for increased risk of thyroid C-cell tumors based on nonclinical carcinogenicity studies.

The Applicant conducted a 2-year rat carcinogenicity study and a 6-month transgenic mouse study (discussed in detail in Dr. Hummer's pharmacology/toxicology review). In the transgenic mouse, increased C-cell hyperplasia (CCH) or neoplasia was not observed. In the rat study, the incidence of thyroid C-cell adenomas was increased over controls at dosages of > 0.5 mg/kg (7-fold the exposure at the MRHD). Additional observations in the thyroid included a numerical increase in thyroid C-cell carcinomas at 5 mg/kg (not statistically significant) and hyperplasia of thyroid C-cells (diffuse and/or focal) at dosages > 0.5 mg/kg. Based on the neoplastic changes occurring in the thyroid, the NOEL for neoplasia in Sprague Dawley rats after 93 weeks of treatment was 0.05 mg/kg, corresponding to an average (Male+Female) AUC_{0-96} of 4.06 µg·hr/mL (approximately 0.5-fold the weekly exposure at the MRHD). As a result of this data taken in combination with the concern for the drug class, the potential for thyroid C-cell tumors remains a concern with dulaglutide.

Patients with a history or a family history of increased risk for medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2), and patients with a screening/baseline serum calcitonin ≥ 20 pg/mL were excluded from the study. Additional safety measures implemented in the development program included serial measurement of calcitonin[8]. Of note, routine calcitonin measurements were not instituted for all of the studies, and measurements of calcitonin were in some instances performed on stored sample. Baseline calcitonin levels were not available at the time of randomization for all of the patients.

a. If at any time point, the serum calcitonin increased by ≥ 50% of the mean of baseline and screening value AND absolute value was ≥ 20 pg/mL AND < 35 pg/mL:

i. Test was to be repeated (central laboratory) within 1 month. If decreasing or stable, patient was to be followed through protocol mandated follow up.
ii. If repeat value was increasing:
- Study drug was to be stopped; patient was not to be rechallenged with study drug.
- Obtained a thyroid ultrasound.
- Obtained appropriate endocrine follow-up for further evaluation and patient management.
- Followed calcitonin values off study drug at 1, 3, and 6 months, and 1 year or until baseline value achieved, whichever occurred first.

b. If at any time point the serum calcitonin increased by ≥ 50% of the mean of baseline and screening and absolute values were >35 pg/mL:
   i. Stop study drug, patient was not to be rechallenged.
   ii. Obtained a thyroid ultrasound.

8 elevations in calcitonin are believe to be predictive of thyroid C-cell hyperplasia, and are used as a marker in medullary thyroid cancer

iii. Obtained appropriate endocrine follow-up for further evaluation and patient management.
iv. Followed calcitonin values off study drug at 1, 3, and 6 months, and 1 year or until baseline value achieved, whichever occurs first.

The Applicant's justification for the assessment point (≥ 50% of the mean of baseline and screening value AND absolute value ≥ 20 pg/mL AND < 35 pg/mL) and stopping criterion (absolute values > 35 pg/mL) was as follows:

"A postbaseline calcitonin value >35 pg/mL was considered a reasonable limit to stop study drug and initiate further clinical evaluation given that the patient was taking an experimental therapy still under investigation and for which the safety profile was not yet known (FDA correspondence dated January 2010). Basal calcitonin values > 50 and < 100 pg/mL have an approximate 50% positive predictive value for CCH/MTC, while a value of 100 pg/mL basal calcitonin is essentially 100% predictive of disease (Costante et al. 2007). There are other clinical situations in which calcitonin may be elevated unrelated to thyroid disease, including the use of proton pump inhibitors, smoking, and renal insufficiency. Thyroid nodules, including asymptomatic "incidentalomas," are very common: approximately 5% prevalence by palpation in older adults (Dillmann 2004), 49% to 57% by autopsy, and 13% to 50% ultrasound (review, Pinchera 2007). However, MTC is rare (Hundahl et al. 1998; Dillmann 2004)."

Reviewer's Comment: Seems acceptable and in-line with other GLP-1 programs

The reference range used to evaluate baseline calcitonin was 0 to 11.5 pg/mL for females and 0 to 18.2 pg/mL for males. The lower limit of quantification for calcitonin was 2 pg/mL. For observations below the lower limit of quantification (BLQ), a value of 1 pg/mL was imputed for analysis purposes.

The analyses of calcitonin included laboratory results from all phase 2/3 studies except GBCJ and GBCK. Data are not available for these Phase 2 Studies because those studies had a ≤ 12-week treatment duration (GBCK), or were conducted before calcitonin monitoring was implemented (GBCJ). These studies were both not more than 16 weeks in duration, and patients from these studies were included for analyses of all thyroid neoplasms. The Applicant reports that Phase 3 Study GBCF had already been initiated at the time the liraglutide toxicology data were made publicly available. The protocol for Study GBCF was amended to implement systematic calcitonin assessments and thus some patients early in the study may not have had screening, baseline, or serial measurements, or did not meet exclusion criteria for MTC. On review of the GBCF study report, this affected patients who were mostly randomized during Stage-1, i.e. baseline samples were unavailable for these patients. No patient in this study reported a calcitonin value ≥ 50 pg/mL at the time points assessed up to 24 months. These issues should not have any significant impact on the acceptability of the thyroid safety evaluation.

In AS1, mean baseline calcitonin values were similar for the placebo and the all dulaglutide group (2.55 pg/mL and 2.64 pg/mL, respectively; see Appendix 9.6 Supportive Tables From the ISS Referenced in the Review- Table ISS.6.48). Through 16 and 26 weeks post-baseline, mean calcitonin changed little within treatments (absolute change <0.3 pg/mL) resulting in similar mean calcitonin values between placebo and all dulaglutide (2.46 pg/mL and 2.67 pg/mL) at 26 weeks.

There was no dose–dependent effect noted for post-treatment calcitonin levels that increased over threshold, as shownin Table 28.

Table 28: Summary of Potentially Clinically Important Calcitonin Values in Phase 2 and 3 Studies[a,b] (Safety Population)

Study Treatment	N	n	%	Patient-Years	n/1000 patient-years
Placebo	605	2	0.3	258	7.75
Metformin	268	0	0	226.7	0
Sitagliptin	439	3	0.7	637.3	4.71
Exenatide BID	276	1	0.4	236.3	4.23
Insulin glargine	558	4	0.7	621.2	6.44
Dula_0.75	1765	11	0.6	1724.2	6.38
Dula_1.5	1733	13	0.8	1683.1	7.72

Abbreviations: BID = twice daily; Dula = dulaglutide; N = total number of patients in specified treatment and category; n = number of patients in specified category..

Note: Dula_x.x refers to x.x mg dulaglutide once weekly.

a Excludes Studies GBCJ and GBCK that took place before calcitonin monitoring was implemented in the dulaglutide clinical program. Therefore, 98 placebo-treated (66 GBCJ, 32, GBCK) and 29 dulaglutide 1.5 mg-treated patients (GBCK) were excluded from these analyses.

b A patient was considered to have potential C-cell hyperplasia if the maximum postbaseline calcitonin was ≥20 pg/mL with an increase ≥50% from mean of baseline and screening.

Source: Table ISS 6.52, page 349

Seven patients had post-baseline elevations of calcitonin over 35 pg/ml (Table 29).

Table 29: Patients with Postbaseline Calcitonin Greater than or Equal to 35 pg/mL in Phase 2 and 3 Studies (Safety Population)

Patients ID	Study Treatment	Patient Characteristics			Calcitonin		Thyroid Event Preferred Term (Actual Term)		Comments
		Sex	Age (y)	DD (y)	Treatment Week	Value (pg/mL)	Thyroid Disorders	Thyroid Neoplasm	
GBCF-013-0701	Dula_2.0	F	56	8	0 26 PTM	91.5 61.7 82.8	--	Thyroid Cancer (Medullary thyroid cancer)	• Positive for RET proto-oncogene germline mutation. • Medullary thyroid carcinoma believed to be preexisting.
GBCF-201-0107	Dula_1.5	M	51	2	0 12 26 39 52 65 78 91	23.4 46.7 25.3 27.2 34.9 14.2 25.8 11.0	--	--	• Only TEAE during study was gastroenteritis reported at 21 months. • No notable history or concomitant medications.
GBCF-203-4108	Dula_0.75	M	66	2	0 12 26 26 39 52 65 78 91 104	14.1 19.7 31.1 35.0 30.2 24.4 30.4 36.4 25.9 24.8	--	Thyroid neoplasm (thyroid nodule)	• After ~1 year of treatment, abdominal and thyroid ultrasound was performed with normal results. • ~78 weeks after the start of the study drug, patient stopped injectable study drug and had another thyroid ultrasound that found left and right lobe thyroid nodules. • No corrective treatments. • ~1 month later, the patient was asymptomatic and had a calcitonin (25.9 pg/mL) and normal thyroid ultrasound
GBCF-203-4116	Dula_0.75	F	61	5	0 12 12 26 PTM PTM PTM	24.7 88.7 40.8 49.1 69.7 39.0 37.5	Goitre (moderate growth of the residual thyroid [simple goiter])	--	• History of medullary thyroid cancer (micromedullary) prior to enrolling in study • Hashimoto's thyroiditis diagnosed by pathology that was performed due to high calcitonin values during study
GBCF-406-5267	Dula_1.5	M	48	4	0 12 26 39	25.4 37.7 13.8 14.3	--	--	• Nausea, vomiting, decreased appetite and fatigue reported at time of elevation (12 weeks) and acute nephritis at 9 months. • No notable history or concomitant medications.
GBDA-060-2971	Dula_0.75	M	70	5	-14 0 13 13 26 39 52	2.6 1.0 42.1 1.0 1.0 1.0 1.0	--	--	• Low values at baseline and all postbaseline visits, including retest, suggest that the 42.1 pg/mL value at Week 13 was laboratory error.
GBDD-036-1854	Insulin glargine	M	65	6	-10 0 2 4 13 19 26 52 PTM	18.2 24.6 27.2 35.6 18.6 22.2 21.8 21.2 19.3	--	Thyroid neoplasm (two 2-mm left thyroid nodules)	• After ~2 months in study, patient was found to have 2 small (2 mm) thyroid nodules. • Study drug discontinued after 3 months and all subsequent calcitonin values approximated baseline value.

Abbreviations: DD = diabetes duration; Dula = dulaglutide; F = female; M = male; PTM = posttreatment measurement; RET = rearranged during transfection; TEAE = treatment-emergent adverse event; y = year.
Source: Table ISS 6.53, page 352

Patient GBCF-013-0701 (dulaglutide 2.0 mg) had a calcitonin level 8-fold ULN prior to study treatment, and was positive for the rearranged during transfection (RET) proto-oncogene germ line mutation which increases the risk for MTC.

Reviewer's assessment of calcitonin elevations:

Numerically more dulaglutide patients exceeded the threshold calcitonin level of 35 pg/ml compared to all comparator. These cases are characterized by elevated baseline calcitonin (5/7 patients), preexisting thyroid disorders or neoplasia (2/7 patients), or single instances of elevated calcitonin after a normal baseline value (1 patient).

Given concerns that thyroid C-cell tumors may be reported simply as a thyroid neoplasm, the Applicant used two search strategies that were applied to TEAEs in the Phase 2 and 3 studies to identify any patient with a potential thyroid abnormality. The first strategy selected MedDRA PTs nested within the high-level term (HLT) Thyroid Disorders Not Elsewhere Classified (NEC). The second search strategy identified MedDRA PTs nested within the HLT Thyroid Neoplasms. The following preferred terms were used:

PT's within Thyroid disorders NEC HLT:

- Calcitonin secretion disorder
- Ectopic thyroid
- Euthyroid sick syndrome
- Goitre
- Goitre congenital
- Haemorrhagic thyroid cyst
- Hypercalcitoninaemia
- Lid lag
- Thyroglossal cyst
- Thyroglossal fistula
- Thyroid C-cell hyperplasia
- Thyroid disorder
- Thyroid dysfunction in pregnancy
- Thyroid fibrosis
- Thyroid hemorrhage
- Thyroid infarction
- Thyroid malformation
- Thyroid mass

- Thyroid pain”

PT’s within Thyroid neoplasm HLT:

- Benign neoplasms of thyroid gland
- Metastases to thyroid
- Thyroid adenoma
- Thyroid cancer
- Thyroid cancer metastatic
- Thyroid cancer recurrent
- Thyroid cancer stage 0-stage 4
- Thyroid cyst,
- Thyroid neoplasm

Thirty patients were identified from review of events coded to these PTs. There were 15 patients with the reported PT “Goiter” (all dulaglutide, n=9 [0.22%]; all comparator, n=6 [0.3%]). There were 15 patients with events included in the “Thyroid neoplasm” HLT (all dulaglutide, n=10 [0.25%]; all comparator, n=5 [0.25%]). Of the 15 patients with events included in the “Thyroid neoplasm” HLT, only three had a diagnosis of thyroid cancer. Calcitonin values were reviewed for the 15 patients with an event of “Goiter” and the 12 patients with a non-thyroid cancer event from the “Thyroid neoplasm” HLT. Only four had an elevation of calcitonin after baseline.

There were three patients with thyroid biopsy results reported on a specific biopsy case report form. None of these patients had an elevated calcitonin. Two of these cases were reported as goiter. The third was initially reported as medullary thyroid cancer, but was supposedly reported in error. The patient had a thyroidectomy and surgical pathology was consistent with papillary thyroid cancer.

Narratives for patients with neoplasms, goiter with calcitonin elevation and biopsy CRF reports were reviewed and are discussed further below. I have separated the cases based on narratives for medullary thyroid cancer, papillary thyroid cancer, goiters with calcitonin elevations and other thyroid biopsy reports.

Medullary thyroid Cancer narrative:

GBCF-013-0701, 57 yr. F, Dulaglutide 2 mg: The patient was a 57-year old white female with no reported family history of endocrine neoplasms, including MEN. The patient was assigned to dulaglutide 2.0 mg during Stage 1 randomization of Study GBCF. After approximately 6 months of blinded study drug, the dose decision for Stage 1 was reached, and the patient’s dulaglutide 2.0 mg dose was discontinued. At the time of discontinuation, the patient’s calcitonin was 61.7 pg/mL. Calcitonin monitoring had not been started at the time this patient was randomized into Stage 1. Thus, this elevated

value at the 6-month discontinuation visit was the first calcitonin value known for this patient. A frozen baseline specimen (collected prior to dosing with study drug) was subsequently assayed, and calcitonin was 91.5 pg/mL. The patient's calcitonin was 82.8 pg/mL three months after discontinuation and an ultrasound revealed multiple small bilateral nodules, many cystic in nature. A fine needle aspiration of a dominant nodule in the left thyroid lobe indicated numerous sheets of thyroid epithelial cells with microfollicles, colloid, and focally numerous macrophages, consistent with a follicular neoplasm. Approximately 1 year after study drug had been initiated and 6 months after it was stopped, the patient underwent a left hemithyroidectomy, and pathology confirmed a left thyroid medullary carcinoma, "0.4 cm in greatest dimension. Stage: pT1, pNX, pMX. Final margins were free of tumor". The patient was subsequently discovered to be heterozygous positive for a RET proto-oncogene mutation associated with MEN2 or familial MTC. The patient's calcitonin values remained elevated following surgery. Due to continued elevation in calcitonin, the presence of RET proto-oncogene mutation, and nodules in the remaining right thyroid lobe, the patient underwent a right hemithyroidectomy and node dissection. A 0.3 cm MTC tumor was found. It was negative for lymphatic and vascular invasion, resection margins free of malignancy. A follow-up calcitonin three-months later was was <2 pg/mL (normal range 5 or less). The event was considered recovered. No other features of MEN2 were reported on investigational work-up.

Reviewer's Comment: Given a baseline value for calcitonin nearly 8x ULN, in a patient positive for a RET proto-oncogene germ line mutation this is likely to be a preexisting cancer. The lack of increasing calcitonin values from baseline suggest that the tumor being stimulated by dulaglutide is unlikely, but this cannot be excluded.

Papillary Thyroid Cancer narratives:

GBCF-608-6653, 46 yr. F, Dulaglutide 1.5 mg: The patient was a 46-year-old Asian female with a family history of thyroid cancer (2 elder sisters). The patient had a history of hyperlipidemia and hypertension. Concomitant medications included atorvastatin, amlodipine, and valsartan. Diabetes background therapy in the study included metformin. Approximately 2 years after the start of study drugs, a thyroid nodule (1.5 cm) was found during a regular checkup. Within 1 week of the nodules discovery, study drugs were stopped and the patient had total thyroidectomy. Pathology confirmed multifocal papillary thyroid cancer. There was no evidence of metastasis and radiotherapy was not started. The patient completed 104 weeks of study participation. At no time during the study did her calcitonin levels exceed 1.0 pg/mL.

Reviewer's Comment:-Possible association with study drug given the 2 years of exposure, although confounded by family history. Papillary thyroid cancer is common and not a class effect associated with GLP-1 based therapies.

GBDB-202-2102, 47 yr F. Dulaglutide 1.5 mg: The patient was a 47-year-old female with history of factor V Leiden deficiency and T2DM diagnosed 10 years prior. Concomitant medications included ramipril, and rosuvastatin calcium. She was taking glimepiride and metformin as concomitant therapy during the study. Approximately 3 months after starting dulaglutide, she was confirmed to have multiple thyroid nodules. A bulky and heterogeneous gland was evident on CT consistent with multinodular goiter. Approximately 5 months after discovering the nodules, the patient discontinued study drug after 8 months on treatment. One week later she underwent thyroidectomy, and follicular variant papillary carcinoma was found on pathology. There was no lymphatic or vascular invasion. She was scheduled for I-131 therapy and taken off the study protocol. During the study, her calcitonin values never exceeded 4.9 pg/mL.

Reviewer's Comment: Nodule with atypia on fine needle aspiration discovered within 6 months on treatment making association to study drug unlikely. Tumor stimulation secondary to dulaglutide cannot be excluded. However, papillary thyroid cancer is more common and not a class effect associated with GLP-1 based therapies

Narratives for Goiter with Blood calcitonin increased:

GBCF -032-1667, 45 yr. F, Dulaglutide 0.75 mg: The patient was a 45-year-old white female with hyperlipidemia, GERD, hypertension, and hypothyroidism (diagnosed two years prior). Concomitant medications included esmeprazole, levothyroxine, ezetimibe/simvastatin, hydrochlorothiazide, and metformin. At baseline her calcitonin level was 16.6 pg/mL (ULN for females=11.5 pg/mL). Calcitonin values were 18.5 pg/mL at 6 months and 16.2 pg/mL at 9 months. Due to these values of calcitonin greater than ULN for female sex, she underwent thyroidectomy. Pathology was consistent with multinodular goiter. Postoperatively she developed iatrogenic hypoparathyoidism. This is reported under an SAE of hypocalcemia. She discontinued from the study due to the SAE of systemic lupus erythematosus after 528 days on therapy.

Reviewer Comment: Calcitonin elevation at baseline with minimal increase post dulaglutide exposure. This is unlikely to be related to dulaglutide.

GBCF-203-4116, 61 yr. F, Dulaglutide 0.75 mg: The patient was a 61-year-old Hispanic female with history of T2DM, previous right hemithyroidectomy (pathology report of adenoma of oxifilic cells, Hashimoto's thyroiditis and medullary microcarcinoma in a 0.5 cm area with surgical margins free of disease), and iatrogenic hypothyroidism. The patient never received neck/head irradiation. Highest blood calcitonin post right hemithyroidectomy was 3.2 pg/mL. Concomitant medications included levothyroxine, estradiol, and metformin (concomitant therapy in the study). She was randomly assigned to treatment in Study GBCF, which was a study initiated prior to the addition of calcitonin, MEN2, and MTC exclusion criteria in dulaglutide studies. Thus, this patient was randomized with a baseline calcitonin of 24.7 pg/mL. At three months, she was noted to have calcitonin of 88.7 pg/mL. Study drug was discontinued. One month later

she had residual thyroid tissue removed. Postoperative diagnosis was consistent with Hashimoto thyroiditis ("clusters of lymphyoplasmacytic inflammatory infiltrate and secondary lymphoid follicles that looked small; several of the follicular cells had eosinophilic granular cytoplasm") and antimicrosomal antibodies were approximately 5x ULN. Positron emission tomography, performed 1 month after surgery due to persistent elevations in calcitonin (49.1 to 69.7 pg/mL), did not show any evidence of residual or metastatic tumor. Two months later, a lymph node dissection of the neck was performed without complications. The pathological study reported follicular and sinus hyperplasia in 34 right lymph nodes and 20 left lymph nodes. There were no malignant cells.

Reviewer's comment: The patient had a prior history of MTC and Hashimoto's thyroiditis, which was again noted in residual thyroid tissue. Calcitonin was elevated at baseline.

GBCF-203-4108, 67 yr. M, Dulaglutide 0.75 mg: The patient was a 67-year-old Hispanic male with a history of dyslipidemia and hypertension treated with pravastatin, lisinopril, and clopidogrel. At baseline, the patient's calcitonin was 14.1 pg/mL and by 3 months, his calcitonin was 19.7 pg/mL. Through the end of the study (24 months), his calcitonin fluctuated between 24.4 pg/mL and 36.4 pg/mL. After approximately 1 year of treatment, the patient underwent abdominal and thyroid ultrasound with a normal result. Approximately 20 months after the start of the study drug, the patient stopped study drug and underwent another thyroid ultrasound that detected left and right lobe thyroid nodules. No corrective treatments were started other than the above noted discontinuation of injectable study drug. Approximately 1 month later, the patient was asymptomatic and had a normal thyroid ultrasound and calcitonin of 25.9 pg/mL.

Reviewer's Comment: This case is confounded by ultrasound operator and technique issues. Temporal association between thyroid nodules and dulaglutide therapy was noted, although calcitonin levels remained elevated on dechallenge (further f/u information not available). A similar case also noted with comparator (insulin glargine).

GBCF-507-6253, 56 yr. M. Dulaglutide 1.5 mg: This patient was a 56-year-old white male with hypertension, dyslipidemia, and T2DM. Concomitant medications included lisinopril, simvastatin, and glimepiride. He had high baseline calcitonin (23.7 pg/mL). Goiter was diagnosed at Visit 9 (6 months of treatment). A thyroid ultrasound was performed showing a very large nodular goiter. An endocrinology consult was suggested (results not known). Calcitonin values varied from 23.7 pg/mL at baseline to 18.2 pg/mL at 3 months and 29.3 pg/mL at the discontinuation visit. A Tc99 thyroid scan was obtained which demonstrated a large asymmetric gland with very little radiotracer uptake, precluding detailed assessment of the gland. No endocrinology consult was obtained. The patient was discontinued from the study due to elevated pancreatic enzymes at 4.5 months of study drug exposure. The investigator reports no new medical problems from the goiter.

Reviewer's Comment: Calcitonin was elevated at baseline with minimal changes post-treatment.

Other Patients with Thyroid Biopsy Reports:

In addition to patient GBDB-202-2102 discussed earlier, fine needle aspiration was done in two patients, associated with nodular disease in the form of preexisting goiter. None of these patients had an elevated calcitonin post-baseline:

GBDD-252-4069, 73 yr. F, dulaglutide1.5 mg: the diagnosis reported was "other". No further information was reported.

GBDD-705-7180, 74 yr. F, dulaglutide 0.75 mg: the diagnoses reported was "benign follicular disease". Further information is not available.

In the 4 month safety update an additional two blinded cases were reported (Table 30). Neither of these events appears to be a thyroid C-cell tumor.

Table 30: Thyroid cancer in ongoing studies:

Trial Alias/ Patient ID	Patient Age - Sex	First Dose to Event	Last Dose to Event	Preferred Term	Outcome	Comments
GBDE-113-1283	43y F	98 days	Not reported	Thyroid cancer	Recovered	• History of thyroid nodules treated with levothyroxine. • Ultrasound showed multinodular gland with dominant right nodule. Decreased activity in dominant nodule on scan with normal RAI overall. • ~81 days after starting study drug, biopsy identified micropapillary carcinoma (1.7 mm). • ~98 days after starting study drug, thyroidectomy performed. • Per investigator, event was not related to study drug. • Per investigator, condition was diagnosed before study enrollment. • Study drug was continued.
GBDJ-941-10414	71y F	299 days	6 days	Papillary thyroid cancer	Recovered	• Non-toxic multinodular goiter ~4 years prior to study. • Stopped study drug for ~5 months due to gastrointestinal events and then restarted study drug. • ~299 days after starting study drug, biopsy with pathology showed follicular variant of papillary carcinoma (1.0 cm) that extended into perithyroidal soft tissue. • Thyroidectomy. • Per investigator, event was not related to study drug as nodule was preexisting. • Study drug was stopped.

Abbreviations: F = female; y = year(s); RAI = radioactive iodine.

Source: Table 11, 4 month safety update

Reviewer's Comment: Since both these patients had pre-existing thyroid nodules and one patient is continuing in the study, unblinding of treatment information was not requested.

Reviewer's Thyroid C-cell safety assessments:

While neither dose of dulaglutide increased mean serum calcitonin compared to placebo, there were numerically more dulaglutide patients with calcitonin > 35 pg/ml than in comparator treated patients. Most of these cases, however, had elevated calcitonin at baseline. The significance of this is unclear. There was one case of MTC in a patient treated with dulaglutide. Causality seems unlikely, however, due to an elevated calcitonin at baseline and detection of a mutation in the RET proto-oncogene. From the available data, there does not appear to be an increased risk for thyroid C-cell proliferation/MTC with dulaglutide. Given the preclinical data and concerns with the drug class, this remains a concern. Similar to other agents in drug class this AE should be addressed with a boxed warning in the package insert and with a Risk Evaluation and Mitigation Strategy (REMS).

- 7.3.2.2 Pancreatitis

There have been concerns regarding the risk for pancreatitis and pancreatic cancer for GLP-1 agonists and for DPP4 inhibitors[9,10,11]. A review of the available non-clinical toxicology studies, clinical trial data, observational studies, and post-marketing studies performed by the European Medicines Agency (EMA) and the FDA have not led to any final conclusions regarding this potential relationship[12]. Both agencies continue to investigate this safety signal.

Pre-clinical studies with dulaglutide did not alleviate concerns for this risk. Modest increases in amylase, increased ductal epithelium, and increase in neutrophilic inflammation of the acinar pancreas were observed in diabetic ZDF rats given dulaglutde at doses up to 5.0 mg/kg/twice weekly for 3 months.

To minimize the risk to patients in the development program, the Applicant excluded patients with a history of acute or chronic pancreatitis. Patients diagnosed by investigators as having pancreatitis were required to be permanently discontinued from study drug, and no rechallenge was allowed.

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9 Sonal Singh, MD, MPH; Hsien-Yen Chang, PhD; Thomas M. Richards, MS; Jonathan P. Weiner, DrPH; Jeanne M. Clark, MD, MPH; Jodi B. Segal, MD, MPH. Glucagon like Peptide 1–Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus. A Population-based Matched Case-Control Study. *JAMA Intern Med. Published online February 25, 2013.*

10. Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies; Michael Elashoff, Aleksey v. Matveyenko, Belinda Gier, Robert Elashoff, and Peter C. Butler; GASTROENTEROLOGY 2011;141:150–156

11. Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors; Alexandra E. Butler, Martha Campbell-Thompson, Tatyana Gurlo, David W. Dawson, Mark Atkinson, and Peter C. Butler. Diabetes 62:2595–2604, 2013

12. Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment. Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D., Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and Curtis Rosebraugh, M.D., M.P.H.

To evaluate the risk of pancreatitis, the Applicant used the following strategy:

1. Investigator-reported adverse events of pancreatitis were identified and collected as an adverse event of special interest. Adverse events of severe and/or serious abdominal pain of unknown origin that were reported in the Phase 2 (Study GBDN) and Phase 3 program were also collected.
2. Repeated lipase and total amylase as well as pancreatic amylase measurements were performed throughout the phase 2 and 3 clinical studies. Serial enzyme measurements were also performed in clinical pharmacology studies. An assessment algorithm for additional follow-up was employed in patients with asymptomatic elevations ≥ 3x upper limit of normal (ULN) in amylase and/or lipase confirmed by repeat testing. Patients with confirmed hyperenzymemia were required to undergo a structured diagnostic work-up which included abdominal imaging.
3. An external committee of physicians with expertise in the field of pancreatitis (clinical endpoint committee [CEC]) was utilized to adjudicate suspected pancreatitis events and thereby characterize the risk for pancreatitis with dulaglutide treatment.

Events were reported using a Pancreatic Follow-up Assessment (PFUA) case report form for patients that met the following criteria:

- Investigator-reported cases of pancreatitis
- Cases of severe and/or serious abdominal pain of unknown origin
- Confirmed elevations (>3x ULN) in lipase, pancreatic amylase, or total amylase, irrespective of symptoms and imaging results

The PFUA forms were submitted along with source information to the CEC for adjudication. The CEC adjudicated events as (1) pancreatitis, (2) not pancreatitis, or (3) unknown if pancreatitis. This last category included instances where it was not possible to obtain sufficient documentation to come to a definitive conclusion regarding the presence of pancreatitis and cases where all required documents were provided but it was not possible to come to a definitive conclusion.

Events of pancreatitis were further classified as (1) acute, (2) chronic, or (3) type unknown using the following criteria:

1. **Acute pancreatitis:** (2 of the following 3 criteria were required for this adjudication outcome):
    - Abdominal pain
    - Serum amylase and/or lipase ≥3x ULN
    - Computed tomography (CT), magnetic resonance imaging (MRI), or other imaging modalities (for example, magnetic resonance

cholangiopancreatography [MRCP], endoscopic ultrasound) showing findings consistent with inflammatory changes in the pancreas

2. **Chronic pancreatitis:**
   - **Clinical Criteria**
     i. Abdominal Pain, Attacks of acute pancreatitis, Diarrhea, Weight loss or Steatorrhea

     OR

     ii. Complications of chronic pancreatitis such as:
       - Bile duct obstruction/stenosis with cholestasis or jaundice
       - Duodenal obstruction/stenosis with clinical signs
       - Vascular obstruction/stenosis with clinical or morphological signs of portal/splenic vein hypertension
       - Pancreatic pseudocysts with clinical signs (compression of adjacent organs, infection, bleeding, etc.)
       - Pancreatic fistula (internal or external)
       - Pancreatogenic ascites
       - Other rare complications related to organs in vicinity (i.e., colonic stenosis, splenic pseudocyst, etc.)
   - **Imaging Criteria:**
     - Plain abdominal x-ray showing pancreatic calcifications
     - Computed tomography, MRI, or other imaging modalities showing ductal and/or parenchymal changes consistent with chronic pancreatitis: diffuse calcification, enlarged/irregular pancreas, dilated pancreatic duct +/- strictures, intrapancreatic cysts, pseudocysts, splenic vein thrombosis
3. **Type Unknown**:
   Events that may have met the definition of pancreatitis but were unable to be classified as either acute or chronic were classified as unknown. This classification is indicated as “Pancreatitis, Unknown Type” in tables and listings

The severity of acute pancreatitis was classified as mild, moderate, severe, or critical using the criteria proposed by Petrov and Windsor[13]. This classification is based on peripancreatic complications (absent, sterile, infectious) and organ failure (absent, transient, persistent).

Reviewer’s Assessment
Overall the measures taken by the Applicant for pancreatic safety assessments seem acceptable.

A total of 151 patients (40 patients treated with placebo or active comparator, 106 patients treated dulaglutide, 5 patients from study GBDA randomized to the

13 Petrov MS, Windsor JA. Classification of the severity of acute pancreatitis: how many categories make sense? *Am J Gastroenterol*. 2010;105(1):74-76.

placebo/dulaglutide sequence) in Phase 2 and 3 studies had events submitted for adjudication and had an adjudication outcome. There were 19 events submitted for adjudication due to an investigator reported TEAE of pancreatitis or pancreatitis-like abnormalities (e.g. pancreatitis, acute pancreatitis, chronic pancreatitis, pancreatic calcification). Seven of these patients came from the comparator treated patients (placebo or active comparator) and twelve came from the dulaglutide treated patients. The remaining 132 patients had other clinical findings that were deemed to merit adjudication.

Of the five adjudicated cases in the placebo/dulaglutide sequence of study GBDA, all the events were adjudicated as “not pancreatitis”. The investigator reported events were “Lipase Increased” for two patients and “Abdominal Pain Upper” or “Abdominal Pain Lower” for three patients. None of the events were investigator reported TEAEs of pancreatitis or pancreatitis-like abnormalities. The events occurred on study drug for three patients and on both therapies for one patient. The narratives were reviewed and the adjudication results seem acceptable. This does not affect the total number of events reported as confirmed pancreatitis or type unknown.

There were 23 patients with PFUA forms submitted for adjudication for which no adjudication response is available. The most common reasons the PFUA forms had no response were:

1. The pancreatic enzyme elevation was unconfirmed by central laboratory;
2. There was another plausible event associated with the qualifying signs/symptoms;
3. The event occurred before the full implementation of adjudication process. Some were classified as non-valid cases, not meeting criteria for adjudication.

These reasons were reviewed and these cases should not affect the validity of the adjudication results.

Of the 151 patients with events with an adjudication outcome, there were138 patients with events that were determined not to be pancreatitis (placebo or active comparator: 34; dulaglutide or placebo/dulaglutide: 104). There were nine patients with an event determined to be pancreatitis (placebo or active comparator-4 patients [all acute pancreatitis]; dulaglutide-5 patients [acute pancreatitis: 2; chronic pancreatitis: 2; type unknown: 1]), and there were four patients adjudicated as “unknown if pancreatitis” (placebo or active comparator: 1; dulaglutide: 3).

Of the cases adjudicated as acute pancreatitis (Table 31), there was one case of hemorrhagic pancreatitis. This occurred in a patient treated with placebo. The narratives for the nine dulaglutide or comparator patients were reviewed. There were no reports of hemorrhagic or necrotizing pancreatitis in the dulaglutide patients.

Reference ID: 3609106

Table 31: Cases of Acute Pancreatitis, Safety Population

USUBJID	Treatment	Severity
GBCF-205-4236	Sitagliptin	Mild
GBCF-706-6954	Sitagliptin	Mild
GBCF-964-3901	Placebo	Mild
GBCK-114-1430	Placebo	Severe[1]
GBDB-003-0128	Dula_0.75	Mild
GBDB-050-0502	Dula_1.5	Mild

[1] hemorrhagic pancreatitis
Source: Adapted from TOSNP- Special Topics, eCTD 5.3.5.3

There were two cases of chronic pancreatitis confirmed by adjudication, both from dulaglutide treated patients.

In the phase 2 studies one patient had pancreatitis adjudicated retrospectively. The case was determined to have mild pancreatitis (type unknown). I will briefly discuss this patient further.

GBCJ-040-4001, 55 yr. M, dulaglutide 0.5mg/1.0 mg: The patient was enrolled in a phase 2 dose-titration study and had an investigator reported AE of elevated lipase. From review of the narrative, the patient was diagnosed to have severe fatty liver with mild pancreatitis on EGD and endoscopic ultrasound. No hemorrhagic or necrotizing changes were reported. This adjudication of pancreatitis-type unknown seems acceptable since reports on symptoms (abdominal pain, nausea etc.) are not available. This does not significantly change my overall assessment of pancreatic safety.

To evaluate the adjudication process, I reviewed cases on dulaglutide treatment reported by the investigator as being a TEAE of pancreatitis but adjudicated as “pancreatitis not confirmed” by the CEC, adjudicated as “unknown if pancreatitis”, Cases with “Abdominal pain” reported as SAEswere reviewed. Based on my review of these cases, the Applicant’s procedures for capture and adjudication seem adequate to identify acute, serious events of pancreatitis. Narrative summaries for these events are discussed further below. Based on review of the narratives the adjudications seem acceptable.

Adjudications with reviewer agreement:

GBCJ-041-4114, 54 yr. M, dulaglutide 0.5/1.0 mg: After 85 days of study drug exposure, the patient experienced nausea and vomiting and diarrhea with abdominal pain that radiated to the back and progressively worsened. He went to the urgent care center for evaluation and treatment. On physical exam diffuse abdominal tenderness worse at the epigastric area with rebound tenderness.was noted. Bowel sounds were normal. He was noted to have elevated serum amylase and lipase at 133 U/L (normal = 16-108 U/L) and 123 U/L (normal = 22-51 U/L) respectively. His glucose was 171 mg/dL. Liver function tests and other serum chemistry laboratory tests were normal. The patient’s

white blood count was 13.7 K/μL (normal = 4.6-10.2 K/μL). The patient underwent a CT scan of the abdomen which showed diffuse fatty infiltration of the liver. There was no specific evidence to suggest pancreatitis. The patient was treated with two liters of normal saline intravenously and metoclopramide and morphine with relief of symptoms. Approximately 3 weeks after the urgent care visit his amylase was 29 U/L (normal = 20=112 U/L) and his lipase was 32 U/L (normal = 0-60 U/L). He was noted to have a triglyceride at that Visit of 616 mg/dL.

Reviewer Comment: Investigator reported AE of pancreatitis. This was adjudicated as unknown if pancreatitis which seems reasonable given the CT scan findings and borderline enzyme elevations.

GBDA-090-4483., 48 yr. M, dulaglutide 0.75 mg: Serum triglycerides at baseline (Visit 5) were 3.97 mmol/L (0.51-2.83 mmol/L) and remained elevated through Visit 10 (3.81 mmol/L) and Visit 12 (3.59 mmol/L). The patient had confirmed elevated pancreatic enzymes (pancreatic amylase 63 IU/L and lipase 138 IU/L) at Visit 9, 92 days after the first dose of the study drug. The patient experienced severe abdominal pain at 320 days after the start of the treatment with normal pancreatic enzymes. The event lasted 6 days and was assessed by the investigator as unrelated to the study drug. Liver function tests were within normal limits throughout the study. Pancreatic imaging was not performed. The patient's last dose of study drug was at Day 358. At LV30, lipase remained elevated at 66 IU/L; amylase and pancreatic amylase values were within normal range.

Reviewer Comment: Adjudicated as "Unknown if pancreatitis". This seems reasonable in the absence of imaging. The patient's baseline risk factor of high triglycerides is a confounder.

GBDA-012-0555, 56 yr. F, dulaglutide 1.5 mg: Investigator reported AE of pancreatic pseudocyst, had pancreatic adenocarcinoma. This case will be discussed further in the discussion of pancreatic cancer events (7.3.2.3 Pancreatic Cancer).

GBDC-105-0501, 61 yr. F, dulaglutide 1.5 mg: The patient had a history of alcoholism, Baseline concurrent medications at Visit 1 included estrogens, norethindrone, metformin, lamotrigine, simvastatin, and aspirin. Serum triglycerides at baseline were 2.70 mmol/L (reference range: 0.51-2.83 mmol/L). She had confirmed pancreatic enzyme elevations (amylase, pancreatic amylase, and lipase) at Visit 4 (32 days) of the study with no pain. Enzymes were normal at the 30-day follow-up visit LV30. Liver function tests were not elevated at any time during the study. Pancreatic imaging was not indicated as the patient was asymptomatic. The patient was terminated from the study due to the adverse event of diarrhea after 29 days on study treatment.

Reviewer Comment: Investigator reported AE of pancreatitis, adjudicated as not pancreatitis. This seems reasonable in the absence of abdominal pain.

GBDC-105-0507, 57 yr. F, dulaglutide 1.5 mg: Patient had symptoms of mild nausea, moderate upper abdominal pain, and moderate dizziness reported at Visit 3 (Week 0). Each symptom was resolved within 24 hours. At 127 days the patient reported experiencing moderate nausea and diarrhea that resolved the next day. She also developed a rash at 120 days. The abdominal pain recurred at 183 days and resolved two days later. Pancreatic enzyme values and liver function tests were within normal limits for the duration of the study. Pancreatic assessment was performed and the Applicant states that pancreatic imaging was not indicated as the patient was asymptomatic and pancreatic enzymes were not elevated. Study drug was discontinued on Day 183 due to the adverse event of rash.

Reviewer Comment: Investigator reported AE of pancreatitis adjudicated as "not pancreatitis". This seems reasonable, based on the short duration of pain and normal enzymes.

GBDB-604-6213, 31 yr. F, dulaglutide 0.75 mg: 5 weeks after receiving study drug, the patient developed chest pain, back pain, respiratory distress, abdominal pain, nausea and melena. She was hospitalized to rule out pancreatitis. Pancreatic enzymes were normal. The patient's final diagnoses were peptic acid disease and spastic colon. X-ray of the chest was normal; ultrasound showed hepatic steatosis and no pancreatic changes reported. Peptic ulcer disease was diagnosed by clinical signs and symptoms of the patient; no H. pylori test, endoscopy or colonoscopy was performed.

Reviewer Comment: SAE of abdominal pain, adjudicated as not pancreatitis. Seems reasonable since enzymes were normal

GBDN-702-7100, 50 yr. F, dulaglutide 0.75 mg: Approximately three months after starting blinded study drug, the patient experienced nausea and stomach pain; and was hospitalized due to intermittent pain in the lower abdomen, and fever. Diarrhea and dysuria in addition to nausea of unknown cause were reported. Urine analysis during hospitalization was positive for leukocytes, nitrite and blood. Other laboratory tests were not done at the hospital of admission. The cause of the abdominal pain was unknown. Pancreatic enzyme results are not reported. The patient was referred to undergo colonoscopy due to the stomach discomfort experienced for two months, the results of which were normal. The patient was treated with pivmecillinam hydrochloride and recovered. Therapy with blinded study drug was resumed.

Reviewer Comment: SAE of lower abdominal pain, appropriately not sent for adjudication. I agree with this decision since the narrative is consistent with UTI and not pancreatitis.

GBCF-021-1101, 42 yr. F, dulaglutide 3 mg: Received dulaglutide 3.0 mg for 24.1 weeks. Pancreatic enzyme elevations were noted on Week 4 which subsequently declined. She complained of moderate abdominal pain along with mild nausea,

dyspepsia, and constipation on week 8. Abdominal CT scan with contrast) revealed a normal pancreas with no pancreatic changes.

Reviewer Comment: Investigator reported AE of abdominal pain, adjudicated as not pancreatitis, Patients on this dose (3mg-GBCF) were discontinued by the DSMB. The adjudication seems reasonable based on imaging results at week 8.

GBCF-009-0511, 54 yr. M, dulaglutide 1.5 mg: The patient had symptoms of severe intermittent upper abdominal pain 1 day after Visit 14 (715 days) without pancreatic enzyme elevations. Pancreatic imaging was not performed. The investigator notes that the pain was localized to the right side with no associated gastrointestinal symptoms or association with food ingestion. The patient reported having similar but less intense episodes of similar pain in the past prior to enrolling in the study. He remained in the study on study drug until study completion.

Reviewer Comment: Investigator reported AE of abdominal pain, adjudicated as not pancreatitis. I agree.

Narrative review for investigator reported AEs of pancreatitis, pancreatic calcification or abdominal pain adjudicated as not pancreatitis, unknown if pancreatitis or not adjudicated, where there is uncertainty about the adjudication, based on reviewer assessments

GBCF-406-5264, 60 yr. M, dulaglutide - 0.75 mg The patient had confirmed increases in pancreatic enzymes (amylase, pancreatic amylase, and lipase) at week 2 and intermittently thereafter, with the highest values at weeks 26, 52, 65 and 104 with a decline in the follow-up visit. Liver function tests were within normal limits throughout the study. Pancreatic imaging (abdominal CT scan with contrast) performed on 10-Jan-2012 (7 days after Visit 15- week 104) revealed no evidence of “native” pancreatitis, but calcification suggesting chronic/subsided cases of pancreatitis. The patient was terminated from the study at 99.1 weeks. The reason for discontinuation was hyperglycemia. Other treatment-emergent adverse events reported during the study included nausea and upper abdominal pain (Day 8); mild hepatic steatosis (Day 19); diarrhea (Day 55).

Reviewer Comment: Investigator reported AE of pancreatic calcification, adjudicated as “not pancreatitis”. This narrative appears consistent with chronic pancreatitis.

GBCF-408-5352, 61 yr. M, dulaglutide -1.5 mg: Patient had history of current alcohol use had confirmed elevated lipase and pancreatic amylase values at Week 0. Lipase was still elevated on repeat testing 6 days later. Lipase was also elevated at weeks 4, 12, and LV30. Pancreatic imaging (abdominal CT scan with contrast) performed on Visit 8.01 revealed a moderately atrophic pancreas with a lobulated contour and decreased density with isolated rod-shaped calcifications in the region of the head of the pancreas

Reference ID: 3609106

as a sign of chronic pancreatitis. The patient was discontinued from the study at Visit 9 due to entry criteria not being met. Concomitant medications included amlodipine, enalapril, metformin and pravastatin.

Reviewer Comment: Investigator reported AE of pancreatic calcification, adjudicated as not pancreatitis. This may be a case of chronic pancreatitis.

GBCF-946-3300, 67 yr. F, dulaglutide -0.75 mg: Patient had symptoms of moderate dyspepsia and diarrhea and mild upper abdominal pain reported at week 52. The dyspepsia and diarrhea had begun after 343 days on therapy and the upper abdominal pain after 379 days on therapy. Study drug was stopped on Visit 11 (51 weeks). An abdominal CT scan without contrast was performed. The imaging results were suggestive of possible chronic pancreatitis without evidence of acute pancreatitis. Pancreatic enzyme values were within normal limits with the exception of an elevated amylase value (118 IU/L; range 20-112 IU/L) at Visit 9 (Month 6). Liver function tests were within normal limits throughout the study. Other TEAE's occurring during the study included abdominal pain, and vomiting (week 26).

Reviewer Comment: Investigator reported AE of chronic pancreatitis, adjudicated as "unknown if pancreatitis". An acute exacerbation of chronic pancreatitis cannot be excluded.

GBCK-109-0905, 61 yr. F, dulaglutide1.5 mg: After receiving the initial dose of study drug, the patient experienced abdominal pain and bloating and nausea. The abdominal pain and bloating were considered to be serious by the investigator as they interfered with daily activities. The last dose of study drug was on Day 8. Central laboratory values for pancreatic enzymes from Day 9 were normal, although local laboratory values included an elevated lipase of 289 U/L (114-286 U/L). A complete blood count was within normal limits. Liver enzymes were normal. Study drug was permanently discontinued on Day 8. The patient was sent home with an order to continue oral omeprazole 20 mg daily. On Day 12, lipase levels from a local lab were elevated. The patient continued to have discomfort above the epigastric area that radiated to the back. She was re-evaluated and an abdominal computed tomography (CT) scan was recommended. On Day 18, the patient withdrew from the study because of continuous discomfort. Central laboratory values for pancreatic enzymes were normal, a CT scan of the abdomen showed bilateral renal cortical cysts; pancreas was unremarkable (considered to be regular scan by investigator). On Day 20, the events of abdominal pain and bloating were reported as recovered.

Reviewer Comment: SAE of abdominal pain, not sent for adjudication. The possibility that is potentially case of resolved pancreatitis cannot be excluded since the CT was done a few days later.

In addition to evaluating pancreatitis, the Applicant looked at pancreatic enzyme elevations. While pancreatic enzyme elevations occur in pancreatitis, their presence alone is not sufficient to make the diagnosis. A trend towards elevated pancreatic enzymes, though, may raise concerns.

The proportion of patients at randomization with lipase values >1x ULN varied across studies, ranging from 2.8% to 25.1%. The proportion of patients with values ≥ 3x ULN at baseline ranged from 0.3% to 2.8%. Fewer patients had pancreatic amylase elevations (defined as > 1x ULN), and patients with total amylase elevations were similarly rare (3.3-11.9% and 2.1-9.9%, respectively) (see 9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.APP.224). Pancreatic amylase is considered to be a more specific biomarker for pancreatitis compared to Total Amylase[14].

The tables below show the percent post-baseline changes in total amylase, pancreatic amylase and lipase over time in the AS1 (compared to placebo) and AS3 datasets (dulaglutide 1.5 mg vs. 0.75 mg). There appears to be a small but consistent dose dependent increase of all enzymes with dulaglutide compared to placebo (i.e. in AS1; Table 32, Table 33 and Table 34). This dose dependent increase was also observed in the AS3 dataset (Table 35).

14 Lipase and pancreatic amylase versus total amylase as biomarkers of pancreatitis: an analytical investigation Majid Y. Moridania,B, Irvin L. Bromberga. Clinical Biochemistry 36 (2003) 31–33.

Table 32: Analysis of Percent Change from Baseline to Each Post-baseline Anchor Timepoint for Lipase, by Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period (AS1)

Variable analyzed: LIPASE (Units/Liter)

		Actual value							Percent Change from Baseline						
Weeks	Treatment	N	Mean	Min	Q1	Median	Q3	Max	Mean	LSM	Min	Q1	Median	Q3	Max
Baseline	Placebo	566	50.3	16	29.0	39.0	52.0	1171							
	Dula_0.75	831	46.0	10	30.0	39.0	51.0	494							
	Dula_1.5	833	45.0	11	30.0	38.0	49.0	425							
	All_Dula	1664	45.5	10	30.0	38.0	50.0	494							
2 - 4*	Placebo	419	46.5	16	30.0	38.0	51.0	359	8.05	-2.03	-91.3	-15.00	0.00	17.65	561.1
	Dula_0.75	532	53.9	14	34.0	43.0	57.5	459	26.80		-95.5	-8.07	9.09	30.00	1539.3
	Dula_1.5	553	54.8	9	34.0	43.0	61.0	559	31.91		-84.2	-2.27	16.10	40.00	1231.0
	All_Dula	1085	54.4	9	34.0	43.0	59.0	559	29.40	14.27	-95.5	-4.88	12.77	36.67	1539.3
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
8	Placebo	394	47.3	17	30.0	39.0	51.0	293	10.86	0.80	-80.6	-12.70	0.00	21.05	605.6
	Dula_0.75	513	54.8	16	34.0	44.0	61.0	520	28.40		-95.0	-4.88	12.73	37.78	663.5
	Dula_1.5	506	54.8	10	35.0	44.0	60.0	600	32.59		-75.5	-3.08	19.48	47.22	916.9
	All_Dula	1019	54.8	10	34.0	44.0	61.0	600	30.48	16.86	-95.0	-3.85	15.22	42.50	916.9
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
12 - 16*	Placebo	512	48.1	9	30.0	38.0	52.0	736	9.46	0.37	-94.4	-14.29	0.00	18.11	863.6
	Dula_0.75	775	56.5	13	34.0	44.0	62.0	582	33.43		-82.9	-7.50	13.79	40.00	1267.5
	Dula_1.5	763	56.3	12	34.0	46.0	63.0	493	39.48		-89.2	0.00	20.00	44.23	1872.0
	All_Dula	1538	56.4	12	34.0	45.0	62.0	582	36.43	19.76	-89.2	-4.66	17.04	42.31	1872.0
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
26	Placebo	489	46.1	16	28.0	37.0	49.0	583	7.38	-1.82	-82.3	-18.18	-2.50	15.19	540.7
	Dula_0.75	768	53.5	9	32.0	44.0	61.0	443	25.56		-81.5	-7.44	11.11	37.00	609.5
	Dula_1.5	745	54.9	10	34.0	44.0	60.0	677	31.47		-89.4	-3.85	18.60	42.11	746.3
	All_Dula	1513	54.2	9	33.0	44.0	61.0	677	28.47	15.81	-89.4	-6.56	14.29	39.22	746.3
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							

Abbreviations: Dula = dulaglutide; LSM = least square mean; Max = maximum; Min = minimum; MMRM = mixed-effects model for repeated measures; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; REML = restricted maximum likelihood; vs = versus.

Source ISS.APP.226-pg 4658

Table 33: Analysis of Percent Change from Baseline to Each Postbaseline Anchor Timepoint for Pancreatic Amylase, by Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period – (AS1)

Variable analyzed: PANCREATIC AMYLASE (Units/Liter)

		Actual value							Percent Change from Baseline						
Weeks	Treatment	N	Mean	Min	Q1	Median	Q3	Max	Mean	LSM	Min	Q1	Median	Q3	Max
Baseline	Placebo	560	29.6	4	19.0	25.0	35.0	410							
	Dula_0.75	823	27.8	3	18.0	24.0	32.0	168							
	Dula_1.5	829	27.8	3	18.0	24.0	33.0	297							
	All_Dula	1652	27.8	3	18.0	24.0	32.0	297							
2 - 4*	Placebo	418	28.2	4	19.0	25.0	34.0	217	4.92	-1.34	-85.4	-11.76	0.00	13.16	309.4
	Dula_0.75	531	32.4	4	20.0	28.0	39.0	150	21.95		-79.6	0.00	12.50	31.71	733.3
	Dula_1.5	551	33.9	6	21.0	29.0	39.0	289	26.79		-69.3	0.00	17.65	40.00	497.1
	All_Dula	1082	33.1	4	21.0	29.0	39.0	289	24.41	16.65	-79.6	0.00	14.71	35.71	733.3
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
8	Placebo	386	28.0	3	18.0	24.0	33.0	173	5.62	-0.35	-72.0	-12.12	0.00	16.67	229.4
	Dula_0.75	500	32.7	4	21.0	29.0	39.0	227	24.77		-80.0	0.00	13.19	35.71	407.7
	Dula_1.5	493	33.4	5	22.0	28.0	39.0	301	26.11		-82.1	1.35	21.05	40.00	360.0
	All_Dula	993	33.0	4	22.0	28.0	39.0	301	25.43	16.66	-82.1	0.00	16.67	38.10	407.7
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
12 - 16*	Placebo	507	29.2	4	19.0	26.0	35.0	161	8.42	2.94	-88.8	-10.53	0.00	18.75	519.2
	Dula_0.75	770	33.8	4	21.0	28.5	40.0	232	27.45		-66.7	0.00	15.19	37.50	466.7
	Dula_1.5	762	34.4	3	22.0	29.0	40.0	286	32.93		-78.7	2.94	19.14	41.67	1195.0
	All_Dula	1532	34.1	3	21.0	29.0	40.0	286	30.18	20.33	-78.7	0.00	17.39	39.34	1195.0
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							

Variable analyzed: PANCREATIC AMYLASE (Units/Liter)

		Actual value							Percent Change from Baseline						
Weeks	Treatment	N	Mean	Min	Q1	Median	Q3	Max	Mean	LSM	Min	Q1	Median	Q3	Max
26	Placebo	484	28.4	4	18.0	25.0	33.0	133	6.02	0.75	-71.6	-12.20	0.00	16.67	242.1
	Dula_0.75	760	32.9	4	20.0	28.0	38.0	210	24.34		-71.1	0.00	13.79	37.27	387.5
	Dula_1.5	740	34.1	3	22.0	28.0	40.0	362	29.05		-95.7	3.23	20.76	42.48	506.3
	All_Dula	1500	33.5	3	21.0	28.0	39.0	362	26.66	18.78	-95.7	0.00	17.39	40.00	506.3
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							

Abbreviations: Dula = dulaglutide; LSM = least square mean; Max = maximum; Min = minimum; MMRM = mixed-effects model for repeated measures; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; REML = restricted maximum likelihood; vs = versus.

Source: ISS.APP.230- page-4580

Table 34: Analysis of Percent Change from Baseline to Each Postbaseline Anchor Timepoint for Total Amylase, by Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period –(AS1)

Variable analyzed: TOTAL AMYLASE (Units/Liter)

		Actual value							Percent Change from Baseline						
Weeks	Treatment	N	Mean	Min	Q1	Median	Q3	Max	Mean	LSM	Min	Q1	Median	Q3	Max
Baseline	Placebo	539	62.2	15	42.0	57.0	75.0	441							
	Dula_0.75	811	62.3	12	43.0	57.0	75.0	227							
	Dula_1.5	813	61.5	11	42.0	56.0	74.0	320							
	All_Dula	1624	61.9	11	43.0	56.5	74.0	320							
2 - 4*	Placebo	402	59.8	16	41.0	54.0	72.0	261	2.10	-2.24	-79.1	-10.77	0.00	12.66	186.8
	Dula_0.75	527	67.6	12	46.0	61.0	81.0	211	11.70		-63.3	-4.65	6.67	20.69	353.8
	Dula_1.5	541	68.9	14	49.0	62.0	83.0	315	13.99		-61.0	-2.25	10.71	25.49	301.6
	All_Dula	1068	68.3	12	48.0	62.0	81.5	315	12.86	9.11	-63.3	-3.85	8.44	23.58	353.8
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
8	Placebo	376	59.9	15	42.0	55.0	72.5	207	4.02	-0.20	-81.8	-10.38	3.01	16.67	136.0
	Dula_0.75	502	69.0	23	48.0	64.0	82.0	298	14.75		-60.0	-2.86	9.55	26.14	227.8
	Dula_1.5	491	69.1	11	49.0	61.0	81.0	333	14.76		-65.9	-2.04	11.11	27.27	222.6
	All_Dula	993	69.1	11	49.0	62.0	81.0	333	14.75	10.39	-65.9	-2.63	10.53	26.67	227.8
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							
12 - 16*	Placebo	489	62.0	15	44.0	59.0	74.0	224	5.82	1.61	-81.9	-10.39	1.89	15.71	366.7
	Dula_0.75	760	69.8	16	48.0	63.0	84.0	268	15.97		-50.4	-3.28	10.32	24.00	395.2
	Dula_1.5	745	69.5	11	49.0	63.0	81.0	307	17.27		-64.9	-2.00	11.67	29.27	497.9
	All_Dula	1505	69.7	11	48.0	63.0	83.0	307	16.62	12.30	-64.9	-2.63	10.71	26.67	497.9
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							

Variable analyzed: TOTAL AMYLASE (Units/Liter)

		Actual value							Percent Change from Baseline						
Weeks	Treatment	N	Mean	Min	Q1	Median	Q3	Max	Mean	LSM	Min	Q1	Median	Q3	Max
26	Placebo	467	61.0	15	43.0	57.0	73.0	211	3.22	-0.64	-73.7	-12.07	0.00	12.70	202.1
	Dula_0.75	749	68.8	19	46.0	63.0	82.0	255	13.24		-58.1	-3.57	8.89	25.42	185.7
	Dula_1.5	727	68.9	8	48.0	62.0	81.0	389	16.54		-66.8	-2.50	12.90	29.41	411.8
	All_Dula	1476	68.9	8	47.0	62.0	82.0	389	14.86	11.28	-66.8	-3.10	11.11	27.72	411.8
	All_Dula vs Placebo LSM Comparison, p-value*a							<.001							

Abbreviations: Dula = dulaglutide; LSM = least square mean; Max = maximum; Min = minimum; MMRM = mixed-effects model for repeated measures; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; REML = restricted maximum likelihood; vs = versus.

Source: ISS.APP.234-page 4592

Table 35:Analysis of Pancreatic Enzymes, All Observations During Planned Treatment Period - Phase 2 and 3 Studies With 0.75 mg and 1.5 mg Dulaglutide (AS3)

	[Mean (Median) at Baseline] LS Mean of %Δ from Baseline		
Time Point	Dula_0.75 (N=1671)	Dula_1.5 (N=1671)	Comparison LS Mean of %Δ from Baseline[b] Dula_1.5 vs. Dula_0.75
Lipase			
BL (U/L)	[44.0 (37.0)]	[45.5 (37.0)]	--
Week 2-4[a]	13.19	18.33	p=0.009
Week 8-16[a]	16.45	19.69	p=0.060
Week 26	14.17	19.44	p=0.002
Week 39	13.53	16.89	p=0.060
Week 52	10.91	15.79	p=0.006
Week 78-104[a]	16.89	16.31	p=0.848
Pancreatic Amylase			
BL (U/L)	[27.0 (24.0)]	[28.2 (24.0)]	--
Week 2-4[a]	14.55	19.10	p=0.004
Week 8-16[a]	17.37	19.60	p=0.117
Week 26	16.67	20.82	p=0.004
Week 39	15.87	18.86	p=0.044
Week 52	13.45	17.87	p=0.003
Week 78-104[a]	16.19	17.85	p=0.500
Total Amylase			
BL (U/L)	[60.6 (55.0)]	[61.8 (56.0)]	--
Week 2-4[a]	8.26	10.43	p=0.046
Week 8-16[a]	10.71	11.52	p=0.400
Week 26	10.17	12.57	p=0.013
Week 39	9.14	11.25	p=0.042
Week 52	8.22	10.36	p=0.042
Week 78-104[a]	9.56	11.10	p=0.408

Abbreviations: %Δ = percent change; BL = baseline; Dula = dulaglutide; LS = least squares; N = total number of patients in specified treatment group; vs. = versus.

[a] Actual timing depending on study, but overall constituting a single anchor time point.

[b] Difference of %LS mean of change from baseline are from mixed-model repeated measures: Log(Actual/Baseline) = Study + Log(Baseline) + Treatment + Week + Treatment*Week (Type III sums of squares). Covariance structure = Unstructured. Estimated percent change from baseline is {exp[estimated(Actual/Baseline)]-1}*100.

Source: ISS 6.43, page 324

Laboratory test results during the safety follow-up visit indicate that the pancreatic enzyme elevations were reversible after cessation of treatment (9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.6.44).

Dulaglutide-treated patients had a numerically higher incidence of treatment-emergent elevations (> 1x ULN) of lipase (placebo-19.9%, dulaglutide 0.75 mg- 33%, dulaglutide 1.5 mg- 35.9%), pancreatic amylase (placebo-9%, dulaglutide 0.75 mg - 16.6%,

dulaglutide 1.5 mg- 18.4%), and total amylase (placebo- 7.5%, dulaglutide 0.75 mg- 12.6%, dulaglutide 1.5 mg- 11.2%) values compared with placebo-treated patients (See Appendix 9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.APP.251). More patients on dulaglutide 1.5 mg had pancreatic amylase and lipase elevations compared to patients on dulaglutide 0.75 mg. Most patients with lipase values above ULN post-baseline had values > 1x to < 3x ULN (placebo: 27.7%; all dulaglutide: 38.5%). The incidence of patients with postbaseline values ≥ 3x to < 5x ULN was higher for all dulaglutide than placebo (4.6% and 2.5%, respectively; See Appendix 9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.APP.256).

Each dulaglutide dose was associated with a consistent increase in pancreatic enzymes across a range of concomitant medications with a trend for dose dependence with lipase elevation in all five phase 3 studies (See Appendix 9.6 Supportive Tables From the ISS Referenced in the Review- Table ISS.6.45). There was no suggestion of interaction between dulaglutide and other antihyperglycemic agents to cause pancreatic enzyme changes.

When compared to the active comparators, the concentration of pancreatic enzymes and incidence of abnormal values was greater with initiation of incretin based therapies (dulaglutide, exenatide BID, and sitagliptin). The observed changes were greater with dulaglutide compared to other therapies. (Table 36).

Table 36: Summary of Abnormal Postbaseline Pancreatic Enzymes - Dulaglutide and Active Comparators in Phase 3 Studies – All Postbaseline Observations Including Follow-up (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD)

	Postbaseline Maximum Value[a]								
	Active Comparator			Dula_0.75			Dula_1.5		
Study (Comparator)	N	>1x to <3x ULN (%)	≥3x ULN (%)	N	>1x to <3x ULN (%)	≥3x ULN (%)	N	>1x to <3x ULN (%)	≥3x ULN (%)
Lipase									
GBDC (Metformin)	267	30.3%	3.4%	268	31.0%	6.0%	266	35.3%	6.8%
GBCF (Sitagliptin)[b]	438	42.7%	9.6%	299	51.8%	11.4%	302	49.7%	12.9%
GBDA (Exenatide BID)[b]	272	34.9%	7.4%	336	39.0%	6.5%	337	38.6%	8.3%
GBDB (Insulin Glargine)	259	35.1%	6.2%	269	46.5%	9.7%	271	45.4%	17.3%
GBDD (Insulin Glargine)	288	27.8%	3.8%	284	31.3%	4.6%	285	35.8%	6.0%
Pancreatic Amylase									
GBDC (Metformin)	267	11.2%	0.7%	268	16.4%	1.1%	266	15.8%	1.5%
GBCF (Sitagliptin)[b]	438	23.7%	0.7%	299	29.1%	2.3%	302	31.5%	2.0%
GBDA (Exenatide BID)[b]	272	21.0%	0.4%	336	20.8%	2.1%	337	22.8%	1.8%
GBDB (Insulin Glargine)	259	19.3%	2.3%	269	29.0%	3.7%	271	24.7%	6.6%
GBDD (Insulin Glargine)	288	15.3%	0.7%	284	16.5%	1.1%	285	24.2%	0.4%
Total Amylase									
GBDC (Metformin)	267	6.7%	0	268	14.6%	0.4%	266	13.2%	0.4%
GBCF (Sitagliptin)[b]	438	18.0%	0	298	23.5%	0.7%	301	20.9%	0
GBDA (Exenatide BID)[b]	272	13.2%	0.4%	336	17.6%	0	337	16.3%	0.6%
GBDB (Insulin Glargine)	259	15.8%	0.4%	269	21.9%	0.7%	271	27.3%	1.5%
GBDD (Insulin Glargine)	288	11.8%	0.7%	284	10.9%	0.4%	285	17.5%	0

Abbreviations: BID = twice daily; Dula = dulaglutide; N = number of patients assigned to this treatment group who received at least 1 dose of study medication who had data; ULN = upper limit of normal.

[a] Percentages based on the number of patients with data (that is, the number of patients with postbaseline lab test available).

[b] Active comparator, Dula_0.75, and Dula_1.5 include any patients with Study GBCF and Study GBDA who began study receiving placebo and reached the time point where they began to received active treatment (Study GBCF=sitagliptin; Study GBDA=dulaglutide 0.75 or 1.5 mg).

Source: Table ISS 6.47, page 333

Narrative Review of Subjects on Dulaglutide, Who Had the PT "Pancreatic Enzymes Increased" reported as an AE by The Investigator:

For pancreatic enzyme elevations, only cases where there is some uncertainty about the adjudication of "not pancreatitis" or a potentially missed event based on timing of imaging versus symptoms are described here (See Appendix 9.5 Narratives for Pancreatic Enzyme Elevations for a complete narrative review of all dulaglutide treated patients with pancreatic enzyme elevations).

GBCF-013-0717, 50 yr. M, dulaglutide 0.75 mg: Serum triglycerides at baseline were 4.64 mmol/L (reference range 0.51-2.83 mmol/L) and 1.94 mmol/L at week 26. The patient reported moderate right upper quadrant abdominal pain at week 4 and was noted to have elevated lipase at the same visit. Liver function tests were within normal limits throughout the study with the exception of the baseline ALT value. Pancreatic imaging (abdominal CT scan with and without contrast) was performed 1 day after repeated enzymes and revealed 2 kidney stones on the right, left lower lobe pneumonia, and a normal pancreas. Lipase remained elevated. Study drug was discontinued at week 71 due to hyperglycemia.

Reviewer Comment: There is uncertainty since the Lipase remained elevated and symptoms are unknown between weeks 4-71.

GBDB-453-4650; 45 yr. M; dulaglutide 0.75 mg: No pain reported in the narrative, pancreatic cyst noted on CT scan with no evidence of pancreatitis.

Reviewer Comment: Pancreatic cyst could imply chronic pancreatitis.

GBDB-751-7552; 51 yr. M; dulaglutide 0.75 mg: Abdominal pain reported in the narrative, study drug discontinued at week 28 due to enzyme elevation, CT scan reported normal.

Reviewer Comment: Timing between abdominal pain report and CT scan is unclear. This could be resolved pancreatitis.

GBDD-207-3825; 66 yr. M; dulaglutide 0.75 mg: Patient had confirmed elevations in amylase, pancreatic amylase, lipase at Day 1 of study drug exposure. Pancreatic enzymes were repeated. Pancreatic imaging (MRI) was performed at 8 days after Visit 11 (26 weeks) and revealed a small benign cyst on the pancreas but no evidence of pancreatitis. The patient was terminated from the study at Visit 12 (39 weeks) due to elevated lipase. Also had upper abdominal pain at Visit 10.

Reviewer Comment: There is uncertainty about adjudication since pancreatic cyst was noted on MRI which could imply possible chronic pancreatitis and there was a delay between episode of pain and scan.

GBDB-501-5054; 53 yr. F; dulaglutide 0.75 mg: The patient had gastritis and diarrhea, abdominal CT scan with and without contrast and ultrasound was within normal limits except for a slightly bulky pancreatic head, but without focal lesions; by ultrasound, the liver was mildly increased in size and echotexture.

Reviewer Comment: Bulky pancreatic head reported on CT scan, hence chronic pancreatitis cannot be excluded.

Reviewer's overall assessment regarding adjudication and capture of pancreatic events and safety concerns related to pancreatitis:

Overall the Applicant's procedures for capture and adjudication seem adequate to identify acute, serious events of pancreatitis. It is possible that some events adjudicated as "unknown" or "not pancreatitis", may have been mild acute exacerbations of chronic pancreatitis for which there are several confounders due to disease and co-morbidities in this patient population, but association to study drug cannot be excluded. It's also possible that there may be some potentially missed cases. This should not have any appreciable impact on the pancreatic safety assessment of dulaglutide. Since acute serious events of

Reference ID: 3609106

fatal, hemorrhagic and necrotizing pancreatitis are unlikely to have been missed by this process of capture and adjudication, there appear to be no events which would appreciably change the benefit- risk profile for dulaglutide compared to other approved GLP-1 agonists.

A dose dependent increase in pancreatic enzymes was seen. However, there was no clear imbalance between dulaglutide and placebo for pancreatitis. Additionally, elevations in pancreatic enzymes did not predict the patients that developed pancreatitis. Labelling and a Risk-Evaluation Mitigation Strategy (REMS) consistent with the other approved products in the class should be sufficient to address concerns regarding pancreatitis.

- 7.3.2.3 Pancreatic Cancer

As discussed 7.3.2.2 Pancreatitis, there has been concern for pancreatic cancer with all GLP-1 based therapies. This section will focus on pancreatic cancers. Other neoplasms will be discussed in 7.3.3.2 Neoplasms.

There were only two cases of pancreatic cancer with dulaglutide in the completed program.

GBCZ-117-1712, 61 yr. old M, Dulaglutide 0.75 mg: Medical history included T2DM (2 years duration) and hypertension. The patient had a 40-year history of tobacco use (pack year history not provided). The day following his first and only dose of study drug, he had elevations in amylase (269 U/L [ULN=112]) and lipase (589 U/L [ULN=60]). These analytes were normal approximately 6 weeks earlier during screening evaluations. One week after randomization, a MRI scan was performed as a work-up for the elevations in pancreatic enzymes and demonstrated a 5-cm tumor consistent with pancreatic carcinoma. A CT scan confirmed the mass as pancreatic carcinoma. The tumor was unresectable; the patient was treated with gemcitabine chemotherapy and then palliative care. The patient died of this carcinoma approximately 5 months after randomization to study drug.

GBDA-012-0555, 56 yr. old F, Dulaglutide 1.5 mg,: Medical historyincluded a 3-year duration of T2DM, hypertension, and hyperlipidemia. She had no history of tobacco use. Approximately 4 months after beginning study drug, the patient reported cramping abdominal pain in left upper quadrant radiating into her back. Pancreatic enzymes were within the limits of normal. Approximately 1 month later, a CT scan of abdomen revealed a pancreatic mass over much of the body and tail of the pancreas. In the clinical trial database, this event was initially coded as a pancreatic pseudocyst, and thus this event progressed through the normal pancreatitis adjudication process and was confirmed to not be pancreatitis. A subsequent biopsy near the time of CT scan confirmed pancreatic carcinoma. Study drug was discontinued at that time (exposure 169 days). Assessment of this tumor determined it to be locally advanced and unresectable. She was treated with chemotherapy (not specified). The patient died of

Reference ID: 3609106

this carcinoma approximately 14 months after randomization of study drug, and ~287 days since last dose of study drug.

An additional 5 cases were reported in the 4-month safety update (Table 37). Treatment for these cases remained blinded. Unblinding of treatment assignments for these cases was requested and performed by the Applicant (Table 38).

Table 37: Blinded cases in ongoing clinical trials reported in 4-month safety update

Trial Alias/ Patient ID	Patient Age - Sex	First Dose to Event	Last Dose to Event	Preferred Term	Outcome	Comments
GBDJ-250-14390	78y M	73 days	10 days	Ductal adenocarcinoma of pancreas	Not recovered	• Ultrasound for unknown reasons showed lesions in liver, around pancreas, near spleen, and on right kidney. • CT scan diagnosed adenocarcinoma, pancreatic tail with liver metastasis. • No biopsy available at last report.
GBDJ-310-10761	54y M	148 days	11 days	Pancreatic carcinoma metastatic	Not recovered	• ~140 days postrandomization, reported hyperglycemia with elevated transaminases and GGT. • 141 days postrandomization, started insulin. • Ultrasound/CT scan performed. • Diagnosed with pancreatic carcinoma head with lymph node metastasis and extensive vascular invasion. • Large tumor (4.5 x 4 cm). • Extensive debulking surgery.
GBDJ-956-13452	74y M	248 days	78 days	Pancreatic carcinoma	Not recovered	• Stopped study drug after 170 days due to increased lipase. • 78 days later, hospitalized with jaundice. • CT scan showed pancreatic tumor (3.5 cm) with narrowing of common bile duct. • Metastasis noted.
GBDJ-825-15328	71y F	123 days	Not reported	Pancreatic carcinoma	Fatal	• 123 day postrandomization, abdominal pain, jaundice. • Ultrasound showed pancreas mass diagnosed as pancreatic carcinoma. • Rapid deterioration of patient, died 1 month later.
Trial Alias/ Patient ID	**Patient Age - Sex**	**First Dose to Event**	**Last Dose to Event**	**Preferred Term**	**Outcome**	**Comments**
GBDP-229-2913	68y F	106 days	Same day	Pancreatic carcinoma	Not recovered	• Weight loss (~6.5 kg). • Tumor markers and ultrasound performed: CEA 6.3 ng/ml (normal: 0-5); CA19-9 2163.4 U/ml (normal: 0-37). • MRCP found 3.8 cm tumor in pancreas tail. • No metastasis, but infiltration of splenic artery and vein. • Chemotherapy.

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computerized tomography; F = female; GGT = gamma glutamyltransferase; M = male; MRCP = magnetic resonance cholangiopancreatography; y = year(s).

Source: 4-month safety update, table 27, page 87

Table 38: Treatment Information for Pancreatic Cancer Cases in 4-Month Safety Update

Trial Alias/ Patient ID	Preferred Term	Mfr. Control #	Study Drug
GBDJ-250-14390	Ductal adenocarcinoma of pancreas	CA201301005214	Placebo
GBDJ-310-10761	Pancreatic carcinoma metastatic	CZ201208007896	Placebo
GBDJ-956-13452	Pancreatic carcinoma	US201304004995	Dulaglutide
GBDJ-825-15328	Pancreatic carcinoma	CO201305009844	Dulaglutide
GBDP-229-2913	Pancreatic carcinoma	JP201305009203	Liraglutide

Source: Table 2.1, Applicant's Response to IR dated April 14, 2014.

Based on the totality of information submitted in the initial NDA submission and in the 4-month safety update, there does not appear to be an imbalance in the incidence of pancreatic cancer. There are four cases of pancreatic cancer reported in dulaglutide treated patients vs. three in all comparators (2 placebo, 1 liraglutide). One case occurred after a single dose of dulaglutide making it unlikely to be related to treatment. Though the available patient exposure is too small to definitively assess the risk for pancreatic cancer with dulaglutide, it seems reasonable to conclude that the incidence in clinical programs to date is comparable to comparator.

Reviewer Assessments on pancreatic cancer:

There is no clear evidence for an increased incidence of pancreatic cancer with dulaglutide. Definite conclusions cannot be made due to the small number of cases. Similar to approved agents in the GLP-1 agonist class, pancreatic cancer should continue to be followed as an AE of special interest in the CV outcome study. Labeling for pancreatic cancer should be consistent with the other members of the drug class.

- 7.3.2.4 Immunogenicity

Immunogenicity is a concern with all injectable peptides and has been observed with approved products in the GLP-1 agonist class. The development of anti-drug antibodies (ADA) can be associated with local or systemic hypersensitivity reactions by triggering an immune response. Development of antibodies with neutralizing activity or cross-reactivity to endogenous GLP-1 may result in reduced efficacy or potential safety issues due to interferences with normal glucose regulation.

In the exenatide, exenatide LAR, liraglutide, and albiglutide clinical programs antidrug antibodies (ADA's) developed in 5.5-40% of patients. Injection site reactions occurred

more frequently in ADA positive patients, but there was no clear relationship to other TEAEs.

(b) (4)

The immunogenicity testing strategy for the dulaglutide program was based on the use of a solid phase extraction with acid dissociation (SPEAD) enzyme-linked immunosorbent assay (ELISA) format and a cell-based assay developed to detect neutralizing ADAs.

Detailed discussion of the methods for detecting and characterizing dulaglutide ADAs can be found in the OBP/CMC review by Dr. Joel Welch.

Blood samples from patients in the Phase 2 and 3 studies were collected and assayed for the detection of dulaglutide ADAs. When detected, titers were determined. Samples with treatment-emergent dulaglutide ADAs were then tested for neutralizing activity against dulaglutide and for their potential to bind to native sequence GLP-1 (nsGLP-1). Samples with cross-reactivity to nsGLP-1 were further tested for neutralizing activity against nsGLP-1.

The assay performance, cut point, and the acceptability of the definition of treatment-emergent ADAs (i.e. 4-fold increase in dulaglutide ADA versus baseline) have all been reviewed by OBP and found to be acceptable.

On average, each patient had samples collected four to six times during study participation (including the safety follow-up visit). Due to the allowance in visit intervals, the interval between the last administered dose of dulaglutide and the collection of the final blood sample at the end of the safety follow up could range from three to six weeks. Some exceptions were as follows:

- In study GBCF, dulaglutide ADA testing at the end of the 30-day safety follow-up (LV30) period occurred only for patients with reported pancreatitis.
- In study GBDA, patients receiving placebo and then dulaglutide were included in the “Other Comparator” and the “All dulaglutide” groups. Treatment emergent ADAs were assessed relative to the original baseline (i.e. at start of study participation, not at time of treatment switch). The denominator for calculating percentage was the number of patients with a follow-up test result for dulaglutide ADAs.

- In Studies GBDB, GBDC and GBDD, patients treated with insulin glargine or metformin were not required by protocol to be tested for ADA. However, some of these patients were tested and these data were included in comparator analyses.

Overall the testing frequency seems acceptable. This was also reviewed by Dr. Joel Welch from OBP/CMC.

There were 115/3606 (3.2%) dulaglutide, 2/269 (0.7%) exenatide and 31/1021 (3.0%) other comparator patients with baseline ADA titers detected. The baseline ADA titers for samples with detected ADAs were generally between 1:2 and 1:16. High titers (≥ 1:128) were detected at baseline in two patients. Neither of these patients had prior exposure to a GLP-1 receptor agonist. Both patients were ultimately randomized to comparator.

The table below (Table 39) provides a complete summary of dulaglutide ADA testing results during the planned treatment and safety follow up periods by type of post baseline exposure (dulaglutide, active comparator exenatide BID, or non-GLP-1 comparator [placebo, active]) for all samples tested. The percent of samples that were positive for dulaglutide ADA increased post baseline in patients exposed to dulaglutide (3.4%) and exenatide BID (5.4%) and remained unchanged (3.0%) in the comparator group.

Table 39: Distribution of Dulaglutide Anti-Drug Antibody Tests at Baseline, at Completion of the Planned Treatment Period, and in the Safety Follow-up Period- Includes Number of Tests Performed, Number Detected and Titer Distribution- Safety Population.

	Number of Tests		
	All_Dula	Exenatide	Other Comparator
Baseline Period			
Number of Test Results *a	3606	269	1021
Not Detected	3491 (96.8)	267 (99.3)	990 (97.0)
Detected	115 (3.2)	2 (0.7)	31 (3.0)
No Titer	2 (<0.1)	0	0
1:2	37 (1.0)	1 (0.4)	6 (0.6)
1:4	31 (0.9)	1 (0.4)	9 (0.9)
1:8	25 (0.7)	0	11 (1.1)
1:16	12 (0.3)	0	2 (0.2)
1:32	5 (0.1)	0	1 (<0.1)
1:64	3 (<0.1)	0	0
1:128	0	0	1 (<0.1)
1:256	0	0	1 (<0.1)

	Number of Tests		
	All_Dula	Exenatide	Other Comparator
Planned Treatment Period			
Number of Test Results *a	10642	756	2942
Not Detected	10277 (96.6)	715 (94.6)	2855 (97.0)
Detected	365 (3.4)	41 (5.4)	87 (3.0)
No Titer	8 (<0.1)	0	1 (<0.1)
1:2	99 (0.9)	8 (1.1)	29 (1.0)
1:4	101 (0.9)	16 (2.1)	27 (0.9)
1:8	69 (0.6)	10 (1.3)	17 (0.6)
1:16	55 (0.5)	3 (0.4)	6 (0.2)
1:32	15 (0.1)	1 (0.1)	2 (<0.1)
1:64	12 (0.1)	3 (0.4)	0
1:128	5 (<0.1)	0	2 (<0.1)
1:256	0	0	2 (<0.1)
1:512	0	0	1 (<0.1)
1:1024	1 (<0.1)	0	0

	Number of Tests		
	All_Dula	Exenatide	Other Comparator
Follow-Up Period			
Number of Test Results *a	2917	232	454
Not Detected	2810 (96.3)	221 (95.3)	438 (96.5)
Detected	107 (3.7)	11 (4.7)	16 (3.5)
No Titer	1 (<0.1)	0	0
1:2	28 (1.0)	2 (0.9)	4 (0.9)
1:4	30 (1.0)	6 (2.6)	5 (1.1)
1:8	24 (0.8)	0	3 (0.7)
1:16	14 (0.5)	1 (0.4)	3 (0.7)
1:32	4 (0.1)	1 (0.4)	1 (0.2)
1:64	3 (0.1)	1 (0.4)	0
1:128	2 (<0.1)	0	0
1:1024	1 (<0.1)	0	0

Note: All_Dula refers to all dulaglutide treatment groups combined. Exenatide group is from study GBDA exclusively. Other Comparator is any non-dulaglutide assigned treatment except exenatide, including placebo. Patients in GBDA who received Placebo initially and subsequently received Dulaglutide are included in both the 'Other Comparator' group and the 'All_Dula' group. The baseline period in this table summarizes observed result without imputation. All percentages are relative to the number of test results, with each period.

Note: Placebo and active comparator patients in studies GBCF, GBDA, and GBDN were tested for ADA. Active comparator patients in studies GBDB, GBDC, and GBDD were not requested to be tested for ADA, but for some patients testing occurred. In addition to placebo and sitagliptin patients required by protocol to be tested in studies GBCF, GBDA, and GBDN, N for 'Other Comparator' includes any active comparator patients from GBDB, GBDC, and GBDD for whom ADA testing was performed, and results from these tests are included in the table. GBCJ patients did not have follow-up visit and are excluded from this table.

*a - Includes all results where Dula ADA is 'Detected' or 'Not Detected'.

Source: Table ISS.APP.318, pg4996

The incidence of treatment emergent dulaglutide ADAs in dulaglutide-treated patients ranged from 0.0% (at any dose in Study GBCJ and Study GBCZ) to a maximum of 3.7% (Study GBDB). The highest incidence of dulaglutide treatment-emergent ADAs in placebo-treated patients was observed in Study GBDA (1.4%). The following observations are made based on review of the data for all post-baseline observations:

- Of the dulaglutide treated patients, 64 (1.6%) developed treatment-emergent dulaglutide ADAs at least once post-baseline versus 8 (0.7%) patients in the comparator treatment group (Table 40).
- Most of the dulaglutide-treated patients with treatment-emergent dulaglutide ADAs did not have detectable ADAs at baseline (Table 41). Nine dulaglutide-treated patients with detectable dulaglutide ADAs at baseline were categorized to have treatment-emergent dulaglutide ADA, defined as baseline titers from 1:2 up to 1:16, with ≥ 4 fold increase in the post-baseline titer.
- The magnitude of the response (change in titer from baseline) was generally 4 to 8 fold (40 patients-63% of patients with detectable ADA). The 24 patients with a > 8 fold increase in titer either did not have detectable ADAs (22 patients) or had titer 1:2 (2 patients) at baseline. All patients with no detectable dulaglutide ADA at baseline had a titer imputed as 1:1. If they had an indeterminable titer after detectable ADA, the titer was then imputed as 1:2.
- Of the four patients who had high treatment-emergent dulaglutide ADA titers (≥ 1:128), none had detectable ADAs at baseline (Table 41*)*. Among the 64 patients treated with dulaglutide and having treatment-emergent ADA at any postbaseline visit, 34 patients developed dulaglutide neutralizing antibodies, 36 patients developed nsGLP-1 cross-reactive antibodies, 4 patients had nsGLP-1 neutralizing ADA and 2 patients had both nsGLP-1 cross-reactive and neutralizing antibodies.

Given that exenatide is also a GLP-1 agonist, the development of dulaglutide ADAs in these patients warrants further discussion. A total of 14 patients (5.2%) in the exenatide BID group developed treatment-emergent dulaglutide ADAs (Table 40). Two of these patients were previously exposed to a GLP-1 agonist. Thirteen of the patients had dulaglutide neutralizing antibodies. Twelve of the patients had nsGLP-1 cross-reactive antibodies, with seven of these thirteen also having nsGLP-1 neutralizing antibodies. All of these patients also had exenatide ADAs. This suggests that the observed dulaglutide ADA activity may be due to cross-reactivity of anti-exenatide ADAs with both exenatide and dulaglutide (i.e. shared epitopes).

Table 40: Summary of Patients with Treatment-Emergent Dulaglutide Anti-Drug Antibodies – Safety Population

Category	All_Dula (N=4006) n (%)	Exenatide (N=276) n (%)	Other Comparator (N=1141) n (%)
Patients with Postbaseline Test *a	3907	270	1114
Patients with >=1 TE Dula ADA *b	64 (1.6)	14 (5.2)	8 (0.7)
TE Dula ADA and Dula Neutralizing	34 (0.9)	13 (4.8)	4 (0.4)
TE Dula ADA and nsGLP1 Cross-Reactive	36 (0.9)	12 (4.4)	3 (0.3)
TE Dula ADA and nsGLP1 Neutralizing	4 (0.1)	7 (2.6)	3 (0.3)
TE Dula ADA and both nsGLP1 Cross-Reactive and Neutralizing	2 (<0.1)	7 (2.6)	2 (0.2)

Abbreviations: ADA = anti-drug antibody; Dula = dulaglutide; N = total number of patients in specified treatment group; n = number of patients in specified category; nsGLP1 = native sequence GLP1; TE = treatment-emergent.

Source: Table ISS 6.65, pg 402

Table 41: Shift Table of Dulaglutide Anti-Drug Antibody Tests from Baseline to Maximum Postbaseline – Safety Population

Frequency| Percent	1	2	4	8	16	32	64	128	1024	Total
1	3702	35	23	10	10	7	1	3	1	3792
	94.75	0.90	0.59	0.26	0.26	0.18	0.03	0.08	0.03	97.06
2	14	14	6	2	1	1	1	0	0	39
	0.36	0.36	0.15	0.05	0.03	0.03	0.03	0.00	0.00	1.00
4	6	3	11	8	3	0	0	0	0	31
	0.15	0.08	0.28	0.20	0.08	0.00	0.00	0.00	0.00	0.79
8	2	0	7	11	5	0	0	0	0	25
	0.05	0.00	0.18	0.28	0.13	0.00	0.00	0.00	0.00	0.64
16	0	0	0	3	8	0	1	0	0	12
	0.00	0.00	0.00	0.08	0.20	0.00	0.03	0.00	0.00	0.31
32	0	0	0	0	2	2	1	0	0	5
	0.00	0.00	0.00	0.00	0.05	0.05	0.03	0.00	0.00	0.13
64	0	0	0	0	0	1	1	1	0	3
	0.00	0.00	0.00	0.00	0.00	0.03	0.03	0.03	0.00	0.08
Total	3724	52	47	34	29	11	5	4	1	3907
	95.32	1.33	1.20	0.87	0.74	0.28	0.13	0.10	0.03	100.00

Note: Y axis shows baseline titers and X-axis shows post-baseline titers. Titer is imputed if unavailable, using 1:1 if Dula ADA test is missing or 'Not Detected', and 1:2 if Dula ADA test result was 'Detected' with no titer available.

Source: Table ISS.6.68-Pg 405

Of the four patients with high titers (either dulaglutide ADAs or dulaglutide neutralizing ADAs), none had a clear immunogenicity related event. Narrative summaries were reviewed for each patient and are discussed further below.

GBCF-878-8407, 39 yr F, dulaglutide 1.5 mg: This patient had no detected ADA at baseline or Week 4; dulaglutide ADA titers of 1:128 were detected at Weeks 12 and 26. By Week 52, the titer was 1:16 and no dulaglutide ADA was detected at Weeks 78 and 104. There were no reported systemic hypersensitivity AEs for this patient. Other adverse events of interest reported were mild cutaneous pruritis at 1-3 months on therapy, judged by the investigator as related to study drug, mild swelling at 2 weeks to

1 month on therapy (related to study drug), mild subcutaneous nodule at 1 month on therapy (related to study drug) and mild to moderate left axillary lymphadenitis at 1-3 months on therapy. These adverse events did not result in discontinuation of study drug and the patient completed all study visits.

Reviewer's Comment: It appears that this patient had an injection site reaction.

GBDB-006-0264, 41 Yr. F,dulaglutide 0.75 mg: The patient did not have dulaglutide ADA at baseline and therefore baseline titer was imputed as 1:1. At Week 72 and at the safety follow up visit (Week 82), the sample titers were 1:128. No possible immunogenicity events were reported.

GBDC-910-9813, 38 yr Fdulaglutide 0.75 mg: The patient did not have dulaglutide ADA at baseline and therefore baseline titer was imputed as 1:1. At Week 52 and at the end of safety follow up (~Week 60), the titers were 1:128. No possible immunogenicity events were reported.

GBDA-016-0789, 70 yr. M, dulaglutide 1.5 mg: had injection site swelling and erythema reported as mild in severity at weeks 4 and 8. This patient had no detected ADA at baseline and by Week 52 had a high dulaglutide ADA titer of 1:1024

One patient met criteria for progressive increase in dulaglutide ADA titers:

GBDN-501-5029, 41 yr. F, dulaglutide 0.75 mg: The patient met criteria for progressive increases in dulaglutide ADA titers. The patient experienced treatment emergent dulaglutide ADA (1:8) beginning at Week 26 that were neutralizing for dulaglutide, and cross-reactive for ns-GLP-1, but not neutralizing for ns-GLP-1. The titer further increased (1:16) at the end of the safety follow up, but remained in low range at both of these visits. There were no reported adverse events to indicate systemic hypersensitivity. The patient reported at Week 8 (57 days on therapy) mild application site erythema of one day duration

The Applicant reports that four dulaglutide-treated patients developed nsGLP-1 neutralizing ADAs. None experienced hypersensitivity events or injection site reactions and all completed the study as planned. These cases are discussed further below.

GBDN-901-8311, 46 yr. F, dulaglutide 0.75 mg: This patient experienced a one-time treatment-emergent nsGLP-1 neutralizing antibody at week 8. At the 30 day follow-up visit (~Week 30) no anti-drug antibodies were detected.

GBDD-106-3259, 65 yr. M, dulaglutide 0.75 mg: This patient developed treatment-emergent dulaglutide ADA and nsGLP-1 neutralizing antibodies at the end of the safety follow-up period (~Week 56). The patient was negative for dulaglutide ADA at all previous visits.

GBDA-013-0610, 58 yr F, placebo/dulaglutide 1.5 mg: This patient developed treatment-emergent dulaglutide ADA (1:8) with nsGLP-1 neutralizing antibodies only at the end of the safety follow up period (~Week 56). The patient was negative for dula ADA at baseline and during the treatment period.

GBDN-047-2407, 42 yr. F, dulaglutide 0.75 mg: This patient experienced treatment emergent dulaglutide ADA beginning at Week 26 that were not neutralizing for ns-GLP-1. The ADA persisted to the 30-day safety follow up visit (~Week 30), at which time the antibodies were neutralizing nsGLP-1. The patient reported mild TEAEs of nasopharyngitis at 128 days and a lower respiratory tract infection occurring at 135 days

The incidence of treatment-emergent dulaglutide ADAs was similar between the two doses studied (dulaglutide 1.5 mg: 26 [1.51%] patients; dulaglutide 0.75 mg: 36 [2.08%] patients) as shown in Table 42 below. This suggests that the development of antibodies is not a dose-dependent effect.

Table 42: Summary of Incidence of Treatment-Emergent Dulaglutide Anti- Drug Antibodies By Dose - All Observations in Planned Treatment Period and in Follow-Up Period – Safety Population

Treatment Once Weekly	Placebo	Dulaglutide <0.75 mg	Dulaglutide 0.75 mg	Dulaglutide ~1.0 mg	Dulaglutide 1.5 mg	Dulaglutide >1.5 mg
Patients Treated	703	191	1765	175	1762	113
Patients with Postbaseline ADA Test	690	189	1726	168	1718	106
Patients with TE ADA anytime Postbaseline (% of those with sample)	3 (0.43)	0 (0.0)	36 (2.08)	1 (0.59)	26 (1.51)	1 (0.94)

Abbreviations: ADA = anti-drug antibody; TE = treatment-emergent.

Source: Table ISS: 6.69, page 406

Reviewer Assessments about Dulaglutide Anti-drug Antibodies:

Based on review of data from the clinical program, the incidence of treatment-emergent ADAs with dulaglutide was low. Treatment-emergent ADA were not associated with any significant systemic hypersensitivity events or injection site reactions

- 7.3.2.5 Hypersensitivity reactions:

The development of antibodies with treatment raises the possibility that hypersensitivity reactions may occur following treatment with dulaglutide. This concern is further amplified by the post marketing cases of anaphylaxis and angioedema reported with other GLP-1 agonists and DPP4 inhibitors.

No cases of anaphylaxis were reported in either the exenatide or exenatide LAR development programs. There were two patients in the liraglutide development program with potentially anaphylactic events, and two patients that discontinued drug due to hypersensitivity. In the albiglutide development program, systemic allergic reactions were balanced, but there was one patient that experienced angioedema and one patient that experienced anaphylaxis. Both were treated with albiglutide. I also reviewed data from two unapproved GLP-1. There were 12 cases of anaphylactic reaction/shock identified by adjudication in the ongoing lixisenatide development program. The observed anaphylaxis rate in the taspoglutide clinical program was 4.3% in phase 2. The Phase 3 program for taspoglutide was halted due to the high frequency of severe hypersensitivity reactions.

Treatment-emergent adverse events (TEAE) indicating potential hypersensitivity reactions resulting from a systemic immune response were assessed using SMQs (Narrow terms for “Anaphylactic Reaction”, “Angioedema”, and “Severe Cutaneous Adverse Reaction”). Adverse event data across all dulaglutide doses (0.1 mg to 3.0 mg) versus placebo, up to 26-weeks of treatment is shown in the Table 43 below.

The Applicant provided a summary of all hypersensitivity events in patients randomized to placebo or dulaglutide using the AS2 dataset. This seems acceptable, since the AS2 dataset contained integrated comparisons of all the dulaglutide doses combined (0.1 mg to 3.0 mg), up to the 26-week time point, and for all Phase 2 and 3 studies that included a placebo comparator. This pool might be expected to provide a more accurate incidence of hypersensitivity reactions compared to placebo.

No imbalance between the dulaglutide treated patients and placebo was noted. The preferred term urticaria was the most frequently reported TEAE for the placebo (2, 0.3%) and all dulaglutide (5, 0.2%) treatment groups.

Table 43: Summary and Analysis of SMQs for Any Hypersensitivity Reaction Through 26 Weeks of the Planned Treatment Period (AS2)

Level 1 Level 2 Level 3 Preferred Term	Placebo (N=703) n (%)	All_Dula (N=2213) n (%)	CMH p-value*a
Any Hypersensitivity Reaction	5 (0.7)	7 (0.3)	.163
Narrow	5 (0.7)	7 (0.3)	.163
Anaphylactic Reaction or Angioedema	5 (0.7)	6 (0.3)	.113
Urticaria	2 (0.3)	5 (0.2)	.836
Lip swelling	0 (0.0)	1 (<0.1)	.618
Face oedema	1 (0.1)	0 (0.0)	.046
Pharyngeal oedema	1 (0.1)	0 (0.0)	.155
Swelling face	1 (0.1)	0 (0.0)	.085
Severe Cutaneous Adverse Reaction	0 (0.0)	1 (<0.1)	.626
Exfoliative rash	0 (0.0)	1 (<0.1)	.626

Source: Table ISS 6.70- page 410

To further explore the incidence of hypersensitivity events, the analysis population was expanded to the entirety of all dulaglutide treated patients in the Phase 2 and 3 studies. There were 19 (0.5%) dulaglutide treated patients who experienced at least one potential treatment-emergent systemic hypersensitivity adverse event, including two serious hypersensitivity reactions (one case each of anaphylaxis and Steven Johnson's syndrome, both are discussed further below). This is compared to 12 (0.6%) events in comparator treated patients. None of the 19 dulaglutide treated patients were positive for treatment-emergent dulaglutide ADAs (Table 44 below). There were no systemic hypersensitivity adverse events reported in any of the 64 dulaglutide-treated patients with treatment-emergent dulaglutide ADAs, including patients with high or progressive treatment-emergent dulaglutide ADA titers.

Table 44: Hypersensitivity Reactions By Dulaglutide Anti-Drug Antibody Status All Phase 2 /3 Studies, All Dulaglutide Dose Groups

Level 1 Level 2 Level 3 Preferred Term	All_Dula TE Dula ADA- (N=3843) n (%)	All_Dula TE Dula ADA+ (N=64) n (%)	All_Dula (N=3907) n (%)	CMH p-value*a
Any Hypersensitivity Reaction	19 (0.5)	0 (0.0)	19 (0.5)	
Narrow	19 (0.5)	0 (0.0)	19 (0.5)	
Anaphylactic Reaction or Angioedema	17 (0.4)	0 (0.0)	17 (0.4)	
Urticaria	14 (0.4)	0 (0.0)	14 (0.4)	
Lip swelling	2 (<0.1)	0 (0.0)	2 (<0.1)	
Anaphylactic shock	1 (<0.1)	0 (0.0)	1 (<0.1)	
Periorbital oedema	1 (<0.1)	0 (0.0)	1 (<0.1)	
Severe Cutaneous Adverse Reaction	2 (<0.1)	0 (0.0)	2 (<0.1)	
Exfoliative rash	1 (<0.1)	0 (0.0)	1 (<0.1)	
Stevens-Johnson syndrome	1 (<0.1)	0 (0.0)	1 (<0.1)	

Abbreviations: ADA = anti-drug antibody; TE Dula ADA+ = treatment-emergent dulaglutide ADA titer; TE Dula ADA- = no treatment-emergent dulaglutide ADA titer; Dula = dulaglutide; N = total number of patients in specified group; n = number of patients with at least one adverse event.

Source: Table ISS 6.72, page 412

The Applicant provided narratives for all hypersensitivity events, irrespective of severity. All hypersensitivity narratives for dulaglutide treated patients were reviewed (Table 45). Specifically the reports were reviewed to determine if any hypersensitivity events for dulaglutide could potentially be anaphylaxis as per the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) criteria[15].

As discussed in the FAAN criteria, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:

15 Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol*. 2006; 117:391-7

a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Table 45: Review of Hypersensitivity events in dulaglutide treated patients:

Patient ID	Reported event	Drug d/c'd?	Antibody?	Pulm/CV sx reported?
GBDA-084-4154	Moderate urticaria	No	No	No
GBDC-124-2429	Severe injection site rash and swelling	Yes[1]	No	No
GBDD-106-3262	Moderate urticaria	No	No	No
GBDN-010-0561	Urticaria	No	No	No
GBCJ-001-0101[2]	Severe urticaria	No	No	No
GBCJ-035-3503	Urticaria	No	No	No
GBCF-302-4565[2]	Lip swelling[3], injection site rash[4]	No	No	No
GBCF-603-6401	Mild urticaria, nasopharyngitis and diarrhea	No	No	No
GBCF-603-6408	Urticaria	Yes[5]	Yes[6]	No
GBCF-701-6713[2]	Anaphylaxis, urticaria (discussed above)	No	No	Yes
GBDA-021-1014	Periorbital edema, injection site pain	No	No	No
GBDC-101-0107	Moderate urticaria	No	No	No
GBDC-301-5011	Urticaria	No	No	No
GBDC-602-7021	Lower lip swelling	No	No	No
GBDC-903-9662	Moderate urticaria	Yes[7]	No	No
GBDD-015-0802	Urticaria	No	No	No

Patient ID	Reported event	Drug d/c'd?	Antibody?	Pulm/CV sx reported?
GBDD-752-7472	Moderate urticaria	No	No	No
GBDN-038-1951	Moderate urticaria	No	No	No
GBCK-113-1317	Exfoliative rash, genital rash	No	Not done	No

ID = identification; d/c'd = discontinued; Pulm/CV sx = pulmonary/cardiovascular symptoms
[1] event occurred on day 107, drug discontinued on day 107; [2] additional details included in summary of narratives that follow; [3] lip swelling and injection site rash occurred on days 153 and 214; [4] injection site rash again reported on day 339; [5] event occurred at week76, drug discontinued at 85 weeks; [6] dulaglutide anti-drug antibodies and native sequence GLP-1 antibodies were detected at baseline [7] event occurred on day 55, study drug discontinued on day 176 due to lack of efficacy.
Source: Adapted from Narratives in Table 3.3: *Significant and Notable Patients: Hypersensitivity and Potentially Immune-Mediated Injection Site Reactions, TOSNP-special topics, eCTD, 5.3.5.3*

No additional cases of potentially serious hypersensitivity reactions were identified during my review. The three narratives for hypersensitivity and potentially immune mediated reactions reported as SAEs or reported to be severe in intensity are described in detail below.

Stevens Johnson syndrome:

GBCF-302-4565,45 yr F, dulaglutide 0.75 mg**:** A 45 year-old white female randomized to dulaglutide 0.75 mg reported an SAE of erythema multiforme with bullous changes (verbatim term) that was coded to the PT Stevens Johnson syndrome. The event occurred approximately 21 months after first exposure to dulaglutide and two days after the most recent dose. Prior to developing erythema multiforme,the patient initially developed an AE of whitlow in her left thumb This was treated with oxacillin for two days. The patient presented with pruritus and erythematous papular rash on trunk and upper limbs without mucosal involvement, within one day of treatment with oxacillin. She recovered without discontinuation of study drug. The patient completed the trial as planned.

Reviewer Comment: Given the temporal association to oxacillin and continued treatment with study drug, associating the event with oxacillin seems more likely than associating it with dulaglutide.

Anaphylactic shock:

GBCF-701-6713,46 yr. F, dulaglutide 0.75 mg: A 46-year-old Asian female randomized to dulaglutide 0.75 mg reported an adverse event of anaphylactic shock approximately 32 weeks (i.e. visit 10) after the start of randomized therapy. According to the investigator, the event was moderate in severity and related to food (i.e. a food allergy). Concomitant medications included metformin, diphenhydramine, epinephrine, ranitidine, and triamcinolone. The event lasted one day and was reported again during the safety follow up period. It again lasted one day. Other TEAEs reported for the patient were food allergy, urticaria, and allergic dermatitis (approximately 40, 48, and 52 weeks after

the start of randomized therapy, respectively). None of these events resulted in discontinuation of study drug and the patient completed the trial as planned. The patient did not have treatment-emergent dulaglutide ADA at any time during the study.

Reviewer Comment: Given the prior history of food allergy and continued treatment with study drug, relationship to dulaglutide is unlikely.

Severe Urticaria:

GBCJ-001-0101, 50 yr. M, dulaglutide 1.0 mg/2.0 mg**:** A 50-year-old Hispanic male patient randomized to dulaglutide 1.0 mg/2.0 mg reported an adverse event of severe urticaria seven days after first exposure to dulaglutide. The patient completed all study visits as planned. The patient did not have any clinically relevant abnormal clinical laboratory values. No respiratory or cardiovascular symptoms were reported. Dulaglutide ADAs were not detected at baseline or at any time during the study.

Reviewer Comment: Since the patient continued study drug and the event resolved, relationship to dulaglutide seems unlikely

Reviewer's Assessment for Treatment-Emergent Adverse Events Indicating Potential Hypersensitivity:

There does not appear to be any new or increased concerns about adverse reactions related to hypersensitivity with dulaglutide compared to approved products in the drug-class. Concerns with regard to hypersensitivity reactions can be mitigated through labeling, similar to the other approved GLP-1 agonists.

- 7.3.2.6 Injection site adverse events

Injection site reactions have been reported with other members of the GLP-1 agonist class of drugs. They have been reported with an increased incidence in patients with positive ADAs.

The Applicant summarized Injection site adverse events for the Phase 2 and -3 studies based on specific MedDRA Preferred Terms (PT) derived from the MedDRA High Level Term (HLT) for "Injection Site Reaction". In addition, the Applicant used a customized MedDRA query. These terms include: Injection site- "Dermatitis", "Erosion", "Erythema", "Hypersensitivity", "Induration", "Pruritis", "Exfoliation", "Vasculitis, "Photosensitivity reaction", "Rash", "Urticaria", "Hypertrophy", "Inflammation", "Irritation", "Edema", "Warmth", "Swelling", "Nodule", "Eczema". Data from patients with events matching these terms were further reviewed for the presence of treatment-emergent dulaglutide ADA, neutralizing anti-dulaglutide ADA, cross-reactive ADA to nsGLP-1 or neutralizing ADA to nsGLP-1.

The Applicant provided a summary of all injection site AEs in patients randomized to placebo or dulaglutide in the Phase 2 and 3 studies up to 26 weeks of treatment (AS2 dataset). This analysis set was used since it contained integrated comparisons of all dulaglutide doses combined (0.1 mg to 3.0 mg) up to the 26-week time point for all Phase 2 and 3 studies that included a placebo comparator. There were 44 patients with an injection site adverse event (Table 46). There were numerically more injection site adverse events in the dulaglutide treatment group (38, 1.7%) compared to the placebo-treated patients (6, 0.9%).

Table 46: Summary and Analysis of MedDRA Query: Injection Site Reactions, Observations Through 26 Weeks of the Planned Treatment Period - All Phase 2 and 3 Placebo-Controlled Studies, All Dulaglutide Doses (AS2)

Level 1 Level 2 Level 3 Preferred Term	Placebo (N=703) n (%)	All_Dula (N=2213) n (%)	CMH p-value*a
Injection Site Reactions	6 (0.9)	38 (1.7)	.108
Injection site haematoma	3 (0.4)	17 (0.8)	.321
Injection site pain	0 (0.0)	6 (0.3)	.176
Injection site erythema	0 (0.0)	4 (0.2)	.316
Injection site haemorrhage	2 (0.3)	3 (0.1)	.389
Injection site irritation	0 (0.0)	3 (0.1)	.319
Injection site pruritus	0 (0.0)	3 (0.1)	.319
Injection site reaction	1 (0.1)	3 (0.1)	.937
Injection site swelling	0 (0.0)	2 (<0.1)	.477
Injection site discomfort	0 (0.0)	1 (<0.1)	.616
Injection site induration	0 (0.0)	1 (<0.1)	.618
Injection site rash	0 (0.0)	1 (<0.1)	.618

Source: Table ISS 6.74-pg 425

In patients treated with dulaglutide, there were no injection site reactions that were reported as an SAE. There were three patients that discontinued study drug due to an injection site reaction. They are each briefly discussed further below. One of the patients was treatment-emergent dulaglutide ADA positive.

GBCF-874-8202, 56 yr. F, dulaglutide 0.75 mg - discontinued from the study due to an adverse event of immediate post-injection reaction reported 1 week after exposure to dulaglutide 0.75 mg reported to be moderate in intensity.

GBDD-013-0720, 65 yr. F, dulaglutide 1.5 mg - discontinued from the study due to an adverse event of injection site pain 1 week after exposure to dulaglutide 1.5 mg reported to be severe in intensity. The patient was tested for dulaglutide ADA at baseline and post-treatment with the same result (positive for dulaglutide ADA at a 1:8 titer).

GBDC-124-2429, 54 yr. F, dulaglutide 1.5 mg - reported a severe TEAE of injection site reaction (injection site rash and injection site swelling) 106 days after treatment with study drug. The patient discontinued study drug (reported as subject decision) after 107 days of treatment.

In addition to looking at AS2, the Applicant explored the relationship of dose to injection site reactions in AS7 which included the entire treatment period for the phase 2 and 3 studies that lasted at least 26 weeks and upto 104 weeks in duration. From AS7, 63 out of 3342 patients treated with 0.75 mg or 1.5 mg dulaglutide reported injection site reactions. There was no difference between the doses (n=31 [1.9%] for 1.5 mg, n=32 [1.9%] for 0.75 mg; Table 47). "Injection site hematoma" was the most frequently reported preferred term for both the 0.75 mg and 1.5 mg groups. The occurrence of injection site reactions was not different in the "All Comparator" group, but it is to be noted that the "All Comparator" included another GLP-1 agonist (i.e. exenatide).

Table 47: All Dulaglutide versus All Comparators Analysis of Treatment-Emergent Adverse Events for High Level Term –Injection site reactions All Postbaseline Observations Including Safety Follow-Up; (AS7)

System Organ Class High Level Term Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Oedema peripheral	43 (2.3)	42 (2.5)	27 (1.6)	69 (2.1)	0.88	.631	.480
Oedema	6 (0.3)	9 (0.5)	4 (0.2)	13 (0.4)	1.20	.073	.712
Generalised oedema	1 (<0.1)	1 (<0.1)	2 (0.1)	3 (<0.1)	1.66	.517	.724
Localised oedema	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Injection site reactions	24 (1.3)	32 (1.9)	31 (1.9)	63 (1.9)	1.46	.218	.163
Injection site haematoma	15 (0.8)	15 (0.9)	10 (0.6)	25 (0.7)	0.92	.142	.693
Injection site pain	3 (0.2)	6 (0.4)	6 (0.4)	12 (0.4)	2.21	.468	.251
Injection site pruritus	1 (<0.1)	4 (0.2)	4 (0.2)	8 (0.2)	4.42	.793	.140
Injection site haemorrhage	3 (0.2)	4 (0.2)	1 (<0.1)	5 (0.1)	0.92	.450	.788
Injection site rash	0 (0.0)	3 (0.2)	3 (0.2)	6 (0.2)			.048
Injection site erythema	0 (0.0)	0 (0.0)	4 (0.2)	4 (0.1)			.131
Injection site reaction	1 (<0.1)	0 (0.0)	3 (0.2)	3 (<0.1)	1.66	.512	.730
Injection site irritation	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)			.223
Injection site swelling	0 (0.0)	0 (0.0)	3 (0.2)	3 (<0.1)			.223
Injection site discomfort	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.482
Injection site macule	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Injection site nodule	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267

Abbreviations: All_Comp = all comparators; CMH = Cochran-Mantel-Haenszel; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event; TEAE = treatment emergent adverse event

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined. All_Comp = metformin for Study GBDC, placebo/sitagliptin or sitagliptin for Study GBCF, exenatide for Study GBDA, insulin glargine for Studies GBDB and GBDD, placebo for Study GBDN. Patient randomized to the Placebo/Dulaglutide switch arms of Study GBDA are excluded from this analysis.

Source: Table APP 5.3, Regulatory Response dated April 21, 2014, page 107

Review of the injection site adverse events in studies that included injectable active comparators (GBDA, GBDB and GBDD) demonstrated that the number of injection site reactions was less compared to exenatide but greater compared to insulin glargine. A summary of the findings for each study follows:

- In Study GBDA, after 52 weeks of treatment, 14 (5.1%) patients treated with exenatide BID, 14 (5.0%) patients treated with dulaglutide 0.75 mg, and 8 (2.9%) of patients treated with dulaglutide 1.5 mg reported injection site adverse event; the most common was hematoma (preferred term)
- In Study GBDB, after 78 weeks of treatment, 4 (0.5%) patients treated with dulaglutide (2 each in the 0.75 mg and 1.5 mg groups) and none of the insulin glargine treated patients reported injection site reactions
- In Study GBDD, after 52 weeks of treatment, 4 (1.4%) of patients treated with dulaglutide 0.75 mg, 1 (0.3%) of patients treated with dulaglutide 1.5 mg, and

none of the insulin glargine treated patients reported an injection site adverse event

To further evaluate the dose dependency for AEs, the "injection site reactions" HLT for dulaglutide 0.75 mg vs. 1.5 mg doses was examined using the placebo-controlled pool (AS1) (Table 48 and Table 49). There were 18 events in each of the dulaglutide doses compared to four with placebo.

Table 48: Injection site reactions HLT, dulaglutide 0.75 mg vs. placebo- placebo controlled pool for studies GBDA, GBCF and GBDN (AS1)

Issue	Type	Score	chi-statistic	Corrected Odds Ratio	OR025_C	A	B	Treatment Subjects	Comparator Subjects	Sex	Age	Race	Dosing Breakdown	Time Frame
Injection site reactions	HLT	0.015956	2.146	2.835	1.006	18	4	836	568	All	All	All	dula0.75 vs placebo	Study Reference Period

Reviewer *Generated using Empirica Study program*

Table 49: Injection site reactions, dulaglutide 1.5 mg vs. placebo- placebo controlled pool for studies GBDA, GBCF and GBDN (AS1)

Issue	Type	Score	chi-statistic	Corrected Odds Ratio	OR025_C	A	B	Treatment Subjects	Comparator Subjects	Sex	Age	Race	Dosing Breakdown	Time Frame
Injection site reactions	HLT	0.015754	2.151	2.842	1.009	18	4	834	568	All	All	All	dula1.5mg vs.pbo	Study Reference Period

Reviewer *Generated using Empirica Study program*

Dulaglutide-treated patients in all phase 2/3 studies with treatment-emergent dulaglutide ADAs (Table 50) had a higher incidence of injection site adverse events (3.1%; 2 of 64 patients) compared to patients who did not develop treatment-emergent dulaglutide ADA (0.5%; 18 of 3843 patients).

Table 50: Potentially Immune-Mediated Injection Site Reactions By Dulaglutide Treatment-Emergent Anti-drug Antibody Status Including All Postbaseline Observations through Safety Follow-up in All Phase 2 and 3 Studies - All Dulaglutide Doses .

Level 1 Preferred Term	All_Dula TE Dula ADA- (N=3843) n (%)	All_Dula TE Dula ADA+ (N=64) n (%)	All_Dula (N=3907) n (%)	CMH p-value*a
Potentially Immune-Mediated Injection Site Reactions	18 (0.5)	2 (3.1)	20 (0.5)	0.005
Injection site pruritus	7 (0.2)	1 (1.6)	8 (0.2)	0.025
Injection site rash	6 (0.2)	0 (0.0)	6 (0.2)	0.754
Injection site erythema	4 (0.1)	1 (1.6)	5 (0.1)	0.001
Injection site irritation	3 (<0.1)	0 (0.0)	3 (<0.1)	0.816
Injection site swelling	2 (<0.1)	1 (1.6)	3 (<0.1)	< 0.001
Injection site induration	1 (<0.1)	0 (0.0)	1 (<0.1)	0.909

Source: Table ISS.6.78-page 431

Reviewer Comment: *The Applicant excluded the PTs of "injection site hematoma", "pain"," hemorrhage", "macule" and "discomfort" from the list of HLT terms. Exclusion of these individual terms seems reasonable.*

As discussed above in section 7.3.2.4 Immunogenicity, four patients developed high treatment-emergent dulaglutide ADA and one patient had a progressive increase in titer for the full duration of treatment. Two out of these five patients (Patient GBDA-016-0789 [dulaglutide 1.5 mg] and Patient GBDN-501-5029 [dulaglutide 0.75 mg]) had injection site adverse events but did not discontinue study treatment.

Reviewer's Assessments about injection site reactions:

Dulaglutide was associated with more injection site reactions than placebo. There was no apparent dose dependency for this, but patients that developed ADAs were more likely to have injection site reactions that those patients that did not develop ADAs. This is consistent with other members of the drug class.

- 7.3.2.7 Renal Safety

While non-clinical studies have not shown direct nephrotoxicity, there are concerns regarding the potential for GLP-1 receptor agonists to cause renal impairment. This is presumably secondary to GI effects and volume depletion resulting in acute renal failure.

In the clinical development program, measures were taken to minimize the risk of renal impairment. For most Phase 2 and 3 studies, patients with serum creatinine ≥1.5 mg/dL (males) or ≥1.4 mg/dL (females), or estimated creatinine clearance (eCrCl) < 60 mL/min were excluded from participation based on label-specific restrictions of concomitant medications (for example, metformin) and limited data available on the use of dulaglutide in patients with renal impairment at the time of implementation of these studies.

Throughout the studies, laboratory assessments were performed to evaluate renal function. Criteria were implemented for discontinuing study drug or the study if patients developed renal disease during the course of the study.

While eCrCl was the measure of renal function specified under exclusion criteria in the protocols for most studies, the effects of dulaglutide in patients with normal renal function and degrees of renal impairment were primarily presented in the ISS using the CKD staging criteria presented in Table ISS.6.117 (Table 51). These categories were based upon the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (NKF KDOQI 2007 [WWW]) for classification of CKD, using estimated GFR (eGFR) calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[16]. Only eCrCl values are reported in several patient narratives.

16 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612

Presence of macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] >300 mg/g) and eGFR ranges were used as markers in distinguishing normal renal function from different stages of renal impairment.

Albumin/creatinine ratio thresholds were used to reflect shifts between normal albuminuria (UACR <30 mg/g), microalbuminuria (defined as UACR ≥ 30 and ≤ 300 mg/g), and macroalbuminuria (UACR >300 mg/g). CKD Stage was determined by adapted CKD-EPI guidelines, using the highest measured value of eGFR (CKD-EPI) and the lowest measured value of UACR from the baseline period. Patients are included in the Macroalbuminuria group if UACR > 300 at all measured time points during baseline, included in the eGFR (CKD-EPI) <60 mL/min/1.73 m^2 group when that criterion is satisfied at all measured time points during baseline, and included in the Renal Impairment group if included in either the Macroalbuminia group or the eGFR (CKD-EPI) < 60 mL/min/1.73 m^2 group.

Table 51: Categories of Chronic Kidney Disease Staging

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

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

a Calculated using Chronic Kidney Disease Epidemiology Collaboration equation.

b Based on spot urine collection.

Source: Table ISS.6.117, page 520

At baseline, 88% (5285 patients) of all randomized patients had normal kidney function. Only 4.4% (265) had an eGFR < 60 mL/min/1.73 m^2, only 3% (181) of patients had macroalbuminuria. The distribution in the dulaglutide treated patients was similar to that seen in the all randomized patients (Table 52 and Table 53).

Table 52: Summary of Renal Characteristics At Baseline of All Phase 2 and 3 Patients, Safety Population

Variable	All Randomized Phase 2 (N=1329)	All Randomized Phase 3 (N=4676)	All Randomized Phase 2 and 3 (N=6005)
CKD Stage at Baseline *a			
Normal	973 (73.2)	4312 (92.2)	5285 (88.0)
Stage 1	9 (0.7)	75 (1.6)	84 (1.4)
Stage 2	13 (1.0)	63 (1.3)	76 (1.3)
Stage 3A	69 (5.2)	161 (3.4)	230 (3.8)
Stage 3B	12 (0.9)	23 (0.5)	35 (0.6)
Unknown	253 (19.0)	42 (0.9)	295 (4.9)
Renal Impairment *b	103 (7.8)	322 (6.9)	425 (7.1)
Macroalbuminuria (UACR >300)	28 (2.1)	153 (3.3)	181 (3.0)
eGFR (CKD-EPI) <60 mL/min/1.73 m²	81 (6.1)	184 (3.9)	265 (4.4)

Abbreviations: CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; N = total number of patients in specified treatment arm; eGFR = estimated glomerular filtration rate; mL/min/1.73 m2 = milliliter per minute per 1.73 square meters of body surface area; n = number of patients in specified category; UACR = urine albumin to creatinine ratio.

Source: Table ISS.6.118- page 522

Table 53: Summary of Patient Characteristics At Baseline, All Observations During the Planned Treatment Period - Phase 2 and 3 Patients who Received Dulaglutide (Safety Population)

Variable	All_Dula (N=4006)
CKD Stage at Baseline *a	
Normal	3516 (87.8)
Stage 1	49 (1.2)
Stage 2	50 (1.2)
Stage 3A	147 (3.7)
Stage 3B	24 (0.6)
Unknown	220 (5.5)
Renal Impairment *b	270 (6.7)
Macroalbuminuria (UACR >300)	111 (2.8)
eGFR (CKD-EPI) <60 mL/min/1.73 m²	171 (4.3)

Source: Table ISS.APP.473- page 5709

The analyses presented by the Applicant for mean eGFR and UACR over time and for categorical assessments were reviewed in comparison to placebo and for the two dulaglutide treatment groups over the long-term compared to baseline. For long-term comparisons, the Applicant only submitted information from the AS3 dataset comparing dulaglutide 1.5 mg to dulaglutide 0.75 mg initially. Information was also requested for mean changes in eGFR and UACR against active comparator (AS7). Categorical shift data was also submitted later. Each of these comparisons will be discussed separately.

Comparison to placebo (AS1):

Baseline mean eGFR values were comparable between the placebo and all dulaglutide groups when calculated using CKD-EPI (89.04 mL/min/1.73 m2 and 89.44 mL/min/1.73

m^2, respectively) (Table 54). No significant difference was observed in LS mean eGFR between the all dulaglutide group and placebo group at baseline or at the last measurement (up to 26 weeks of exposure).

Table 54: ANCOVA Analysis of Baseline to Postbaseline Anchor Timepoint of eGFR CKD-EPI By Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period (AS1)

Variable analyzed: eGFR estimated by CKD-EPI (mL/min/1.73 m^2)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Baseline	Placebo	568	89.04		18.85	77.65	90.52	101.68	129.65						
	Dula_0.75	836	89.30		35.61	78.19	91.22	101.48	131.42						
	Dula_1.5	833	89.59		42.63	77.23	92.05	101.84	136.54						
	All_Dula	1669	89.44		35.61	77.62	91.61	101.70	136.54						
16 - 26*	Placebo	551	88.22	86.51	33.23	75.86	90.40	101.61	133.05	-0.82	-42.25	-5.66	-0.37	4.49	71.53
	Dula_0.75	811	87.79		27.50	76.50	90.86	100.48	133.51	-1.37	-62.26	-5.44	-1.02	3.14	27.24
	Dula_1.5	811	87.77		35.74	75.00	89.37	100.32	136.07	-1.90	-48.96	-6.92	-1.08	2.92	36.34
	All_Dula	1622	87.78	85.57	27.50	75.52	90.30	100.40	136.07	-1.64	-62.26	-6.15	-1.05	3.02	36.34

All_Dula vs Placebo LSM Comparison, p-value*a .075

Abbreviations: ANCOVA = analysis of covariance; CKD-EPI = chronic kidney disease epidemiology collaboration; Dula = dulaglutide; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; LSM = least square mean; Max = maximum; Min = minimum; mL/min/1.73 m^2 = milliliter per minute per 1.73 square meters of body surface area; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; vs = versus; UACR = urine albumin to creatinine ratio.

Source: Table ISS.6.120- page 525

Based on shifts in eGFR values from baseline to the lowest postbaseline value, the proportions of patients shifting to higher eGFR category or lower eGFR category were comparable between the all dulaglutide and placebo groups (Table 55). Notably, there were two patients in the dulaglutide 0.75 mg group shifted from normal (eGFR>60 ml/min/1.73m^2) to Stage 4 CKD (eGFR < 30 ml/min/1.73m^2) respectively versus none with placebo, the narratives are discussed below.

Table 55: Shift of Estimated Glomerular Filtration Rate from Minimum Baseline to Minimum Postbaseline, Observations Through 26 Weeks of the Planned Treatment Period - (AS1)

Lab Test (unit) = ESTIMATED GLOMERULAR FILTRATION RATE -- CKD-EPI (mL/min/1.73 m2)

Treatment	Minimum Baseline	Minimum Postbaseline: < 30 n (%)	>= 30 to < 45 n (%)	>= 45 to < 60 n (%)	>= 60 to < 90 n (%)	>= 90 n (%)	Total n (%)
Placebo (N=551)	< 30	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
	>= 30 to < 45	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>= 45 to < 60	0 (0.0)	10 (1.8)	20 (3.6)	13 (2.4)	0 (0.0)	43 (7.8)
	>= 60 to < 90	0 (0.0)	1 (0.2)	14 (2.5)	197 (35.8)	54 (9.8)	266 (48.3)
	>= 90	0 (0.0)	1 (0.2)	2 (0.4)	39 (7.1)	199 (36.1)	241 (43.7)
	Total	0 (0.0)	12 (2.2)	36 (6.5)	250 (45.4)	253 (45.9)	551 (100.0)
Dula_0.75 (N=811)	< 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>= 30 to < 45	0 (0.0)	2 (0.2)	5 (0.6)	1 (0.1)	0 (0.0)	8 (1.0)
	>= 45 to < 60	1 (0.1)	8 (1.0)	30 (3.7)	16 (2.0)	0 (0.0)	55 (6.8)
	>= 60 to < 90	1 (0.1)	1 (0.1)	23 (2.8)	303 (37.4)	72 (8.9)	400 (49.3)
	>= 90	1 (0.1)	0 (0.0)	0 (0.0)	47 (5.8)	300 (37.0)	348 (42.9)
	Total	3 (0.4)	11 (1.4)	58 (7.2)	367 (45.3)	372 (45.9)	811 (100.0)

Lab Test (unit) = ESTIMATED GLOMERULAR FILTRATION RATE -- CKD-EPI (mL/min/1.73 m2)

Treatment	Minimum Baseline	Minimum Postbaseline: < 30 n (%)	>= 30 to < 45 n (%)	>= 45 to < 60 n (%)	>= 60 to < 90 n (%)	>= 90 n (%)	Total n (%)
Dula_1.5 (N=811)	< 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>= 30 to < 45	0 (0.0)	4 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	6 (0.7)
	>= 45 to < 60	0 (0.0)	5 (0.6)	30 (3.7)	20 (2.5)	1 (0.1)	56 (6.9)
	>= 60 to < 90	0 (0.0)	1 (0.1)	21 (2.6)	296 (36.5)	70 (8.6)	388 (47.8)
	>= 90	0 (0.0)	0 (0.0)	2 (0.2)	72 (8.9)	287 (35.4)	361 (44.5)
	Total	0 (0.0)	10 (1.2)	55 (6.8)	388 (47.8)	358 (44.1)	811 (100.0)
All_Dula (N=1622)	< 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>= 30 to < 45	0 (0.0)	6 (0.4)	7 (0.4)	1 (<0.1)	0 (0.0)	14 (0.9)
	>= 45 to < 60	1 (<0.1)	13 (0.8)	60 (3.7)	36 (2.2)	1 (<0.1)	111 (6.8)
	>= 60 to < 90	1 (<0.1)	2 (0.1)	44 (2.7)	599 (36.9)	142 (8.8)	788 (48.6)
	>= 90	1 (<0.1)	0 (0.0)	2 (0.1)	119 (7.3)	587 (36.2)	709 (43.7)
	Total	3 (0.2)	21 (1.3)	113 (7.0)	755 (46.5)	730 (45.0)	1622 (100.0)

Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; mL/min/1.73 m² = milliliter per minute per 1.73 square meters of body surface area; N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in the specified category.

Source: Table ISS.6.122, page 528

Shift from Normal to CKD Stage 3b:

GBDN-944-9154, 56 yr. F, Dulaglutide 0.75 mg: This patient was a 56-year-old Asian female with a 3-year duration of T2DM. Past medical history included hypertension. Concomitant medications included acarbose, atenolol, glimepiride, and metformin. Renal function laboratory tests were normal at baseline (Visit 3) (serum creatinine was 1.0 mg/dL, eCrCl was 82 mL/min, BUN was 5.0 mmol/L, urinary albumin to creatinine ratio was 24.78 mg/g). Abnormal laboratory renal function tests were reported at Visit 7 (16 Weeks) and Visit 8 (26 weeks). On Visit 7 (16 weeks), serum creatinine was 1.7 mg/dL, eCrCl was 45 mL/min, urinary albumin to creatinine ratio was 604.5. On Visit 8 (26 weeks), serum creatinine was 2.0 mg/dL, eCrCl was 39 mL/min, and BUN was 9.6 mmol/L. No other adverse event was reported in association with these abnormal laboratory values.

Shift from Normal to CKD Stage 4:

GBCF-944-3205, 69 yr. M, Dulaglutide 0.75 mg): This was a 69-year-old West Asian male with a 9-year duration of T2DM. Past medical history included hypertension.

Concomitant medications included atenolol. Abnormal urinary microscopic exam, calcium oxalate crystals, protein, and occult blood were reported at the randomization visit (Visit 4). Renal function laboratory testswere normal at baseline (Visit 4) (serum creatinine was 0.8 mg/dL, eCrCl was 89 mL/min, BUN was 8.2 mmol/L, urinary albumin to creatinine ratio was 12.3 mg/g). At Visit 9 (6 month), abnormal renal function laboratory tests were reported (serum creatinine was 2.3 mg/dL, eCrCl was 30 mL/min, BUN was 10.4 mmol/L, urinary albumin to creatinine ratio was 76.1). Treatment was stopped at 6 months. No AEs are reported.

Reviewer's Comment: No other AEs are reported for these patients. Further follow-up information is not available.

Albuminuria:

Mean and median changes from baseline for UACR for dulaglutide 1.5 mg and 0.75 mg in the placebo-controlled pool (AS1) were comparable to placebo (Table 56).

Table 56: ANCOVA Analysis of Baseline to Postbaseline Anchor Timepoint of UACR By Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period (AS1)

Variable analyzed: Urine Albumin to Creatinine Ratio (milligram/gram)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Baseline	Placebo	557	55.676		0.89	5.310	8.850	21.240	3533.81						
	Dula_0.75	818	48.868		0.89	4.425	8.850	24.780	5045.39						
	Dula_1.5	813	55.166		0.89	4.425	8.850	23.895	7267.62						
	All_Dula	1631	52.007		0.89	4.425	8.850	23.895	7267.62						
16 - 26*	Placebo	527	56.142	10.719	0.89	4.425	7.965	23.895	2316.05	2.381	-1226.61	-5.310	-0.443	3.540	1140.77
	Dula_0.75	774	46.361		0.89	4.425	7.080	18.585	8553.53	-4.000	-1459.37	-7.080	-1.770	1.770	3508.14
	Dula_1.5	774	56.242		0.44	4.425	7.965	20.355	6698.57	-0.384	-1496.54	-7.523	-1.328	2.655	1865.58
	All_Dula	1548	51.301	9.641	0.44	4.425	7.965	20.355	8553.53	-2.192	-1496.54	-7.080	-1.770	2.655	3508.14

All_Dula vs Placebo LSM Comparison, p-value*a .023

Abbreviations: ANCOVA = analysis of covariance; Dula = dulaglutide; HbA1c = hemoglobin A1c; LSM = least square mean; Max = maximum; Min = minimum; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; vs = versus; UACR = urine albumin to creatinine ratio.

Source: Table ISS 6.123, page 531

Categorical shifts in albuminuria:

One patient in the dulaglutide 0.75 mg group and 4 patients in the dulaglutide 1.5 mg group shifted from normal albuminuria to macroalbuminuria versus none on placebo (Table 57). The shifts from micro-to macroalbuminuria were numerically less than placebo.

Table 57: Shift of Urine Albumin to Creatinine Ratio from Maximum Baseline to Maximum Postbaseline, Observations Through 26 Weeks of the Planned Treatment Period - (AS1)

Lab Test (unit) = URINE ALBUMIN to CREATININE RATIO (milligram/gram)

		Maximum Postbaseline			
		< 30 mg/g	>= 30 to <= 300 mg/g	> 300 mg/g	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)
Placebo (N=527)	< 30 mg/g	391 (74.2)	22 (4.2)	0 (0.0)	413 (78.4)
	>= 30 to <= 300 mg/g	32 (6.1)	53 (10.1)	11 (2.1)	96 (18.2)
	> 300 mg/g	0 (0.0)	4 (0.8)	14 (2.7)	18 (3.4)
	Total	423 (80.3)	79 (15.0)	25 (4.7)	527 (100.0)
Dula_0.75 (N=774)	< 30 mg/g	558 (72.1)	22 (2.8)	1 (0.1)	581 (75.1)
	>= 30 to <= 300 mg/g	71 (9.2)	93 (12.0)	5 (0.6)	169 (21.8)
	> 300 mg/g	1 (0.1)	10 (1.3)	13 (1.7)	24 (3.1)
	Total	630 (81.4)	125 (16.1)	19 (2.5)	774 (100.0)
Dula_1.5 (N=774)	< 30 mg/g	557 (72.0)	34 (4.4)	4 (0.5)	595 (76.9)
	>= 30 to <= 300 mg/g	73 (9.4)	78 (10.1)	4 (0.5)	155 (20.0)
	> 300 mg/g	0 (0.0)	8 (1.0)	16 (2.1)	24 (3.1)
	Total	630 (81.4)	120 (15.5)	24 (3.1)	774 (100.0)
All_Dula (N=1548)	< 30 mg/g	1115 (72.0)	56 (3.6)	5 (0.3)	1176 (76.0)
	>= 30 to <= 300 mg/g	144 (9.3)	171 (11.0)	9 (0.6)	324 (20.9)
	> 300 mg/g	1 (<0.1)	18 (1.2)	29 (1.9)	48 (3.1)
	Total	1260 (81.4)	245 (15.8)	43 (2.8)	1548 (100.0)

Abbreviations: mg/g = milligram per gram; N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in a specified category.

Source: Table ISS 6.124-Page 532

Long-term Renal function finding in studies ≥ 26 weeks duration (AS3) and (AS7):

Except for week 26, when there appears to be a greater decline renal function for the dulaglutide 1.5 mg group, the mean/median change in eGFR is comparable to all comparators at all time points (Table 58)

Table 58: Repeated Measures Analysis of Baseline to Postbaseline Anchor Timepoint of eGFR CKD-EPI, MMRM by Treatment and Anchor Timepoint - All Observations During the Planned Treatment Period, All Comparator Comparison (AS7)

Variable analyzed: eGFR estimated by CKD-EPI (mL/min/1.73 m^2)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Baseline	All Comparator	1844	89.56		36.98	78.23	92.04	101.59	134.17						
	Dula_0.75	1671	88.91		31.08	77.57	90.86	101.18	132.78						
	Dula_1.5	1670	89.40		27.74	77.95	91.72	101.70	138.82						
	All_Dula	3341	89.16		27.74	77.74	91.27	101.42	138.82						
26	All Comparator	1782	88.03	86.25	24.34	76.36	90.45	100.49	135.44	-1.51	-49.77	-6.20	-1.25	3.47	55.34
	Dula_0.75	1609	86.98		17.85	75.09	89.56	100.01	133.51	-1.93	-62.26	-6.10	-1.60	2.75	27.71
	Dula_1.5	1612	87.12		21.36	74.94	89.21	99.84	136.07	-2.33	-48.96	-7.20	-1.74	2.58	36.34
	All_Dula	3221	87.05	85.60	17.85	75.09	89.45	99.94	136.07	-2.13	-62.26	-6.56	-1.65	2.64	36.34
	All_Dula vs All Comparator LSM Comparison, p-value*a								.029						

Variable analyzed: eGFR estimated by CKD-EPI (mL/min/1.73 m^2)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
52	All Comparator	1320	87.39	85.29	26.64	76.06	89.87	99.37	133.02	-2.34	-50.50	-7.44	-1.57	2.88	37.14
	Dula_0.75	1239	86.45		28.94	74.54	88.85	98.77	137.16	-2.46	-50.46	-7.13	-1.78	2.51	35.17
	Dula_1.5	1206	87.31		26.84	75.96	89.63	99.91	133.25	-2.54	-63.00	-7.29	-1.92	2.71	31.38
	All_Dula	2445	86.87	85.00	26.84	75.22	89.35	99.31	137.16	-2.50	-63.00	-7.21	-1.88	2.58	35.17
	All_Dula vs All Comparator LSM Comparison, p-value*a								.417						
78 - 104*	All Comparator	588	88.48	84.73	32.50	77.42	91.00	99.32	126.01	-3.37	-45.55	-8.09	-3.01	2.02	25.97
	Dula_0.75	487	88.94		30.28	78.12	91.54	100.96	138.21	-2.19	-50.74	-7.23	-1.70	2.89	87.23
	Dula_1.5	478	90.78		31.92	81.61	93.99	101.48	132.21	-2.94	-47.15	-7.53	-2.27	2.19	29.11
	All_Dula	965	89.85	84.51	30.28	79.73	92.49	101.36	138.21	-2.56	-50.74	-7.23	-2.00	2.52	87.23
	All_Dula vs All Comparator LSM Comparison, p-value*a								.657						

Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; Dula = dulaglutide; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; LSM = least square mean; Max = maximum; Min = minimum; mL/min/1.73 m^2 = milliliter per minute per 1.73 square meters of body surface area; MMRM = mixed-effects model for repeated measures; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; REML = restricted maximum likelihood; vs = versus; UACR = urine albumin to creatinine ratio.

Source: Table APP 5.6, Response to IR dated 4/21/14

Based on shifts of eGFR values from baseline to the lowest post-baseline value, proportions of patients shifting to higher eGFR category or lower eGFR category were comparable between dulaglutide 1.5 mg and dulaglutide 0.75 mg (Table 59). One patient on dulaglutide 0.75 mg shifted from > 90 to < 30ml/min/m^2. Six patients in total on dulaglutide shifted from > 60 to < 30 ml/min/1.73 m^2 compared to one on all comparator.

Table 59: Shift of Estimated Glomerular Filtration Rate from Minimum Baseline to Minimum Post-baseline, All Dulaglutide Observations During the Planned Treatment Period - (AS7)

Lab Test (unit) = ESTIMATED GLOMERULAR FILTRATION RATE -- CKD-EPI (mL/min/1.73 m2)

		Minimum Postbaseline					
Treatment	Minimum Baseline	< 30 n (%)	>= 30 to < 45 n (%)	>= 45 to < 60 n (%)	>= 60 to < 90 n (%)	>= 90 n (%)	Total n (%)
All Comparator (N=1789)	< 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>= 30 to < 45	2 (0.1)	9 (0.5)	3 (0.2)	1 (<0.1)	0 (0.0)	15 (0.8)
	>= 45 to < 60	1 (<0.1)	22 (1.2)	67 (3.7)	30 (1.7)	0 (0.0)	120 (6.7)
	>= 60 to < 90	1 (<0.1)	9 (0.5)	72 (4.0)	634 (35.4)	97 (5.4)	813 (45.4)
	>= 90	0 (0.0)	0 (0.0)	7 (0.4)	225 (12.6)	609 (34.0)	841 (47.0)
	Total	4 (0.2)	40 (2.2)	149 (8.3)	890 (49.7)	706 (39.5)	1789 (100.0)
Dula_0.75 (N=1620)	< 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>= 30 to < 45	1 (<0.1)	9 (0.6)	7 (0.4)	1 (<0.1)	0 (0.0)	18 (1.1)
	>= 45 to < 60	1 (<0.1)	20 (1.2)	58 (3.6)	29 (1.8)	0 (0.0)	108 (6.7)
	>= 60 to < 90	3 (0.2)	9 (0.6)	70 (4.3)	620 (38.3)	67 (4.1)	769 (47.5)
	>= 90	1 (<0.1)	0 (0.0)	4 (0.2)	173 (10.7)	547 (33.8)	725 (44.8)
	Total	6 (0.4)	38 (2.3)	139 (8.6)	823 (50.8)	614 (37.9)	1620 (100.0)
Dula_1.5 (N=1617)	< 30	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
	>= 30 to < 45	1 (<0.1)	11 (0.7)	8 (0.5)	0 (0.0)	1 (<0.1)	21 (1.3)
	>= 45 to < 60	0 (0.0)	12 (0.7)	67 (4.1)	21 (1.3)	1 (<0.1)	101 (6.2)
	>= 60 to < 90	2 (0.1)	4 (0.2)	70 (4.3)	604 (37.4)	70 (4.3)	750 (46.4)
	>= 90	0 (0.0)	0 (0.0)	5 (0.3)	187 (11.6)	551 (34.1)	743 (45.9)
	Total	4 (0.2)	28 (1.7)	150 (9.3)	812 (50.2)	623 (38.5)	1617 (100.0)
All_Dula (N=3237)	< 30	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
	>= 30 to < 45	2 (<0.1)	20 (0.6)	15 (0.5)	1 (<0.1)	1 (<0.1)	39 (1.2)
	>= 45 to < 60	1 (<0.1)	32 (1.0)	125 (3.9)	50 (1.5)	1 (<0.1)	209 (6.5)
	>= 60 to < 90	5 (0.2)	13 (0.4)	140 (4.3)	1224 (37.8)	137 (4.2)	1519 (46.9)
	>= 90	1 (<0.1)	0 (0.0)	9 (0.3)	360 (11.1)	1098 (33.9)	1468 (45.4)
	Total	10 (0.3)	66 (2.0)	289 (8.9)	1635 (50.5)	1237 (38.2)	3237 (100.0)

Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; mL/min/1.73 m² = milliliter per minute per 1.73 square meters of body surface area; N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in the specified category.

Source Table 4.1, Applicant's response dated June 24, 2014

When compared to all comparator, there was a statistically significantly greater decline in UACR in the dulaglutide 1.5 mg group and dulaglutide 0.75 mg which was maintained at all time-points (Table 60).

Table 60: Repeated Measures Analysis of Baseline to Postbaseline Anchor Timepoint of UACR, MMRM by Treatment and Anchor Timepoint - All Observations During the Planned Treatment Period, All Comparator Comparison - (AS7)

Variable analyzed: Urine Albumin to Creatinine Ratio (milligram/gram)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Baseline	All Comparator	1825	65.571		0.44	5.310	9.735	27.435	5625.06						
	Dula_0.75	1653	58.003		0.89	4.425	8.850	24.780	6341.03						
	Dula_1.5	1647	73.093		0.44	4.868	9.735	27.435	7267.62						
	All_Dula	3300	65.535		0.44	4.425	8.850	26.550	7267.62						
26	All Comparator	1732	55.336	11.110	0.44	4.425	8.629	24.780	3169.19	-6.307	-5171.94	-7.080	-0.885	3.540	2100.11
	Dula_0.75	1565	55.186		0.44	4.425	7.965	20.355	8553.53	-3.585	-2233.74	-7.080	-1.328	2.655	3508.14
	Dula_1.5	1564	58.732		0.44	4.425	7.965	21.683	6698.57	-12.888	-4387.83	-8.850	-1.770	2.213	1865.58
	All_Dula	3129	56.958	10.266	0.44	4.425	7.965	21.240	8553.53	-8.235	-4387.83	-7.965	-1.770	2.213	3508.14
	All_Dula vs All Comparator LSM Comparison, p-value*a								.005						

Variable analyzed: Urine Albumin to Creatinine Ratio (milligram/gram)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
52	All Comparator	1297	55.388	11.006	0.44	4.425	7.965	23.895	3668.33	-3.045	-3232.91	-7.080	-0.885	3.540	1455.83
	Dula_0.75	1210	50.641		0.89	3.983	7.965	21.240	4950.69	-0.954	-1623.98	-7.080	-0.885	3.098	3047.94
	Dula_1.5	1180	45.738		0.44	3.983	7.965	21.240	4430.31	-23.887	-7255.23	-9.735	-1.770	1.770	1779.74
	All_Dula	2390	48.220	10.154	0.44	3.983	7.965	21.240	4950.69	-12.277	-7255.23	-7.965	-1.328	2.655	3047.94
	All_Dula vs All Comparator LSM Comparison, p-value*a								.015						
78 - 104*	All Comparator	561	48.569	11.082	0.44	4.425	8.850	24.780	2850.59	2.911	-677.91	-7.080	-0.885	4.425	1299.18
	Dula_0.75	461	86.649		0.89	4.425	8.850	28.320	7283.55	25.657	-1422.20	-6.195	0.000	6.195	6172.88
	Dula_1.5	457	37.300		0.44	3.540	7.080	21.240	1470.87	-14.554	-2422.25	-9.735	-1.770	2.655	407.99
	All_Dula	918	62.082	10.148	0.44	4.425	8.850	25.665	7283.55	5.639	-2422.25	-7.965	-0.885	4.425	6172.88
	All_Dula vs All Comparator LSM Comparison, p-value*a								.085						

Abbreviations: Dula = dulaglutide; HbA1c = hemoglobin A1c; LSM = least square mean; Max = maximum; Min = minimum; MMRM = mixed-effects model for repeated measures; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; REML = restricted maximum likelihood; vs = versus; UACR = urine albumin to creatinine ratio.

Source: Table APP 5.7- response to IR dated April 21, 2014

Based on maximum postbaseline UACR values, the proportions of patients with normal albuminuria, microalbuminuria, and macroalbuminuria were comparable between the dulaglutide 0.75 mg group, 1.5 mg group and all comparators (dulaglutide 0.75 mg: 74%, 22.3%, 3.7%; dulaglutide 1.5 mg: 72.2%, 23.1%, 4.7% ; comparator: 72.3%, 23.3%, 4.4% respectively). A comparable number of patients shifted from normal to macroalbuminuria or from micro- to macroalbuminuria. Numerically more patients on dulaglutide 1.5 mg shifted from microalbuminuria to normal compared to dulaglutide 0.75 mg or comparator (9% vs 7.4%, 6.8%) but shifts from macroalbuminura to normal were comparable (Table 61).

Table 61: Shift of Urine Albumin to Creatinine Ratio from Maximum Baseline to Maximum Postbaseline, All Observations During the Planned Treatment Period (AS7)

Lab Test (unit) = URINE ALBUMIN to CREATININE RATIO (milligram/gram)

		Maximum Postbaseline			
		< 30 mg/g	>= 30 to <= 300 mg/g	> 300 mg/g	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)
All Comparator (N=1759)	< 30 mg/g	1146 (65.2)	121 (6.9)	5 (0.3)	1272 (72.3)
	>= 30 to <= 300 mg/g	120 (6.8)	262 (14.9)	27 (1.5)	409 (23.3)
	> 300 mg/g	2 (0.1)	18 (1.0)	58 (3.3)	78 (4.4)
	Total	1268 (72.1)	401 (22.8)	90 (5.1)	1759 (100.0)
Dula_0.75 (N=1593)	< 30 mg/g	1054 (66.2)	119 (7.5)	6 (0.4)	1179 (74.0)
	>= 30 to <= 300 mg/g	118 (7.4)	217 (13.6)	20 (1.3)	355 (22.3)
	> 300 mg/g	1 (<0.1)	16 (1.0)	42 (2.6)	59 (3.7)
	Total	1173 (73.6)	352 (22.1)	68 (4.3)	1593 (100.0)
Dula_1.5 (N=1582)	< 30 mg/g	1034 (65.4)	102 (6.4)	6 (0.4)	1142 (72.2)
	>= 30 to <= 300 mg/g	142 (9.0)	206 (13.0)	18 (1.1)	366 (23.1)
	> 300 mg/g	2 (0.1)	26 (1.6)	46 (2.9)	74 (4.7)
	Total	1178 (74.5)	334 (21.1)	70 (4.4)	1582 (100.0)
All_Dula (N=3175)	< 30 mg/g	2088 (65.8)	221 (7.0)	12 (0.4)	2321 (73.1)
	>= 30 to <= 300 mg/g	260 (8.2)	423 (13.3)	38 (1.2)	721 (22.7)
	> 300 mg/g	3 (<0.1)	42 (1.3)	88 (2.8)	133 (4.2)
	Total	2351 (74.0)	686 (21.6)	138 (4.3)	3175 (100.0)

Abbreviations: mg/g = milligram per gram; N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in a specified category.

Source: Table 4,2, Applicants response dated June 24, 2014

Reviewer's assessment on renal function:

There was no apparent decline in renal function with dulaglutide 1.5 mg or dulaglutide 0.75 mg as measured by eGFR or UACR compared to placebo or to all comparator with in the clinical program. No dose-dependent effect was observed for eGFR. For albuminuria, there was a statistically significant greater decline in UACR in the dulaglutide 1.5 mg group compared to all comparator and dulaglutide 0.75 mg which was maintained at all time-points. This may be a result of better glycemic control, rather than a direct effect on urine albumin excretion.

Renal Adverse Events:

In addition to evaluating changes in renal laboratory tests, the incidence of treatment emergent adverse events was assessed. Events reported in the "Renal and urinary disorders" SOC and PTs from the "Acute renal failure and impairment" HLT were similar between dulaglutide and all comparators.

Table 62: All Dulaglutide versus All Comparator Analysis of Treatment-Emergent Adverse Events in Renal and Urinary Disorders System Organ Class, By Descending Frequency of Preferred Term within High-Level Term–(AS7)

System Organ Class / High Level Term / Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Renal and urinary disorders	94 (5.1)	71 (4.2)	90 (5.4)	161 (4.8)	0.94	.232	.817
Urinary abnormalities	32 (1.7)	25 (1.5)	26 (1.6)	51 (1.5)	0.88	.416	.650
Haematuria	13 (0.7)	8 (0.5)	7 (0.4)	15 (0.4)	0.64	.382	.268
Microalbuminuria	9 (0.5)	7 (0.4)	9 (0.5)	16 (0.5)	0.98	.049	.908
Proteinuria	2 (0.1)	5 (0.3)	7 (0.4)	12 (0.4)	3.32	.713	.073
Pyuria	2 (0.1)	4 (0.2)	0 (0.0)	4 (0.1)	1.10	.280	.992
Urine odour abnormal	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)			.222
Albuminuria	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			.036
Chromaturia	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55		.610
Leukocyturia	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.55	.156	.617
Glycosuria	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.368
Hypercalciuria	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.482
Crystalluria	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Ketonuria	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Renal lithiasis	13 (0.7)	14 (0.8)	17 (1.0)	31 (0.9)	1.32	.387	.470
Nephrolithiasis	13 (0.7)	14 (0.8)	17 (1.0)	31 (0.9)	1.32	.387	.470
Bladder and urethral symptoms	20 (1.1)	15 (0.9)	13 (0.8)	28 (0.8)	0.77	.813	.472
Dysuria	10 (0.5)	6 (0.4)	4 (0.2)	10 (0.3)	0.55	.281	.206
Pollakiuria	7 (0.4)	5 (0.3)	5 (0.3)	10 (0.3)	0.79	.302	.687
Urinary incontinence	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	1.10	.476	.789
Micturition urgency	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)			.320
Stress urinary incontinence	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)			.253
Urinary retention	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)			.253
Urinary hesitation	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.482
Bladder irritation	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Bladder spasm	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.149
Mixed incontinence	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Nephropathies and tubular disorders NEC	11 (0.6)	5 (0.3)	19 (1.1)	24 (0.7)	1.21	.389	.413
Diabetic nephropathy	8 (0.4)	4 (0.2)	16 (1.0)	20 (0.6)	1.38	.648	.295
Nephropathy	3 (0.2)	1 (<0.1)	2 (0.1)	3 (<0.1)	0.55	.074	.503
Nephropathy toxic	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.368
Renal neoplasms	4 (0.2)	8 (0.5)	6 (0.4)	14 (0.4)	1.94	.695	.231
Renal cyst	4 (0.2)	7 (0.4)	6 (0.4)	13 (0.4)	1.80	.616	.287
Renal cyst haemorrhage	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.482
Urinary tract signs and symptoms NEC	8 (0.4)	9 (0.5)	5 (0.3)	14 (0.4)	0.97	.499	.859
Renal colic	4 (0.2)	5 (0.3)	3 (0.2)	8 (0.2)	1.10	.571	.915
Nocturia	1 (<0.1)	3 (0.2)	1 (<0.1)	4 (0.1)	2.21	.666	.531
Polyuria	2 (0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.28	.218	.215
Renal pain	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.55	.211	.747
Urinary tract lithiasis (excl renal)	3 (0.2)	5 (0.3)	8 (0.5)	13 (0.4)	2.40	.629	.118
Calculus ureteric	3 (0.2)	4 (0.2)	3 (0.2)	7 (0.2)	1.29	.317	.605
Calculus bladder	0 (0.0)	0 (0.0)	3 (0.2)	3 (<0.1)			.224
Calculus urinary	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)			.147
Renal failure and impairment	8 (0.4)	4 (0.2)	7 (0.4)	11 (0.3)	0.76	.276	.557
Renal failure	3 (0.2)	2 (0.1)	2 (0.1)	4 (0.1)	0.74	.203	.726
Renal failure acute	2 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0.55	.258	.476
Renal impairment	0 (0.0)	0 (0.0)	3 (0.2)	3 (<0.1)			.179
Renal failure chronic	3 (0.2)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.18	.553	.103
Anuria	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Renal obstructive disorders	3 (0.2)	1 (<0.1)	3 (0.2)	4 (0.1)	0.74	.275	.795
Hydronephrosis	3 (0.2)	1 (<0.1)	3 (0.2)	4 (0.1)	0.74	.275	.795
Bladder disorders NEC	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)			.318
Bladder perforation	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.482
Bladder prolapse	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.478
Genital and urinary tract disorders NEC	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Urinary tract disorder	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Nephritis NEC	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.368
Nephritis	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.368
Renal vascular and ischaemic conditions	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Renal artery stenosis	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Ureteric disorders NEC	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.55	.154	.603
Ureteric dilatation	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.482
Ureteric stenosis	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.149
Bladder infections and inflammations	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267

System Organ Class High Level Term Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Cystitis noninfective	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Myoneurogenic bladder disorders	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.041
Hypertonic bladder	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.041
Renal disorders NEC	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.116
Renal disorder	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Renal mass	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Renal structural abnormalities and trauma	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.159
Kidney enlargement	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.159
Structural and obstructive urethral disorders (excl congenital)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.149
Urethral stenosis	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.149

Abbreviations: All_Comp = all comparators; CMH = Cochran-Mantel-Haenszel; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event; TEAE = treatment emergent adverse event

Source Table APP.5.3, response to IR dated April 24, 2014

In a narrow SMQ search conducted by the Applicant for ARF in all Phase 2 and 3 studies, dulaglutide-treated patients who reported ARF (SMQs [only narrow terms]) included 7 patients in dulaglutide 1.5 mg, 4 patients in dulaglutide 0.75 mg, and 1 patient in dulaglutide 0.5 mg.

In the AS7 dataset numerically more patients treated with dulaglutide 1.5 mg reported ARF SMQs (narrow terms of acute renal failure, renal impairment and renal failure) compared to patients treated with dulaglutide 0.75 mg (dulaglutide 1.5 mg: 6 patients [0.4%]; dulaglutide 0.75 mg: 3 patients [0.2%]). The number of events was similar to all comparators (5 patients [0.27%]; see Table 62).

Narrative Review of Subjects Dulaglutide treated subjects with PT of Acute Renal Failure:

These narratives were provided by the Applicant in tabular format in the ISS. Under SAE narratives there was only one report of acute renal failure for a placebo treated patient (GBDN-008-0458). These narratives were reviewed to determine if there were any cases where I would disagree with the Applicant's opinion that could change the comparison.

GBCF-014-0759, 58 yr. F, Dulaglutide 1.5 mg: 58 yr. old female with 20 yr. duration of Type 2 DM. AE of toxic nephropathy was reported 15 months after starting treatment). Concomitant medications included cetirizine, ezetimibe, glipizide, guaifenesin, multivitamin, olmesartan, omega-3 marine triglycerides, thyroid, hydrochlorothiazide, choline and azithromycin. Minimum eGFR was 31 ml/min/1.73 m^2 at month 15 and 54 ml/min/1.73 m^2 at month 18. This patient completed the study.

Reviewer Comment: The assessment for association to dulaglutide is confounded by multiple other medications.

GBCF-017-0904, 40 yr. M, Dulaglutide 0.5 mg: The AE of renal failure was reported (at randomization). The patient discontinued study drug and from the study 3 months later

due to sponsor decision (i.e. the patient's dose was not selected for further study in the phase 3 program). Minimum eGFR was 76 ml/min/1.73 m^2.

GBCF-021-1117, 64 yr F, Dulaglutide 1.5 mg: The AE of renal impairment was reported at randomization (creatinine clearance of 61ml/min at screening, 53ml/min at randomization). The patient stopped study drug (after approximately 55 week's exposure) due to renal impairment (decreased renal function, creatinine clearance-52 ml/min). Other associated AEs included dyspepsia, abdominal discomfort, vomiting, and diarrhea. At the last visit (Visit 12, month 15), creatinine clearance value was 55 mL/min.

Reviewer Comment: This AE was reported at randomization and last creatinine clearance was 55 ml/min.

GBCF-401-5012, 65 yr. M, Dulaglutide 0.75 mg: The patient had an SAE of pulmonary embolism 86 days after starting treatment); in association with this SAE, the patient had an AE of renal failure and elevated SCr (1.32 mg/dl) recorded on Visit 8. The patient reported additional SAEs of pulmonary embolism, urinary retention, prostatic adenoma, and urinary tract infection at visit 9 and urinary retention and hematuria at Visit 10

Reviewer Comment: This AE was associated with urinary retention and UTI.

GBCF-706-6955, 60 yr F, Dula 1.5 mg- The patient reported proteinuria at randomization. Treatment was stopped on Day 197 due to serious AE of lower gastrointestinal hemorrhage and associated AE of renal failure

Reviewer Comment: AE associated with lower GI bleed.

GBDA-038-1850, 64 yr. M, Dula 0.75 mg: The patient reported an AE of renal failure 379 days after starting treatment and 20 days after stopping treatment, Only S. Creatinine is available- 1.83 mg/dl at week 52 and 1.5 mg/dl at LV30

GBDC-103-0311, 70 yr F, Dula 0.75 mg: 231 days after starting treatment, the patient reported an SAE of dysphagia with AEs of acute renal failure and dehydration and discontinued treatment. Reported eGFR was 56ml/min/1.73 m^2. As part of work-up an esophageal manometry was performed, which was suggestive of achalasia.

Reviewer Comment: ARF secondary to GI side effects of dulaglutide is possible.

GBDC-406-6139, 72 yr. F, Dulaglutide 1.5 mg: An AE of renal failure was reported 198 days after starting treatment and treatment discontinued at 28 weeks. eGFR ranged from 53-59 ml/min/1.73 m^2.

Reviewer Comment: eGFR did not change significantly.

GBDD- 002-0153, 68 yr. F, Dulaglutide 1.5 mg: 68 yr. old F had AE of renal impairment reported 30 days after completing study treatment. At the 30-day safety follow up visit (LV30), AEs of renal impairment, myalgia, and urinary tract infection were reported .Kidney function laboratory values included SCr (1.26 mg/dL) and eGFR (51 mL/min/1.73 m^2, 44 ml/min/1.73m^2 at baseline) and abnormal urinary microscopic exam.

Reviewer Comment: No change in eGFR.

GBDD-012-0661, 60 yr. F, Dulaglutide 0.75 mg- Adverse events of polyuria and anuria, and peripheral edema were reported 244 days after starting treatment. Treatment was stopped 3 months later. eGFR or Serum Creatinine is not reported

GBDD- 107-3225, 58 yr. M, Dulaglutide1.5 mg: Renal impairment was reported 8 and16 days after starting treatment and treatment was discontinued. eGFR was 33 and 27 ml/min/1.73 m^2 respectively at screening and randomization.

Reviewer Comment: eGFR *low at randomization.*

GBDD-554-6150, 67 yr. F, Dulaglutide 1.5 mg- Three months after starting study treatment, the patient was hospitalized because of sepsis due to erysipelas; acute renal failure was reported in association with this event and was confirmed to be due to the sepsis. Study treatment was discontinued. eGFR was 59 ml/min/m^2 at baseline and was 46 ml/min/m^2 at week 26.

Reviewer Comment: AE associated with sepsis.

Reviewer's assessment for acute renal failure AE's:
Numerically more patients on dulaglutide 1.5 mg had ARF reported, but the numbers were similar to all comparators in the AS7 dataset. Several of the cases reported had low eGFR or Creatinine clearance at baseline, and there was no significant change. Some of the cases were associated with other acute events like sepsis, UTI, GI bleed, and were confounded by concomitant medications.

No SAEs of acute renal failure or renal impairment were reported with dulaglutide. There was one SAE of "acute nephritis" with dulaglutide 1.5 mg. Information is incomplete in some of these reports, but none of the patients are reported to have required dialysis or organ transplantation. The narratives for SAEs and discontinuation due to AEs (TOSNPs, eCTD 5.3.5.3) were also searched to confirm absence of these reports.

To further evaluate the renal safety of dulaglutide, the sub-population of patients with a baseline eGFR < 60 ml/min/1.73 m^2 was separately evaluated. As patients that already have renal impairment are felt to be at greater risk for further deterioration of renal

Reference ID: 3609106

function secondary to volume depletion from GI adverse events, there may be a greater impact in these patients. As shown in Table 52 and Table 53, around 425 subjects in the entire phase 2/3 program and 270 dulaglutide treated subjects had an eGFR < 60 ml/min/1.73m^2 and/or macroalbuminuria. Table 63 below shows data from placebo controlled studies. Given the small sample size, limited conclusions can be drawn from this data.

Maximum baseline and postbaseline serum creatinine values were comparable between placebo and the dulaglutide groups (Table 63). Baseline minimum and postbaseline minimum eGFR were also comparable when comparing placebo and dulaglutide groups in this sub-population. Similar values were also seen on comparing dulaglutide 1.5 and 0.75 mg in the AS3 dataset (9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.6.144).

Table 63: Change from Baseline Analysis of Renal Markers (Creatinine: Max-to-Max; eGFR: Min-to-Min), Observations Through 26 Weeks of the Planned Treatment Period - Placebo Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide in patients with eGFR < 60 ml/min/1.73m^2 and/or macroalbuminuria

Value	Placebo N=40	Dula 0.75 N=52	Dula 1.5 N=47	All Dula N=99
Mean Creatinine (mg/dl)				
Baseline Maximum	1.15	1.17	1.14	1.16
Postbaseline Maximum	1.18	1.21	1.16	1.19
Change Max-to-Max	0.03	0.02	0.02	0.03
Estimated Glomerular Filtration Rate -- CKD-EPI (mL/min/1.73 m^2)				
Baseline Minimum	62.31	61.84	63.86	62.80
Postbaseline Minimum	61.14	61.23	62.68	61.93
Change Min-to-Min	-0.70	-0.85	-1.18	-1.01

Source: Table ISS.6.140-page 580

Based on the change from maximum baseline UACR value to maximum postbaseline UACR value, no significant change in albuminuria was observed in the all dulaglutide group compared to placebo in both renal subpopulation 1 (eGFR <60 mL/min/1.73 m^2 at baseline) and renal subpopulation 2 (UACR>300mg/g). However in the renal impairment subpopulation with either condition (renal subpopulation 3), a small decrease in albuminuria was observed in both dulaglutide groups compared to placebo (Table 64) and numerically more patients shifted from macroalbuminuria to microalbuminura with both doses (placebo-1 [2.6%]; dulaglutide 0.75 mg-7 [14%]; dulaglutide 1.5 mg-6 [13.3%]). (9.6 Supportive Tables From the ISS Referenced in the Review- Table ISS.6.142).

Table 64: Maximum to Maximum Change Analysis of Renal Markers, Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide Renal Subpopulations 1, 2, and 3, Studies GBCF, GBDA, GBDN)

Urine Albumin/Creatinine (UACR) (mg/g)					
	Placebo	Dula_0.75	Dula_1.5	All_Dula	
Value	Median	Median	Median	Median	p-value*
Renal Subpopulation 1	(N=26)	(N=34)	(N=29)	(N=63)	
Baseline Maximum	6.64	15.05	15.93	15.05	
Postbaseline Maximum	12.83	12.83	9.74	10.62	
Change Max-to-Max	-1.99	-5.31	-3.54	-4.43	0.18
Renal Subpopulation 2	(N=16)	(N=20)	(N=21)	(N=41)	
Baseline Maximum	715.08	608.88	769.07	656.67	
Postbaseline Maximum	763.76	365.06	500.03	367.28	
Change Max-to-Max	-117.71	-198.24	-213.29	-213.29	0.67
Renal Impairment (Renal Subpopulation 3)	(N=40)	(N=52)	(N=47)	(N=99)	
Baseline Maximum	46.02	79.65	90.27	90.27	
Postbaseline Maximum	30.53	59.74	53.99	59.30	
Change Max-to-Max	-1.99	-23.01	-15.05	-19.47	0.03

Abbreviations: Dula = dulaglutide; max = maximum; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; UACR = urinary albumin-to-creatinine ratio.

Source: Table ISS .6.141-page 583

Overall the AEs in this sub-population seem consistent with AEs in all patients in the Applicant's analyses. Given the small sample size and limited number of events in each SOC available no definitive conclusions can be made about all drug-disease interactions in the renal impairment sub-population.

Given the concern about post-marketing reports of acute renal failure with the drug class secondary to nausea, vomiting and dehydration, this HLT under the GI SOC were analyzed using MAED (MedDRA Adverse Event Diagnostic Service) software (Table 65).

Table 65: Gastrointestinal HLTs in Renal Subpopulation-3 (macroalbuminuria or eGFR< 60ml/min/m^2)

	Group 1 (N = 121)			Group 2 (N = 152)			Group 0 (N = 154)			Group1 Vs.Group 0	Group2 Vs.Group 0
HLT	Ev	Su	P (%)	Ev	Su	P (%)	Ev	Su	P (%)	RD (CI)	RD (CI)
Nausea and vomiting symptoms	76	21	**17.4**	126	39	**25.7**	47	18	**11.7**	5.67 (-2.78_ +14.11)	13.97 (5.37_22.57)

Ev=number of events, Su=number of subjects, P=proportion (%), Group 0= all comparators, Group 1=dulaglutide ≤0.75 mg, Group 2= Dulaglutide> 0.75 mg, RD=risk difference
Source: Reviewer generated using MAED

Reviewer's Assessment for gastrointestinal AEs in renal sub-population:

Dose dependency of nausea/vomiting (discussed under common adverse events-section 7.4.1 and section 7.5.1) seems to also occur in the renal sub-population. Given the increased risk for acute renal failure secondary to AEs in this sub-population, it may be prudent to initiate therapy with the 0.75 mg dose in this sub-population and titrate based on tolerability and need for additional glycemic control.

To further evaluate the use of dulaglutide in patients with renal impairment, the Applicant is conducting a Phase 3 study (H9X-MC-GBDX [GBDX]). Study GBDX is currently ongoing and is designed to assess the effects of dulaglutide treatment over 52 weeks in patients with T2DM and moderate or severe chronic kidney disease (CKD). The following information is being collected in this study for Renal event adjudication (Table 66):

Table 66: Renal Events and Information Collected for Adjudication in Study GBDX

	Imaging Study Reports (e.g., CT, MRI)
Renal Events (Protocol H9X-MC-GBDX only)	Renal Event CRF Laboratory results (blood and urinalysis) Microscopic examination of urine sediment Urinary indices (Urine sodium, creatinine, FeNa, FeUrea, urine osm etc.) Imaging: Ultrasound, CT scan, renal angiography, etc. Renal biopsy report Nephrology consultation notes Discharge Summary

Source: Table-1, (b) (4) CEC charter, CV Metaanalyses report- page 247

The effect of dulaglutide on renal function in patients with CKD stage 3 or worse can be better assessed when the dedicated renal study (GBDX) in patients with moderate and severe renal impairment is complete.

Reviewer's Assessments about Renal Safety:

There does not appear to be an effect of dulaglutide on renal function. There was no apparent decline in renal function as assessed by eGFR, or by UACR. There was also no apparent increased risk for development of acute renal failure. The assessment is limited by the small number of patients with renal impairment at baseline, but this can be better assessed in the CV outcome study (study GBCJ, where more patients with moderate renal impairment are enrolled) and in study GBDX (a dedicated study in patients with moderate/severe renal impairment). Given concerns for an increased risk of acute renal failure secondary to AEs in patients already with renal impairment, it may be prudent to initiate therapy with the 0.75 mg dose and titrate based on tolerability and need for additional glycemic control.

- 7.3.2.8 Hypoglycemia

With any antidiabetic agent, hypoglycemia is a concern. GLP-1 agonists are no exception, and severe hypoglycemia can occur when GLP-1 agonists are used with an insulin secretagogue (e.g. a sulfonylurea) or insulin. Lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia is advised in the warning and precautions section of the approved GLP-1 agonist PI's.

To analyze hypoglycemic risk, the Applicant used two plasma glucose cutoffs. The principal set of analyses is based on the 70 mg/dL (3.9 mmol/L) cutoff, as recommended by the American Diabetes Association (ADA)[17] and adopted by the FDA and the EMA. A second set of analyses is based on a < 54 mg/dL (3 mmol/L) cutoff. The Applicant indicates this cut-off was used as it is a prevailing criterion for reporting hypoglycemia in the literature. Only the 70 mg/dL cut-off analyses set was reviewed since it is consistent with the ADA guidelines.

During Phase 3 development, episodes of hypoglycemia were collected on a hypoglycemia-specific CRF. Cases of severe hypoglycemia were required to be reported as SAEs. Severe hypoglycemia was defined as a hypoglycemic event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, as judged by investigators. Though confirmatory plasma glucose measurements may not have been available during such an event, neurologic recovery attributable to the restoration of normal glucose levels was considered sufficient evidence that the event was induced by low plasma glucose.

Per the 2013 ADA Consensus Statement, non-serious events were classified based on symptoms suggestive of hypoglycemia and availability of diagnostic plasma glucose values.

In the main analyses presented by the Applicant, hypoglycemia data were censored at the time patients initiated an alternative antihyperglycemic medication (i.e. rescue therapy), and thus excluded events reported during the period when rescue therapy was used. This is a standard approach to prevent confounding by the use of rescue medication and seems acceptable.

Categories of hypoglycemia:

The categories of hypoglycemia that the Applicant defined are listed in the table below. I focused on documented symptomatic hypoglycemia and severe hypoglycemia. Nocturnal hypoglycemia rates were also reviewed. Since the rates of nocturnal hypoglycemia mirrored the trends for documented symptomatic hypoglycemia, these data are not presented in the review.

17 Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care, Online, April 15, 2013

Table 67: Categories of Hypoglycemia in Integrated Analyses of Phase 2 and 3 Studies by Required Criteria

	Criteria Required			
Category of Hypoglycemia[a]	Glucose Value?[b]	Symptoms Present?	Time of Day?	Required Assistance?
Total[c]	Summary category of all events reported			
Documented symptomatic	Known and below threshold	Yes	Any	No, if not severe
Asymptomatic	Known and below threshold	No	Any	No
Severe[d]	Known and below threshold, or missing	Yes	Any	Yes
Probable symptomatic	Unknown or missing	Yes	Any	No, if not severe
Nocturnal	Known and below threshold, unknown, or missing	Yes	Between bedtime and waking	No, if not severe
Non-nocturnal	Known and below threshold, unknown, or missing	Yes	Between waking and bedtime	No, if not severe

[a] Patients may have had events that were counted in more than one category.
[b] For categories of hypoglycemia requiring blood glucose measurements, separate reports were produced using ≤70 mg/dL (3.9 mmol/L) and <54 mg/dL (3 mmol/L) as cutoff values.
[c] This category represents overall hypoglycemia and includes any event meeting the definition of symptomatic documented, asymptomatic, probable, or severe hypoglycemia.
[d] Severe hypoglycemia has two clinical presentations 1) symptoms of severe hypoglycemia with confirmatory glucose value, or 2) symptoms of severe hypoglycemia with recovery upon the institution of therapy but without confirmatory glucose. The diagnosis is reported based on the investigator's opinion, which could supercede the other criteria described.

Source: Table ISS.6.55 page 362

The Applicant presented the data by background therapies in comparison to placebo and active comparators. This is acceptable.

To assess the hypoglycemic risk of dulaglutide compared to placebo, hypoglycemic episodes reported in Studies GBCF and GBDA for patients receiving placebo, dulaglutide 0.75 mg, or 1.5 mg (separately and combined) through 26 weeks of planned treatment, which was the duration of the placebo controlled period, were analyzed. Study GBCF included metformin as concomitant (background) OAM, while Study GBDA included metformin plus TZD in combination as concomitant (background) OAMs. The table below (Table 68) presents the incidence and estimated rates per 30 days and per year based on plasma glucose ≤70 mg/dL, excluding episodes that occurred post-rescue.

Table 68 : Summary of Hypoglycemia Episode Incidence, Estimated Rates, and Odds Ratios By Treatment - Placebo Comparison, Observations Through 26 Weeks of the Planned Treatment Period (GBDA, GBCF)

Study (Background) / Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBCF (MET)								
Total Hypo (PG <=70 mg/dL)								
Placebo	177	2	(1.1)	7	0.01	0.08		
Dula_0.75	302	12	(4.0)	27	0.01	0.18	Dula_0.75 vs Pla	3.62
Dula_1.5	304	24	(7.9)	59	0.03	0.39	Dula_1.5 vs Pla	7.50
All_Dula	606	36	(5.9)	86	0.02	0.28	All_Dula vs Pla	5.53
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Placebo	177	2	(1.1)	7	0.01	0.08		
Dula_0.75	302	8	(2.6)	19	0.01	0.13	Dula_0.75 vs Pla	2.38
Dula_1.5	304	17	(5.6)	40	0.02	0.26	Dula_1.5 vs Pla	5.18
All_Dula	606	25	(4.1)	59	0.02	0.19	All_Dula vs Pla	3.77
Asymptomatic Hypo (PG <=70 mg/dL)								
Placebo	177	0	(0.0)	0	0.00	0.00		
Dula_0.75	302	5	(1.7)	8	0.00	0.05	Dula_0.75 vs Pla	
Dula_1.5	304	5	(1.6)	12	0.01	0.08	Dula_1.5 vs Pla	
All_Dula	606	10	(1.7)	20	0.01	0.07	All_Dula vs Pla	
Severe Hypo								
Placebo	177	0	(0.0)	0	0.00	0.00		
Dula_0.75	302	0	(0.0)	0	0.00	0.00	Dula_0.75 vs Pla	
Dula_1.5	304	0	(0.0)	0	0.00	0.00	Dula_1.5 vs Pla	
All_Dula	606	0	(0.0)	0	0.00	0.00	All_Dula vs Pla	

Study (Background) / Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBDA (MET+TZD)								
Total Hypo (PG <=70 mg/dL)								
Placebo	141	5	(3.5)	12	0.03	0.35		
Dula_0.75	280	30	(10.7)	136	0.09	1.09	Dula_0.75 vs Pla	3.26
Dula_1.5	279	29	(10.4)	62	0.04	0.44	Dula_1.5 vs Pla	3.16
All_Dula	559	59	(10.6)	198	0.06	0.77	All_Dula vs Pla	3.21
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Placebo	141	2	(1.4)	4	0.00	0.06		
Dula_0.75	280	13	(4.6)	25	0.01	0.18	Dula_0.75 vs Pla	3.38
Dula_1.5	279	14	(5.0)	31	0.02	0.22	Dula_1.5 vs Pla	3.67
All_Dula	559	27	(4.8)	56	0.02	0.20	All_Dula vs Pla	3.53
Asymptomatic Hypo (PG <=70 mg/dL)								
Placebo	141	3	(2.1)	5	0.02	0.26		
Dula_0.75	280	16	(5.7)	95	0.06	0.68	Dula_0.75 vs Pla	2.79
Dula_1.5	279	16	(5.7)	26	0.02	0.19	Dula_1.5 vs Pla	2.80
All_Dula	559	32	(5.7)	121	0.04	0.43	All_Dula vs Pla	2.79
Severe Hypo								
Placebo	141	0	(0.0)	0	0.00	0.00		
Dula_0.75	280	0	(0.0)	0	0.00	0.00	Dula_0.75 vs Pla	
Dula_1.5	279	0	(0.0)	0	0.00	0.00	Dula_1.5 vs Pla	
All_Dula	559	0	(0.0)	0	0.00	0.00	All_Dula vs Pla	

Source: Table ISS 6.56, page 365

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Compared to placebo, patients treated with dulaglutide had an increased rate of documented symptomatic hypoglycemia. There was a trend for dose dependency in Study GBCF, as more events of symptomatic hypoglycemia were seen with dulaglutide 1.5 mg. This was not observed in study GBDA. There were no severe hypoglycemia events, thus no comparison between dulaglutide and placebo can be made for severe hypoglycemia.

As part of the development program, dulaglutide was compared to active comparators. Active comparators studied included metformin, sitagliptin, exenatide, and insulin glargine.

The incidences of total, symptomatic and severe hypoglycemia are shown in Table 69 below. Data that included post-rescue visits were also reviewed and the trends were

similar (See Appendix 9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.APP 298 and ISS.APP.299).

Reviewer's Comment: It is to be noted that unlike clinical programs for some of the approved products in the GLP-1 agonist class, the add-on to insulin lispro and SU studies have insulin glargine as an active comparator and not placebo. This has to be considered before making any cross-trial comparisons for hypoglycemic rates, since the rate of hypoglycemia in the comparator arms may be increased, thus minimizing the apparent hypoglycemia risk with dulaglutide.

Table 69: Summary of Hypoglycemia Episode Incidence, Estimated Rates, and Odds Ratios by Treatment,– Active Comparison by Study, All Observations During the Planned Treatment Period (Studies GBCF, GBDA, GBDB, GDBC, GBDD)

Study (Background) / Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBDC (Monotherapy)								
Total Hypo (PG <=70 mg/dL)								
Metformin	268	34	(12.7)	69	0.02	0.28	0.75 vs Met	0.86
Dula_0.75	270	30	(11.1)	103	0.04	0.47	1.5 vs 0.75	1.12
Dula_1.5	269	33	(12.3)	95	0.07	0.89	1.5 vs Met	0.96
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Metformin	268	13	(4.9)	22	0.01	0.09	0.75 vs Met	1.24
Dula_0.75	270	16	(5.9)	34	0.01	0.15	1.5 vs 0.75	1.07
Dula_1.5	269	17	(6.3)	23	0.05	0.62	1.5 vs Met	1.32
Asymptomatic Hypo (PG <=70 mg/dL)								
Metformin	268	21	(7.8)	44	0.01	0.18	0.75 vs Met	0.99
Dula_0.75	270	21	(7.8)	64	0.02	0.30	1.5 vs 0.75	1.00
Dula_1.5	269	21	(7.8)	64	0.02	0.24	1.5 vs Met	1.00
Severe Hypo								
Metformin	268	0	(0.0)	0	0.00	0.00	0.75 vs Met	
Dula_0.75	270	0	(0.0)	0	0.00	0.00	1.5 vs 0.75	
Dula_1.5	269	0	(0.0)	0	0.00	0.00	1.5 vs Met	

Study (Background) / Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBCF (MET)								
Total Hypo (PG <=70 mg/dL)								
Sitagliptin	315	27	(8.6)	105	0.02	0.20	0.75 vs Sita	1.00
Dula_0.75	302	26	(8.6)	125	0.02	0.21	1.5 vs 0.75	1.56
Dula_1.5	304	39	(12.8)	125	0.02	0.26	1.5 vs Sita	1.57
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Sitagliptin	315	18	(5.7)	91	0.01	0.17	0.75 vs Sita	1.11
Dula_0.75	302	19	(6.3)	110	0.02	0.18	1.5 vs 0.75	1.81
Dula_1.5	304	33	(10.9)	87	0.02	0.19	1.5 vs Sita	2.01
Asymptomatic Hypo (PG <=70 mg/dL)								
Sitagliptin	315	3	(1.0)	8	0.00	0.01	0.75 vs Sita	3.19
Dula_0.75	302	9	(3.0)	13	0.00	0.02	1.5 vs 0.75	0.99
Dula_1.5	304	9	(3.0)	29	0.00	0.06	1.5 vs Sita	3.17
Severe Hypo								
Sitagliptin	315	0	(0.0)	0	0.00	0.00	0.75 vs Sita	
Dula_0.75	302	0	(0.0)	0	0.00	0.00	1.5 vs 0.75	
Dula_1.5	304	0	(0.0)	0	0.00	0.00	1.5 vs Sita	

GBDA (MET+TZD)								
Total Hypo (PG <=70 mg/dL)								
Exenatide	276	51	(18.5)	307	0.09	1.13	0.75 vs Exen	0.80
Dula_0.75	280	43	(15.4)	218	0.07	0.90	1.5 vs 0.75	0.79
Dula_1.5	279	35	(12.5)	110	0.03	0.40	1.5 vs Exen	0.63
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Exenatide	276	37	(13.4)	205	0.06	0.75	0.75 vs Exen	0.42
Dula_0.75	280	17	(6.1)	39	0.01	0.14	1.5 vs 0.75	1.07
Dula_1.5	279	18	(6.5)	53	0.02	0.19	1.5 vs Exen	0.45
Asymptomatic Hypo (PG <=70 mg/dL)								
Exenatide	276	28	(10.1)	98	0.03	0.36	0.75 vs Exen	0.87
Dula_0.75	280	25	(8.9)	157	0.05	0.56	1.5 vs 0.75	0.79
Dula_1.5	279	20	(7.2)	49	0.01	0.18	1.5 vs Exen	0.68
Severe Hypo								
Exenatide	276	2	(0.7)	2	0.00	0.01	0.75 vs Exen	0.00
Dula_0.75	280	0	(0.0)	0	0.00	0.00	1.5 vs 0.75	
Dula_1.5	279	0	(0.0)	0	0.00	0.00	1.5 vs Exen	0.00
GBDB (MET+SU)								
Total Hypo (PG <=70 mg/dL)								
Glargine	262	187	(71.4)	2424	0.57	6.90	0.75 vs Glar	0.52
Dula_0.75	272	154	(56.6)	1479	0.34	4.18	1.5 vs 0.75	1.08
Dula_1.5	273	160	(58.6)	1524	0.35	4.27	1.5 vs Glar	0.57
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Glargine	262	134	(51.1)	1034	0.25	3.02	0.75 vs Glar	0.61
Dula_0.75	272	106	(39.0)	515	0.14	1.67	1.5 vs 0.75	1.06
Dula_1.5	273	110	(40.3)	609	0.14	1.67	1.5 vs Glar	0.64
Asymptomatic Hypo (PG <=70 mg/dL)								
Glargine	262	142	(54.2)	1358	0.31	3.80	0.75 vs Glar	0.65
Dula_0.75	272	118	(43.4)	911	0.20	2.38	1.5 vs 0.75	1.04
Dula_1.5	273	121	(44.3)	884	0.21	2.51	1.5 vs Glar	0.67
Severe Hypo								
Glargine	262	2	(0.8)	2	0.00	0.01	0.75 vs Glar	0.00
Dula_0.75	272	0	(0.0)	0	0.00	0.00	1.5 vs 0.75	
Dula_1.5	273	2	(0.7)	2	0.00	0.01	1.5 vs Glar	0.96
GBDD (Lispro +/- MET)								
Total Hypo (PG <=70 mg/dL)								
Glargine	296	266	(89.9)	15543	4.70	57.17	0.75 vs Glar	1.03
Dula_0.75	293	264	(90.1)	12738	3.97	48.38	1.5 vs 0.75	0.68
Dula_1.5	295	254	(86.1)	11293	3.43	41.74	1.5 vs Glar	0.70
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Glargine	296	247	(83.4)	11106	3.36	40.95	0.75 vs Glar	1.15
Dula_0.75	293	250	(85.3)	9423	2.93	35.66	1.5 vs 0.75	0.69
Dula_1.5	295	236	(80.0)	8466	2.55	31.06	1.5 vs Glar	0.79
Asymptomatic Hypo (PG <=70 mg/dL)								
Glargine	296	208	(70.3)	3998	1.18	14.39	0.75 vs Glar	0.88
Dula_0.75	293	198	(67.6)	3082	0.98	11.88	1.5 vs 0.75	0.89
Dula_1.5	295	192	(65.1)	2572	0.80	9.71	1.5 vs Glar	0.79
Severe Hypo								
Glargine	296	15	(5.1)	22	0.01	0.09	0.75 vs Glar	0.46
Dula_0.75	293	7	(2.4)	15	0.00	0.05	1.5 vs 0.75	1.43
Dula_1.5	295	10	(3.4)	11	0.00	0.06	1.5 vs Glar	0.66

Abbreviations: d = days; Dula = dulaglutide; Exen = Exenatide; Glar = glargine; Hypo = hypoglycemia; Met = metformin; mg/dL = milligrams per deciliter; N = total number of patients in specified treatment group; n = number of patients with at least one hypoglycemia episode; PG = plasma glucose; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione; vs = versus.

Source: Table ISS.6.57, page 368

In the monotherapy study (study GBDC), there were numerically more patients with documented symptomatic hypoglycemic events with dulaglutide than with metformin (metformin 13 [4.9%], dula 0.75mg- 16 [5.9%], dula 1.5 mg- 17 [6.3%]). No severe hypoglycemic events occurred.

In the add-on to metformin study (study GBCF), there were numerically more patients with documented symptomatic hypoglycemic episodes with dulaglutide 1.5 mg compared to sitagliptin (sitagliptin 18 [5.7%], dula 1.5 mg 33 [10.9%]). No substantial difference was seen between dulaglutide 0.75 mg (n=19, 6.3%) and sitagliptin. No severe hypoglycemic events occurred.

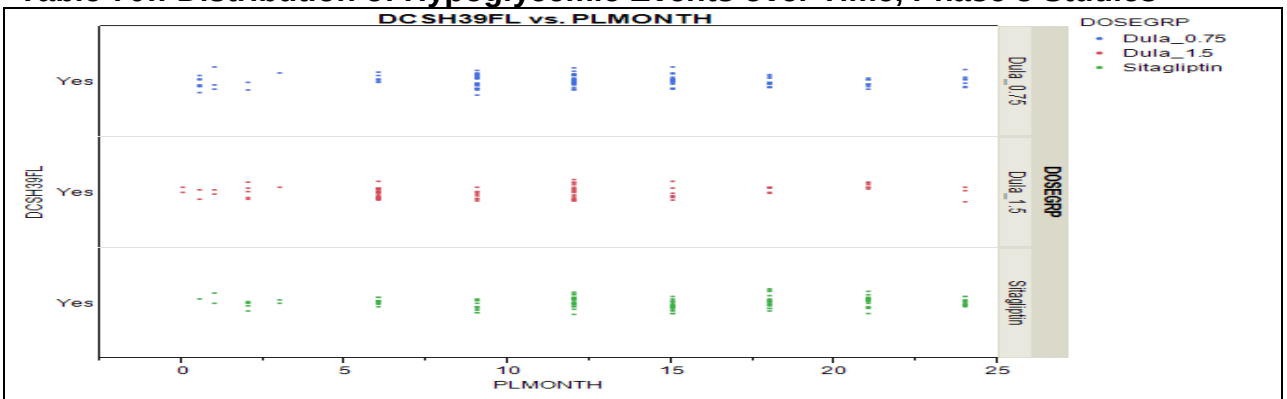
In the add-on to metformin and TZD study (study GBDA), there were more documented symptomatic hypoglycemic episodes in patients treated with exenatide compared to dulaglutide (exenatide 37 [13.4%], dulaglutide 0.75 mg-17 [6.1%], dulaglutide 1.5 mg - 18 [6.5%]). Two patients reported severe hypoglycemic events with exenatide, none with dulaglutide.

In the add-on to metformin and SU study (study GBDB), there were more documented symptomatic hypoglycemic events with insulin glargine than with dulaglutide (glargine 134 [5.1%], dula 0.75 mg-106 [3.9%], dula1.5 mg – 110 [4.0%]. Two episodes of severe hypoglycemia occurred during the study, one each with insulin glargine and dulaglutide 1.5 mg.

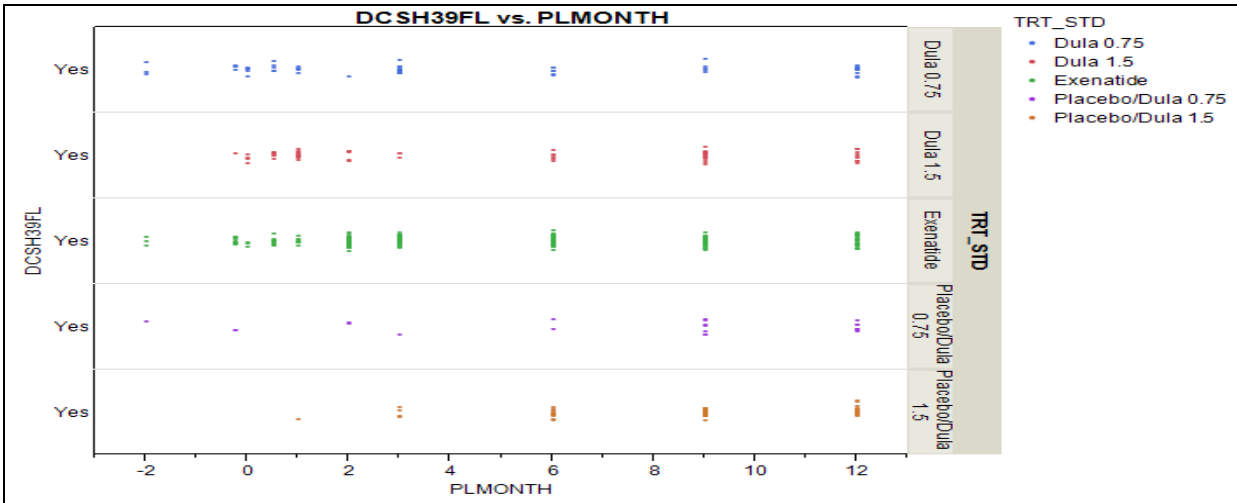
In the add-on to insulin lispro with or without metformin study (study GBDD) documented symptomatic hypoglycemia occurred in similar numbers (>80%) of patients in all three groups (insulin glargine: 247 [83.4%], dula 0.75: 250 [85.3%], dula 1.5: 236 [80.0%]). Severe hypoglycemic episodes occurred more frequently in the insulin glargine treated patients than in the dulaglutide treated patients (insulin glargine-15 [5.1%], dula 0.75 mg- 7 [2.4%], dula 1.5 mg 10 [3.4%]).

The graphs (Table 70) shown below illustrate that for all studies (including GBDD), hypoglycemic events were reported over the course of the studies and not just in the early phase alone. This includes severe hypoglycemic events, the majority of which occurred in study GBDD.

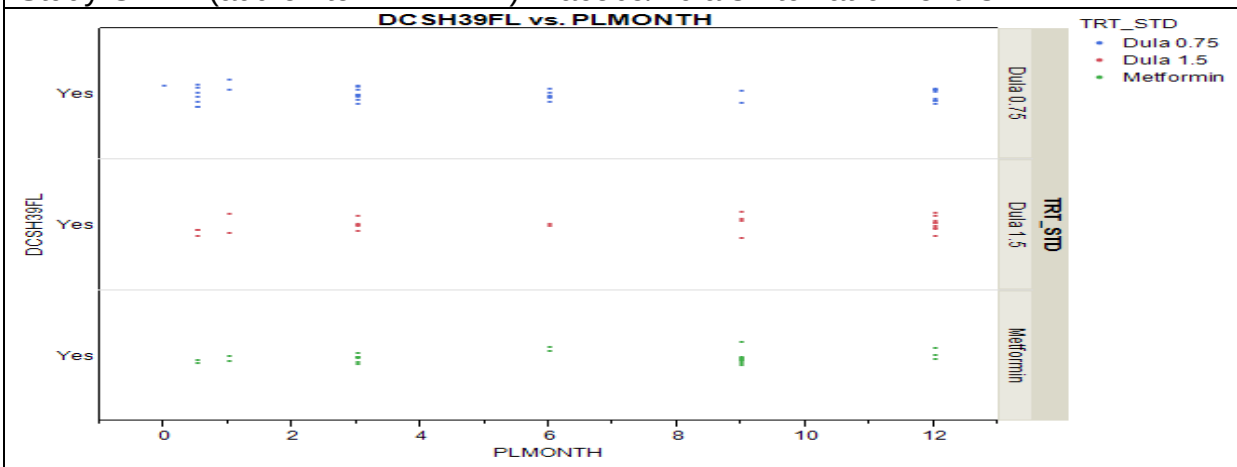
Table 70:: Distribution of Hypoglycemic Events over Time, Phase 3 Studies



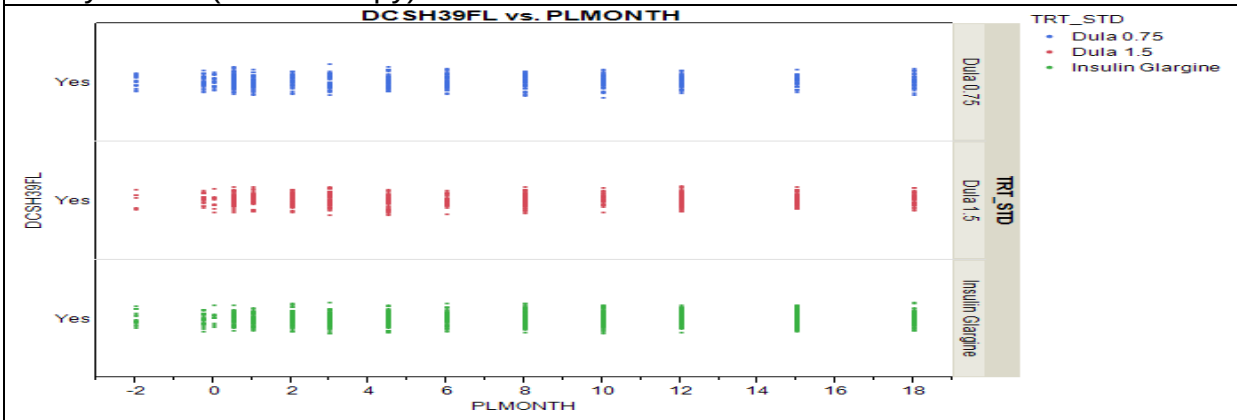
Study GBCF(add on to MET,sitagliptin 0-6 months included placebo)



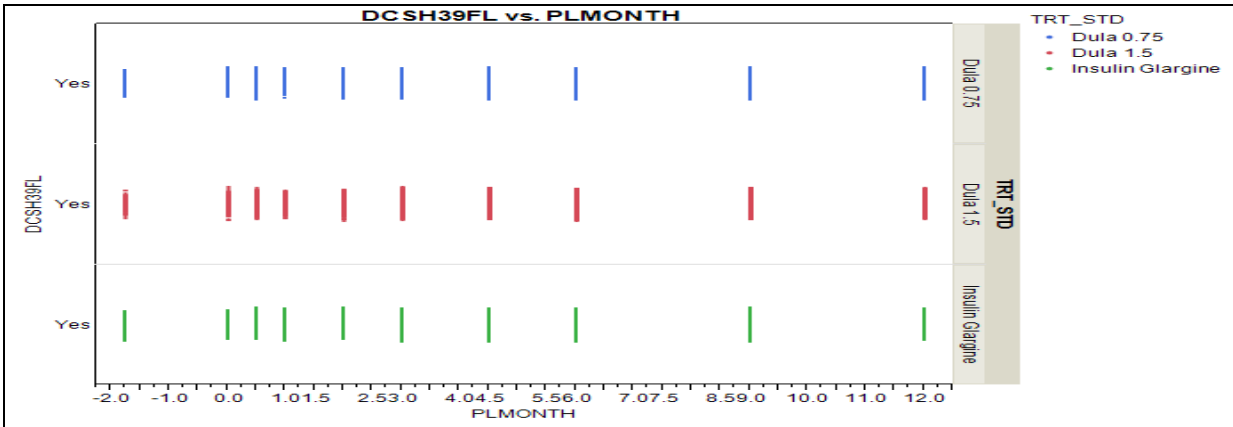
Study GBDA (add on to MET+TZD)-Placebo/Dula switch at 6 months



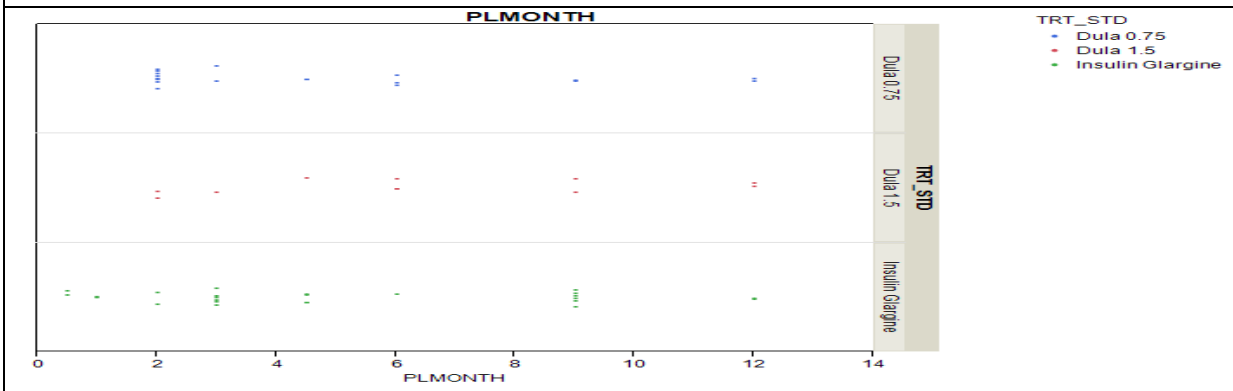
Study GBDC (Monotherapy)



Study GBDB (add on to MET+SU)



Study GBDD (add on to insulin lispro± MET)



Severe Hypoglycemia in study GBDD

DSHL39FL = documented symptomatic hypoglycemia with blood glucose less than 3.9 mmol/L, PLMONTH = planned number of months.
Source: Reviewer generated using JMP software using the provided hypo xpt dataset

Severe Hypoglycemia:

The Applicant reports that 62 events of severe hypoglycemia were reported for 41 patients in the Phase 2 and 3 program (Table 71), as determined by the investigator and captured on the "Hypoglycemic event" CRF. Of these, eight events occurred after initiation of rescue therapy. These were excluded from analysis, due to the confounding effect of rescue therapy.

Table 71: Listing of Severe Hypoglycemic Events

USUBJID	Treatment	Glucose (mg/dL)	IV glucose or glucagon	Days on therapy	LOC
GBDA-051-0000002528	Exenatide	39	IV glucose	355	
GBDA-071-0000003500	Exenatide			41	
GBDB-008-0000000371	Insulin Glargine	25		326	
GBDB-008-0000000395	Dula 1.5	45	IV glucose	448	Y
GBDB-053-0000000656	Insulin Glargine			115	
GBDB-150-0000001500	Dula 1.5	34	IV glucose	3	Y

USUBJID	Treatment	Glucose (mg/dL)	IV glucose or glucagon	Days on therapy	LOC
GBDD-002-0000000157	Dula 0.75	27		163	Y
GBDD-002-0000000159	Insulin Glargine	32	IV glucose + glucagon injection	84	Y
GBDD-004-0000000263	Dula 0.75	19	IV glucose	68	
GBDD-008-0000000460	Insulin Glargine	34		55	
GBDD-010-0000000553	Dula 0.75	50		52	
GBDD-015-0000000800	Dula 0.75	30	IV glucose	219	
GBDD-015-0000000815	Dula 1.5	26	IV glucose	55	Y
GBDD-018-0000000951	Insulin Glargine	44		209	
GBDD-019-0000001004	Insulin Glargine	35		77	
GBDD-023-0000001202	Insulin Glargine	46		126	
GBDD-027-0000001417	Dula 1.5	23	IV Glucose	151	Y
GBDD-027-0000001417	Dula 1.5	29	Glucagon injection	153	
GBDD-028-0000001452	Insulin Glargine	39	IV glucose	192	Y
GBDD-029-0000001505	Insulin Glargine	24	IV glucose + glucagon injection	24	Y
GBDD-031-0000001612	Insulin Glargine	28	Unknown	193	Y
GBDD-033-0000001719	Insulin Glargine			92	
GBDD-033-0000001719	Insulin Glargine	47	Glucagon injection	157	Y
GBDD-106-0000003268	Insulin Glargine			43	
GBDD-250-0000004015	Dula 0.75	33	IV glucose	108	Y
GBDD-250-0000004015	Dula 0.75	22	IV glucose	135	
GBDD-251-0000004030	Dula 1.5	48		75	Y
GBDD-251-0000004035	Dula 1.5	32	IV glucose	302	Y
GBDD-251-0000004045	Dula 1.5		IV glucose	120	Y
GBDD-251-0000004049	Dula 1.5	28	IV glucose	219	Y
GBDD-252-0000004250	Dula 1.5	34	IV glucose	253	Y
GBDD-253-0000004090	Insulin Glargine	25	IV glucose	131	Y
GBDD-253-0000004090	Insulin Glargine	36		229	
GBDD-253-0000004090	Insulin Glargine	29		267	
GBDD-253-0000004090	Insulin Glargine	40		273	
GBDD-254-0000004111	Insulin Glargine	52		12	
GBDD-254-0000004111	Insulin Glargine	41		45	
GBDD-254-0000004111	Insulin Glargine			107	Y
GBDD-454-0000005356	Dula 1.5		IV glucose	50	Y
GBDD-457-0000005428	Insulin Glargine	30.6	IV glucose	75	Y
GBDD-501-0000005601	Dula 1.5	40	IV glucose	358	Y
GBDD-504-0000005701	Dula 0.75	40	IV glucose	327	Y
GBDD-504-0000005755	Dula 1.5	30	IV glucose	142	Y
GBDD-752-0000007470	Insulin Glargine	37.8	IV glucose	350	Y
GBDD-800-0000008006	Insulin Glargine		IV glucose	25	Y
GBDD-800-0000008006	Insulin Glargine	33	glucagon injection	348	
GBDD-801-0000008026	Dula 0.75	25		51	

USUBJID	Treatment	Glucose (mg/dL)	IV glucose or glucagon	Days on therapy	LOC
GBDD-801-0000008026	Dula 0.75	22		56	
GBDD-801-0000008026	Dula 0.75	27		72	
GBDD-801-0000008026	Dula 0.75	25		90	
GBDD-801-0000008026	Dula 0.75	29		135	
GBDD-801-0000008026	Dula 0.75	34		137	
GBDD-801-0000008026	Dula 0.75	48		199	
GBDD-801-0000008026	Dula 0.75	23		342	
Events after Rescue Therapy was Initiated:					
GBDA-021-0000001008	Placebo/Dula 0.75			82	
GBDD-051-0000002740	Dula 0.75	28	glucagon injection	10	
GBDD-051-0000002740	Dula 0.75	53		10	
GBDD-051-0000002740	Dula 0.75	41		10	
GBDD-051-0000002740	Dula 0.75	27		10	
GBDD-551-0000006076	Insulin Glargine	24		74	
GBDD-551-0000006076	Insulin Glargine	35		74	
GBDD-551-0000006076	Insulin Glargine	46		74	

LOC- Loss of consciousness (if reported)
Source file: hypo.xpt, Days on treatment from Applicant's table, ISS 6.59, page 380 and narratives review from TOSNP-SAE, eCTD 5.3.5.3.

After excluding the post-rescue events, in study GBDD, there were 22 events in patients on insulin glargine, 15 events in patients on dulaglutide 0.75 mg, 11 events in patients on dulaglutide 1.5 mg; In study GBDA there were 2 events in patients on exenatide and none on dulaglutide treated patients; In study GBDB, there were 2 events each in patients treated with insulin glargine and dulaglutide 1.5 mg.

While the prespecified definition of severe hypoglycemia is requiring third-party assistance, this is also dependent on the patient's mobility and availability of third party assistance. There were 27 events treated with food/drink and oral glucose. Events requiring IV glucose or glucagon were separately reviewed since they would presumably be more objective in identifying cases of severe hypoglycemia (see Table 71). There were 27 events that were treated with either IV glucose or glucagon injection, 12 occurred in patients on dulaglutide 1.5 mg , 9 events in patients on insulin glargine, 5 events on patient's treated with dulaglutide 0.75 mg and one event in a patient treated with exenatide. This also suggests a dose dependency for hypoglycemic AEs between dulaglutide 1.5 mg to 0.75 mg.

Reviewer's Hypoglycemia Assessments:

The risk for hypoglycemia with dulaglutide is consistent with the drug class. It is to be noted that unlike clinical programs for some of the approved products in the GLP-1 agonist class, the add-on to insulin lispro and SU studies have insulin glargine as an active comparator and not placebo. This may increase the rate of hypoglycemia in the

Reference ID: 3609106

comparator arms. Compared to placebo, patients on dulaglutide had an increased rate of documented symptomatic hypoglycemia. Some studies showed a suggestion of dose dependency. This is based on the observation that there was more documented symptomatic hypoglycemia with dulaglutide 1.5 mg vs. 0.75 mg in studies GBCF, GBDC, and severe hypoglycemic episodes in studies GBDD and GBDB.

- 7.3.2.9 Cardiac Safety

All drugs developed for the treatment of Type 2 DM are required to exclude unacceptable CV risk as specified by the FDA guidance [18]. This is discussed in the following section. Other cardiac effects (e.g. effects on heart rate and conduction) observed with dulaglutide and other agents in drug class will be discussed after the discussion of cardiovascular risk.

Cardiovascular risk:

The risk for major cardiovascular events was separately reviewed by Dr. Janelle Charles. Refer to CV safety statistical review by Dr. Janelle Charles dated May 15, 2014 for detailed discussion of the methodology, analysis plan and verification of meta-analyses results.

The Applicant has submitted a CV meta-analysis report based on data from the nine completed phase 2 and 3 trials. 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 Guidance for Industry 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 (H9X-MC-GBDJ-REWIND). As 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, the second planned meta-analysis was not performed. 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 that was reviewed and agreed upon by the FDA (FDA correspondence dated June 12, 2012). The agreed

18 FDA Guidance for Industry *Diabetes Mellitus –Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* dated December 2008

upon primary safety endpoint (End-of Phase 2 Meeting Minutes-January 19, 2010) of this meta-analysis was MACE+, a composite endpoint comprised of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina (HUA). A key secondary endpoint was MACE, a composite endpoint comprising CV death, non-fatal MI, or non-fatal stoke. All CV events included in the meta-analysis were based on positively adjudicated events determined by an independent blinded Clinical Event Committee (CEC) 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 primary meta-analysis measure was the time to first occurrence (after randomization) of the composite of MACE+. The analysis model for the primary and additional meta-analysis endpoints was a Cox proportional hazards regression model for the time to the first occurrence of an endpoint event, stratified by study (with all Phase 2 trials forming 1 stratum) and with treatment as a fixed effect. 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 the statistical review are based on two-sided alpha-adjusted 98.02% confidence intervals (CIs).

For the meta-analysis, there were a total of 3,885 patients randomized to dulaglutide. Of these, 26 patients (0.7%) experienced a MACE+ event. A total of 2,125 patients were randomized to a comparator. Of these, 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 estimated hazard ratio for MACE yielded consistent results (Table 72). The Applicant has excluded the pre-marketing risk margin of 1.8.

Table 72: Summary of Meta-analysis Results of MACE+ and MACE

Outcome	Number of Patients with Events		HR
	Dulaglutide[1], N=3885 n (%)	Comparator[2], N=2125 n (%)	(98.02% CI)
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
[1]Pooled dulaglutide doses
[2]Pooled active and placebo comparators

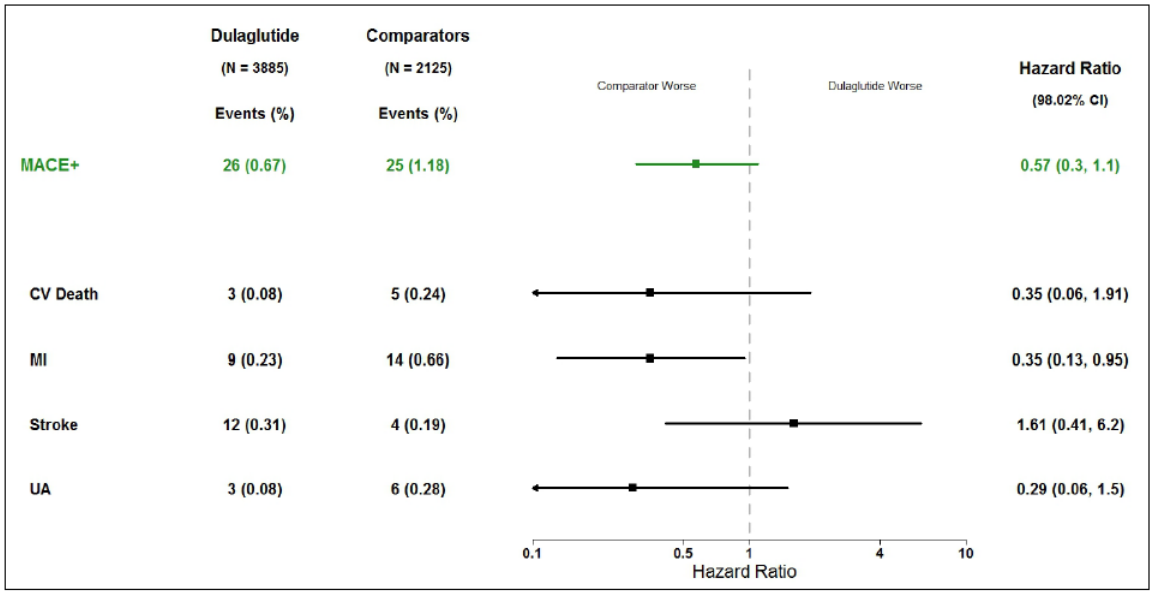
Source: Created by the reviewer using dataset "cv_all.xpt"

Source: Table-1 in Dr. Janelle Charles' dulaglutide CV statistical review

Reference ID: 3609106

For all components, other than non-fatal stoke, the point estimates of the HR were less than one (Figure 12). However, given the small number of events, these results should be interpreted with caution. The estimated HR for all-cause mortality was 0.50 with a corresponding 98.02% CI of 0.15 to 1.67.

Figure 12: Forest Plot of MACE + Component Analysis



MI=myocardial infarction, UA=unstable angina, CV=cardiovascular
Source: Created by the reviewer using dataset "cv_all.xpt

Source: Figure 4, Dr. Charles' statistical review of cardiovascular risk

The results of subgroup analyses for gender, race, age, region, CV risk factors (BMI, duration of diabetes, smoking history, CV disease history), and dulaglutide dose are presented in Tables 8, 9 and 10 of the Dr. Charles' statistical review of cardiovascular risk with unadjusted 95% CIs as they are considered exploratory. Given the small number of events, no definitive conclusions can be drawn from these results.

Review of the meta-analyses endpoints and adjudication process, statistical methodology and analyses plan, patient disposition, demographics, baseline characteristics for CV risk, meta-analyses results for MACE and MACE+ including sensitivity analyses and sub-group analyses conducted by the Applicant and by the FDA statistical reviewer are discussed in the Dr. Janelle Charles's statistical review of cardiovascular risk. My clinical assessment will focus on the acceptability of the end-point adjudication process.

The Clinical Event Classification (CEC) Group consisted of physicians selected from (b) (4) Physicians from

outside (b) (4) were selected as necessary. No Sponsor representatives were to serve on the CEC.

The CEC was responsible to adjudicate defined clinical events, in a blinded, consistent and unbiased manner across these studies. The (b) (4) CEC created and maintained the CEC Charter and collaborated with the Applicant to ensure accurate adjudication and classification of the following CV events:

1. All Deaths
    - Cardiovascular (CV)
    - Noncardiovascular
2. Acute Coronary Syndromes
    - Myocardial Infarction (MI)
    - Hospitalization for Unstable Angina
3. Cerebrovascular Events
    - Stroke
    - Transient Ischemic Attack (TIA)
4. Coronary Revascularization Procedures
    - Coronary Artery Bypass Grafting
    - Percutaneous Coronary Interventions
5. Hospitalization for Heart Failure

The CV event definitions used in the (b) (4) and the REWIND CEC Charters were adapted from the October 2010 draft document "Standardized Definitions for Endpoint Events in Cardiovascular Trials" authored by members of the Standardized Data Collection for Cardiovascular Trials Initiative task force.

Since initiating the CEC charter, there have been updated definitions for the CV endpoints[19]. The Applicant's definitions for endpoints with updated definitions are presented below.

Biomarker Elevations (MI)

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the URL is not available, then the URL for myocardial necrosis should be used. If the 99th percentile of the URL, or the URL for myocardial necrosis is not available, the MI decision limit for that laboratory should be used. CKMB and troponin are preferred; CK may be used in the absence of CKMB and troponin.

19 Draft Definitions for Testing November 9, 2012. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials. Karen A. Hicks, H. M. James Hung, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Norman L. Stockbridge, Shari L. Targum, Robert Temple; on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative

Hospitalization for Unstable Angina (HUA)

Unstable angina requiring hospitalization will be defined as ischemic symptoms meeting the following criteria:

1. Lasting > 10 minutes and considered to be myocardial ischemia on final diagnosis

AND

2. Requiring an unscheduled visit to a healthcare facility and overnight admission (including chest pain observation units) within 24 hours of the most recent symptoms.

AND

3. At least one of the following:

- New or worsening ST or T wave changes on ECG
- ST elevation: New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: > 0.2 mV in men (> 0.25 mV in men < 40 yr.) or > 0.15 mV in women in leads V2-V3 and/or > 0.1 mV in other leads.
- ST depression and T wave changes: New horizontal or downsloping ST depression > 0.05 mV in two contiguous leads; and/or new T inversion > 0.1mV in two contiguous leads.
    - Ischemia evidence on stress testing with or without cardiac imaging
    - Angiographic evidence of > 70% lesion and/or thrombus in an epicardial coronary artery
    - Coronary artery revascularization during same hospital stay

    AND
    - No evidence of acute myocardial infarction

Transient Ischemic Attack

Transient ischemic attack (TIA) will be defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction, and no new defect on neuroimaging (and it did not result in death).

These were compared with the updated standardized definitions. While there is some variation in the ECG criteria measurements for ST-depression and T wave inversion, the Applicant's criteria appear to be more inclusive (lower voltage specification). While the Applicant's HUA criteria specify absence of evidence of acute MI, the latest update to the standardized definitions specifies negative cardiac biomarkers with no evidence of acute MI. These differences are not likely to have significantly impacted the findings of the meta-analysis.

Source documents used by the CEC were as follows (Table 73):

Table 73: Source Documents Used by the Clinical Events Committee, CV Meta-analyses

Event	Source Documents
Death	Autopsy report (if done) Death certificate Discharge /Death summary (if in-hospital death)
Myocardial Infarction, Hospitalization for Unstable Angina	Discharge Summary ER reports/Admission History and Physical Cardiac Biomarkers and other laboratory results with reference ranges (all Troponin I or T, CK-MB) ECG tracings (all, including baseline and event) Procedural Reports (if done)
Coronary Revascularization Procedures	Cardiac Catheterization Report/PCI Report Surgical Report Discharge Summary
Hospitalization for Heart Failure	Discharge Summary Admission History and Physical All medication reports and treatments Chest x-ray reports Cardiac Biomarkers with reference ranges (all Troponin I or T, CK-MB) Other laboratory values (e.g., BNP) with reference ranges ECG tracings (all, including baseline and event) Description or report of all relevant procedures and diagnostic studies (i.e. IABP insertion, dialysis, Pulmonary Artery Monitoring line insertion, echocardiograms, chest x-rays, etc)
Stroke or TIA	Discharge Summary Admission History and Physical, including the time of symptom onset and resolution Imaging Study Report(s) (e.g., CT, MRI, angiography) Neurological consultation report

Source: Table-1, (b) (4) CEC charter, CV Metaanalyses report- page 247

Investigator reported vs. CEC adjudicated Events:

The investigator reported vs. CEC adjudicated events are compared in the Figure 13 below. The endpoints with the highest number of events reported by the investigators but not confirmed by the CEC were ACS and cerebrovascular events.

Figure 13: Disposition of all investigator-reported and CEC-Adjudicated cardiovascular events; dulaglutide cardiovascular meta-analysis.

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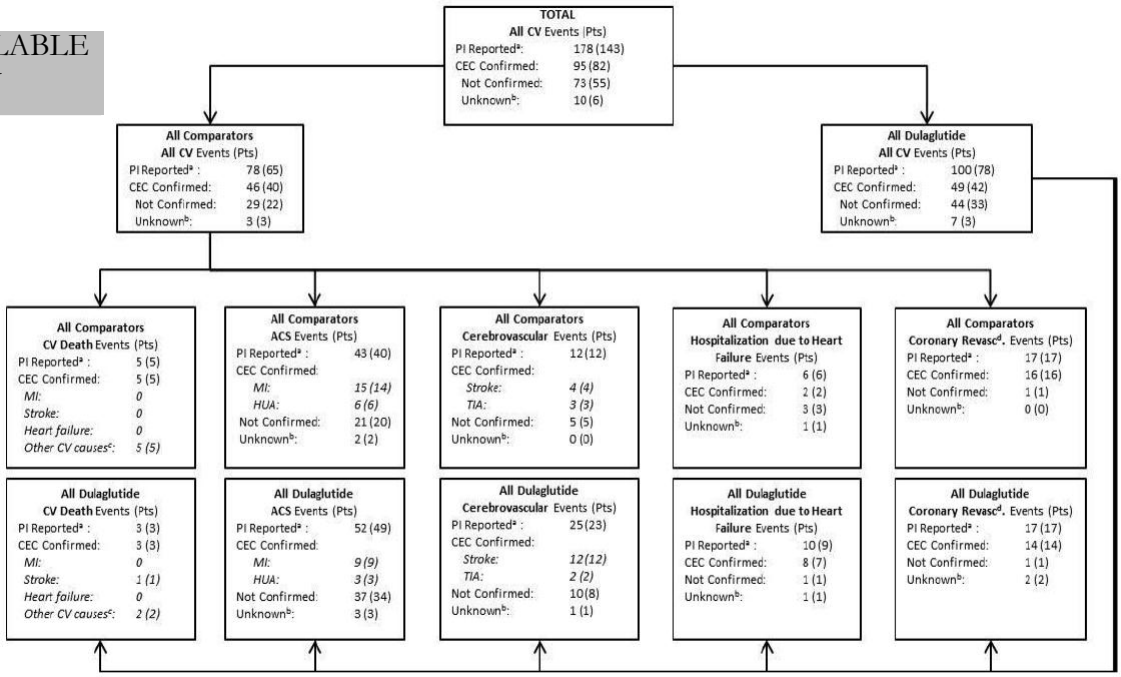


Source Figure 4.1, CV meta-analyses report, page 30

Of the 95 ACS events and 37 cerebrovascular events (Figure 13), events in dulaglutide treated patients where there was difference or agreement between investigator reported diagnosis and adjudicator opinions were identified (Table 8.27, CV Meta-analysis Report), and then reviewed at random to assess the adjudication process. The reviewed cases were separated by event and are discussed further below (Table 74 and Table 75). Adverse events of cardiovascular death, congestive heart failure, and coronary revascularization were not included in the pool of cases for random selection as there was little disagreement between the investigator reported event and the adjudicated outcome. In addition, CHF hospitalization was not part of the primary endpoint.

Table 74: Review of Randomly Selected Dulaglutide Cases Reported as Stroke by the Investigator but Adjudicated as "Stroke Not Confirmed" or "Unknown" or Vice-Versa.

SUBJ-ID	Age	Sex	Exposure (weeks)	AE Report	Symptoms and Stroke work-up/ adjudication report
GBDA-204-6205	61	F	4	Syncope, CVA not confirmed	Adjudicated asIschemic stroke based on facial deviation to the right
GBDB-702-7101.	65	F	52	Left hemi-paresis syndrome	"Brain scan did not show significant modification for stroke". Adjudicated as unknown if stroke since no duration of symptoms provided.
GBDC-404-6206	66	F	32	Transient ischemic attack	The patient presented with transient hemiansopsia-right and amnesic aphasia (anomia) for one hour accompanied by headache. MRI negative for ischemia. Adjudicated as TIA, stroke not confirmed
GBCF-508-6277.	50	M	104	TIA X 2	Weakness and dizziness on Day 121, dizziness, stiffness and numbness in left hand and fingers for 15 minutes 1 week later. Carotid doppler normal. Only second episode adjudicated as TIA.
GBDA-084-4155.	76	M	8, 12	Stroke/sei-zure /atrial fibrillation at week 8 Subdural hematoma 1 month later	Patient with hx of head injury, surgery of skull and atrial fibrillation. History of lightheadedness, fainting and generalized seizure at week 8, diagnosed with bilateral subdural hematoma at week 12. Both events adjudicated as not CVA or TIA including the first event on the basis of symptoms.
GBDD-028-1451	64	M	46	Metabolic encephalo-pathy	Narrative review consistent with metabolic encephalopathy secondary to sinusitis, adjudicated as stroke not confirmed
GBDB-453-4662	63	M	78	Carotid artery stenosis	The patient was diagnosed with stenosis of right ACII 90% (right internal carotid artery) when he was hospitalized. The patient underwent elective surgery 5 days later. Adjudicated as stroke not confirmed based on absence of clinical symptoms reported.
GBDC-117-1701	72	F	4	Right middle cerebral artery Infarction	complaints of blurred vision and drooling from the left side of her mouth. CT with contrast reported that "middle cerebral artery infarct can be sub-acute" and MRI "–acute right middle cerebral artery infarct involving the insula, posterior-rt frontal lobe and frontoparietal junction". Adjudicated as stroke not confirmed based on "Patient woke up with drooling - No reported neuro deficits based on available records. Not a stroke despite compelling imaging"
GBDC-117-1715	50	M	20	Left sided numbness of left Upper extremity	Adjudication –stroke not confirmed, based on "Patient had old stroke with no new symptoms and no stroke identified on brain CT/MRI"

SUBJ-ID	Age	Sex	Exposure (weeks)	AE Report	Symptoms and Stroke work-up/ adjudication report
GBDD-254-4117	54	M	57 (37 days after last dose)	Hemorr-hagic stroke	Narrative reported as case not valid since over 30 days after trial completion. Adjudication- "Pt with no clinical symptoms provided and imaging concerning for traumatic injuries. Given no clinical symptoms and concerning trauma findings, no stroke"
GBDD-502-5655	65	F	20	Transient ischemic attack	Chorea type movements and dysarthria. Not adjudicated as stroke or TIA. Description of modest dysarthria for a few hours and two hours after presenting with involuntary movements in the limbs. CT scan was normal. In the neurological exam the speech was considered normal

Source: Reviewer generated, adapted from narratives in the TOSNP, eCTD 5.3.5.3

There were several cases of investigator reported stroke and TIA submitted for adjudication which were adjudicated as "TIA, stroke not confirmed" or "Stroke,TIA not confirmed". This likely accounts for several of the CEC unconfirmed cerebrovascular events. Based on the cases reviewed, there may be some uncertainty regarding TIAs based on the narratives for some patients (e.g. GBDD-502-5655, GBDC-117-1701), but overall the adjudication seem acceptable.

Table 75: Review of Randomly Selected Investigator Reported Myocardial Infarction (MI) and Hospitalization for Unstable Angina (HUA) Adjudicated as HUA or MI not Confirmed and Vice- Versa

SUBJ ID	Investigator reported AE	ECG findings, Cardiac Enzymes, Coronary Revascularization Procedures and Adjudicator opinion
GBCF-924-9705	Non-Q wave MI	New anterior T wave changes on ECG;Troponin reported normal; No procedures; Adjudicated as HUA, MI not confirmed
GBDB-003-0144	Ventricular Tachycardia	Monomorphic ventricular tachycardia, cardiorespiratory arrest on ECG; Troponin 9.96 ng/ml, CK-MB-57.1 IU/L(high); Coronary angiography normal; Cardioversion/defibrillation performed. Adjudicated as Type 2 MI, HUA not confirmed, -"No ECG's, Type 2 since normal coronaries, likely primary arrhythmia as event"
GBDD-010-0554.	Angina pectoris-Day 310	Normal ECG; Troponin 0.03 and 0.5 (no units reported), Negative thallium stress test and nuclear myocardial perfusion scan. Adjudicated as Type 1 MI.
	Angina- day 336	No changes on ECG; Troponin 0.92 (high) and 0.5 (no units- reported in CRF form); Normal stress echo with second episode. Adjudicated as MI and HUA unconfirmed.
GBCF-402-5060	Coronary artery disease and mitral valve incompetence	ECG changes not reported; Troponin reported normal in CRF; c/o dyspnea, Coronary angiography- left anterior ascending rhythm idioventricular stenosis (RIVA-stenosis). Adjudicated as HUA.

SUBJ ID	Investigator reported AE	ECG findings, Cardiac Enzymes, Coronary Revascularization Procedures and Adjudicator opinion
GBDD-302-4350	Non-sustained Ventricular tachycardia	ECG-sinus rhythm, with wide complex beats; Troponin negative; Presented with chest pain, dyspnea and dizziness. Coronary angiography positive for disease in Left coronary branches. Treated with mexelitine, radiofrequency ablation and flecainide; Adjudicated as HUA and MI not confirmed "admitted for VT...CP symptoms. W/u revealed small vessel with dx, but probably not enough to cause VT, so not really UA"
GBDC-867-8849.	Unstable angina 10 day history of chest pain	ECG-No report available; Normal Troponin; Coronary angiogram- 40-50% stenosis of the left coronary artery (LCA) trunk and 50% restenosis in stents implanted in the LAD. Adjudicated as HUA Not Confirmed-"max coronary stenosis= 50%, no ischemic ECGs"
GBDB-006-0274	Unstable Angina (Precordial pain)	ECG- Sinus rhythm, no ST-T wave changes; Troponin-Normal; Adjudicated as HUA and MI not confirmed- "No EKG changes, No troponins, CKMBs reported. Cath without significant obstruction. No event."
GBCF-853-7453.	Cardiac Ischemia- (dyspnea on climbing stairs)	1 mm horizontal ST depression in III, AVF, V5 and V6 with resolution to baseline in recovery in cardiac stress test; Troponin not reported. Adjudicated as MI and HUA not confirmed " No event"
GBDB-002-0075	Acute Coronary Syndrome (no symptoms reported)	ECG- No signs of acute ischemia; CPK- 123, CPK-MB-8.7(no units reported); Angiography showed a muscular bridge over the middle third of anterior descending artery. Adjudicated as MI and HUA not confirmed "CKMB/CK ratio = 7.3%. ULN = 10% so no to MI. Cath showed muscle bridge w/o stenosis- no for UA"
GBDB-051-0553	Angina Pectoris "exacerbation of angina"	ECG-Sinus rhythm; Troponin not reported; the patient was hospitalized due to exacerbation of angina requiring coronary angioplasty and stent placement. Adjudicated as MI and HUA not confirmed "chest pain not at rest".

Source: Reviewer generated, adapted from narratives in the TOSNP, eCTD 5.3.5.3

Overall, based on review of the narratives presented in Table 75, the adjudication seems acceptable.

Patients in study GBDA that switched from placebo to dulaglutide were assessed separately since cardiovascular events occurring after patients switched from placebo to dulaglutide were not included in the Applicant's analysis.

There were only three patients in study GBDA with MACE+ events occurring after the switch from placebo to dulaglutide and therefore they are not included in the primary CV meta-analysis.

- GBDA70-3462: The reported angina event occurring in this patient were not confirmed by the CEC (MI not confirmed and HUA not confirmed)
- GBDA85-4210.: The reported chest pain event occurring in this patient was not confirmed by the CEC (MI not confirmed and HUA not confirmed).
- GBDA 200-6024: The reported acute MI event occurring in this patient was confirmed as MI by the CEC (MI confirmed and HUA not confirmed).

Reviewer's Comment-Only one MI in a patient who switched from placebo to dulaglutide was CEC confirmed, but not included in the meta-analysis. This should have minimal impact on the meta-analyses results.

Reviewer's Assessments about the cardiovascular risk:

The identification of cases and adjudication process for cardiovascular risk appears acceptable. The estimated HR for MACE+ (the primary endpoint) was 0.57 with a corresponding 98.02% CI of 0.30 to 1.10. The meta-analysis has ruled out the pre-market risk margin of 1.8 set forth in the FDA Guidance to establish CV safety of new antidiabetic products. Further evaluation of the CV risk of dulaglutide post-approval will be performed. This evaluation will be based on data from the REWIND trial, which is designed to exclude a 30% increase in CV risk based on the MACE endpoint and conducted in a high risk population.

Other Cardiac Events:

Other cardiac events were evaluated by review of reported adverse events. A comparison of adverse events for AS1 and for AS7 (Table 76 and Table 77) is presented below. The effect on lipids, Heart Rate, BP and ECG intervals will be discussed in sections 7.4.2, 7.4.3 and 7.4.4.

Table 76: Summary and Analysis of TEAEs, By Descending Frequency of Preferred Term within System Organ Class, Observations Through 26 Weeks of the Planned Treatment Period – (AS1)

System Organ Class / Preferred Term	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Cardiac disorders	19 (3.3)	23 (2.8)	22 (2.6)	45 (2.7)	0.80	.128	.459
Palpitations	3 (0.5)	7 (0.8)	3 (0.4)	10 (0.6)	1.13	.519	.707
Tachycardia	1 (0.2)	3 (0.4)	5 (0.6)	8 (0.5)	2.73	.578	.350
Myocardial infarction	1 (0.2)	1 (0.1)	4 (0.5)	5 (0.3)	1.70	.697	.563
Angina pectoris	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.2)			.372
Atrial fibrillation	3 (0.5)	1 (0.1)	2 (0.2)	3 (0.2)	0.34	.363	.087
Atrioventricular block first degree	1 (0.2)	1 (0.1)	2 (0.2)	3 (0.2)	1.02	.344	.898
Ventricular extrasystoles	2 (0.4)	2 (0.2)	1 (0.1)	3 (0.2)	0.51	.504	.582
Cardiac failure congestive	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)			.477
Extrasystoles	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)			.376
Sinus tachycardia	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)			.376
Aortic valve incompetence	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.589
Aortic valve stenosis	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)			.589
Atrial flutter	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.482
Bradycardia	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)			.616
Bundle branch block left	1 (0.2)	1 (0.1)	0 (0.0)	1 (<0.1)	0.34	.213	.482
Cardiac arrest	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.616
Cardiomegaly	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)			.616
Coronary artery disease	2 (0.4)	1 (0.1)	0 (0.0)	1 (<0.1)	0.17	.494	.086
Mitral valve incompetence	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)			.616
Myocardial ischaemia	1 (0.2)	1 (0.1)	0 (0.0)	1 (<0.1)	0.34	.142	.323
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.589
Ventricular fibrillation	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)			.616
Bundle branch block right	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			.046
Cardiomyopathy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			.046
Sinus bradycardia	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)			.044
Supraventricular extrasystoles	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Ventricular tachycardia	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)			.018

Abbreviations: CMH = Cochran-Mantel-Haenszel; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event; TEAE = treatment emergent adverse event.

Source: ISS.APP.55, page 1111

Table 77: All Dulaglutide versus All Comparator Analysis of Treatment-Emergent Adverse Events, By Descending Frequency of Preferred Term within High-Level Term/System Organ Class – (AS7)

System Organ Class / High Level Term / Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Cardiac disorders	103 (5.6)	85 (5.1)	73 (4.4)	158 (4.7)	0.84	.305	.217
Ischaemic coronary artery disorders	33 (1.8)	27 (1.6)	15 (0.9)	42 (1.3)	0.70	.109	.140
Angina pectoris	17 (0.9)	16 (1.0)	5 (0.3)	21 (0.6)	0.68	.442	.222
Myocardial infarction	9 (0.5)	1 (<0.1)	7 (0.4)	8 (0.2)	0.49	.852	.156
Angina unstable	2 (0.1)	5 (0.3)	2 (0.1)	7 (0.2)	1.93	.270	.439
Acute myocardial infarction	3 (0.2)	3 (0.2)	2 (0.1)	5 (0.1)	0.92	.213	.928
Myocardial ischaemia	2 (0.1)	3 (0.2)	0 (0.0)	3 (<0.1)	0.83	.238	.911
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Prinzmetal angina	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Rate and rhythm disorders NEC	9 (0.5)	15 (0.9)	16 (1.0)	31 (0.9)	1.91	.221	.071
Tachycardia	6 (0.3)	12 (0.7)	12 (0.7)	24 (0.7)	2.22	.427	.056
Bradycardia	2 (0.1)	4 (0.2)	1 (<0.1)	5 (0.1)	1.38	.548	.801
Extrasystoles	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)			.255
Arrhythmia	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Nodal rhythm	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Cardiac signs and symptoms NEC	15 (0.8)	19 (1.1)	8 (0.5)	27 (0.8)	0.99	.314	.979
Palpitations	15 (0.8)	19 (1.1)	8 (0.5)	27 (0.8)	0.99	.314	.979
Supraventricular arrhythmias	20 (1.1)	7 (0.4)	18 (1.1)	25 (0.7)	0.69	.276	.217
Atrial fibrillation	9 (0.5)	4 (0.2)	7 (0.4)	11 (0.3)	0.67	.528	.369
Atrial flutter	3 (0.2)	1 (<0.1)	2 (0.1)	3 (<0.1)	0.55	.460	.436
Supraventricular extrasystoles	4 (0.2)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0.28	.407	.131
Sinus bradycardia	3 (0.2)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0.37	.231	.201
Sinus tachycardia	1 (<0.1)	0 (0.0)	3 (0.2)	3 (<0.1)	1.66	.625	.562
Sinus arrhythmia	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)			.315
Sick sinus syndrome	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.55	.156	.612

System Organ Class / High Level Term / Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Supraventricular tachyarrhythmia	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.368
Coronary artery disorders NEC	16 (0.9)	8 (0.5)	7 (0.4)	15 (0.4)	0.52	.236	.051
Coronary artery disease	12 (0.7)	4 (0.2)	4 (0.2)	8 (0.2)	0.37	.279	.021
Arteriosclerosis coronary artery	1 (<0.1)	3 (0.2)	2 (0.1)	5 (0.1)	2.76	.102	.337
Coronary artery stenosis	3 (0.2)	0 (0.0)	2 (0.1)	2 (<0.1)	0.37	.127	.252
Coronary artery insufficiency	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Cardiac conduction disorders	12 (0.7)	6 (0.4)	8 (0.5)	14 (0.4)	0.64	.648	.285
Atrioventricular block first degree	2 (0.1)	1 (<0.1)	5 (0.3)	6 (0.2)	1.66	.773	.463
Bundle branch block right	5 (0.3)	2 (0.1)	1 (<0.1)	3 (<0.1)	0.33	.058	.114
Bundle branch block left	3 (0.2)	2 (0.1)	0 (0.0)	2 (<0.1)	0.37	.296	.243
Atrioventricular block second degree	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)			.324
Atrioventricular block complete	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55		.620
Conduction disorder	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Heart failures NEC	5 (0.3)	6 (0.4)	5 (0.3)	11 (0.3)	1.21	.665	.884
Cardiac failure	2 (0.1)	4 (0.2)	3 (0.2)	7 (0.2)	1.93	.539	.499
Cardiac failure congestive	2 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)	1.10	.269	.992
Cardiogenic shock	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.159
Ventricular arrhythmias and cardiac arrest	10 (0.5)	3 (0.2)	4 (0.2)	7 (0.2)	0.38	.779	.053
Ventricular extrasystoles	7 (0.4)	2 (0.1)	2 (0.1)	4 (0.1)	0.31	.513	.066
Ventricular tachycardia	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	1.10	.224	.991
Ventricular fibrillation	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.55	.159	.616
Cardiac arrest	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.482
Cardio-respiratory arrest	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Mitral valvular disorders	1 (<0.1)	3 (0.2)	0 (0.0)	3 (<0.1)	1.66	.625	.562
Mitral valve incompetence	1 (<0.1)	3 (0.2)	0 (0.0)	3 (<0.1)	1.66	.625	.562
Myocardial disorders NEC	4 (0.2)	3 (0.2)	0 (0.0)	3 (<0.1)	0.41	.904	.210
Left ventricular hypertrophy	2 (0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.28	.253	.282
Cardiomegaly	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55	.159	.616
Right atrial dilatation	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Diastolic dysfunction	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Left atrial dilatation	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.149
Aortic valvular disorders	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)			.202
Aortic valve incompetence	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.368
Aortic valve stenosis	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.368
Cardiomyopathies	2 (0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.28	.220	.213
Cardiomyopathy	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.481
Congestive cardiomyopathy	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.149
Ischaemic cardiomyopathy	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.155
Left ventricular failures	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Left ventricular failure	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Noninfectious pericarditis	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Pericarditis	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Pericardial disorders NEC	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55	.161	.605
Pericardial effusion	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55	.161	.605
Right ventricular failures	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Cor pulmonale chronic	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.488
Tricuspid valvular disorders	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Tricuspid valve incompetence	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478

Abbreviations: All_Comp = all comparators; CMH = Cochran-Mantel-Haenszel; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event; TEAE = treatment emergent adverse event

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined. All_Comp = metformin for Study GBDC, placebo/sitagliptin or sitagliptin for Study GBCF, exenatide for Study GBDA, insulin glargine for Studies GBDB and GBDD, placebo for Study GBDN. Patient randomized to the Placebo/Dulaglutide switch arms of Study GBDA are excluded from this analysis.

*a - Mantel-Haenszel Odds Ratio. All_Dula is numerator, All_Comp is denominator.
*b - Heterogeneity of odds ratios across studies was assessed using the Breslow-Day test.
*c - p-values are from Cochran-Mantel-Haenszel (CMH) test comparing All_Dula to All_Comp stratified by study.

Source: Table APP.5.3, Sponsor's response to IR – April 21, 2014

In the placebo controlled dataset (AS1), the PT "tachycardia" was the most frequent AE with dulaglutide. This is consistent with other members in class. Except for tachycardia and supraventricular arrhythmias, there was no apparent dose-dependency observed for Cardiac AEs with dulaglutide. Overall in both the placebo controlled (AS1) and the all comparator (AS7) dataset, events other than the PT tachycardia (see rate and rhythm disorders discussed below) seem balanced between dulaglutide and placebo or all comparators. These include the PTs under the ischemic coronary artery disorders, conduction disorders, cardiomyopathies and valvular disorders HLTs.

Since increased heart-rate (HR) is a GLP-1 class effect, AEs related to rate and rhythm were closely reviewed. On review of the Applicant's custom queries for any term in arrhythmia-related investigations and signs and symptoms (Table 78:), numerically more subjects in the dulaglutide 1.5 mg dose (4, 0.5%) experienced syncope compared to placebo (1, 0.2%) and dulaglutide 0.75 mg (1, 0.1%). The number of events, however, was small. In addition, syncope can also occur from non-cardiac causes.

Table 78: Summary and Analysis of Medical Query: Any Term in Arrhythmia-Related Investigations and Signs and Symptoms, Observations Through 26 Weeks of the Planned Treatment Period – Placebo- Controlled Studies with Dulaglutide 0.75 and 1.5 mg (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Level 1 Level 2 Level 3 Preferred Term	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)	CMH p-value*a
Any Term in Arrhythmia-Related Investigations and Signs and Symptoms	6 (1.1)	13 (1.6)	16 (1.9)	29 (1.7)	.237
Broad	6 (1.1)	13 (1.6)	16 (1.9)	29 (1.7)	.237
Palpitations	3 (0.5)	7 (0.8)	3 (0.4)	10 (0.6)	.707
Tachycardia	1 (0.2)	3 (0.4)	5 (0.6)	8 (0.5)	.350
Syncope	1 (0.2)	1 (0.1)	4 (0.5)	5 (0.3)	.624
Heart rate increased	2 (0.4)	1 (0.1)	2 (0.2)	3 (0.2)	.483
Bradycardia	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	.616
Cardiac arrest	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	.616
Electrocardiogram change	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	.482
Loss of consciousness	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	.616

Source: ISS Table 6.94, page 458

On review of the medical queries for the broad and narrow SMQ search "any supraventricular arrhythmias" numerically more subjects on dulaglutide 1.5 mg had AEs compared to dulaglutide 0.75 mg, in both the AS1 and AS3 datasets (Table 79 and Table 80), although the number of events in the "all dulaglutide group" was balanced against placebo or all comparator. As expected, all the reported PT's were tachyarrhythmias. Ventricular tachyarrhythmias were balanced between all treatment groups *(*Table 77*).*

Table 79: Summary and Analysis of Medical Query: Any Supraventricular Arrhythmia, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with Dulaglutide 0.75 and 1.5 mg (Safety Population, (AS1)

Level 1 Level 2 Level 3 Preferred Term	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)	CMH p-value*a
Any Supraventricular Arrhythmia	4 (0.7)	1 (0.1)	8 (1.0)	9 (0.5)	.645
Narrow	4 (0.7)	1 (0.1)	5 (0.6)	6 (0.4)	.270
Any supraventricular tachyarrhythmia	4 (0.7)	1 (0.1)	3 (0.4)	4 (0.2)	.088
Atrial fibrillation	3 (0.5)	1 (0.1)	2 (0.2)	3 (0.2)	.087
Atrial flutter	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	.482
Supraventricular extrasystoles	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	.155
Any non-specified tachyarrhythmia	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)	.376
Extrasystoles	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)	.376
Broad	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.2)	.300
Any supraventricular tachyarrhythmia	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.2)	.300
Sinus tachycardia	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)	.376
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	.589

Abbreviations: N = total number of patients in specified treatment arm; n = number of patients with at least one treatment-emergent adverse event.

Source: Table ISS.6.102-page 479

Table 80: Summary and Analysis of Medical Query: Any Supraventricular Arrhythmia, All Observations During the Planned Treatment Period – Phase 2 and 3 Studies With 0.75 mg and 1.5 mg Dulaglutide (AS3)

Level 1 Level 2 Level 3 Preferred Term	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	CMH p-value*a
Any Supraventricular Arrhythmia	4 (0.2)	16 (1.0)	20 (0.6)	.007
Narrow	4 (0.2)	12 (0.7)	16 (0.5)	.046
Any supraventricular tachyarrhythmia	4 (0.2)	10 (0.6)	14 (0.4)	.109
Atrial fibrillation	3 (0.2)	6 (0.4)	9 (0.3)	.320
Atrial flutter	1 (<0.1)	2 (0.1)	3 (<0.1)	.563
Supraventricular extrasystoles	1 (<0.1)	1 (<0.1)	2 (<0.1)	.999
Supraventricular tachyarrhythmia	0 (0.0)	1 (<0.1)	1 (<0.1)	.318
Any non-specified tachyarrhythmia	0 (0.0)	2 (0.1)	2 (<0.1)	.157
Extrasystoles	0 (0.0)	2 (0.1)	2 (<0.1)	.157
Broad	0 (0.0)	4 (0.2)	4 (0.1)	.046
Any supraventricular tachyarrhythmia	0 (0.0)	4 (0.2)	4 (0.1)	.046
Sinus tachycardia	0 (0.0)	3 (0.2)	3 (<0.1)	.083
Supraventricular tachycardia	0 (0.0)	1 (<0.1)	1 (<0.1)	.319

Abbreviations: N = total number of patients in specified treatment arm; n = number of patients with at least one treatment-emergent adverse event.

Source: Table ISS.6.103-page 480

Given the effect of the drug on heart rate and the dose-dependent imbalance in supra-ventricular arrhythmias, all supraventricular and ventricular arrhythmias reported as SAEs were reviewed. In addition to the cases decribed below from the phase 2/3 program, in the TQT study, a healthy volunteer developed atrial fibrillation within 1 day of receiving dulaglutide 4 mg.

Table 81: Supraventricular and Ventricular arrhythmias with Dulaglutide Reported as SAE's:

Subject ID Age Treatment	Event	Details
GBCF-006-0354 55 yr. M Dula 1.5 mg	Supra-ventricular Tachycardia (SVT)	Patient with no known history or prior CAD presented to the emergency department with intermittent feelings of pressure in his chest, During one of these episodes, a short episode of supraventricular narrow complex tachycardia at a rate of 150/minute was noted. Treated with metoprolol and diltiazem, catheter ablation planned. Acute coronary syndrome (ACS) was excluded. Hydrochlorthiazide was discontinued due to mild hyponatremia. Sodium level was 135 at the time of discharge. Study drug was continued
GBDA-028-1374 56 yr. M Dula 1.5 mg	Atrial Fibrillation	Patient with no prior history of atrial fibrillation was diagnosed with new –onset atrial fibrillation after 9 months of study drug exposure. Cardiac enzymes were normal. Study drug was continued
GBDA-084-4155 76 yr. M Dula 1.5 mg	Atrial Fibrillation	Patient had prior history of atrial fibrillation and head injury. Case discussed earlier with stroke adjudications. Recurrent atrial fibrillation with seizures and sub-dural hematoma
GBDA-064-3151 61 yr. M Dula 1.5 mg	Cardiac arrest Atrial fibrillation Inferior MI	CV death in patient with no known prior CAD presenting initially with possible atrial fibrillation, congestive heart failure (CHF), inferior MI based on initial evaluation at primary care physician office and later developed ventricular fibrillation and cardiac arrest.
GBDD-028-1451 64 yr. M Dula 1.5 mg	Atrial Fibrillation	Case discussed earlier with HUA adjudications, developed metabolic encephalopathy secondary to sinusitis and also developed atrial fibrillation with rapid ventricular rate during the hospitalization.
GBCK-114-1437 66 yr. M Dula 1 mg	Atrial flutter	Patient had no known prior CAD with sinus rhythm on prior ECG. Developed atrial flutter 10 weeks after starting study drug with occasional ventricular premature depolarization, non-specific intra-ventricular conduction delay, and variable atrial-ventricular block. Treated with synchronized cardioversion and recovered.
GBCF-029-1518 55 yr. M Dula 0.75 mg	Atrial fibrillation	Patient had possible history (not confirmed) of prior symptomatic arrhythmias. Developed atrial fibrillation with rapid ventricular response 15 days after starting study treatment which was discontinued. Defibrillation was unsuccessful, patient remained in atrial fibrillation and continued warfarin.
GBDD-553-6132 73 yr. M Dula 0.75 mg	Atrial flutter	Patient with history of prior atrial flutter, CAD, MI, reduced ejection fraction and prophylactic ICD. Was on warfarin therapy. Developed recurrent atrial flutter after 1 year on study treatment.
GBDA-079-3914. 67 yr. M Placebo/dula 1.5mg	Atrial Fibrillation	Patient had no previous history of atrial fibrillation. Developed atrial fibrillation, flutter episodes while on placebo (Day 183) and dulaglutide (month 12) per narrative.

Subject ID Age Treatment	Event	Details
GBDA-041-2008. 66 yr. M Placebo/ dula 0.75 mg	Atrial Fibrillation	Patient had a prior history of atrial flutter, fibrillation and CAD. Hospitalized for treatment of recurrent/persistent atrial fibrillation with mapping and ablation on Day 107 of exposure (placebo).
GBDD-302-4350 55 yr. M Dula 0.75 mg	Ventricular tachycardia	Patient had a history of prior CAD (unstable angina). 7 days after receiving the last dose of study drug, the patient developed non-sustained ventricular tachycardia (VT). Case discussed earlier with MI adjudications
GBDB-003-0144 48 yr. old male Dula 1.5 mg	Ventricular tachycardia	Patient had a prior history of paroxysmal supraventricular tachycardia, dilated cardiomyopathy. Case discussed earlier with MI adjudications. Developed ventricular tachycardia and cardiorespiratory arrest from which he recovered and completed the study. Adjudicated as Type 2 MI

Source: Reviewer generated, adapted from TOSNP, eCTD 5.3.5.3.

Reviewer's Assessment for supraventricular arrhythmias:

- Numerically comparable number patients on dulaglutide (8, 0.19%) had supraventricular tachycardia, atrial flutter or atrial fibrillation reported as an SAE compared to all comparators (4 [0.2%] in total; placebo-2 [discussed above], metformin-1 [atrial fibrillation], exenatide-1 [supraventricular extrasystole associated with hypokalemia]).
- Of the dulaglutide treated patients, three on dulaglutide 1.5 mg and one patient on dulaglutide 1 mg had no history of prior atrial fibrillation or CAD; this compares to one patient on placebo and one patient on dulaglutide 0.75 mg with a unconfirmed history of prior symptomatic arrhythmias.
- In addition, one patient on Dula 1.5 mg (GBDN-108-3358) was discontinued from the study at 4 months due to sinus tachycardia. The patient had recurrent sinus tachycardia, intermittent atrial flutter with rapid ventricular response in a prior visit and other ECG changes compared to baseline.
- As discussed earlier, in the TQT study, a healthy volunteer developed atrial fibrillation within 1 day of receiving dulaglutide 4 mg.
- Based on review of the SAEs, although the number of TEAEs reported under the supraventricular arrhythmias HLT was balanced compared to all comparator in the AS7 dataset, review of individual patient narratives is suggestive of a dose dependent effect. This can be further evaluated as an AE of special interest in the CV outcome trial.

As discussed earlier, clinically important conduction disorders were balanced between dulaglutide and comparator. However, since PR interval prolongation has been observed with dulaglutide and other GLP1 agonists, SAEs and other significant AEs reported for dulaglutide patients are discussed below.

Second-Degree AVB:

GBDB-006-0282, 64 yr. F, Dulaglutide 1.5 mg: The patient had a history of right branch block, arterial hypertension, obesity, and dyslipidemia. Concomitant medications included metformin, glimepiride, furosemide, and amlodipine. The patient's baseline PR interval was normal (178 msec; normal range 112 to 204 msec). Approximately 3.5 months after starting study drug, the patient was admitted to the hospital for cardiac arrhythmia and was diagnosed with 2nd degree AVB. Coronary angiography revealed no significant lesions; Echo doppler showed mural venous thrombosis (date of imaging unknown; event not considered SAE by investigator). The patient required temporary and later permanent pacemaker placement and recovered. Study drug was continued, and the patient completed the study.

3rd Degree AVB:

GBDD-252-4057, 63 yr. M, Dulaglutide 0.75 mg: This was a 63-year-old white male. His medical history included hypertension and T2DM. His concomitant medications included metformin, atenolol, enalapril, and simvastatin. His baseline PR interval was normal (172 msec; normal range 120 to 200 msec). Approximately 8 months after randomization and 2 days after most recent dose, he was hospitalized with syncope and found to have intermittent 3rd degree AVB. A cardiac catherization revealed normal coronary arteries. He had a permanent pacemaker implanted and recovered without sequelae. He completed the study.

Variable AVB with atrial flutter:

GBCK-114-1437, 66 yr. M, Dulaglutide 1.0 mg: This was a 66‑ year-old white male. Medical history included hypertension, hyperlipidemia, and T2DM. Concomitant medications included lisinopril, lovastatin, metformin, tadalafil, vicodin, and aspirin. He did not have a history of palpitation, arrhythmia, or syncope, and previous ECGs were noted to have normal sinus rhythm. At his last patient visit in study and approximately 10 weeks after starting study drug, he was asymptomatic but found to have atrial flutter with a rate of 75 to 82, variable AVB, and nonspecific intraventricular conduction delay.

Dyspnea:

GBDN-030-1560, 75 yr. M, Dulaglutide 0.75 mg: This patient was a 75-year-old white male randomly assigned to receive dulaglutide 0.75 mg. He had a history of MI with coronary revascularization, included atenolol, hydrochlorothiazide, diovan, allopurinol, metformin and glipizide, gemfibrozil, simvastatin, oxybutynin, and ticlopidine. Baseline ECG showed a 1st degree AVB (PR interval 306 msec) and evidence of anterior lateral myocardial ischemia. At 16 weeks, the patient's study ECG showed a 2nd degree AV block, Mobitz-1. Approximately 5 months after starting study drug, the patient was

Reference ID: 3609106

admitted to the hospital with shortness of breath presumed due to atrial flutter which progressed to atrial fibrillation with resultant anterior ischemia noted on ECG, but with reported “good left ventricular function” on echocardiogram. Second degree block was still apparent with long pauses. He was treated with pacemaker placement and discontinued from study. Throughout the patient’s participation, ECGs showed variable anterior lateral ischemia.

Patients with baseline AV block:

GBDN-008-0456; 61 yr. F, dulaglutide 1.5 mg: At baseline she had atrial fibrillation and Mobitz-1 2nd degree AVB. Atrial fibrillation persisted but by Week 4, the Mobitz-1 2nd degree AVB was not apparent; she had 1st degree AVB recorded throughout the remainder of study

GBDA-031-1508, 74 yr. M, dulaglutide 1.5 mg: This patient with prior history of MI had second degree Atrio-ventricular block (AVB) –Mobitz-1 at screening ECG and 1st degree AVB with PR interval at 308 msec on randomization. At 26 weeks, he had Mobitz-1 2nd degree AVB with PR interval 404 msec. Mobitz-1 2nd degree AVB persisted at 52 weeks.

Reviewer’s Cardiac Safety assessments for other cardiac events:

- Compared to placebo, tachycardia was the most frequent AE, consistent with drug class. Other Cardiac AEs were balanced compared to all comparators.
- On review of the medical queries for the broad and narrow SMQ search “ any supraventricular arrhythmias “ numerically more subjects on dulaglutide 1.5 mg had AEs compared to dulaglutide 0.75 mg, in both the AS1 and AS3 datasets . As expected, all the reported PT’s were tachyarrhythmias. This was not observed for ventricular tachyarrhythmias.
  Although the number of TEAEs reported under the supraventricular arrhythmias HLT was balanced compared to all comparator in the AS7 dataset, review of individual patient narratives for SAEs and discontinuations due to AEs, taken together with the class effect on heart rate is suggestive of a dose dependent effect with dulaglutide. This can be further evaluated as an AE of special interest in the CV outcome trial.

- 7.3.2.10 Skin and Soft Tissue infections

Recently serious injection site reactions (abscesses/large nodules) requiring surgery have been reported with exenatide LAR. On review of the PT’s under the Infections and Infestations SOC, there was an imbalance in skin and soft tissue infections HLT not favoring dulaglutide, specifically for the PT subcutaneous abscess (see Table 82 below). Given the recent concern with exenatide LAR, this was examined further.

Table 82: All Dulaglutide versus All Comparators Analysis of Select Treatment-Emergent Adverse Events Within Infections and Infestations SOC; All Post-baseline Observations Including Safety Follow-Up (AS7)

System Organ Class • High Level Term ○ Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)
• Dental and oral soft tissue infections (HLT)	27 (1.5)	34 (2.0)	29 (1.7)	63 (1.9)
• Infections NEC (HLT)				
○ Abscess limb	5 (0.3)	1 (<0.1)	2 (0.1)	3 (<0.1
○ Incision site infection	1 (<0.1)	1 (<0.1)	0 (0.0)	1(<0.1)
○ Abscess	3 (0.2)	1(<0.1)	1 (<0.1)	2 (<0.1
○ Injection site infection	1 (< 0.1)	0	0	0
○ Injection site abscess	1 (< 0.1)	0	0	0
• Bacterial Infections NEC (HLT)				
○ Cellulitis	17 (0.9)	8 (0.5)	10 (0.6)	18 (0.5)
• Skin structures and soft tissue infections (HLT)	9 (0.5)	16 (1.0)	17 (1.0)	33 (1.0)
○ Subcutaneous abscess	0 (0.0)	5 (0.3)	4 (0.2)	9 (0.3)
○ Skin infection	0 (0.0)	4 (0.2)	2 (0.1)	6 (0.2)

Source Table App 5.3, Applicant's response to IR dated April 21, 2014.

Skin infections listed under other HLT terms (e.g. cellulitis, PTs under Infections NEC) seemed balanced. Abscesses were reported with increased frequency in the comparator group under the Infections-NEC HLT.

Narratives for subcutaneous abscesses reported as SAEs were reviewed to determine if they were injection-site related: Two cases of subcutaneous abscess were reported as SAEs. Patient GBDA-100-5000 had a scalp abscess and GBDA-104-5235 had an abscess in the back. None of the skin infections reported as SAEs seem related to injection site.

Reviewer's Assessment of skin infections/abcess:

The incidence of specific PTs (injection site infection/abscess) was not increased. Skin infections under other HLT terms were balanced and subcutaneous abscesses are common AEs in patients with T2DM. This was likely a chance finding and not evaluated further.

7.3.3 Significant Adverse Events

Based on the ICH-E3 guidance[20] these events are defined as "Marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events."

20 ICH guidance for industry *E3 Structure and Content of Clinical Study Reports*

Nausea and vomiting and discontinuations as a result of nausea and vomiting will be discussed in Section 7.4.1 (Common adverse events).

- 7.3.3.1 Hepatic Safety

Delayed gall bladder emptying and cholestasis has been observed with other agents in the GLP-1 agonist class. There has also been a report of drug-induced autoimmune hepatitis in the literature with associated with liraglutide[21].

To evaluate the hepatic safety of dulaglutide in the clinical program, samples were collected through the Phase 2 and 3 clinical studies for assessment of hepatic analytes (i.e. alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, direct bilirubin, gamma-glutamyl-transpeptidase [GGT], and alkaline phosphatase [AP]). The time course of these analytes was summarized. The number and proportion of patients with treatment-emergent values outside the normal range and patients with values exceeding critical thresholds (e.g. ≥ 3x, ≥ 5x, and ≥ 10x ULN for AST and ALT; ≥ 2x ULN for total bilirubin) were determined. Potentially clinically significant patients are described in more detail below. In addition, integrated analyses of adverse events potentially associated with hepatic injury in these studies were conducted by the Applicant using MedDRA SMQs. This approach seems acceptable. Hepatic TEAEs for dulaglutide vs. all comparators in the AS7 dataset are listed Table 83 below.

21 Liraglutide-Induced Autoimmune Hepatitis . Emily Kern, MD; Lisa B. VanWagner,MD, MS; Guang-Yu Yang,MD, PhD; Mary E. Rinella, MD. JAMA Internal Medicine Published online April 14, 2014

Table 83: Hepatic TEAEs-Dulaglutide vs. All Comparators in Studies over 26 weeks (AS7 dataset):

System Organ Class / High Level Term / Preferred Term	All Comp (N=1844) n (%)	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Hepatobiliary disorders	34 (1.8)	37 (2.2)	34 (2.0)	71 (2.1)	1.16	.656	.375
Hepatocellular damage and hepatitis NEC	17 (0.9)	17 (1.0)	20 (1.2)	37 (1.1)	1.20	.232	.422
Hepatic steatosis	15 (0.8)	16 (1.0)	20 (1.2)	36 (1.1)	1.33	.445	.291
Non-alcoholic steatohepatitis	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55	.109	.746
Hepatitis	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.267
Cholecystitis and cholelithiasis	12 (0.7)	17 (1.0)	15 (0.9)	32 (1.0)	1.48	.867	.200
Cholelithiasis	9 (0.5)	15 (0.9)	13 (0.8)	28 (0.8)	1.72	.644	.104
Cholecystitis	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)			.223
Cholecystitis acute	2 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0.55	.366	.479
Cholecystitis chronic	2 (0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.28	.082	.220
Hepatic and hepatobiliary disorders NEC	4 (0.2)	5 (0.3)	2 (0.1)	7 (0.2)	0.97	.474	.996
Liver disorder	3 (0.2)	2 (0.1)	1 (<0.1)	3 (<0.1)	0.55	.488	.514
Hepatic cyst	1 (<0.1)	2 (0.1)	0 (0.0)	2 (<0.1)	1.10	.319	.901
Biliary polyp	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)			.482
Hepatic calcification	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Hepatic lesion	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.159
Hepatic enzymes and function abnormalities	1 (<0.1)	2 (0.1)	1 (<0.1)	3 (<0.1)	1.66	.628	.566
Hepatic function abnormal	1 (<0.1)	2 (0.1)	1 (<0.1)	3 (<0.1)	1.66	.628	.566
Gallbladder disorders NEC	4 (0.2)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.14	.628	.037
Gallbladder polyp	2 (0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.28	.468	.289
Gallbladder disorder	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.045
Hepatic fibrosis and cirrhosis	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Nodular regenerative hyperplasia	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.488
Hepatic vascular disorders	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	0.55		.620
Portal vein thrombosis	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)			.478
Portal hypertension	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.159
Hepatobiliary signs and symptoms	4 (0.2)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.14	.208	.049
Hepatomegaly	4 (0.2)	0 (0.0)	1 (<0.1)	1 (<0.1)	0.14	.208	.049
Bile duct infections and inflammations	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.045
Biliary colic	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.045
Cholestasis and jaundice	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.156
Hyperbilirubinaemia	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)			.156

Abbreviations: All_Comp = all comparators; CMH = Cochran-Mantel-Haenszel; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event; TEAE = treatment emergent adverse event

Source: Table APP 5.3, Applicant's response to IR dated April 24, 2014

Hepatobiliary events seem balanced between dulaglutide and all comparators and no dose-dependent effects were noted.

Hepatic Analytes:

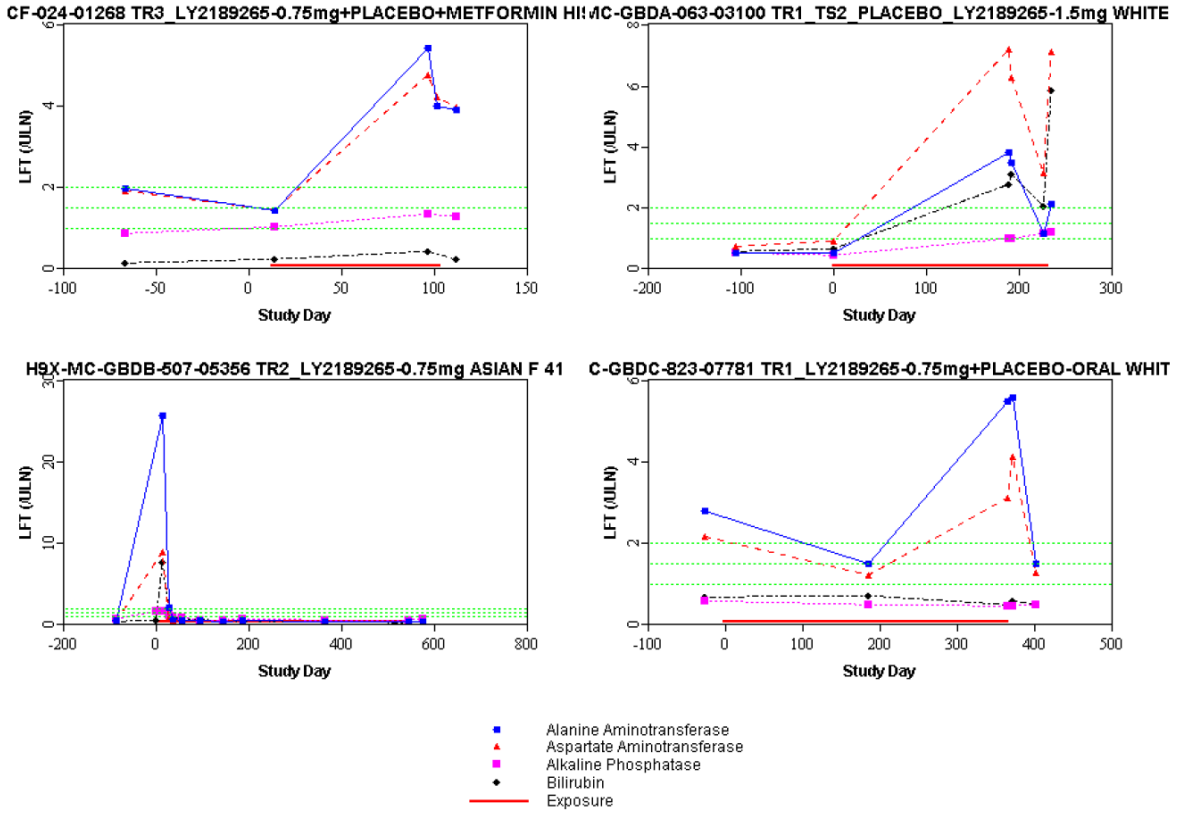
Since specific hepatic enzyme elevations patterns may indicate hepatocellular injury or biliary obstruction, these analytes were reviewed for mean changes and categorical shifts.

There was no clinically significant change in mean or median values for hepatic enzymes compared to baseline (See Appendix 9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.APP.681).

Treatment-emergent ALT, AST, GGT and total bilirubin elevations were comparable between placebo and dulaglutide (AS1), and between the two dulaglutide doses (AS3) (see Appendix 9.6 Supportive Tables From the ISS Referenced in the Review-Table ISS.6.155-157).

Narratives for individual patients in all phase 2/3 studies who had clinically important enzyme elevations (fulfilled Hy's law criteria, ALT elevations over 5 xULN, ALT elevations over 3 x ULN on at-least 3 consecutive visits and total bilirubin over 3 xULN) are discussed below. Plots of enzyme elevations in ALT over 5 x ULN in individual dulaglutide patients, along with AST, bilirubin and AP, with their time course are also shown below (Figure 14).

Figure 14: Plots of Liver enzymes over time in Dulaglutide Treated Patients with ALT elevations over 5 X ULN or fulfilled Hy's Law Criteria



Source: Reviewer Generated using WebSDM software, data source: SDTM datasets from phase 2 and 3 studies.

The particular laboratory profile of ALT elevation >3x ULN seen concurrently with bilirubin >2x ULN has been referred to as Hy's Law. It has been used to identify a drug likely to cause severe drug-induced liver injury (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases[22]. A key caveat to use of Hy's Law is that in addition to lab abnormalities, there needs to be no other explanation for the laboratory test abnormalities. Elevations in ALT > 5x ULN are also considered a concerning finding. Only dulaglutide treated patients fulfilled Hy's law laboratory test criteria or had ALT elevations over 5x ULN. Narratives of these patients follow.

22 FDA Guidance for industry, Drug –Induced liver injury: pre-marketing evaluation; July 2009

Patients meeting Hy's law laboratory criteria:

GBDA-063-3100, 63 yr. M, Placebo/Dulaglutide 1.5 mg): This was a 63-year-old white male with a medical history of T2DM with neuropathy, hypertension, hypercholesterolemia, atrial fibrillation, and obesity. Concomitant medications included metoprolol and simvastatin. He was taking metformin and pioglitazone as background study medications. At baseline, all of his hepatic analytes were within the normal limits (ALT: 26 U/L; AST: 41 U/L; total bilirubin: 14 μ mol/L; AP: 64 U/L) except GGT which was 154 U/L (>3x ULN). At his 26-week visit, at the end of the placebo treatment period, his ALT was 3.8x ULN, AST 7.2x ULN, and total bilirubin 2.8x ULN. Alkaline phosphatase was not elevated, but GGT was remarkably elevated (>43x ULN). Repeat testing confirmed an AST >3x ULN and total bilirubin >2x ULN without a significant elevation in AP, but with a GGT >17x ULN. At 26 weeks, the patient began treatment with dulaglutide 1.5 mg and received 5 doses. At Week 39, laboratory values for ALT were 2.1x ULN, for AST 7.1x ULN, for total bilirubin 5.9x ULN, and for GGT >23x ULN. At that time, the patient was discontinued from the study due to admitting that he had a significant binge alcohol drinking problem.

Reviewer's comment: The patient had alcoholic liver disease consistent with the pattern of abnormal analytes (high baseline GGT and relatively higher AST versus ALT). Since similar severe elevations in AST, GGT, and bilirubin occurred during placebo period, association to dulaglutide is not likely.

GBDB-507-5356, 41 yr. F, Dulaglutide 0.75 mg: This was a 41-year-old female patient and her medical history included dyslipidemia and T2DM. There was no history of viral hepatitis or other liver disease. Concomitant medications included atorvastatin, miglitol, and glimeperide. At baseline, all hepatic analytes were normal. Approximately 1 week after randomization, she reported fever and jaundice and hepatic analytes were found to be remarkably abnormal: ALT >25x ULN, AST >8x ULN, total bilirubin >7x ULN, and AP <2x ULN. Study drug was temporarily held pending further evaluation of these acute abnormalities. Viral serology was consistent with an acute infection with hepatitis E. The abnormal analytes returned to normal within 4 weeks. After discussion with the investigator, because a clear cause of the elevations in analytes was determined, the study drug was rechallenged. No further elevations were recorded, and the patient completed the study

Reviewer's comment: This patient's clinical presentation and laboratory work-up is consistent with viral hepatitis.

ALT elevation > 5 X ULN:

GBCF-024-1268, 60 yr. F, Dulaglutide 0.75 mg: This case involves a 60-year-old female and medical history included T2DM and hypercholesterolemia. Concomitant

medications included lovastatin and “nictinam”. The patient was taking metformin as study concomitant therapy. ALT and AST were approximately 2x ULN at screening. Total bilirubin and AP were normal. By 12 weeks, ALT was >5x ULN and AST >4x ULN. Total bilirubin and AP were <2x ULN. Alanine aminotransferase and AST were approximately 4x ULN at the time of last report (Week 26). The patient stopped participation in the study due to the increased hepatic enzymes.

Reviewer’s comment: This case is confounded by baseline elevations of hepatic enzymes and concomitant intake of lovastatin. However, association to dulaglutide cannot be excluded.

GBDC-823-7781, 55 yr. M, Dulaglutide 0.75 mg: This case concerns a 55-year-old male with T2DM. Concomitant medications included bromazepam. This patient had normal total bilirubin and AP, with other hepatic analytes elevated at baseline (ALT: 2.8x ULN; AST: 2.2x ULN; GGT: approximately 6x ULN). At 26 weeks, the values had decreased (ALT: 1.5x ULN; AST: 1.2x ULN; GGT: approximately 2x ULN). At 52 weeks, the values were elevated closer to baseline. However, ALT did reach 5.5x ULN at this time point. The patient completed the study without any reported hepatic adverse events. By 30 days after the Patient’s last visit (LV30), values were less than baseline.

Reviewer’s comment: This case is confounded by baseline enzyme elevations and fluctuations on treatment, but association to dulaglutide cannot be excluded since enzymes were normal at LV30.

To review all potential signals for cholestasis or hepatocellular injury, patient narratives for ALT/AST over 3 X ULN and elevated bilirubin were also reviewed.

Additional Patients with ALT or AST More than 3x ULN on at least 3 Consecutive Visits/Measurements:

One patient on dulaglutide and 3 comparator patients (sitagliptin-2, placebo-1) fulfilled these criteria. The narrative for the dulaglutide treated patient was as follows:

GBDB-703-7162, 69 yr. F, Dulaglutide 0.75 mg: This case involved a 69-year-old female with a medical history of *hepatic steatosis,* hypertension, and dyslipidemia. Concomitant medications included indapamide, perindopril, amlodipine, candesartan, amiloride and silimarina (milk thistle extract). Increases from baseline to 3x to 3.2x ULN in ALT observed at 44weeks were confirmed and remained present at safety follow-up (LV30). Alkaline phosphatase and total bilirubin were not >2x ULN.

Other dulaglutide treated patients with total bilirubin ≥ 2X ULN:

There were numerically more cases of patients with a total bilirubin ≥ 2x ULN in the dulaglutide treated (dulaglutide-7 [0.17%], comparator-1 [0.05%]) but they all had bilirubin elevations at baseline or a diagnosis of Gilbert's syndrome. There was one patient (patient GBDB-453-4677) where the increase from baseline values in total bilirubin secondary to study drug cannot be excluded since there was a positive de-challenge. All other cases had alternate explanations and none had elevations in AP (which would suggest cholestasis) or concomitant ALT elevations > 3X ULN. A review of these cases follows:

GBCJ-015-1500, 29 yr. F, Dulaglutide 1.0 mg/1.0 mg): This was a 29-year-old Hispanic female with a history of Gilbert's syndrome. Total bilirubin was 2.1x ULN (44 mmol/L) at screening and remained elevated at 16 weeks (1.4x ULN [29 mmol/L]). The increased bilirubin was primarily indirect bilirubin (37 mmol/L screening, 24 mmol/L at 16 weeks) which is consistent with Gilbert's syndrome. Alkaline phosphatase (AP) and transaminases were within normal limits throughout study participation.

GBDB-201-2058, 55 yr. M, Dulaglutide 1.5 mg: This is a 55-year-old white male with a medical history of bipolar disorder. This patient had elevated values for total bilirubin and direct bilirubin at screening (2.0x ULN [41 mmol/L], 1.4x ULN [7 mmol/L], respectively) and throughout the study. No elevations in transaminases or AP were reported.

GBDB-453-4677, 68 yr. M, Dulaglutide 1.5 mg: This case concerns a 68-year-old male. His medical history included hypertension. This patient had elevations in total bilirubin at baseline (1.3x ULN) that generally persisted throughout the study. At the 52-week visit the only elevations in transaminases were observed (ALT 2.0x ULN; AST 1.1x ULN). At this visit total bilirubin was 2.9x ULN and direct bilirubin remained stable at 1.8x ULN. These abnormal analytes were repeated and back to baseline within 1 week, but his direct bilirubin remained in the range of 1.4x to 1.8x ULN.

GBDD-304-4402, 75 yr. M, Dulaglutide 0.75 mg: This case refers to a 75-year-old male. His medical history included hepatic steatosis, coronary artery disease, and Gilbert's syndrome. While exposed to study drug, the patient's total bilirubin and direct bilirubin remained near 2x ULN.

Patient GBCZ-121-2104, 58 yr. M, Dulaglutide 0.75 mg): This case pertains to a 58-year old male. The patient had a history of hyperlipidemia, hypertension, and panic disorder. concomitant medications were metformin, amlodipine besilate, candesartan cilexetil, atorvastatin calcium and paroxetine for panic disorder. The patient entered the study with total bilirubin 46 μ mol/L and GGT 108 U/L, each approximately 2x ULN. The total bilirubin values continued to be elevated throughout study (1.2x to 2.1x ULN). Transaminases, ALT, and AST remained less than ULN throughout the study as did AP. The patients direct bilirubin was near normal (<1.5x ULN) throughout the study.

Reference ID: 3609106

Other Hepatic SAEs:

There was one case of an SAE related to hepatic failure. This case came from the hepatic impairment clinical pharmacology study.

Hepatic steatosis and abdominal pain:

GBDD-017-0910, 64 yr. F, Dulaglutide 1.5 mg: This was a 64-year-old white female. Medical illnesses included T2DM, peripheral neuropathy, hyperlipidemia, hepatic steatosis, and history of cholecystectomy. She was taking gabapentin and fenofibrate as concomitant medications. The patient was exposed to 49 weeks of treatment with dulaglutide 1.5 mg. Approximately 4 months after completing the study, she reported serious abdominal pain and was hospitalized for the same. Work up revealed normal blood chemistries including ALT, AST, bilirubin, amylase, hemoglobin, hematocrit, white blood cells, and platelets. Abdominal ultrasound revealed hepatosplenomegaly and patent hepatic, splenic, and portal veins. She improved and was discharged as recovered with post-study SAEs recorded as hepatic steatosis and abdominal pain.

Reviewer's Comment: Medical history of hepatic steatosis was reported, although a contributory association to dulaglutide for progression to cirrhosis cannot be excluded.

Reviewer's Hepatic Safety Assessments:

Though there were two patients on dulaglutide with hepatic enzyme elevations that satisfied Hy's Law criteria, alternate etiologies (alcoholic liver disease and viral hepatitis) were present to explain the elevations. An additional five patients on dulaglutide had total bilirubin elevations > 2X ULN. None of these had concomitant elevations of AP to suggest cholestasis, and all had baseline elevations or a diagnosis of Gilbert's syndrome. Although the overall exposure with dulaglutide does not allow any definitive conclusions regarding drug-induced liver injury or cholestasis, there does not appear to be a significant hepatic safety signal based on available data.

- 7.3.3.2 Neoplasms

(Pancreatic cancer and thyroid cancer are discussed in Section 7.3.2)

Concerns have arisen that various diabetes treatments may be associated with malignancies[23],[24],[25]. As a result, the dulaglutide program was reviewed for imbalances in any malignancy.

The total number of neoplasms was small (n=89). Overall the incidence of neoplasms appeared balanced between dulaglutide and all comparators (Table 84:). Dose dependency could not be assessed due to the small number of events.

23 Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, Vaughn DJ, Nessel L, Selby J, Strom BL. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care.* 2011;34(4):916-922.

24 Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia*. 2009; 52(9):1732-1744.

25.http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl

Table 84: Exposure Adjusted Incidence of Patients with Treatment-Emergent Malignancies and Unspecified Tumors, All Post-baseline Observations Through Safety Follow-up – Phase 2 and 3 Studies (Safety Population)

	Number (%) of Patients [Number of Events/1000 Patient-Years of Exposure]					
		Active Comparator				
Location of Cancer Cancer Type	Placebo (N=703)	Metformin (N=268)	Sitagliptin (N=439)[a]	Exenatide BID (N=276)	Insulin Glargine (N=558)	Dulaglutide (N=4006)[b]
Patient Year Exposure(pt-yrs)	284	227	637	236	621	3531
Number (%) of patients with any malignancy or unspecified tumor[c]	**7 (1.0) [24.6]**	**0**	**9 (2.1) [14.1]**	**3 (1.1) [12.7]**	**12 (2.2) [19.3]**	**48 (1.2)[d,e] [13.6]**
Thyroid	**0**	**0**	**1 (0.2) [1.57]**	**1 (0.4) [4.23]**	**2 (0.4) [3.22]**	**7 (0.2)[d] [1.98]**
Thyroid neoplasm	0	0	1 (0.2) [1.57]	1 (0.4) [4.23]	2 (0.4) [3.22]	5 (0.1) [1.42]
Thyroid cancer	0	0	0	0	0	3 (0.1)[h] [0.85]
Breast	**0**	**0**	**1 (0.2)[1.57]**	**0**	**2 (0.4) [3.22]**	**6 (0.1) [1.70]**
Breast cancer	0	0	1 (0.2) [1.57]	0	2 (0.4) [3.22]	4 (0.1) [1.13]
Breast cancer in situ	0	0	0	0	0	1 (<0.1)[f] [0.28]
Breast cancer metastatic	0	0	0	0	0	1 (<0.1) [0.28]
Skin	**4 (0.6) [14.08]**	**0**	**1 (0.2) [1.57]**	**0**	**1 (0.2) [1.61]**	**10 (0.2) [2.83]**
Basal cell carcinoma	0	0	1 (0.2) [1.57]	0	0	7 (0.2)[e] [1.98]
Neoplasm skin	2 (0.3) [7.04]	0	0	0	0	0
Malignant melanoma	2 (0.3) [7.04]	0	0	0	0	0
Skin cancer	0	0	0	0	1 (0.2) [1.61]	1 (<0.1) [0.28]
Squamous cell carcinoma of skin	0	0	0	0	0	1 (<0.1) [0.28]
Bowen's disease	0	0	0	0	0	1 (<0.1) [0.28]
Ear, nose, or throat	**0**	**0**	**1 (0.2) [1.57]**	**0**	**0**	**1 (<0.1) [0.28]**
Laryngeal cancer stage 3	0	0	1 (0.2) 1.57]	0	0	0
Vocal cord neoplasm	0	0	0	0	0	1 (<0.1) [0.28]

	Number (%) of Patients [Number of Events/1000 Patient-Years of Exposure]					
		Active Comparator				
Location of Cancer Cancer Type	Placebo (N=703)	Metformin (N=268)	Sitagliptin (N=439)	Exenatide BID (N=276)	Insulin Glargine (N=558)	Dulaglutide (N=4006)
Gastrointestinal	**1 (0.1) [3.52]**		**1 (0.2) [1.57]**	**1 (0.4) [4.23]**	**2 (0.4) [3.22]**	**11 (0.3) [3.12]**
Tongue neoplasm[g]	0	0	0	0	0	1 (<0.1) [0.28]
Tongue carcinoma stage 1	0	0	0	0	0	1 (<0.1) [0.28]
Oesophageal adenocarcinoma	1 (0.1) [3.52]	0	0	0	0	0
Colon cancer	0	0	0	1 (0.4) [4.23]	0	2 (<0.1) [0.57]
Rectal neoplasm	0	0	0	0	0	1 (<0.1) [0.28]
Gastrointestinal stromal tumour	0	0	0	0	0	1 (<0.1) [0.28]
Gastric neoplasm	0	0	0	0	0	1 (<0.1) [0.28]
Rectal cancer	0	0	0	0	2 (0.4) [3.22]	0
Gallbladder cancer	0	0	0	0	0	1 (<0.1) [0.28]
Gastric cancer	0	0	1 (0.2) [1.57]	0	0	1 (<0.1) [0.28]
Pancreatic carcinoma	0	0	0	0	0	2 (<0.1) [0.57]
Lung	**0**	**0**	**2 (0.5) [3.14]**	**0**	**2 (0.4) [3.22]**	**2 (<0.1) [0.57]**
Lung neoplasm	0	0	2 (0.5) [3.14]	0	1 (0.2) [1.61]	2 (<0.1) [0.57]
Non-small cell cancer of lung	0	0	0	0	1 (0.2) [1.61]	0
Other	**2 (0.3) [7.04]**	**0**	**2 (0.5) [3.14]**	**1 (0.4) [4.23]**	**3 (0.5) [4.83]**	**12 (0.3) [3.40]**
Non-secretory adenoma of pituitary	1 (0.1)[f] [3.52]	0	0	0	0	0
Chronic lymphocytic leukemia	0	0	0	0	0	1 (<0.1) [0.28]
Prostate cancer	1 (0.1) [3.52]	0	1 (0.2) [1.57]	1 (0.4) [4.23]	1 (0.2) [1.61]	1 (<0.1) [0.28]
Prostate cancer stage 0	0	0	0	0	0	2 (<0.1) [0.57]
Uterine cancer	0	0	1 (0.2) [1.57]	0	0	0
Liposarcoma	0	0	0	0	0	1 (<0.1)[e] [0.28]
Squamous cell carcinoma	0	0	0	0	0	1 (<0.1) [0.28]

Location of Cancer Cancer Type	Number (%) of Patients [Number of Events/1000 Patient-Years of Exposure]					
		Active Comparator				
	Placebo (N=703)	Metformin (N=268)	Sitagliptin (N=439)	Exenatide BID (N=276)	Insulin Glargine (N=558)	Dulaglutide (N=4006)
Other (concluded)	--	--	--	--	--	--
Adenocarcinoma	0	0	0	0	0	1 (<0.1) [0.28]
Testicular seminoma (pure)	0	0	0	0	0	1 (<0.1) [0.28]
Transitional cell carcinoma	0	0	0	0	0	1 (<0.1) [0.28]
Multiple myeloma	0	0	0	0	0	1 (<0.1) [0.28]
Non-Hodgkins lymphoma	0	0	0	0	0	1 (<0.1) [0.28]
Vaginal neoplasm	0	0	0	0	1 (0.2) [1.61]	0
B-cell small lymphocytic lymphoma	0	0	0	0	1 (0.2) [1.61]	0
Renal neoplasm	0	0	0	0	0	1 (<0.1) [0.28]

Abbreviations: BID = twice daily; N = number of patients with event in specified location.

Source: ISS Table 6.158, page 637

Data from the 4 month safety update remains blinded (Table 85). The incidence of neoplasms in the blinded studies were reviewed and compared to the incidence in the completed program to determine whether unblinding of treatment assignments was needed for the neoplasms reported. Most malignancies had an incidence comparable to that seen in the completed program. There were a few numerical imbalances noted, where more blinded cases were reported in the 4-month safety update:

- Lung cancer: There were seven cases of malignant lung neoplasm in the blinded data submitted with the 4 month safety update compared to none reported in the dulaglutide treated patients and one case of non-small cell lung cancer in a patient treated with insulin glargine from the completed studies.
- Breast cancer: There were nine cases of breast cancer in the blinded data submitted with the 4 month safety update compared to six cases in the dulaglutide treated patients and three cases in the “all comparator” group from the completed studies.
- Prostate cancer: There were 14 cases of prostate cancer in the blinded data submitted with the 4 month safety update compared to three cases in the dulaglutide treated patients and four in the “all comparator” group from the completed studies.

Given the large size of the safety population and the still relatively small number of cases, these additional cases are unlikely to substantially change the incidence or event-rate for these malignancies. I did not think it necessary or useful to unblind these additional cases.

Table 85: Summary and Analysis of Medical Query: Any Malignant or Unspecified Tumor – All Observations During the Planned Treatment Period (Safety Population)

Level 1 Level 2 Level 3 Preferred Term	Completed All_Dula (N=4006) n (%)	Ongoing Blinded, excluding GBDJ (N=3310) n (%)	Ongoing Blinded, GBDJ (N=9776) n (%)
Any Malignant or Unspecified Tumour	46 (1.1)	17 (0.5)	90 (0.9)
Narrow	46 (1.1)	17 (0.5)	90 (0.9)
Basal cell carcinoma	7 (0.2)	0 (0.0)	10 (0.1)
Thyroid neoplasm	5 (0.1)	2 (<0.1)	5 (<0.1)
Breast cancer	4 (<0.1)	0 (0.0)	8 (<0.1)
Colon cancer	2 (<0.1)	2 (<0.1)	0 (0.0)
Lung neoplasm	2 (<0.1)	0 (0.0)	1 (<0.1)
Pancreatic carcinoma	2 (<0.1)	1 (<0.1)	2 (<0.1)
Prostate cancer stage 0	2 (<0.1)	0 (0.0)	0 (0.0)
Thyroid cancer	2 (<0.1)	0 (0.0)	1 (<0.1)
Adenocarcinoma	1 (<0.1)	0 (0.0)	1 (<0.1)
Bowen's disease	1 (<0.1)	0 (0.0)	0 (0.0)
Breast cancer metastatic	1 (<0.1)	0 (0.0)	1 (<0.1)
Chronic lymphocytic leukaemia	1 (<0.1)	1 (<0.1)	1 (<0.1)
Gallbladder cancer	1 (<0.1)	0 (0.0)	1 (<0.1)
Gastric cancer	1 (<0.1)	2 (<0.1)	2 (<0.1)
Gastric neoplasm	1 (<0.1)	0 (0.0)	0 (0.0)
Gastrointestinal stromal tumour	1 (<0.1)	0 (0.0)	0 (0.0)
Liposarcoma	1 (<0.1)	0 (0.0)	0 (0.0)
Multiple myeloma	1 (<0.1)	0 (0.0)	0 (0.0)
Non-Hodgkin's lymphoma	1 (<0.1)	0 (0.0)	0 (0.0)
Prostate cancer	1 (<0.1)	2 (<0.1)	12 (0.1)
Rectal neoplasm	1 (<0.1)	0 (0.0)	0 (0.0)
Renal neoplasm	1 (<0.1)	0 (0.0)	0 (0.0)
Skin cancer	1 (<0.1)	0 (0.0)	2 (<0.1)
Squamous cell carcinoma	1 (<0.1)	0 (0.0)	1 (<0.1)
Squamous cell carcinoma of skin	1 (<0.1)	0 (0.0)	4 (<0.1)
Testicular seminoma (pure)	1 (<0.1)	0 (0.0)	0 (0.0)
Tongue carcinoma stage I	1 (<0.1)	0 (0.0)	0 (0.0)
Tongue neoplasm	1 (<0.1)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	1 (<0.1)	0 (0.0)	0 (0.0)
Vocal cord neoplasm	1 (<0.1)	0 (0.0)	0 (0.0)
Adrenal neoplasm	0 (0.0)	0 (0.0)	1 (<0.1)
Angiosarcoma	0 (0.0)	0 (0.0)	1 (<0.1)
Basosquamous carcinoma of skin	0 (0.0)	0 (0.0)	1 (<0.1)
Bile duct cancer	0 (0.0)	1 (<0.1)	0 (0.0)
Bladder cancer	0 (0.0)	1 (<0.1)	2 (<0.1)
Bladder neoplasm	0 (0.0)	0 (0.0)	2 (<0.1)
Bladder transitional cell carcinoma	0 (0.0)	0 (0.0)	1 (<0.1)
Bone neoplasm	0 (0.0)	0 (0.0)	1 (<0.1)
Breast neoplasm	0 (0.0)	0 (0.0)	1 (<0.1)
Cardiac neoplasm unspecified	0 (0.0)	0 (0.0)	1 (<0.1)
Cervix carcinoma stage III	0 (0.0)	0 (0.0)	1 (<0.1)
Colon neoplasm	0 (0.0)	1 (<0.1)	2 (<0.1)
Colorectal cancer	0 (0.0)	0 (0.0)	1 (<0.1)
Diffuse large B-cell lymphoma	0 (0.0)	0 (0.0)	1 (<0.1)
Duodenal neoplasm	0 (0.0)	1 (<0.1)	0 (0.0)
Fibrosarcoma	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatic neoplasm	0 (0.0)	0 (0.0)	1 (<0.1)
Intestinal adenocarcinoma	0 (0.0)	0 (0.0)	1 (<0.1)
Keratoacanthoma	0 (0.0)	0 (0.0)	1 (<0.1)
Laryngeal cancer	0 (0.0)	0 (0.0)	1 (<0.1)
Lung cancer metastatic	0 (0.0)	0 (0.0)	1 (<0.1)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	6 (<0.1)
Malignant melanoma	0 (0.0)	0 (0.0)	3 (<0.1)
Metastases to adrenals	0 (0.0)	0 (0.0)	1 (<0.1)
Metastases to liver	0 (0.0)	0 (0.0)	3 (<0.1)
Nasal sinus cancer	0 (0.0)	0 (0.0)	1 (<0.1)
Neoplasm	0 (0.0)	1 (<0.1)	0 (0.0)
Neoplasm malignant	0 (0.0)	0 (0.0)	1 (<0.1)
Neoplasm prostate	0 (0.0)	0 (0.0)	1 (<0.1)
Oesophageal adenocarcinoma	0 (0.0)	0 (0.0)	1 (<0.1)
Oesophageal carcinoma	0 (0.0)	0 (0.0)	1 (<0.1)

Level 1 Level 2 Level 3 Preferred Term	Completed All_Dula (N=4006) n (%)	Ongoing Blinded, excluding GBDJ (N=3310) n (%)	Ongoing Blinded, GBDJ (N=9776) n (%)
Ovarian cancer	0 (0.0)	1 (<0.1)	0 (0.0)
Ovarian neoplasm	0 (0.0)	1 (<0.1)	0 (0.0)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	1 (<0.1)
Rectal cancer	0 (0.0)	1 (<0.1)	0 (0.0)
Renal cancer	0 (0.0)	0 (0.0)	2 (<0.1)
Renal cell carcinoma	0 (0.0)	0 (0.0)	1 (<0.1)
Soft tissue neoplasm	0 (0.0)	1 (<0.1)	0 (0.0)
Tonsil cancer	0 (0.0)	0 (0.0)	1 (<0.1)
Urinary tract neoplasm	0 (0.0)	0 (0.0)	1 (<0.1)

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Abbreviations: Dula = dulaglutide; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event.

Note: Safety population refers to safety population of both completed submission studies and ongoing blinded studies. Completed submission studies include GBCF, GBCJ, GBCK, GBCE, GBDA, GBDB, GBDC, GBDD and GBDN; Ongoing blinded studies include GBCG, GBDE, GBDG, GBDJ, GBDK, GBDP, GBDQ, GBDX, and GBDY.
Completed All_Dula refers to all dulaglutide treatment groups combined in completed submission studies.
Ongoing blinded refers to all treatment groups combined in ongoing blinded studies.

MedDRA Version 15.0 for completed submission studies and MedDRA Version 16.0 for ongoing blinded studies.

GBDJ- Ongoing CV outcome study.
Source: Table 26, 4-month Safety Update report, Page-83

The listings in the ISS were reviewed to determine if there might be any unusual presentations of solid tumors or hematologic malignancies in terms of age/sex for patients exposed to dulaglutide. Narratives under SAEs were also reviewed (see Appendix 9.6 Supportive Tables From the ISS Referenced in the Review- Table ISS.APP.731). Narratives reported as SAEs (excluding pancreatic and thyroid cancers, which were discussed earlier) were reviewed for any unusual presentations (e.g. unexpected age at diagnosis), and presentations in patients with no known risk factors. Overall the solid tumors and hematologic malignancies occurred in the expected age-groups, with no unexpected presentation or findings which would suggest a safety signal.

<u>Reviewer's Conclusions about Neoplasms (other than pancreatic and thyroid cancers):</u>

Based on the available data, there is no apparent signal of concern for solid tumor or hematological malignancies.

7.3.4 Other Nonfatal Serious Adverse Events

Nonfatal serious adverse events in the placebo controlled (AS1) pool and all comparator pools (AS7), that occurred in two or more persons and more frequently with dulaglutide treated patients are listed below (Table 86 and Table 87). Though these events had numerically more patients treated with dulaglutide, the incidences were not markedly different. This is due to the small number of events and the size of the study population.

Table 86: Summary of Serious Adverse Events by Preferred Term, Occurring in Two or More Dulaglutide-Treated Patients, Observations Through 26 Weeks of the Planned Treatment Period – (AS1)

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

Abbreviations: Dula = dulaglutide; N = total number of patients in specified treatment arm; SAE = serious adverse event.

Source Table ISS.6.19, page 225

Table 87: All Dulaglutide versus All Comparator Analysis of Serious Adverse Events, By Preferred Term within System Organ Class ≥ 2 and More Frequent in dulaglutide treated persons, All Postbaseline Observations Including Safety Follow-Up (AS7) (Cardiac Disorders, Cerebrovascular Accidents under Nervous System Disorders, Hepatobiliary disorders, and Neoplasms excluded)

SOC • **PT**	**All Comp (N=1844) n (%)**	**Dula 0.75 (N=1671) n (%)**	**Dula 1.5 (N=1671) n (%)**	**All Dula (N=3342) n (%)**
Gastrointestinal disorders:				
• Gastrointestinal hemorrhage	0 (0.0)	2 (0.1)	0 (0.0)	2 (<0.1)
• Lower gastrointestinal hemorrhage	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)
• Gastritis	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)
• Colitis	0 (0.0)	2 (0.1)	0 (0.0)	2 (<0.1)
General disorders and administration site conditions				
• Non-cardiac chest pain	3 (0.2)	3 (0.2)	4 (0.2)	7 (0.2)
• Fatigue	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)

SOC • **PT**	**All Comp (N=1844) n (%)**	**Dula 0.75 (N=1671) n (%)**	**Dula 1.5 (N=1671) n (%)**	**All Dula (N=3342) n (%)**
Infections and infestations				
• Appendicitis	2 (0.1)	4 (0.2)	4 (0.2)	8 (0.2)
• Pneumonia	3 (0.2)	8 (0.5)	2 (0.1)	10 (0.3)
• Urinary Tract Infection	2 (0.1)	5 (0.3)	2 (0.1)	7 (0.2)
• Pyelonephritis acute	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1
• Cystitis	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
• Cellulitis	2 (0.1)	2 (0.1)	3 (0.2)	5 (0.1)
• Localized infection	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)
• Sepsis	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
• Subcutaneous abscess	0 (0.0)	2 (0.1)	0 (0.0)	2 (<0.1)
Injury, poisoning and procedural complications				
• Fall	1 (<0.1)	3 (0.2)	4 (0.2)	7 (0.2)
• Meniscus lesion	0 (0.0)	2 (0.1	2 (0.1)	4 (0.1)
• Subdural hematoma	0 (0.0)	2 (0.1)	1 (<0.1)	3 (<0.1)
• Overdose	0 (0.0)	0 (0.0)	3 (0.2)	3 (<0.1)
Investigations				
• Blood calcitonin increased	0 (0.0)	3 (0.2)	0 (0.0)	3 (<0.1)
Metabolism and nutrition disorders				
• Hyperglycemia	1 (<0.1)	0 (0.0)	4 (0.2)	4 (0.1)
• Dehydration	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Musculoskeletal and connective tissue disorders:				
• Neck pain	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)
• Intervertebral disc protrusion	0 (0.0)	1 (<0.1)	2 (0.1)	3 (<0.1)
Nervous System disorders:				
• Syncope:	1 (<0.1)	5 (0.3)	2 (0.1)	7 (0.2)
• Sciatica	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Pregnancy, Puerperium and Perinatal conditions:				
• Pregnancy	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)
Renal and urinary disorders				
• Calculus ureteric	1 (<0.1)	3 (0.2)	3 (0.2)	6 (0.2)
• Hematuria	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Respiratory, thoracic and mediastinal disorders				
• Dyspnea	0 (0.0)	4 (0.2)	0 (0.0)	5 (0.1)
Surgical and medical procedures				
• Knee arthroplasty	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)

Source: Data from Table APP.5.2, Applicant's response to IR dated April 21, 2014

Nonfatal serious gastrointesinal events:

Due to the known effect of GLP-1 agonists on GI motility, the SAEs for gastritis, GI bleed and colitis were reviewed for any unusual presentations and for adverse events that could be linked to delayed gastric emptying or reduced GI motility (Table 88). Narratives for SAEs with the PT "Abdominal pain" are discussed in 7.3.2.2 Pancreatitis.

Table 88: Narrative Review for Gastrointestinal Disorders Reported as SAEs

USUBJID	Exposure	Details for PTs of Gastritis, GI bleed and Colitis
GBCF-946-3308 56 Yr. F Dula 1.5 mg	5 days	Reported as drug induced gastritis, no known risk factors, history of vomiting and loss of appetite.
GBDA-104-5241. 72 yr. F Dula 1.5 mg	3 months	The patient was hospitalized with dehydration, uncontrollable vomiting, acute gastritis, and rule out gastroparesis. an endoscopy revealed mild edematous gastritis, no history of known risk factors
GBDA-007-0329 53 yr. M Dula 1.5 mg	330 days	Hospitalized for vomiting and dehydration. Erosive gastritis/esophagitis /diverticulum on EGD. Had history of GERD
GBCF-706-6955 60 yr. old F Dula 1.5 mg	7 months	Lower GI bleed (source not identified) with no prior history of GI disorder. Attributed to aspirin and study drug, discontinued study drug one month later.
GBDD-554-6150 67 yr. old F Dula 1.5 mg	5 months	GI (hemorrhoid) bleed associated with sepsis hospitalization secondary to erysipelas.
GBDB-402-4101 63 yr. F Dula 1.5 mg	10 months	History of CAD on clopidogrel, hospitalized for anemia and GI bleed. Colonoscopy- angioplasia of cecum, EGD- enteric metaplasia and gastritis.
GBDD-250-4022 59 yr. F Dual 0.75 mg	One month	History of gastritis, on ASA for CAD. Hospitalized for GI bleed (+occult blood in stool), anemia and worsening CAD. Study drug discontinued
GBDC-123-2300 52 yr. F Dual 0.75	5 months	Hospitalized for abdominal pain bloody diarrhea. Treated for colitis with antibiotics..
GBDD-004-0263 53 yr. old F Dula 0.75 mg.	2 months	History of colitis and GERD. Hospitalized for exacerbation of colitis- presented with nausea, vomiting , diarrhea, fever and dehydration

Source: Reviewer generated, adapted from the TOSNP, eCTD 5.3.5.3.

Reviewer's Comment: The three SAEs of gastritis on dulaglutide 1.5 mg appear to be associated to study drug.

Narratives for appendicitis were reviewed (Table 89) to confirm diagnosis and to look for any potential missed cases of gastrointestinal intolerance/pancreatitis.

Table 89: Narrative Review for Appendicitis SAEs on Dulaglutide

USUBJ ID	Age/Sex	Dose	Diagnosis
GBCF-205-4227.	47/F	Dula 1.5 mg	Tubo-ovarian abscess and reactive appendicitis
GBDA-082-4064	37/M	Dula 1.5 mg	Appendicitis-presentation and w/u unavailable. Study drug continued
GBDC-102-0207	44/F	Dula 1.5 mg	CT report –"thickening and dilation of the appendix with acute inflammation, consistent with acute appendicitis"
GBDN-101-3004	51/M	Dula 1.5 mg	Acute gangrenous appendicitis on pathology report.
GBDA-007-0329	53/M	Dula 0.75 mg	Post-operative diagnosis was" Acute perforated appendicitis"
GBDA-021-1021	51/M	Dula 0.75 mg	Presented with abdominal pain, had appendectomy, study drug continued.
GBDA-302-7208	55/M	Dula 0.75 mg	Hospitalized for right flank pain with nausea/vomiting, had an open appendectomy, study drug continued
GBDD-101-3086.	53/M	Dula 0.75 mg	Intraoperative diagnosis-"acute gangrenous appendicitis"

Source: Reviewer generated, adapted from the TOSNP, eCTD 5.3.5.3.

Reviewer's Comment: All the narratives appear consistent with appendicitis, Except for two patients for whom study drug was continued, none of the presentations are suggestive of appendicitis as an incidental diagnosis with upper abdominal pain secondary to study drug.

Nonfatal serious pneumonia events:

An imbalance in pneumonia events was noted in the albiglutide clinical program (1.8% with albiglutide vs. 0.8% with all comparator, more SAEs on albiglutide [0.4% vs. 0.1%]). This was not seen with other approved drugs in class. Albiglutide is the only other approved GLP-1 agonist that's also a fusion protein. There were 33 (1.0%) events with all dulaglutide compared to 15 (0.8%) with all comparator. The imbalance seems minimal in this program, but clinical events reported as SAEs were reviewed for any unusual presentations (Table 90).

Table 90: Narrative review for Pneumonias on Dulaglutide

USUBJID	Age/Sex	Dose	Details (including fatal or requiring respiratory support etc.)
GBDB-700-7007	44/M	Dula 1.5 mg	Hospitalized for bronchopneumonia, 80 pack year smoking history
GBDC-118-1818	*64/F*	Dula 1.5 mg	Right upper lobe pneumonia (streptococcus) with bacteremia. No report of respiratory failure.
GBDD-150-3401	62/M	Dula 1.5 mg	Hospitalized for Pneumonia, current smoker, No report of respiratory failure.
GBCJ-001-0114	39/M	Dula 1.0/ 2 mg	Hospitalized for Community-acquired Pneumonia, no risk-factors, No report of respiratory failure.
GBDA-051-2529	50/F	Dula 0.75 mg	History of morbid obesity, asthma, bronchitis, obstructive sleep apnea. Hospitalized for asthma and Pneumonia. , No report of respiratory failure. Study drug was discontinued.
GBDA-060-2971.	69/M	Dula 0.75 mg	History of paroxysmal atrial fibrillation/atrial flutter. Hospitalized for Pneumonia and congestive heart failure, early interstitial lung disease-possibly amniodarone induced, No report of respiratory failure. Study drug discontinued
GBDB-653-6665	64/F	Dula 0.75 mg	History of CAD, Parkinson's disease and heart failure. Hospitalized for Pneumonia. No report of respiratory failure.
GBDD-002-0160	50/M	Dula 0.75 mg	Hospitalized for Pneumonia and congestive heart failure. No report of respiratory failure. History of CAD, lymphoma , pleural effusions and radiation fibrosis
GBDD-007-0402	*56/M*	Dula 0.75 mg	Hospitalized for Pneumonia. No report of respiratory failure. History of GERD and sleep apnea syndrome.
GBDD-007-0408	61/M	Dula 0.75 mg	Died due to interstitial pneumonia and respiratory failure after 10 weeks on study drug. Had a history of pulmonary fibrosis

Reference ID: 3609106

USUBJID	Age/Sex	Dose	Details (including fatal or requiring respiratory support etc.)
GBDD-551-6075	65/F	Dula 0.75 mg	Hospitalized for Pneumonia after 3 months on study drug, study drug continued. No report of respiratory failure. No known risk factors.
GBDN-044-2256	35/F	Dula 0.75 mg	Hospitalized for Pneumonia after one month on study drug, study drug continued. No report of respiratory failure. No known risk factors other than BMI>35.
GBCF-031-1600	65/M	Dula 0.5 mg	History of CAD and tobacco use. Hospitalized for community-acquired Pneumonia. No report of respiratory failure
GBDA-049-2416	66/M	Placebo/Dula 0.5mg	Hospitalized for Pneumonia after 1 month on study drug (placebo), study drug continued. No report of respiratory failure. No known risk factors.

Source: Reviewer generated, adapted from the TOSNP, eCTD 5.3.5.3.

Reviewer's Comment: Some events occurred with patients with no known risk factors for pneumonia (e.g. smoking, lung disease), but overall, these presentations can be expected in patients with Type 2 DM and associated co-morbid conditions.

Nonfatal serious urinary infections:

Since SAEs of UTI, cystitis, and pyelonephritis occurred in numerically more patients treated with dulaglutide, they were also reviewed for any unusual presentations and for potential missed cases of GI intolerance or pancreatitis. There were no unusual presentations. Most events were associated with prior history or nephrolithiasis and might be expected in patients with diabetes. None of the cases appeared to be pancreatitis or GI intolerance.

SAEs of UTI, pyelonephritis and cystitis occurred in the following dulaglutide treated patients (Table 91):

Table 91: SAES of UTI, Pyelonephritis and Cystitis in Dulaglutide Treated Patients

Subject ID	Age/Sex	Details
GBDA-041-2026	50/F	UTI with nephrolithiasis and gastroenteritis
GBDC-201-4027	44/F	UTI, history of nephrolithiasis
GBCF-301-4503	60/F	UTI and Ureteric Calculus

Subject ID	Age/Sex	Details
GBCF-401-5012	65/M	UTI associated with urinary retention and obstructive prostatic adenoma
GBDD-404-5106	59/F	UTI with history of nephrolithiasis, Crohns disease and aseptic pyuria.
GBDD-702-7104	60/M	UTI and dehydration post LV30
GBDD-750-7406	63/F	UTI with no prior history or risk factors
GBCF-706-6960	40/F	acute pyelonephritis with history of prior UTI
GBCF-706-6963	54/F	acute pyelonephritis and Ureteric calculus. The patient's medical history included: acute pyelonephritis and bilateral ureter stone, post-surgical extracorporeal shock wave lithotripsy.
GBCF-003-0210	56/F	Pyelonephritis, history of intermittent urinary tract infection
GBDC-822-7751	71/F	Acute pyelonephritis with no prior history of UTI or nephrolithiasis
GBCF-401-5013	60/M	Cystitis with hematuria and prostatic adenoma
GBDD-551-6075	65/F	Cystitis

Source: Reviewer generated, adapted from the TOSNP, eCTD, 5.3.5.3

Reviewer's Comment: Most events were associated with prior history or nephrolithiasis and can be expected in patients with diabetes.

Nonfatal serious falls:

Since falls were more frequent with dulaglutide treated patients, they were reviewed to determine if any were due to syncope, hypoglycemia, arrhythmias or orthostatic hypotension that could be associated with study drug (Table 92). Events of subdural hematomas are also included here.

Table 92: Narrative review of Falls and Sub-dural Hematoma

USUBJID	Age/Sex	Dose	Details
GBDA-002-0055	59/M	Dula 0.75mg	Right sub-dural hematoma after a fall, history of Von Willebrand's disease.
GBDA-048-2350	61/M	Dula 0.75 mg	Left sub-dural hematoma after a fall on ice, the patient was found unconscious.
GBDA-084-4155	76/M	Dula 1.5 mg	Bilateral subdural hematoma and prior history of atrial fibrillation- discussed in section 7.3.3.1
GBCF-409-5411	78/F	Dula 1.5 mg	Fall and right forearm fracture

USUBJID	Age/Sex	Dose	Details
GBCF-604-6465	53/F	Dula 1.5 mg	Fall and fracture neck of radius. No history of impairment reported prior to fall
GBDB-856-8620	71/F	Dula 1.5 mg	Medical history of osteoporosis. Fall and knee fracture due false step, no history of dizziness
GBDC-830-8000	67/M	Dula 1.5 mg	Fall (reported as accidental) and humerus fracture.
GBCF-873-8155	60/F	Dula 0.75 mg	Fall and thoracic vertebral fracture after accidental fall.
GBCF-946-3301	63/F	Dula 0.75 mg	History of prior CVA, Fall and right humerus fracture reported as accidental- No report of hypoglycemia or loss of consciousness
GBDD-455-5385	64/M	Dula 0.75 mg	Lumbar Vertebral fracture after fall from tree

Source: Reviewer generated, adapted from the TOSNP, eCTD, 5.3.5.3

Reviewer's Comment: Seven dulaglutide treated patients had "fall" reported as an SAE vs. one patient in all comparators. In the AS7 dataset, the total number of falls reported as TEAEs were balanced (17-dulaglutide, 10-all comparator, 0.5% each). There are no reports of hypoglycemia or syncope/pre-syncope in the narratives and these events occurred in both dulaglutide dose groups.

Nonfatal serious syncopal events:

Due to known drug effects of dehydration secondary to GI intolerance, changes in blood pressure, chronotropic effects, and hypoglycemia, I also reviewed SAEs of syncope (Table 93).

Table 93: Narrative Review of Syncope:

USUBJID Age/Sex	Exposure	Dose	Details
GBDA-204-6205 61/F	1 month	Dula 1.5 mg	Hospitalized to rule-out CVA (symptoms not reported). CT scan, Carotid Doppler and Holter reported normal. Diagnosis changed to syncope. Study drug continued
GBDB-004-0175 74/M	4 1/2 months	Dula 1.5 mg	Syncopal episode lasted 2 minutes. Hypoglycemia and hypotension were excluded. History of vertiginous syndrome. Study drug continued

USUBJID Age/Sex	Exposure	Dose	Details
GBDC-404-6090 61/M	3 months	Dula 1.5 mg	Presyncope with nausea and vomiting reported. Study drug continued.
GBDC-134-3402 57/F	7 months	Dula 0.75 mg	Syncopal episode. No history of chest pain, palpitations, seizure or hypoglycemia. Reported as vasovagal episode. Patient was lost to follow-up
GBDC-822-7751 71/F	9 months	Dula 0.75 mg	Post-operative pain followed by syncope-reported as vagal episode.
GBDD-004-0254 64/M	3 months	Dula 0.75 mg	The patient's medical history included benign polycythemia and frequent phlebotomy. Lost consciousness for approximately 15 seconds during phlebotomy. His blood pressure was at 74/40 transiently and resolved spontaneously with Trendelenburg maneuver. His heart rhythm was normal throughout the encounter, no chest pain suggesting angina. Upon sitting up he again lost consciousness. Neurological and cardiac work-up was normal. Study drug was discontinued.
GBDD-004-0260 70/F	3 months	Dula 0.75 mg	Developed worsening of chronic diarrhea with nausea and vomiting followed by orthostatic syncope. Study drug was discontinued.
GBDD-021-1104 63/F	49 days	Dula 0.75 mg	The patient reported that her blood pressure got very low and she passed out about 30 minutes after eating lunch. Her blood glucose was 84 prior to the meal and 89 (units and normal range not reported) after she passed out. She had started on hydrocholorothiazide for blood pressure treatment 10 days earlier

Source: Reviewer generated, adapted from the TOSNP, eCTD, 5.3.5.3

Reviewer Comment: Eight dulaglutide treated patients had "presyncope/syncope" reported as an SAE vs. one patient in all comparators. The events occurred in both dose groups and were related to gastrointestinal side effects in two patients. In all the other episodes, association to dulaglutide (BP, chronotropic effects, hypoglycemia) is confounded, but cannot be excluded. In the AS7 dataset, the total number of syncopal episodes reported as TEAEs were also more frequent with dulaglutide, but no dose effect was observed (dulaglutide-14 [0.4%], all comparator-4 [0.2%]).

Reviewer's Assessments about nonfatal SAEs:

Other than serious adverse events specific to the drug-class, most SAEs were balanced. Some imbalances were noted, and include:

- *SAEs of gastritis, gastrointestinal bleed were numerically more frequent with dulaglutide (3 [<0.1%] vs. 0 on comparator). Gastritis appeared to be related to the gastrointestinal side effects of dulaglutide secondary to delayed gastric emptying. There was no unusual presentation for the GI bleeds that warrant further exploration.*
- *Appendicitis (8 [0.2%] vs. 2 [0.1%]), pneumonia (10 [0.3%] vs.3 [0.2%]) and UTI/pyelonephritis/cystitis (12 [0.35%], vs. 2 [0.1%]) were also more frequent with dulaglutide, but these events are common in patients with diabetes and other co-morbid conditions. The presentations for appendicitis did not suggest any missed cases of pancreatitis or GI intolerance.*
- *Syncope was more frequent in dulaglutide treated patients (8 [0.24%] vs. 1 [0.05%]). Two of the events appeared secondary to gastrointestinal side-effects of dulaglutide.*

Overall, given the low incidence of these events in this patient population, these imbalances do not appear to be concerning.

7.3.5 Dropouts and/or Discontinuations

In four of the five Phase 3 studies, patients were permitted to continue in the study if they stopped study drug to facilitate continued monitoring of safety parameters. Thus, patients who completed the study or discontinued from the study may have discontinued study drug at an earlier time and for a reason that was different from the reason for discontinuing the study. Subject disposition in the placebo controlled pool (AS1) is presented as a combined discontinuation of study drug and discontinuation from the study (Table 94).

Table 94: Summary and Analysis of Reasons for Patient Discontinuation from Study or Study Drug, Observations Through 26 Weeks of the Planned Treatment Period) (AS1)

Disposition	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)	Overall p-value*a
Completed 26 Weeks	451 (79.4)	746 (89.2)	710 (85.1)	1456 (87.2)	
Discontinued Prior to 26 Weeks	117 (20.6)	90 (10.8)	124 (14.9)	214 (12.8)	<.001
Adverse Event	40 (7.0)	26 (3.1)	55 (6.6)	81 (4.9)	
Subject Decision	30 (5.3)	31 (3.7)	35 (4.2)	66 (4.0)	
Sponsor Decision	1 (0.2)	2 (0.2)	0 (0.0)	2 (0.1)	
Lost to Follow-Up	13 (2.3)	14 (1.7)	8 (1.0)	22 (1.3)	
Physician Decision	14 (2.5)	11 (1.3)	11 (1.3)	22 (1.3)	
Entry Criteria Not Met	3 (0.5)	2 (0.2)	7 (0.8)	9 (0.5)	
Lack of Efficacy	9 (1.6)	0 (0.0)	3 (0.4)	3 (0.2)	
Protocol Violation	7 (1.2)	3 (0.4)	3 (0.4)	6 (0.4)	
Death	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.2)	

Source: Table ISS.APP.34, page 1057.

In the placebo controlled pool, discontinuations due to an adverse event were more frequent with dulaglutide 1.5 mg compared to 0.75 mg. Overall, the discontinuation due to an adverse event was greater with placebo. Discontinuations due to subject decision, lost to follow-up, physician decision, are comparable between the groups. More subjects on placebo discontinued due to lack of efficacy and protocol violations.

In the placebo controlled pool, gastrointestinal disorders led to discontinuation more frequently in the all dulaglutide than placebo group (2.4% and 0.2%, respectively) (Table 95).

Table 95: Summary and Analysis of Adverse Events by Preferred Term Reported as the Reason for Discontinuation from Study or Study Drug, Observations Through 26 Weeks of the Planned Treatment Period in 2 or more persons– Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

System Organ Class • **Preferred Term**	**Placebo (N=568) n(%))**	**Dula 0.75 (N=836) n (%)**	**Dula 1.5 (N=834) n (%)**	**All Dula (N=1670) n (%)**
Total Patients discontinued due to AE	40 (7.0)	24 (2.9)	55 (6.6)	79 (4.7)
Gastrointestinal disorders	1 (0.2)	11 (1.3)	29 (3.5)	40 (2.4)
• Nausea	0 (0.0)	6 (0.7)	12 (1.4)	18 (1.1)
• Vomiting	0 (0.0)	2 (0.2)	6 (0.7)	8 (0.5)
• Abdominal pain	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.2)
• Dyspepsia	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.2)
• Abdominal Pain Upper	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
• Diarrhea	1 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)
• Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Cardiac disorders	0 (0.0)	1 (0.1)	3 (0.4)	4 (0.2)
• Atrial fibrillation	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
• Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)
• Sinus tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)

System Organ Class • **Preferred Term**	**Placebo (N=568) n(%))**	**Dula 0.75 (N=836) n (%)**	**Dula 1.5 (N=834) n (%)**	**All Dula (N=1670) n (%)**
Investigations	4 (0.7)	6 (0.7)	4 (0.5)	10 (0.6)
• Pancreatic enzymes increased	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.2)
• Lipase increased	3 (0.5)	0 (0.0)	1 (0.1)	1 (<0.1)
Metabolism and nutrition disorders	19 (3.3)	3 (0.4)	5 (0.6)	8 (0.5)
• Hyperglycemia	18 (3.2)	1 (0.1)	4 (0.5)	5 (0.3)
• Decreased appetite	0 (0.0)	2 (0.2)	1 (0.1)	3 (0.2)
Pregnancy, puerperium and perinatal conditions				
• Pregnancy	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Renal and Urinary Disorders	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders:				
• Hypertension	4 (0.7)	0 (0.0)	3 (0.4)	3 (0.2)

Source: Table ISS.6.222, page 232

The major reason for dulaglutide discontinuations compared to placebo was gastrointestinal side effects. Discontinuations due to PTs in the GI disorders SOC were dose-dependent (placebo 1 [0.2%], dulaglutide 0.75 mg- 11 [1.3%], dulaglutide 1.5 mg-29 [3.5%]). The majority of the events were due to nausea (placebo-0, dulaglutide 0.75 mg -6 [0.7%], dulaglutide 1.5 mg-12 [1.4%]), followed by vomiting (placebo-0, dulaglutide 0.75 mg -2 [0.2%], dulaglutide 1.5 mg-6 [0.7%]). None of these events were reported as SAEs. These will be discussed in more detail under common adverse events (7.4.1 Common Adverse Events).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the placebo controlled pool (AS1), the profiles of TEAEs by descending frequency of PT reported for at least 2% of patients are presented in the table below (Table 96). The most common TEAE's reported were nausea, vomiting, diarrhea, nasopharyngitis, decreased appetite, headache, dyspepsia, UTI and back pain. Of these, the most common TEAE's that occurred more frequently in the dulaglutide treated patients compared to placebo were nausea (16.8% and 5.3%), vomiting (9.3% and 2.3%), diarrhea (10.7% and 6.7%), decreased appetite (6.8% and 1.6%), dyspepsia (4.9% and 2.3%), constipation (3.7% and 0.7%), dizziness (3.7% and 2.3%), fatigue (3.1% and 1.8%), upper abdominal pain (2.8% and 1.6%), and abdominal distension (2.6% and 0.7%).

Table 96: Summary and Analysis of Treatment-Emergent Adverse Events Occurring in at Least 2% of Patients By Descending Frequency of Preferred Term - Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Preferred Term	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)	Odds Ratio*a	Heterogeneity p-value*b	CMH p-value*c
Patients with >=1 TEAE	379 (66.7)	569 (68.1)	597 (71.6)	1166 (69.8)	1.15	.744	.235
Nausea	30 (5.3)	104 (12.4)	176 (21.1)	280 (16.8)	3.61	.317	<.001
Diarrhoea	38 (6.7)	74 (8.9)	105 (12.6)	179 (10.7)	1.67	.964	.003
Vomiting	13 (2.3)	50 (6.0)	105 (12.6)	155 (9.3)	4.37	.005	<.001
Nasopharyngitis	42 (7.4)	65 (7.8)	65 (7.8)	130 (7.8)	1.06	.778	.703
Headache	40 (7.0)	50 (6.0)	67 (8.0)	117 (7.0)	0.99	.820	.682
Decreased appetite	9 (1.6)	41 (4.9)	72 (8.6)	113 (6.8)	4.51	.797	<.001
Dyspepsia	13 (2.3)	34 (4.1)	48 (5.8)	82 (4.9)	2.20	.620	.006
Urinary tract infection	21 (3.7)	32 (3.8)	35 (4.2)	67 (4.0)	1.09	.778	.754
Back pain	29 (5.1)	33 (3.9)	32 (3.8)	65 (3.9)	0.75	.551	.223
Upper respiratory tract infection	20 (3.5)	33 (3.9)	30 (3.6)	63 (3.8)	1.07	.047	.875
Dizziness	13 (2.3)	31 (3.7)	31 (3.7)	62 (3.7)	1.65	.597	.079
Constipation	4 (0.7)	30 (3.6)	31 (3.7)	61 (3.7)	5.35	.246	<.001
Fatigue	10 (1.8)	22 (2.6)	29 (3.5)	51 (3.1)	1.76	.716	.109
Arthralgia	17 (3.0)	26 (3.1)	22 (2.6)	48 (2.9)	0.96	.421	.906
Abdominal pain upper	9 (1.6)	19 (2.3)	28 (3.4)	47 (2.8)	1.80	.257	.097
Abdominal distension	4 (0.7)	24 (2.9)	19 (2.3)	43 (2.6)	3.73	.542	.006
Abdominal pain	11 (1.9)	17 (2.0)	25 (3.0)	42 (2.5)	1.31	.387	.436
Abdominal discomfort	8 (1.4)	16 (1.9)	24 (2.9)	40 (2.4)	1.72	.030	.113
Flatulence	8 (1.4)	12 (1.4)	28 (3.4)	40 (2.4)	1.72	.346	.151
Cough	15 (2.6)	20 (2.4)	19 (2.3)	39 (2.3)	0.88	.487	.724
Influenza	10 (1.8)	22 (2.6)	17 (2.0)	39 (2.3)	1.33	.168	.359
Lipase increased	10 (1.8)	15 (1.8)	24 (2.9)	39 (2.3)	1.33	.273	.331
Gastrooesophageal reflux disease	3 (0.5)	14 (1.7)	17 (2.0)	31 (1.9)	3.56	.236	.017
Pain in extremity	14 (2.5)	16 (1.9)	13 (1.6)	29 (1.7)	0.70	.565	.204
Asthenia	4 (0.7)	10 (1.2)	17 (2.0)	27 (1.6)	2.32	.880	.082
Oedema peripheral	11 (1.9)	18 (2.2)	5 (0.6)	23 (1.4)	0.71	.509	.192
Oropharyngeal pain	13 (2.3)	9 (1.1)	14 (1.7)	23 (1.4)	0.60	.118	.154
Non-cardiac chest pain	12 (2.1)	11 (1.3)	10 (1.2)	21 (1.3)	0.59	.337	.251
Weight decreased	1 (0.2)	3 (0.4)	17 (2.0)	20 (1.2)	6.87	.367	.033
Muscle spasms	12 (2.1)	10 (1.2)	6 (0.7)	16 (1.0)	0.45	.899	.025
Hyperglycaemia	30 (5.3)	5 (0.6)	5 (0.6)	10 (0.6)	0.11	.067	<.001

Abbreviations: CMH = Cochran-Mantel-Haenszel; N = total number of patients in specified treatment arm; n = number of patients with at least one treatment emergent adverse event; TEAE = treatment emergent adverse event.

Source: Table ISS.6.10- page 206.

Gastrointestinal (GI) disorders:

Adverse events secondary to delayed gastric emptying are the most commonly reported AEs in the GLP-1 class. Hence they were reviewed in detail to determine if there were any dose-dependent effects or for any features unique to dulaglutide compared to other drugs in class.

Subjects who had a known clinically significant gastric emptying abnormality (e.g. severe diabetic gastroparesis, gastric outlet obstruction), undergone gastric bypass (bariatric) surgery, or chronically take drugs that directly reduce gastrointestinal motility were excluded from the trials.

As mentioned earlier, TEAEs within the GI disorders SOC were the most frequently reported adverse events with more patients in the dulaglutide group compared to

placebo with clear dose-dependence as shown in the table below. Nausea and vomiting occurred about twice as frequently with dulaglutide 1.5 mg compared to dulaglutide 0.75 mg: 21.1% vs. 12.4% for nausea, 12.6% vs. 6% for vomiting. Diarrhea also occurred more frequently on dulaglutide treated patients compared to placebo (dula 1.5 mg-12.6%, dula 0.75 mg-8.9%, placebo-6.7%).

Table 97: Summary and Analysis of Common Gastrointestinal Adverse Events through 26 Weeks of the Planned Treatment Period Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups, Safety Population, Studies GBCF, GBDA, GBDN:

Preferred Term	Placebo (N=568) n (%)	Dula 0.75 (N=836) n (%)	Dula 1.5 (N=834) n (%)	All Dula (N=1670) n (%)
Nausea	30 (5.3)	104 (12.4)	176 (21.1)	280 (16.8)
Diarrhea	38 (6.7)	74 (8.9)	105 (12.6)	179 (10.7)
Vomiting	13 (2.3)	50 (6.0)	105 (12.6)	155 (9.3)
Dyspepsia	13 (2.3)	34 (4.1)	48 (5.8)	82 (4.9)
Constipation	4 (0.7)	30 (3.6)	31 (3.7)	61 (3.7)
Abdominal pain upper	9 (1.6)	19 (2.3)	28 (3.4)	47 (2.8)
Abdominal distension	4 (0.7)	24 (2.9)	19 (2.3)	43 (2.6)
Abdominal pain	11 (1.9)	17 (2.0)	25 (3.0)	42 (2.5)
Abdominal discomfort	8 (1.4)	16 (1.9)	24 (2.9)	40 (2.4)
Flatulence	8 (1.4)	12 (1.4)	28 (3.4)	40 (2.4)
Gastrooesophageal reflux disease	3 (0.5)	14 (1.7)	17 (2.0)	31 (1.9)

Source: Adapted from Table ISS.6.8, page 201.

Discontinuations due to Common Gastrointestinal events related to delayed gastric emptying:

As discussed in section 7.3.5 Dropouts and/or Discontinuations, discontinuations due to nausea and vomiting in dulaglutide treated patients were clearly dose dependent. Discontinuations due to diarrhea were comparable to placebo.
Other PTs related to delayed gastric emptying (e.g. abdominal pain, dyspepsia, GERD) resulting in discontinuation and more frequent with dulaglutide are reviewed here to assess if dose-dependence was consistent.

Table 98: Narrative Review for other Gastrointestinal Events Linked to Delayed Gastric Emptying that resulted in discontinuation:

USUBJID	Age/Sex	Dose	Exposure	Details
Abdominal Pain:				
GBCF-029-1502.	52/M	Dula 1.5 mg	4 days	Abdominal pain and diarrhea which resolved with dechallenge
GBCK-109-0905	61/F	Dula 1.5 mg	7 days	Abdominal pain (epigastric), nausea and distention/bloating. Pancreatic enzymes normal
GBDA-104-5202	60/F	Dula 1.5 mg	8 days	Severe abdominal pain, nausea, vomiting and distention. Pancreatic enzymes normal
GBDN-024-1262	54/F	Dula 1.5 mg	8 days	Upper abdominal pain, nausea, headache and eructation. Pancreatic enzymes normal
GBDN-048-2455	40/M	Dula 1.5 mg	14 days	upper abdominal pain, severe diarrhea, moderate nausea, and severe projectile vomiting, The patient's lipase elevated to 63 U/L (range 0-60) 10 days after discontinuing study drug but decreased later.
GBDB-856-8603	66/F	Dula 1.5 mg	24 days	Moderate abdominal discomfort and anorexia, normal pancreatic enzymes.
GBDB-001-0001.	53/F	Dula 0.75 mg	5 months	mild nausea and moderate abdominal pain and confirmed pancreatic enzymes (amylase and pancreatic amylase) elevation. Imaging was negative for pancreatitis.
GBDB-401-4056	62/F	Dula 0.75 mg	14 days	Upper abdominal pain, nausea, and constipation. Pancreatic enzymes normal
GBDN-033-1716	51/M	Dula 0.75 mg	21 days	decreased appetite and severe abdominal pain, headache, GERD. Pancreatic enzymes normal
GBDC-931-4737	61/M	Dula 0.75 mg	68 days	"Mild" abdominal pain. Normal pancreatic enzymes
Dyspepsia:				
GBDA-074-3656	68/M	Dula 1.5 mg	148 days	Moderate dyspepsia that started on day 23
GBDD-052-2754	59/M	Dula 1.5 mg	62 days	Nausea, abdominal pain, dyspepsia and diarrhea starting on Day 1, pancreatic enzymes normal
GBDD-504-5756	56/F	Dula 1.5 mg	2 days	Vomiting (resolved) and dyspepsia reported.
GBDN-853-7404	40/F	Dula 1.5 mg	7 days	mild to moderate dyspepsia, mild constipation, and eructation
GBCF-946-3300	67/F	Dula 0.75 mg	51 weeks	Confirmed pancreatitis
GBDA-044-2161	57/M	Dula 0.75 mg	57 days	Recurrence of severe dyspepsia (previous medical condition)
Gastroesphageal Reflux disease (GERD):				
GBCF-850-	48/M	Dula 1.5 mg	One year	Worsening gastroesophageal reflux

USUBJID	Age/Sex	Dose	Exposure	Details
7312				(History of GERD). Presented with nausea vomiting diarrhea and severe heartburn.
GBDN-034-1756	45/F	Dula 1.5 mg	4 months	Worsening of GERD
GBDN-701-7061	51/M	Dula 1.5 mg	51 days	Developed GERD 2 days after starting study drug.
GBCF-940-3023	44/M	Dula 1.5 mg	15 days	Developed hyperchlorohydria (increased gastric acidity) along with fatigue and loss of appetite

Source: Reviewer generated, adapted from TOSNP for Discontinuations due to Adverse Events- eCTD 5.3.5.3

Reviewer's Comment : Except for confirmed pancreatitis in patient GBCF-946-3300, most of the events of abdominal pain, new-onset or recurrent dyspepsia and GERD causing study drug discontinuation appear to be related to delayed gastric emptying secondary to study drug and occurred with increasing frequency with dulaglutide 1.5 mg compared to dulaglutide 0.75 mg and all comparator.

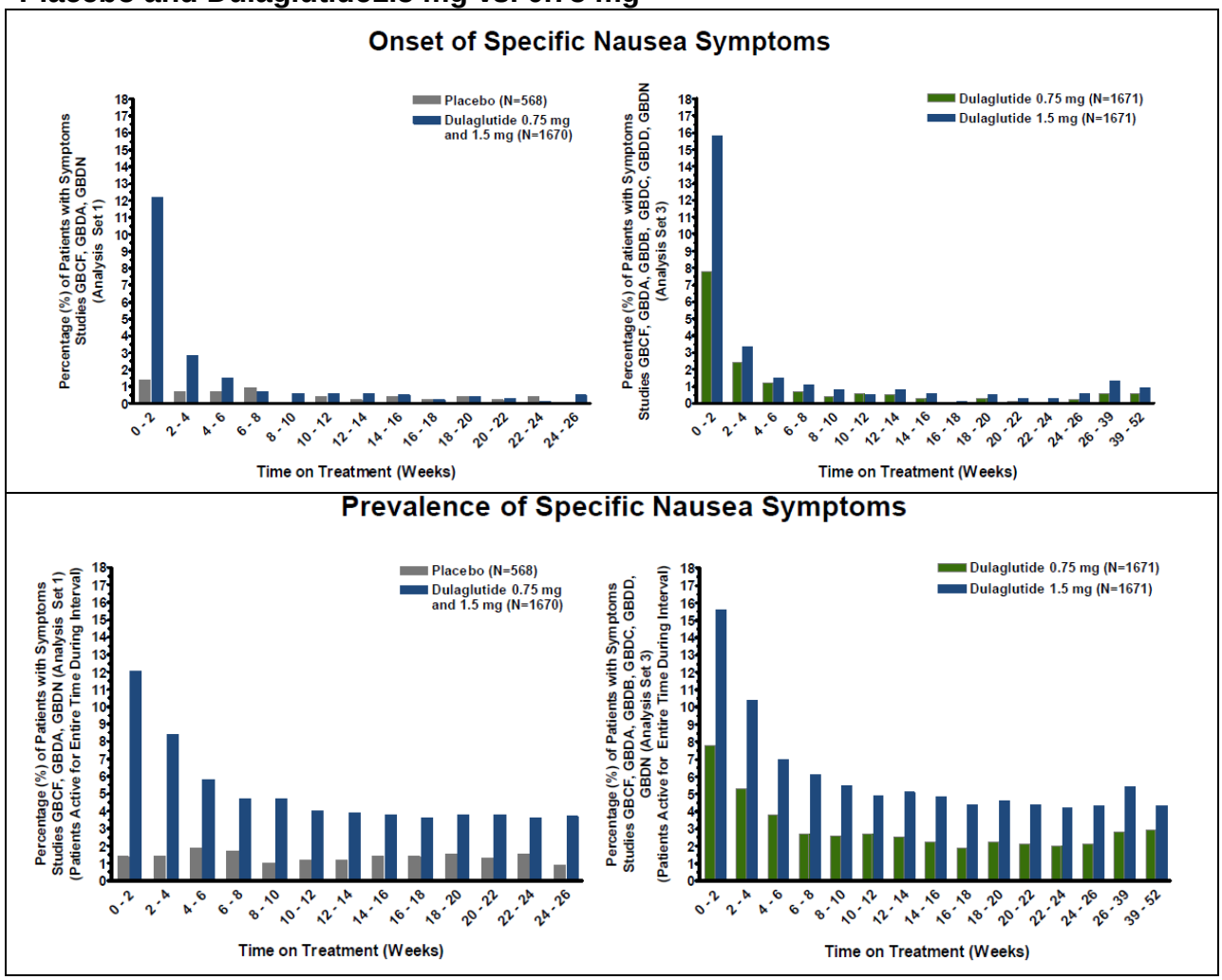
Reviewer's Assessment about discontinuations due to GI side effects:

The major reason for dulaglutide discontinuation compared to placebo was gastrointestinal side effects. Discontinuations due to PTs in the GI disorders SOC were dose-dependent (placebo 1 [0.2%], dulaglutide 0.75 mg- 11 [1.3%], dulaglutide 1.5 mg- 29 [3.5%]). The majority of the events were due to nausea. This suggests that there is improved tolerability with the 0.75 mg dose and favors approval of the lower dose in addition to the 1.5 mg dose.

Time course of nausea and vomiting:

With the GLP-1 receptor agonists, nausea and vomiting have an early onset and typically improve with continued treatment. The Applicant's figures below (Figure 15) show the onset and prevalence of specific nausea symptoms in the AS1 and AS3 datasets. In the first figure, patients within each interval represent those who reported their first event of specific nausea during the discrete interval or who reported a subsequent event of specific nausea when all previous events had resolved within a previous interval. The time course of nausea with dulaglutide is consistent with approved products and peaks at 2 weeks. The proportion of patients experiencing nausea was dose dependent, and prevalence over time is higher in the dulaglutide 1.5 mg dose group compared to the 0.75 mg dose group.

Figure 15: Onset and Prevalence of Specific Nausea Symptoms, Dulaglutide vs. Placebo and Dulaglutide1.5 mg vs. 0.75 mg



Source: Figure ISS.6.5, page 262

Dose Titration and GI tolerability:

Dose titration is recommended for other approved GLP-1 agonists (e.g. exenatide, liraglutide, albiglutide) to mitigate GI side-effects. Exenatide LAR is approved for a single dose and is not up titrated.

The effect of dose titration on GI side effects was evaluated in a Phase 2 study, Study GBCJ. In this study, patients were assigned to 4 sequences: placebo to placebo; dulaglutide 0.5 mg to 1.0 mg; dulaglutide 1.0 mg to 1.0 mg; and dulaglutide 1.0 mg to 2.0 mg. they received 1 dose weekly for 4 weeks and a second dose weekly for 12 weeks. In this study, the Applicant reports that escalating to the higher dulaglutide doses after 4 weeks of lower dosing did not significantly reduce the incidence of GI

adverse events. In addition, the Applicant has conducted exposure-response modeling to compare the probability of nausea and vomiting if treatment with dulaglutide is initiated at 0.75 mg and continued once weekly for 1 to 4 weeks before starting 1.5 mg doses versus treatment initiated with the 1.5 mg dose. This is based on data from 4 clinical pharmacology studies on patients with type 2 DM and healthy subjects. As shown in the table below (Table 99), the Applicant asserts that based on model estimates, a titrated regimen would only reduce the overall incidence of nausea (absolute difference 3.0%) and vomiting (absolute difference 1.7%) in the first week, and that by starting with the optimal therapeutic dose of 1.5 mg, patients could develop tolerance over the first 2 weeks of treatment.

Table 99: Model-Estimated Cumulative Incidence of Nausea/Vomiting by Week for Once Weekly Dulaglutide Dosing Regimens with No Titration and Up-Titration

	Model-Estimated Cumulative Incidence of Nausea and Vomiting per Week (%)			
Event	**Nausea**		**Vomiting**	
Week/Dosing Regimen	**Week 1**	**Week 2**	**Week 1**	**Week 2**
No titration[a]	10.9	7.9	7.0	5.9
Up-titration[b]	7.9	8.3	5.3	6.0
Absolute Difference[c] (Up titration – No titration)	*3.0*	*0.4*	*1.7*	*0.1*

[a] Patients received 1.5 mg once weekly for 2 weeks.
[b] Patients received 0.75 mg once during Week 1 and 1.5 mg during Week 2.
[c] Percent difference for up-titration - no titration.
Source: Summary of Clinical Pharmacology Studies, Module 2.7.2.3.6.3.

Source: Table 4.3, Applicant's Submission dated April 22, 2014

Reviewer's Comment: The clinical pharmacology studies had limited patient exposure. Based on the placebo controlled phase 3 data, discontinuations due to nausea and vomiting were higher with dulaglutide 1.5 mg. Initiating therapy at 0.75 mg should be considered for improved treatment adherence.

Comparison to other drugs in Class:

In their response dated April 22, 2014 to justify a single approved dose of 1.5 mg, the Applicant submitted data indicating that GI side effects with dulaglutide 1.5 mg was comparable to exenatide, exenatide LAR and lixisenatide, liraglutide, based on product information or the European Public Assessment report (Table 100).

Table 100: Applicant's comparison of gastrointestinal side-effects for dulaglutide and other GLP-1 agonists

	Dulaglutide Clinical Program (~26 wk Treatment Duration)			Marketed GLP-1 receptor agonists[a] (Treatment Duration)			
TEAE	Dula 1.5 mg	Dula 0.75 mg	Placebo	Victoza® (≥26 wk)	Byetta® (30 wk)	Bydureon® (24-30 wk)	Lyxumia (24 wk)
GI Disorders (%)	41.0	31.6	21.3	41	NR	NR	NR
Nausea (%)	21.1	12.4	5.3	20	51	20	26.1
Vomiting (%)	12.6	6.0	2.3	8	19	8	10.5
Events Leading to Withdrawals							
Adverse Events (%)	6.6	2.9	7.0	7.8	8	4.9	7.4
GI Disorders (%)	3.5	1.3	0.2	5	NR	NR	NR
Nausea (%)	1.4	0.7	0.0	2.8	4	0.5	3.1

Abbreviations: Dula = dulaglutide; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; NR = not reported; TEAE = treatment-emergent adverse event; wk = week.

[a] Source: Victoza®, Byetta®, Bydureon® and Lyxumia product information or European Public Assessment Report.

Note: Dulaglutide data are for Analysis Set 1 (integrated assessment of Dula_0.75 and Dula_1.5 vs. placebo for observations through 26 weeks of planned treatment in placebo-controlled studies of planned duration ≥26 weeks).

Source: Clinical Overview (Table 2.5.5.4).

Source: Regulatory Response dated April 22, 2014.

Three of the products listed by the Applicant in Table 100 are short-acting or administered once-daily. I compared nausea and vomiting incidence in the dulaglutide program with approved GLP-1 analogs administered once-weekly (Table 101). Separate data from albiglutide 30 mg and albiglutide 50 mg were unavailable, since subjects in the albiglutide clinical trials evaluating both doses were either optionally or force-titrated from 30 mg to 50 mg once-weekly.

Table 101: Incidence in percent for gastrointestinal adverse events compared to placebo with long-acting GLP-1 receptor agonists

Adverse Event	Dulaglutide			Albiglutide		Exenatide LAR
	Dula 1.5	Dula0.75	Placebo	Albiglutide	Placebo	ExenatideLAR*
Nausea	21.1	12.4	5.3	11.1	9.6	25.3
Vomiting	12.6	6.0	2.3	4.2	2.6	11
Withdrawal from nausea	1.4	0.7	0.0	0.3	0.4	0.3
Withdrawal from vomiting	0.7	0.2	0.0	0.2	0.0	0.3
Withdrawal from GI disorders	3.5	1.3	0.2	1.7	1.7	0.8

*Comparator data not included for Bydureon
Source: Table ISS.6.22 - page 232, Table ISS.6.8-page 201, Albiglutide (BLA125431-November 4, 2013) and exenatide LAR primary reviews (NDA-22200- Feb 22, 2010)- and USPI's

Reviewer's Assessment for dose-dependence of GI side effects:

Although cross-trial comparisons have limitations, the gastrointestinal side effects with the 1.5 mg dose are comparable to Bydureon but more frequent than what was observed in the albiglutide clinical program compared to placebo. Withdrawals from gastrointestinal events were more frequent with dulaglutide 1.5 mg. The 0.75 mg dose had a lower incidence for gastrointestinal events and for withdrawals due to gastrointestinal events. Based on this data, I would favor initiating therapy at the 0.75 mg dose and titrating upwards based on tolerability and the need for additional glycemic control.

Reviewer's Overall Assessment of GI side effects:

- Consistent with drug class, nausea and vomiting were the most common adverse events with dulaglutide compared to placebo.
- Nausea and vomiting were clearly dose dependent: occurred about twice as frequently with dulaglutide 1.5 mg compared to dulaglutide 0.75 mg : 21.1% vs. 12.4%, 12.6% vs. 6% respectively.
- The time course of nausea and vomiting with dulaglutide is consistent with approved products and peaked at 2 weeks. However, prevalence over time was still higher with the dulaglutide 1.5 mg dose group.
- Initiating therapy at 0.75 mg dose may be considered for improved treatment adherence.
- Initiating therapy at the 0.75 mg dose and titrating upwards based on tolerability and the need for additional glycemic control could be considered a reasonable approach to treatment.
- Labeling for gastrointestinal adverse events should be consistent with approved products in class.

7.4.2 Laboratory Findings

Laboratory assessments associated with adverse events of special interest are discussed in the following sections:

Lipase and amylase -7.3.2.2 Pancreatitis
Calcitonin-7.3.2.1 Potential thyroid C-cell proliferation
eGFR and urine albumin-7.3.2.7 Renal Safety
Hepatic Safety-7.3.3.1 Hepatic Safety

Since serum lipids (total cholesterol, HDL-C, LDL-C, triglycerides, and total cholesterol/HDL-C) are accepted biomarkers of cardiovascular risk, analyses of median changes from baseline and treatment emergent abnormal values were reviewed.

Table 102: Mean Changes from Baseline in Serum Lipids, AS1 and AS3 datasets

	[Mean (Median) Baseline] Mean Change from Baseline to Last Postbaseline Observation				ANCOVA LOCF[b]
Analyte (Units)	Placebo	Dula_0.75	Dula_1.5	All_Dula	LSM Difference (95% CI), p-value
			Analysis Set 1[a]		(All_Dula vs. Placebo)
Cholesterol (mmol/L)	[4.495 (4.35)] 0.009	[4.550 (4.45)] -0.092	[4.573 (4.48)] -0.149	[4.562 (4.48)] -0.121	-0.150 (-0.230, -0.069) p<0.001
HDL cholesterol (mmol/L)	[1.200 (1.17)] 0.011	[1.221 (1.19)] 0.014	[1.204 (1.17)] 0.026	[1.212 (1.19)] 0.020	-0.001 (-0.021, 0.019) p=0.890
LDL cholesterol (mmol/L)	[2.482 (2.33)] -0.007	[2.533 (2.43)] -0.073	[2.545 (2.46)] -0.090	[2.539 (2.46)] -0.082	-0.089 (-0.157, -0.022) p=0.010
Triglycerides (mmol/L)	[1.929 (1.665)] 0.0	[1.951 (1.64)] -0.135	[2.009 (1.65)] -0.254	[1.980 (1.645)] -0.194	-0.169 (-0.280, -0.058) p=0.003
Total cholesterol/ HDL cholesterol	[3.953 (3.737)] -0.033	[3.958 (3.781)] -0.151	[4.014 (3.773)] -0.203	[3.986 (3.777)] -0.177	-0.129 (-0.224, -0.033) p=0.008
			Analysis Set 3[a]		(Dula_1.5 vs. Dula_0.75)
Cholesterol (mmol/L)	--	[4.592 (4.51)] -0.047	[4.617 (4.51)] -0.052	[4.605 (4.51)] -0.050	0.005 (-0.048, 0.058) p=0.851
HDL cholesterol (mmol/L)	--	[1.212 (1.170)] 0.021	[1.208 (1.170)] 0.033	[1.210 (1.170)] 0.027	0.011 (-0.002, 0.024) p=0.101
LDL cholesterol (mmol/L)	--	[2.556 (2.460)] -0.058	[2.568 (2.460)] -0.030	[2.562 (2.460)] -0.044	0.031 (-0.014, 0.077) p=0.177
Triglycerides (mmol/L)	--	[1.961 (1.68)] -0.044	[2.005 (1.66)] -0.167	[1.983 (1.67)] -0.105	-0.092 (-0.156, -0.028) p=0.005
Total cholesterol/ HDL cholesterol	--	[4.010 (3.803)] -0.104	[4.034 (3.794)] -0.153	[4.022 (3.802)] -0.128	-0.034 (-0.095, 0.027) p=0.275

Source: Table ISS.6.116, page 512

There were no clinically concerning mean or median changes in LDL-cholesterol, HDL cholesterol or triglycerides from baseline compared to placebo (AS1) or over the long-term in patients on dulaglutide 1.5 mg or 0.75 mg (AS3).

Treatment emergent abnormal lipid values listed in the ISS appendices for the AS1 and AS3 datasets were reviewed. All treatment groups had comparable number of patients

with treatment-emergent abnormal values above threshold (LDL >1xULN- placebo-6.5%, dulaglutide 0.75 mg-5.8%, dulaglutide 1.5 mg- 7.2%; HDL <1 xULN- placebo-9.1%, dulaglutide 0.75 mg-7.3%, dulaglutide 1.5 mg- 7.7%; Triglycerides > 1XULN-placebo-6.8%, dulaglutide 0.75 mg-6.7%, dulaglutide 1.5 mg-4.2%); see 9.6 Supportive Tables From the ISS Referenced in the Review- Table ISS.APP.459).

7.4.3 Vital Signs

HR changes are also discussed in 7.4.4 Electrocardiograms (ECGs)

GLP-1 receptor agonists have been associated with increases in heart rate (HR). These effects are described in the package insert of the approved products. In the heart, the GLP-1 receptor was localized in myocytes of the sinoatrial node in primates[26], making direct chronotropic or conduction effects plausible. The long-term effects of the increase in pulse rate have not been established

Dose-dependent and statistically significant increases in HR and variable effects on diastolic BP (DBP) were observed with dulaglutide in healthy subjects and patients with T2DM in early clinical studies. Due to these early clinical findings, the Applicant included both DBP and HR among the four response measures used in the adaptations and dose selection criteria in Study GBCF. In Phase 2 Study GBDN, the effects of dulaglutide on SBP, DBP, and HR were characterized over a 26-week period in 755 patients with T2DM and relatively controlled blood pressure using 24-hour ABPM. Sitting vital sign measurements were collected in triplicate in the Phase 2 and 3 studies. Standing and supine blood pressure measures were collected as single measurements.

The Applicant presented both the ABPM data and the integrated safety data from the phase 2/3 studies. Consistent with other members of the drug class, a dose dependent decrease in systolic BP (SBP) was noted in the ABPM study, as shown in Table 103 below. Mean 24-hour DBP in the dulaglutide 0.75 mg and 1.5 mg groups were not different from placebo at 16 or 26 weeks. Using a non-inferiority margin of 3 bpm, dulaglutide 0.75 mg group was non-inferior to placebo at 16 and 26 weeks. Non-inferiority to placebo was not achieved with the dulaglutide 1.5 mg group. Small increases in LS mean HR were observed in the dulaglutide 1.5 mg group compared to placebo at 16 weeks (difference 2.84 bpm) and 26 weeks (difference 3.50 bpm).

26 GLP-1 Receptor Localization in Monkey and Human Tissue: Novel Distribution Revealed With Extensively Validated Monoclonal Antibody Charles Pyke, R. Scott Heller, Rikke K. Kirk, Cathrine Ørskov, Steffen Reedtz-Runge, Peter Kaastrup, Anders Hvelplund, Linda Bardram, Dan Calatayud, and Lotte Bjerre Knudsen: Endocrinology, April 2014, 155(4):1280–1290

Table 103: Summary and Analysis of Mean 24-Hour Systolic and Diastolic Blood Pressure, and Heart Rate, Measured with Ambulatory Blood Pressure Monitoring at 4, 16, and 26 Weeks, Mixed-Model Repeated Measures Analysis (Intent-to- Treat Population, Study H9X-MC-GBDN

Time Point	Placebo (N=250)		Dula_0.75 (N=254)		Dula_1.5 (N=251)	
	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)	Mean (SD)	ΔLSM (SE)
Systolic Blood Pressure (mm Hg)						
Baseline	131.13 (11.23)	--	132.08 (12.97)	--	130.85 (12.14)	--
Week 4	130.84 (11.82)	-0.34 (0.53)	130.39 (11.82)	-1.85 (0.53)	127.10 (12.00)	-3.73 (0.53)
Week 16	130.36 (11.79)	-0.63 (0.59)	130.38 (12.29)	-1.70 (0.58)	127.23 (12.58)	-3.41 (0.61)
Week 26	130.83 (11.63)	0.15 (0.62)	130.67 (12.11)	-1.56 (0.60)	127.75 (11.94)	-2.51 (0.63)
Diastolic Blood Pressure (mm Hg)						
Baseline	75.96 (7.79)	--	76.64 (8.38)	--	76.29 (8.39)	--
Week 4	75.84 (8.13)	-0.06 (0.34)	76.76 (8.15)	0.28 (0.33)	75.83 (8.03)	-0.16 (0.34)
Week 16	75.07 (8.44)	-0.55 (0.37)	76.23 (7.70)	-0.13 (0.37)	75.69 (8.85)	-0.23 (0.38)
Week 26	75.20 (7.91)	-0.24 (0.39)	76.49 (8.33)	-0.09 (0.38)	75.84 (8.40)	0.26 (0.40)
Heart Rate (beat per minute)						
Baseline	79.91 (9.97)	--	79.01 (9.75)	--	79.86 (10.83)	--
Week 4	80.07 (9.78)	0.28 (0.40)	81.80 (9.05)	2.71 (0.40)	84.47 (10.51)	4.61 (0.40)
Week 16	80.40 (9.46)	0.86 (0.44)	81.48 (8.99)	2.48 (0.43)	83.65 (10.16)	3.70 (0.45)
Week 26	80.46 (9.64)	0.68 (0.47)	81.00 (9.69)	1.94 (0.46)	83.72 (11.14)	4.18 (0.47)

Abbreviations: ΔLSM = change in least squares mean from baseline within treatment group; Dula = dulaglutide; N= number of patients in specified treatment group; SD = standard deviation; SE = standard error.

Source: ISS.6.80, page 441 and Table ISS.6.83-page 444 and Table ISS 6.84, page 445.

Additional observations with regard to vital signs for dulaglutide compared to placebo include:

- Statistically significant decreases in SBP were observed for each dose of dulaglutide versus placebo (LS mean [95% CI] difference at 26 weeks for dulaglutide 1.5 mg: -2.58 [-3.88, -1.28] mm Hg; for dulaglutide 0.75 mg: -2.14 [-3.45, -0.83] mm Hg). In both dulaglutide dose groups, the reductions in SBP observed at 2 to 4 weeks and 8 weeks were numerically greater than those at later time points such that by 52 weeks, these changes in SBP from baseline were < 1 mm Hg (AS3).
- Small non-significant changes in DBP (LS mean change from baseline <1 mm Hg) were observed with both placebo and all dulaglutide through 26 weeks of treatment.

- For HR at 26 weeks for both dulaglutide 0.75 mg and dulaglutide 1.5 mg groups when each was compared separately with placebo (LS mean [95% CI] difference from placebo with dulaglutide 1.5 mg: 3.37 bpm [2.48, 4.25]; dulaglutide 0.75 mg: 2.15 bpm [1.30, 3.01]).

On review of the threshold analyses of heart rate (HR), more subjects on dulaglutide 1.5 mg compared to dulaglutide 0.75 mg or placebo, had HR measured to be above the prespecified threshold, demonstrating a dose-dependent effect (5.6% at any time post-baseline [PBL] ,2.2% at two consecutive visits PBL and 1.6% more than twice PBL). Dose dependence was also observed for subjects with sitting heart rate > 100 bpm and increase of over 15 bpm from baseline (placebo-0.7%, dulaglutide 0.75mg-1.3%, dulaglutide 1.5 mg-2.2%)(See 9.6 Supportive Tables From the ISS Referenced in the Review- Table ISS.6.91).

Patients exceeding threshold values for BP were comparable between the groups (Table 104). Similar observations were seen in the AS3 dataset.

Table 104: Threshold Analysis of Vital Signs, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with Dulaglutide 0.75 and 1.5 mg (AS1)

Vital Sign Threshold Level 1 Threshold Level 2	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)
Office-Measured Sitting Systolic BP (mm Hg)				
Pts with data *a	567	828	823	1651
>180 mm Hg				
with Incr >=10 mm Hg at least once PBL	4 (0.7)	3 (0.4)	1 (0.1)	4 (0.2)
with Incr >=10 mm Hg at 2 Con PBL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<90 mm Hg				
with Decr at least 10 mm Hg at least once PBL	1 (0.2)	8 (1.0)	4 (0.5)	12 (0.7)
with Decr at least 10 mm Hg at 2 Con PBL	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
Office-Measured Sitting Diastolic BP (mm Hg)				
Pts with data *a	567	828	823	1651
>100 mm Hg				
with Incr >=10 mm Hg at least once PBL	10 (1.8)	9 (1.1)	11 (1.3)	20 (1.2)
with Incr >=10 mm Hg at 2 Con PBL	1 (0.2)	2 (0.2)	3 (0.4)	5 (0.3)
<60 mm Hg				
with Decr at least 10 mm Hg at least once PBL	17 (3.0)	27 (3.3)	20 (2.4)	47 (2.8)
with Decr at least 10 mm Hg at 2 Con PBL	0 (0.0)	3 (0.4)	1 (0.1)	4 (0.2)
Vital Sign Threshold Level 1 Threshold Level 2	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)
Office-Measured Heart Rate (bpm)				
Pts with data *a	567	828	823	1651
>100 bpm				
at any time PBL	17 (3.0)	23 (2.8)	46 (5.6)	69 (4.2)
at 2 Con PBL	3 (0.5)	6 (0.7)	18 (2.2)	24 (1.5)
more than twice PBL	1 (0.2)	3 (0.4)	13 (1.6)	16 (1.0)
>=130 bpm				
at any time PBL	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)
at 2 Con PBL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
more than twice PBL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BP = blood pressure; bpm = beats per minute; Con = consecutive visits; Decr = decrease from baseline; Dula = dulaglutide; Incr = increase from baseline; mm Hg = millimeters of mercury; N = number of patients in specified treatment group; n = number of patients in specified category; PBL = postbaseline; Pts = patients.

Source: Table ISS.6.89, page 450

Adverse events related to HR and BP effects (syncope, arrhythmias are discussed in sections 7.3.3 and 7.3.4

Reviewer Assessment about vital signs:

- Consistent with approved products, there was an increase in HR that was dose-dependent: (LS mean [95% CI] difference from placebo with dulaglutide 1.5 mg: 3.37 bpm [2.48, 4.25]; dulaglutide 0.75 mg: 2.15 bpm [1.30, 3.01]). In addition, more treat-emergent abnormal outliers were noted with on categorical analyses with dulaglutide- 1.5 mg. sitting heart rate > 100 bpm and increase of over 15 bpm from baseline (placebo-0.7%, dulaglutide 0.75mg-1.3%, dulaglutide 1.5 mg-2.2%)

- There was a dose dependent decrease in systolic BP with dulaglutide. Statistically significant decreases in SBP were also observed for each dose of dulaglutide versus placebo (LS mean [95% CI] difference at 26 weeks for dulaglutide 1.5 mg: -2.58 [-3.88, -1.28] mm Hg; for dulaglutide 0.75 mg: -2.14 [-3.45, -0.83] mm Hg. These changes from baseline peaked early in treatment and declined to less than 1mm Hg compared to baseline after 26 weeks. There were no differences between dulaglutide and placebo treated groups for treatment – emergent abnormal values for systolic or diastolic BP.
- The heart rate effect should be labelled, consistent with other approved GLP-1 agonists.

7.4.4 Electrocardiograms (ECGs)

In the thorough QT study (study GBCC) submitted to IND 70930, no QT prolongation effect was observed with LY2189265 4mg or 7 mg. The largest upper bounds of the 2-sided 90% CI for the mean difference between LY2189265 (4 mg and 7 mg) and placebo did not exceed 10 msec, the threshold for regulatory concern as described in ICH E14 guidelines (see Table 105 below). The QT- Inter-disciplinary Review team (QT-IRT) had reservations regarding assay sensitivity demonstration with moxifloxacin, however since the confidence intervals for both supratherapeutic LY2189265 doses and moxifloxacin effects do not overlap, they were reassured that LY2189265 does not prolong the QTc interval.

Table 105: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for LY2189265 (4 mg and 7 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
LY2189265 4 mg	2	0.8	(-1.2, 2.8)
LY2189265 7 mg	12	1.8	(-0.1, 3.8)
Moxifloxacin 400 mg*	8	7.4	(5.7, 9.1)

Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 time points is 5.2 ms.

Source: Table 1, QT-IRT review, IND 70930, September 14, 2009.

In this three-period (dulaglutide, moxifloxacin and placebo), single dose, cross-over study, both 4 mg and 7 mg LY2189265 caused significant increase in heart rate (>10 bpm). The peak increase occurred at 24 hours post-dose.

Due to poor GI tolerability and pancreatic enzyme elevations there were several discontinuations in this study which was initiated at 7 mg but later the dulaglutide dose evaluated was switched to 4 mg. Enough data was gathered by the Applicant to conduct the ECG interval analyses before discontinuing the study. The reviewer of this QT study

agreed that there was sufficient data. In addition, one subject developed atrial fibrillation one day after dulaglutide 4 mg but converted to sinus rhythm spontaneously.

Prolongation of PR interval was seen in clinical studies with dulaglutide. In Study H9X-MC-GBCO, a clinical pharmacology study in healthy volunteers, the effects of dulaglutide in combination with metoprolol compared to metoprolol alone on PR interval were assessed. Nonsignificant LS mean increases in PR interval were observed with both dulaglutide and metoprolol (2 to 3 msec for both). The greatest increase in PR interval was observed when dulaglutide and metoprolol were co-administered (LS mean increase 15 msec).

In Study GBDN, small LS mean increases from baseline were observed for PR interval at 16 and 26 weeks with both dulaglutide 0.75 mg (3.67 msec and 3.17 msec, respectively) and 1.5 mg (4.96 msec and 3.32 msec, respectively). The majority (>91%) of patients who had a normal PR interval (≤ 220 msec) at baseline remained in this category post-baseline. Approximately 2% of patients in Study GBDN had prerandomization PR interval >220 msec. Only one patient at each subsequent time point had a PR interval >220 msec with an increase from baseline that was greater than 25%.

The categorical analyses for PR intervals conducted by the sponsor was reviewed (Table 106) for changes over 220 msec with over 25% change from baseline. In the placebo controlled pool there were three dulaglutide 1.5 mg patients who met this criterion. In the AS3 data-set, numerically more outliers were again observed in dulaglutide 1.5 mg treated patients.

Table 106: Threshold Analyses of PR interval- AS1 and AS3 datasets

ECG Parameter / Threshold Level 1 / Threshold Level 2	Placebo (N=568) n (%)	Dula_0.75 (N=836) n (%)	Dula_1.5 (N=834) n (%)	All_Dula (N=1670) n (%)
PR Interval (msec)				
Pts with data *a	535	797	788	1585
>=220 msec				
at 2 Con PBL	3 (0.6)	12 (1.5)	10 (1.3)	22 (1.4)
and 0 < Incr <=25%	4 (0.7)	20 (2.5)	24 (3.0)	44 (2.8)
and Incr >25%	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.2)

ECG Parameter / Threshold Level 1 / Threshold Level 2	Dula_0.75 (N=1671) n (%)	Dula_1.5 (N=1671) n (%)	All_Dula (N=3342) n (%)
PR Interval (msec)			
Pts with data *a	1594	1580	3174
>=220 msec			
at 2 Con PBL	34 (2.1)	22 (1.4)	56 (1.8)
and 0 < Incr <=25%	45 (2.8)	49 (3.1)	94 (3.0)
and Incr >25%	2 (0.1)	6 (0.4)	8 (0.3)

Abbreviations: bpm = beats per minute; Chg = change from baseline; Con = consecutive visits; Dula = dulaglutide; ECG = electrocardiogram; Incr = increase from baseline; msec = milliseconds; N = number of patients in specified treatment group; n = number of patients in specified category; PBL = postbaseline;
Source: Table: ISS.6.111 and 6.112, page- 494.

In addition, in the sponsor's analyses of qualitative ECG findings in the AS1 dataset, more subjects on dulaglutide 1.5 mg developed first degree AV block (placebo 0.9%, dulaglutide 0.75 mg-1.8%, dulaglutide 1.5 mg-2.3%). This was also seen in the AS3 dataset (dulaglutide 0.75 mg 1.5%, dulaglutide 1.5 mg- 2.4%).

Clinically significant AEs under the conduction disorders HLT were balanced (discussed earlier in 7.3.2.9 Cardiac Safety).

Reviewer assessment of ECG interval effects:

- Dulaglutide does not prolong the QTc interval.
- Small mean increases in PR interval (3-4 msec) were noted with dulaglutide in the placebo controlled studies.
- More subjects on dulaglutide 1.5 mg developed first degree AV block (AS1: placebo 0.9%, dulaglutide 0.75 mg-1.8%, dulaglutide 1.5 mg-2.3%; AS3: dulaglutide 0.75 mg 1.5%, dulaglutide 1.5 mg- 2.4%).
- Clinically significant AEs under the conduction disorders HLT were balanced.
- The clinical significance of these observations would be best seen in elderly patients, patients with underlying ischemic heart disease, sick-sinus or other pre-excitation syndromes, conduction disorders or on baseline beta-blocker/calcium channel blocker therapy. Hence conduction disorders should be studied as an AE of special interest in the ongoing CV outcome study (GBDJ-REWIND).

7.4.5 Special Safety Studies/Clinical Trials

Other than the Thorough QT and ABPM studies, no special safety studies were conducted by the Applicant

7.4.6 Immunogenicity

See 7.3.2.4 Immunogenicity

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Definitive dose dependency (i.e. increased adverse events with dulaglutide 1.5 mg vs. 0.75 mg) was observed for the following adverse effects:

Discontinuations due to adverse events-discussed in

- 7.3.5 Dropouts and/or Discontinuations
- Nausea and vomiting- discussed in 7.4.1 Common Adverse Events
- Pancreatic enzyme elevations- discussed in 7.3.2.2 Pancreatitis
- Heart rate effects:- discussed in 7.4.3 Vital Signs

A trend or suggested dose-dependency of adverse effects was observed for:

- Hypoglycemia- discussed in 7.3.2.8 Hypoglycemia
- Supraventricular arrhythmias –discussed in 7.3.2.9 Cardiac Safety
- PR interval prolongation- discussed in 7.4.4 Electrocardiograms (ECGs)

Reviewer's Assessment of dose dependency:

There was a dose dependent increase for elevations in pancreatic enzymes, but the clinical significance of the pancreatic enzyme elevations is unclear since they were not predictive for pancreatitis. All the other AEs with apparent dose dependence listed here have some clinical relevance, except for PR prolongation. The clinical relevance of the observed dose dependent PR prolongation may be better evaluated with the cardiovascular outcomes study.

Although the dulaglutide 1.5 mg dose has demonstrated superior effects on the primary and secondary efficacy end-points in some trials, I would recommend initiating therapy at the 0.75 mg dose and titrating based on tolerability and need for additional glycemic control based on my concerns around these dose dependent safety signals. Given the uncertainties with some of the safety signals listed above, it seems prudent to avoid a higher dose in patients who do not require additional glycemic control. This can be re-evaluated once the CV outcome trial is complete.

Additionally, while no significant imbalance in acute renal failure (ARF) was observed and GI side-effects were not worse in the sub-population with eGFR<60ml/min/1.73m^2 or macroalbuminuria, the dose-dependency for gastrointestinal side-effects is preserved in this sub-population. Given the post-marketing reports for acute renal failure in this class, it would be prudent to start at 0.75 mg and dose-titrate with close clinical monitoring based on tolerability and need for further glycemic control while use in patients with renal impairment is assessed further. This can be re-evaluated once the results of Study GBDX are available.

7.5.2 Time Dependency for Adverse Events

The most relevant AES that were time dependent were nausea and vomiting. These have been discussed in 7.4.1 Common Adverse Events.

7.5.3 Drug-Demographic Interactions

For the PT decreased appetite, there was an exaggerated difference between dulaglutide 1.5 mg and 0.75 mg in the ≥ 65 years group (9.6% and 3.2%) compared to the <65 years group (7.3% and 5.5%,).

A treatment interaction with BMI was noted for the PT nausea and vomiting with an exaggerated difference between doses in the lower BMI group (≤ 30 kg/m^2).

7.5.4 Drug-Disease Interactions

Adverse events in subjects with chronic kidney disease have been discussed in 7.3.2.7 Renal Safety.

7.5.5 Drug-Drug Interactions

Consistent with class effect, dulaglutide slows gastric emptying and, as a result, may reduce the extent and rate of absorption of orally co-administered medications. This would affect drugs which are dependent on threshold concentrations for efficacy, such as antibiotics, or medications with narrow therapeutic index. In clinical pharmacology studies, the Applicant reports that dulaglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree and does not recommend any dose adjustment. The clinical pharmacology reviewers agree with the Applicant's assessment.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This has been discussed in:

7.3.2.3 Pancreatic Cancer
7.3.2.1 Potential thyroid C-cell proliferation
7.3.3.2 Neoplasms

7.6.2 Human Reproduction and Pregnancy Data

No studies of dulaglutide have been conducted in pregnant or nursing women. There have been seven pregnancies in completed studies in the dulaglutide clinical program. Five of these pregnancies occurred during dulaglutide treatment and two during active comparator treatment (insulin glargine; sitagliptin). Fetal exposure was restricted to the first trimester in all cases. Two of the pregnancies were voluntarily terminated. The other 5 pregnancies resulted in live births. No complications were reported for infants.

One mother in study GBDD experienced the following maternal complications: mild hypertension, cholestasis, and hyperglycemia. The infant remained hospitalized for 15 days due to low weight, and no other complications were reported.

One pregnancy (Patient GBDY-327-2703) has been reported in the ongoing Phase 3 studies. Fetal exposure was limited to the first trimester, and no complications were reported for the mother or offspring in this ongoing study.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted to date.

The Applicant has submitted a request for a partial waiver for pediatric studies in children less than 10 years; and a request for deferral of studies in children with T2DM ages 10 to <18 years until juvenile toxicology studies are completed and the agency concludes that there is sufficient evidence for efficacy and safety in adults. This is consistent with the Division of Metabolism and Endocrinology Product's (DMEP's) approach to other products for the treatment of type 2 diabetes mellitus.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for abuse of dulaglutide, resulting in overdose, withdrawal or rebound is low. However, there is concern for off-label use for weight loss.

There were 23 patients who reported taking more than the designated dose of dulaglutide, including one patient who took 13 consecutive daily doses of 1.5 mg. Events temporally associated with these overdoses were primarily GI events (for example., nausea, vomiting, flatulence), hypoglycemia (reported as non-severe), and small elevations in pancreatic and hepatic analytes (<3x ULN).

Three of the overdose events were reported as serious using the criterion "other reasons". An SAE (moderate myofascial pain syndrome) was reported approximately 1 month after dulaglutide overdose (1.5 mg dose; assigned dose 0.75 mg; Patient GBCF-029-1511). This event led to study discontinuation

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

Not applicable

9 Appendices

9.1 Literature Review/References

References cited are included as footnotes in the relevant sections.

9.2 Labeling Recommendations

Labelling discussions were ongoing at the time this review was completed. It is expected that labelling will be consistent with other GLP-1 agonists.

Broadly, section 6 and section 14 will have to be revised to include information on the 0.75 mg and 1.5 mg dose. I would also recommend revising section 2 (dosing) to indicate that 0.75 mg qweekly is the recommended dose for initiating therapy with up-titration to 1.5 mg in patients needing additional glycemic control.

9.3 Advisory Committee Meeting

Not applicable

9.4 Financial disclosure reviews

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA-125469

Submission Date(s): September 17, 2013

Applicant: Eli Lilly and Company

Product: Trulicity (dulaglutide)

Reviewer: William Chong, MD

Date of Review: March 14, 2014

Covered Clinical Study (Name and/or Number):

1. H9X-MC-GBCJ: The effect of dose titration of LY2189265 (GLP-1 analog IV-Fc) in overweight and obese patients with type 2 diabetes mellitus (the EGO Study)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 135		
Number of investigators who are sponsor employees (including both full-time and		

part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 75		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 135 investigators that participated in study H9X-MC-GBCJ. There were 75 investigators who did not provide financial information to the Applicant despite two emails and a letter delivered by UPS requiring a signature. The majority were sub-investigators (n=63), with 12 of 39 principal investigators not providing financial disclosure information. Of the 262 patients enrolled, 50 came from sites where financial disclosure information could not be obtained from any of the investigators.

Any potential bias that might result from this is minimized by the fact that study H9X-MC-GBCJ is not one of the pivotal trials, and makes up a small percentage of the overall patient population in the development program.

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBCJ is adequate.

2. H9X-MC-GBCK: Assessment of dose-dependent effects of LY2189265 on glycemic control in patients with type 2 diabetes treated only with lifestyle interventions

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 135		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 135 investigators that participated in study H9X-MC-GBCK. None of the investigators had disclosable financial interests/arrangements

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

Reference ID: 3609106

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBCK is adequate.

3. H9X-JE-GBCZ: Assessment of dose-dependent effects of LY2189265 on glycemic control in Japanese patient with type 2 diabetes

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 34		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 15		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 34 investigators that participated in study H9X-JE-GBCZ. There were 15 investigators who did not provide financial information to the Applicant. All of these were sub-investigators. All of these sub-investigators left the investigational site before providing financial disclosure information.

Reference ID: 3609106

Any potential bias that might result from this is minimized by the fact that study H9X-JE-MBCZ is not one of the pivotal trials, and makes up a small percentage of the overall patient population in the development program.

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-JE-GBCZ is adequate.

4. H9X-MC-GBDB: A randomized, open-label, parallel-arm, noninferiority comparison of the effects of two doses of LY2189265 and insulin glargine on glycemic control in patients with type 2 diabetes on stable doses of metformin and glimepiride (AWARD-2: Assessment of weekly administration of LY2189265 in diabetes – 2)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 276		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:		from applicant)

The Applicant has submitted a list of 276 investigators that participated in study H9X-MC-GBDB. There were four investigators who received significant payments as defined in 21 CFR 54.2(f). All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the study (multi-center), size of the trial (829 enrolled patients), and the small contribution from each of these investigators (each < 1% of the total number of subjects).

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBDB is adequate.

5. H9X-MC-GBDD: The impact of LY2189265 versus insulin glargine both in combination with insulin lispro for the treatment to target of type 2 diabetes mellitus (AWARD-4: Assessment of weekly administration of LY2189265 in diabetes – 4)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 349		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 349 investigators that participated in study H9X-MC-GBDD. There were seven investigators who received significant payments as defined in 21 CFR 54.2(f). All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the study (multi-center), size of the trial (892 enrolled patients), and the small contribution from each of these investigators (each < (b) (6) of the total number of subjects).

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBDD is adequate.

6. H9X-MC-GBCF: A phase 2/3, placebo-controlled, efficacy and safety study of once-weekly, subcutaneous LY2189265 compared to sitagliptin in patients with type 2 diabetes mellitus on metformin

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 406		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 11		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 406 investigators that participated in study H9X-MC-GBCF. There were 11 investigators who received significant payments as defined in 21 CFR 54.2(f). All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the study (multi-center), size of the trial (1202 enrolled patients), and the small contribution from each of these investigators (each < (b) (6) of the total number of subjects).

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBCF is adequate.

7. H9X-MC-GBDN: The effect of LY2189265 on blood pressure and heart rate, as assessed by ambulatory blood pressure monitoring in patients with type 2 diabetes mellitus

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 297		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined		

in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 297 investigators that participated in study H9X-MC-GBDN. There were three investigators who received significant payments as defined in 21 CFR 54.2(f). All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the study (multi-center), size of the trial (755 enrolled patients), and the small contribution from each of these investigators (each (b) (6) of the total number of subjects).

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBDN is adequate.

8. H9X-MC-GBDC: The impact of LY2189265 versus metformin on glycemic control in early type 2 diabetes mellitus (AWARD-3: Assessment of weekly administration of LY2189625 in diabetes – 3)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 345		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 345 investigators that participated in study H9X-MC-GBDC. There were three investigators who received significant payments as defined in 21 CFR 54.2(f). All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the study (multi-center), size of the trial (807 enrolled patients), and the small contribution from each of these investigators (each (b) (6) of the total number of subjects).

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBDC is adequate

9. H9X-MC-GBDA: A randomized, placebo-controlled comparison of the effects of two doses of LY2189265 or exenatide on glycemic control in patients with type 2 diabetes on stable doses of metformin and pioglitazone (AWARD-1: Assessment of weekly administration of LY2189265 in diabetes – 1)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

Reference ID: 3609106

		applicant)
Total number of investigators identified: 424		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 15		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 15 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 424 investigators that participated in study H9X-MC-GBDA. There were 15 investigators who received significant payments as defined in 21 CFR 54.2(f). All of these investigators received payments > $25,000 in non-grant financial payments for speaker fees, honoraria, and/or consulting fees. Any potential bias that might result from this is minimized by the design of the study (multi-center), size of the trial (978 enrolled patients), and the small contribution from each of these investigators (each (b) (6) of the total number of subjects).

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBDA is adequate.

10. H9X-MC-GBDT: Comparative pharmacokinetics of dulaglutide after administration via an auto-injector and a manual syringe in healthy subjects.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 4		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of four investigators that participated in study H9X-MC-GBDT. None of these investigators had a disclosable financial arrangement with the Applicant.

This information is not likely to influence the outcome of the study or affect the review of the NDA product.

The disclosure of financial arrangements and interests for the investigators that participated in study H9X-MC-GBDT is adequate.

9.5 Narratives for Pancreatic Enzyme Elevations

Table 107: Narrative Review of Subjects on Dulaglutide, Who Had the PT "Pancreatic Enzymes Increased" Reported as an AE by The Investigator, Adjudicated as "Not Pancreatitis"

USUBJID	TRT_STD	Key symptoms, Imaging (Normal implies no pancreatic changes)
GBCF-013-0717	Dula 0.75	Serum triglycerides at baseline were 4.64 mmol/L (0.51-2.83 mmol/L) and 1.94 mmol/L at week 26. He reported moderate right upper quadrant abdominal pain at week 4 and was noted to have elevated lipase at the same visit. Liver function tests were within normal limits throughout the study with the exception of the baseline ALT value. Pancreatic imaging (abdominal CT scan with and without contrast) was performed on (b) (6) (1 day after repeated enzyme labs) and revealed 2 kidney stones on the right, left lower lobe pneumonia, and a normal pancreas. Lipase remained elevated , discontinued at week 71 due to hyperglycemia
GBCF-019-1023	Dula 0.75	Discontinued at week 78 due to hyperglycemia. No pain reported. Serum triglycerides at baseline (Visit 4) were 1.66 mmol/L (0.51-2.83 mmol/L); at week 26, triglycerides were elevated at 3.20 mmol/L . The patient had confirmed pancreatic (pancreatic amylase and lipase) enzyme elevation at 30 days on study drug. Liver function tests (with the exception of increased GGT levels on Visits, 4, 8, and 9 and ALT at week 26) were within normal limits throughout study. Pancreatic imaging (abdominal CT scan without contrast) obtained (17 days after Visit 6) revealed no pancreatic changes
GBDA-005-0203	Dula 0.75	No pain reported, normal CT scan
GBDA-017-0808	Dula 0.75	No pain reported, MRI scan normal
GBDA-028-1356	Dula 0.75	No pain reported, normal CT scan
GBDB-001-0001	Dula 0.75	*Had nausea and moderate abdominal pain on Day 32, study drug discontinued at week 22 for recurrent pain, also had recurrent pancreatic enzyme elevations which was normal at LV30*. CT scan, ultrasound and MRIx2 were negative for pancreatitis
GBDB-006-0297	Dula 0.75	No pain reported, normal CT scan
GBDB-205-2258	Dula 0.75	No pain reported, normal CT scan
GBDB-453-4650	Dula 0.75	No pain reported, CT scan- pancreatic cyst, no evidence of pancreatitis
GBDB-302-3109	Dula 0.75	No pain reported, CT scan and MRI- both revealing a known inherited malformation of the pancreas (pancreas divisum) and no signs of infection or other pathologies
GBDB-751-7552	Dula 0.75	*Abdominal pain reported, study drug discontinued at week 28 due to enzyme elevation, CT scan normal*
GBDB-856-8616	Dula 0.75	No pain reported, normal CT scan
GBDB-954-9515	Dula 0.75	No pain reported, ovarian cystadenoma diagnosed during CT scan, normal pancreas.
GBDC-303-5123	Dula 0.75	No pain reported, normal CT scan
GBDC-129-2916	Dula 0.75	No pain reported, normal CT scan

USUBJID	TRT_STD	Key symptoms, Imaging (Normal implies no pancreatic changes)
GBDC-404-6095	Dula 0.75	Had AE of cerebellar infarction and diarrhea, no pain reported, normal CT scan.
GBDD-033-1703	Dula 0.75	Lipase increased (max 174 IU/L), normal ultrasound.
GBDD-207-3825	Dula 0.75	*He had confirmed elevations in amylase, pancreatic amylase, lipase at Day1 of study drug exposure. Pancreatic enzymes were repeated. Pancreatic imaging (MRI) was performed on 8 days after Visit 11 (26 weeks) and revealed a small benign cyst on the pancreas but no evidence of pancreatitis. The patient was early terminated at Visit 12 (39 weeks) due to elevated lipase. Also had upper abdominal pain at Visit 10*
GBDN-023-1208	Dula 0.75	No pain reported, CT scan normal. The patient was early terminated at Visit 7 (106 days; 12.1 weeks on therapy on therapy) due to the elevations in pancreatic enzymes
GBDN-045-2305	Dula 0.75	No pain reported, CT scan normal
GBCF-854-7508	Dula 1.5	No pain, CT normal at 2 weeks , had recurrent pancreatic enzyme elevation, normal at LV30. Discontinued at week 78 due to hyperglycemia
GBCF-201-0102	Dula 1.5	No pain, CT scan normal
GBCF-015-0817	Dula 1.5	Lipase increased, CT scan normal
GBCF-507-6253	Dula 1.5	No pain, CT scan normal
GBCF-872-8103	Dula 1.5	Recurrent elevated pancreatic enzymes with normal CT scan X2 (week 78 and 3 months after week 91)
GBDA-007-0303	Dula 1.5	No pain reported, CT normal
GBDA-019-0900	Dula 1.5	Enzymes increased at screening, CT scan normal X 2, no pain reported.
GBDA-055-2713	Dula 1.5	nausea and gastroesophageal reflux reported, CT scan normal
GBDA-084-4154	Dula 1.5	Nausea/vomiting that resolved in 1 day but no pain, MRI- normal
GBDB-005-0202	Dula 1.5	No pain reported, CT normal
GBDB-005-0213	Dula 1.5	No pain reported, renal cyst, hepatic steatosis, CT normal
GBDB-006-0266	Dula 1.5	No pain reported, CT scan normal X 2
GBDB-154-1706	Dula 1.5	Dyspepsia/gastritis, nausea and upper abdominal pain, MRI normal X 3
GBDB-206-2326	Dula 1.5	No pain reported, CT-fatty liver and renal cyst, negative for pancreatitis
GBDB-206-2335	Dula 1.5	Abdominal discomfort and gastroenteritis, CT normal
GBDB-501-5054	Dula 1.5	Gastritis and diarrhea, abdominal CT scan with and without contrast and ultrasound was within normal limits except for a slightly bulky pancreatic head, but without focal lesions; by ultrasound, the liver was mildly increased in size and echotexture
GBDB-507-5370	Dula 1.5	No pain reported, CT scans normal X 2
GBDB-602-6105	Dula 1.5	No pain reported, CT scan normal
GBDB-602-6116	Dula 1.5	No pain reported, CT scan normal
GBDB-603-0000006176	Dula 1.5	Had upper abdominal pain, CT scan normal
GBDB-855-8556	Dula 1.5	Abdominal pain, constipation and fecaloma, CT scan normal

USUBJID	TRT_STD	Key symptoms, Imaging (Normal implies no pancreatic changes)
GBDC-106-0600	Dula 1.5	No abdominal pain reported, Pancreatic imaging (abdominal CT scan with contrast) revealed an anomaly of the pancreas but no inflammation. an endoscopy was performed and biopsies of a gastric nodule and a pancreatic cyst were obtained. Surgical pathology reported gastritis with moderate Helicobactor pylori and the pancreatic cyst biopsy contained only degenerated debris. An abdominal MRI was performed and revealed diffuse fatty infiltrate of the liver but no inflammatory pancreatic changes
GBDC-206-4267	Dula 1.5	No pain, ultrasound normal
GBDC-831-8028	Dula 1.5	No pain, CT-normal pancreas, hepatic steatosis and cholelithiasis
GBDD-002-0153	Dula 1.5	No pain, CT- normal
GBDD-031-1610	Dula 1.5	Severe hypoglycemia, dehydration and confusional state reported, CT and MRI normal
GBDD-051-2725	Dula 1.5	lipase values peaking at 1170 IU/L at 13 days on study drug, CT scan normal, discontinued by subject decision at 4 weeks, drug stopped at day 7.. Lipase normal at follow-up
GBDN-008-0852	Dula 1.5	No pain reported, abdominal ultrasound normal
GBDN-043-2228	Dula 1.5	Lipase increased, no pain reported, CT scan normal
GBN-101-3030	Dula 1.5	No pain reported, CT scan normal, discontinued due to physician decision.
GBDN-860-7783	Dula 1.5	No pain, CT scan normal, patient was discontinued due to enzyme elevation.

9.6 Supportive Tables From the ISS Referenced in the Review

Table ISS.6.48. Summary of Actual Value and Change from Baseline to each Postbaseline Anchor Timepoint for Calcitonin, By Treatment and Anchor Timepoint, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with 0.75 and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Summary and Analysis of Calcitonin by Time 08MAY2013 11:04
Summary by Anchor Timepoint with ANCOVA of Postbaseline Last Observation
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDN

Variable analyzed: CALCITONIN (Picogram/Milliliter)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Baseline	Placebo	516	2.55		1.0	1.00	1.00	3.15	26.8						
	Dula_0.75	788	2.52		1.0	1.00	1.00	3.10	32.7						
	Dula_1.5	775	2.76		1.0	1.00	1.00	3.20	30.2						
	All_Dula	1563	2.64		1.0	1.00	1.00	3.10	32.7						
4 - 16*	Placebo	485	2.37		1.0	1.00	1.00	2.80	17.4	-0.23	-12.2	0.00	0.00	0.00	6.3
	Dula_0.75	736	2.60		1.0	1.00	1.00	3.00	42.1	0.07	-15.1	0.00	0.00	0.00	41.1
	Dula_1.5	726	2.73		1.0	1.00	1.00	3.20	46.7	-0.01	-11.5	0.00	0.00	0.00	23.3
	All_Dula	1462	2.66		1.0	1.00	1.00	3.10	46.7	0.03	-15.1	0.00	0.00	0.00	41.1
26	Placebo	419	2.46		1.0	1.00	1.00	2.90	29.6	-0.04	-9.7	0.00	0.00	0.00	18.2
	Dula_0.75	695	2.67		1.0	1.00	1.00	3.20	32.3	0.13	-16.1	0.00	0.00	0.00	17.2
	Dula_1.5	662	2.68		1.0	1.00	1.00	3.00	29.3	0.06	-11.6	0.00	0.00	0.00	9.3
	All_Dula	1357	2.67		1.0	1.00	1.00	3.10	32.3	0.10	-16.1	0.00	0.00	0.00	17.2

Variable analyzed: CALCITONIN (Picogram/Milliliter)

		Actual value								Change from Baseline					
Weeks	Treatment	N	Mean	LSM	Min	Q1	Median	Q3	Max	Mean	Min	Q1	Median	Q3	Max
Postbaseline Last Observation	Placebo	498	2.49	2.54	1.0	1.00	1.00	3.00	29.6	-0.07	-12.0	0.00	0.00	0.00	18.2
	Dula_0.75	757	2.67		1.0	1.00	1.00	3.10	32.3	0.15	-16.1	0.00	0.00	0.00	17.2
	Dula_1.5	745	2.80		1.0	1.00	1.00	3.10	46.7	0.03	-11.6	0.00	0.00	0.00	23.3
	All_Dula	1502	2.73	2.71	1.0	1.00	1.00	3.10	46.7	0.09	-16.1	0.00	0.00	0.00	23.3

All_Dula vs Placebo LSM Diff, 95% CI (lower, upper)*a 0.17 (-0.03, 0.36)
All_Dula vs Placebo LSM Diff, p-value*a .092

Abbreviations: ANCOVA = analysis of covariance; CI = Confidence interval; Diff = difference; Dula = dulaglutide; LSM = least square mean; Max = maximum; Min = minimum; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group; Q1 = first quartile; Q3 = third quartile; vs = versus.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined. The last non-missing observation in planned treatment period for analysis set including unscheduled visit is used in the analysis for Postbaseline Last Observation.

* = Actual timing depending on study, but overall constituting a single anchor time point.
*a = 95% CI and p-value of difference (All_Dula - Placebo) of LS Means are from an ANCOVA model:
Last Actual Value in Planned Treatment for Analysis Set = Baseline + Study + Treatment + Treatment*Study (Type III sums of squares).

Program Location: [Dula_ISS_prd]:/mcalc1.sas
Output Location: [Dula_ISS_prd]:/tfl_output/safety/sm_calcitonin_as1.rtf
Data Location: [Dula_IDB_prd]:/data/ads/subjinfo.sas7bdat, safety_minmax.sas7bdat, visit.sas7bdat

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Table ISS.APP.224. Collage of Maximum Values of Pancreatic Enzymes during Baseline Period – All Screened Patients and All Randomized Patients in Phase 2 and 3 Studies GBCJ, GBCK, GBCZ, GBDN, GBCF, GBDA, GBDB, GBDC, and GBDD

Collage of Maximum Values of Pancreatic Enzymes During Baseline Period 13MAY2013 11:47
All Screened Patients and All Randomized Patients
Studies GBCJ, GBCK, GBCZ, GBDN, GBDC, GBCF, GBDA, GBDB, GBDD

Study: GBCJ, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	510	262
Patients with data	441	262
Mean	46.1	43.3
Min	14	14
Q1	28.0	30.0
Median	37.0	37.0
Q3	50.0	49.0
Max	493	204
> ULN n (%) *a	58 (13.2)	31 (11.8)
>= 3X ULN n (%) *a	9 (2.0)	2 (0.8)

Study: GBCJ, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	510	262
Patients with data	441	262
Mean	60.8	58.2
Min	15	20
Q1	42.0	42.0
Median	55.0	53.0
Q3	71.0	67.0
Max	283	263
> ULN n (%) *a	24 (5.4)	10 (3.8)
>= 3X ULN n (%) *a	0 (0.0)	0 (0.0)

Study: GBCK, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	460	167
Patients with data	447	167
Mean	43.1	43.6
Min	12	16
Q1	28.0	28.0
Median	36.0	38.0
Q3	47.0	49.0
Max	444	444
> ULN n (%) *a	52 (11.6)	18 (10.8)
>= 3X ULN n (%) *a	4 (0.9)	1 (0.6)

Study: GBCK, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	460	167
Patients with data	447	167
Mean	27.1	27.2
Min	4	9
Q1	18.0	19.0
Median	24.0	25.0
Q3	31.0	32.0
Max	123	94
> ULN n (%) *a	23 (5.1)	8 (4.8)
>= 3X ULN n (%) *a	0 (0.0)	0 (0.0)

Study: GBCK, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	460	167
Patients with data	387	157
Mean	62.4	62.5
Min	19	20
Q1	43.0	44.0
Median	58.0	60.0
Q3	75.0	76.0
Max	271	137
> ULN n (%) *a	16 (4.1)	5 (3.2)
>= 3X ULN n (%) *a	0 (0.0)	0 (0.0)

Study: GBCZ, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	219	145
Patients with data	214	145
Mean	38.7	38.6
Min	15	16
Q1	27.0	28.0
Median	33.0	33.0
Q3	41.0	41.0
Max	589	589
> ULN n (%) *a	9 (4.2)	4 (2.8)
>= 3X ULN n (%) *a	1 (0.5)	1 (0.7)

Study: GBCZ, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	219	145
Patients with data	214	145
Mean	69.2	64.9
Min	29	29
Q1	49.0	48.0
Median	62.0	60.0
Q3	77.0	74.0
Max	337	269
> ULN n (%) *a	10 (4.7)	3 (2.1)
>= 3X ULN n (%) *a	1 (0.5)	0 (0.0)

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Study: GBDN, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1497	755
Patients with data	756	748
Mean	44.8	43.4
Min	11	11
Q1	29.0	29.0
Median	38.0	38.0
Q3	50.0	50.0
Max	1139	200
> ULN n (%) *a	107 (14.2)	106 (14.2)
>= 3X ULN n (%) *a	3 (0.4)	2 (0.3)

Study: GBDN, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1497	755
Patients with data	755	747
Mean	28.0	27.8
Min	3	3
Q1	18.0	18.0
Median	25.0	25.0
Q3	33.0	33.0
Max	297	297
> ULN n (%) *a	42 (5.6)	41 (5.5)
>= 3X ULN n (%) *a	2 (0.3)	1 (0.1)

Study: GBDN, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1497	755
Patients with data	756	748
Mean	61.2	61.0
Min	11	11
Q1	42.0	42.0
Median	56.0	56.0
Q3	74.0	74.0
Max	320	320
> ULN n (%) *a	33 (4.4)	32 (4.3)
>= 3X ULN n (%) *a	0 (0.0)	0 (0.0)

Study: GBDC, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1396	807
Patients with data	1376	807
Mean	42.9	42.6
Min	11	11
Q1	28.0	29.0
Median	37.0	37.0
Q3	48.0	48.0
Max	654	573
> ULN n (%) *a	152 (11.0)	90 (11.2)
>= 3X ULN n (%) *a	9 (0.7)	4 (0.5)

Study: GBDC, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1396	807
Patients with data	1375	807
Mean	26.9	26.5
Min	4	4
Q1	18.0	18.0
Median	24.0	24.0
Q3	31.0	31.0
Max	424	398
> ULN n (%) *a	53 (3.9)	27 (3.3)
>= 3X ULN n (%) *a	3 (0.2)	1 (0.1)

Study: GBDC, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1396	807
Patients with data	1376	807
Mean	60.2	59.6
Min	12	12
Q1	42.0	43.0
Median	55.0	55.0
Q3	71.5	71.0
Max	495	432
> ULN n (%) *a	57 (4.1)	26 (3.2)
>= 3X ULN n (%) *a	2 (0.1)	1 (0.1)

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Study: GBCF, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	2195	1202
Patients with data	2005	1200
Mean	49.5	51.7
Min	11	11
Q1	31.0	32.0
Median	40.0	41.5
Q3	54.0	57.0
Max	676	676
> ULN n (%) *a	373 (18.6)	256 (21.3)
>= 3X ULN n (%) *a	32 (1.6)	23 (1.9)

Study: GBCF, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	2195	1202
Patients with data	2000	1156
Mean	29.1	30.2
Min	2	4
Q1	19.0	20.0
Median	25.0	26.0
Q3	34.0	35.0
Max	297	297
> ULN n (%) *a	128 (6.4)	81 (7.0)
>= 3X ULN n (%) *a	7 (0.4)	5 (0.4)

Study: GBCF, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	2195	1202
Patients with data	1756	1015
Mean	63.8	64.9
Min	11	11
Q1	44.0	45.0
Median	57.0	59.0
Q3	77.0	77.0
Max	372	358
> ULN n (%) *a	103 (5.9)	61 (6.0)
>= 3X ULN n (%) *a	2 (0.1)	1 (<0.1)

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Study: GBDA, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	2129	978
Patients with data	2079	978
Mean	54.4	58.6
Min	10	10
Q1	31.0	32.0
Median	41.0	44.0
Q3	56.0	60.0
Max	1171	1171
> ULN n (%) *a	435 (20.9)	241 (24.6)
>= 3X ULN n (%) *a	51 (2.5)	25 (2.6)

Study: GBDA, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	2129	978
Patients with data	2079	978
Mean	31.9	32.9
Min	3	3
Q1	19.0	20.0
Median	26.0	27.0
Q3	37.0	38.0
Max	410	410
> ULN n (%) *a	201 (9.7)	98 (10.0)
>= 3X ULN n (%) *a	11 (0.5)	6 (0.6)

Study: GBDA, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	2129	978
Patients with data	2079	978
Mean	66.2	67.2
Min	11	16
Q1	43.0	44.0
Median	59.0	61.0
Q3	80.0	80.0
Max	617	441
> ULN n (%) *a	156 (7.5)	69 (7.1)
>= 3X ULN n (%) *a	4 (0.2)	3 (0.3)

Abbreviations: Max = maximum; MET = Metformin; Min = minimum; n = number of patients in specified category; OAM = oral antihyperglycemic medication; Q1 = first quartile; Q3 = third quartile ; SU = sulfonylurea, TZD = thiazolidinedione; ULN = upper limit of normal.

*a - Percentages based upon the number of patients with data, i.e. the number of patients with baseline lab test available.

Program Location: [Dula_ISS_prd]:/mmaxbpe.sas
Output Location: [Dula_ISS_prd]:/tfl_output/safety/co_pancenz_max_dur_bsl.rtf
Data Location: [Dula_IDB_prd]:/data/ads/subjinfo.sas7bdat, safety_minmax.sas7bdat

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Study: GBDB, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1273	810
Patients with data	1268	810
Mean	54.0	57.6
Min	8	8
Q1	31.0	32.0
Median	42.0	43.0
Q3	57.0	61.0
Max	626	626
> ULN n (%) *a	282 (22.2)	203 (25.1)
>= 3X ULN n (%) *a	28 (2.2)	23 (2.8)

Study: GBDB, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1273	810
Patients with data	1268	810
Mean	33.1	34.1
Min	2	2
Q1	20.0	20.0
Median	27.0	27.0
Q3	37.0	39.0
Max	455	239
> ULN n (%) *a	128 (10.1)	96 (11.9)
>= 3X ULN n (%) *a	10 (0.8)	7 (0.9)

Study: GBDB, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1273	810
Patients with data	1268	810
Mean	68.1	69.5
Min	13	14
Q1	45.0	46.0
Median	60.0	61.5
Q3	80.5	83.0
Max	732	278
> ULN n (%) *a	109 (8.6)	80 (9.9)
>= 3X ULN n (%) *a	1 (<0.1)	0 (0.0)

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Study: GBDD, Variable: Maximum Lipase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1237	884
Patients with data	1218	884
Mean	51.0	50.7
Min	7	7
Q1	28.0	29.0
Median	38.0	39.0
Q3	55.0	55.0
Max	1327	640
> ULN n (%) *a	243 (20.0)	188 (21.3)
>= 3X ULN n (%) *a	26 (2.1)	17 (1.9)

Study: GBDD, Variable: Maximum Pancreatic Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1237	884
Patients with data	1218	884
Mean	29.3	29.7
Min	4	4
Q1	18.0	18.0
Median	24.5	25.0
Q3	34.0	35.0
Max	345	198
> ULN n (%) *a	88 (7.2)	66 (7.5)
>= 3X ULN n (%) *a	5 (0.4)	2 (0.2)

Study: GBDD, Variable: Maximum Total Amylase (Units/Liter) During Baseline Period

	All Screened Patients	All Randomized Patients
Total patients	1237	884
Patients with data	1218	884
Mean	65.6	66.2
Min	13	15
Q1	44.0	46.0
Median	59.0	61.0
Q3	79.0	80.0
Max	425	270
> ULN n (%) *a	85 (7.0)	62 (7.0)
>= 3X ULN n (%) *a	1 (<0.1)	0 (0.0)

Abbreviations: Max = maximum; MET = Metformin; Min = minimum; n = number of patients in specified category; OAM = oral antihyperglycemic medication; Q1 = first quartile; Q3 = third quartile ; SU = sulfonylurea, TZD = thiazolidinedione; ULN = upper limit of normal.

*a - Percentages based upon the number of patients with data, i.e. the number of patients with baseline lab test available.

Program Location: [Dula_ISS_prd]:/mmaxbpe.sas
Output Location: [Dula_ISS_prd]:/tfl_output/safety/co_pancenz_max_dur_bsl.rtf
Data Location: [Dula_IDB_prd]:/data/ads/subjinfo.sas7bdat, safety_minmax.sas7bdat

ISS page 4554-4562

Table ISS.6.44. Summary of Pancreatic Enzymes At Baseline, Last On-Study Visit, and Follow-Up – All Patients with Received Dulaglutide in Phase 2 and 3 Studies (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

Summary of Pancreatic Enzymes 14MAY2013 11:35
At Baseline, Last Planned Treatment Period Visit and Follow-up
All Phase 2 and 3 Patients Who Received Dulaglutide and Had Available Measurements At All 3 Timepoints
Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN

			Actual value						
Variable analyzed	Treatment	Timepoint	M	Mean	Min	Q1	Median	Q3	Max
LIPASE	All_Dula	Baseline	2911	44.6	7	28.0	37.0	49.0	589
		Last Visit*a	2911	51.5	6	31.0	42.0	58.0	944
		Follow-up	2911	47.0	5	29.0	39.0	53.0	902
AMYLASE, PANCREAS DERIVED	All_Dula	Baseline	2778	27.5	2	17.0	23.5	32.0	398
		Last Visit*a	2778	32.2	2	20.0	27.0	37.0	255
		Follow-up	2778	29.2	2	19.0	25.0	34.0	240
AMYLASE, TOTAL	All_Dula	Baseline	2803	61.0	11	42.0	55.0	73.0	432
		Last Visit*a	2803	66.6	4	46.0	61.0	80.0	406
		Follow-up	2803	62.6	10	44.0	57.0	75.0	307

Abbreviations: Dula = dulaglutide; Max=maximum; Min=minimum; M=total number of patients with non-missing value at baseline, last visit and at the follow-up timepoint; Q1 = first quartile; Q3 = third quartile

Note: All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.

*a - Last visit is defined as the patient's last planned treatment period visit.

Program Location: [Dula_ISS_prd]:/msumpe2.sas
Output Location: [Dula_ISS_prd]:/tfl_output/safety/sm_pancenz_fu_as6.rtf
Data Location: [Dula_IDB_prd]:/data/ads/subjinfo.sas7bdat, safety_minmax.sas7bdat, visit.sas7bdat.

Source: ISS page- 325

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Table ISS.APP.251. Summary of Treatment-Emergent Abnormal High Pancreatic Enzymes, Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Summary of Treatment-Emergent Abnormal High Pancreatic Enzymes 12MAY2013 22:48
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDN

Lab Test (units) Abnormality Direction	Placebo (N=568) m	M	(%)	Dula_0.75 (N=836) m	M	(%)	Dula_1.5 (N=834) m	M	(%)	All_Dula (N=1670) m	M	(%)
LIPASE (Units/Liter)												
>1X ULN	88	443	(19.9)	213	646	(33.0)	239	665	(35.9)	452	1311	(34.5)
AMYLASE, PANCREAS DERIVED (Units/Liter)												
>1X ULN	46	513	(9.0)	124	746	(16.6)	139	755	(18.4)	263	1501	(17.5)
AMYLASE, TOTAL (Units/Liter)												
>1X ULN	38	507	(7.5)	94	749	(12.6)	84	751	(11.2)	178	1500	(11.9)

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Abbreviations: Dula = dulaglutide; M = number of patients with baseline not in the specified direction of treatment-emergent abnormality and at least one post-baseline result; m =number of patients in specified category; N = total number of patients in specified treatment group; ULN = Upper Limit of Normal.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.

Program Location: [Dula_ISS_prd]:/mtsabnpe.sas
Output Location: [Dula_ISS_prd]:/tfl_output/safety/ss_pancenz_te_abnormhigh_as1.rtf
Data Location: [Dula_IDB_prd]:/data/ads/subjinfo.sas7bdat, visit.sas7bdat, safety_minmax.sas7bdat

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Table ISS.APP.256. Shift of Pancreatic Analytes from Maximum Baseline to Maximum Postbaseline, Observations Through 26 Weeks of the Planned Treatment Period –Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Shift of Pancreatic Analytes from Maximum Baseline to Maximum Postbaseline Page 1 of 6
Observations Through 26 Weeks of the Planned Treatment Period 14:41 24MAY2013
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDN

Lab Test (unit) = LIPASE (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Placebo (N=563)	<=1x ULN	355 (63.1)	82 (14.6)	3 (0.5)	3 (0.5)	0 (0.0)	443 (78.7)
	>1 to <3x ULN	27 (4.8)	67 (11.9)	8 (1.4)	3 (0.5)	1 (0.2)	106 (18.8)
	>=3 to <5x ULN	2 (0.4)	5 (0.9)	2 (0.4)	1 (0.2)	0 (0.0)	10 (1.8)
	>=5 to <10x ULN	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)
	>=10x ULN	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)
	Total	384 (68.2)	156 (27.7)	14 (2.5)	7 (1.2)	2 (0.4)	563 (100.0)
Dula_0.75 (N=820)	<=1x ULN	433 (52.8)	191 (23.3)	18 (2.2)	4 (0.5)	0 (0.0)	646 (78.8)
	>1 to <3x ULN	25 (3.0)	112 (13.7)	18 (2.2)	7 (0.9)	0 (0.0)	162 (19.8)
	>=3 to <5x ULN	0 (0.0)	3 (0.4)	1 (0.1)	2 (0.2)	0 (0.0)	6 (0.7)
	>=5 to <10x ULN	0 (0.0)	3 (0.4)	0 (0.0)	2 (0.2)	0 (0.0)	5 (0.6)
	>=10x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Total	458 (55.9)	310 (37.8)	37 (4.5)	15 (1.8)	0 (0.0)	820 (100.0)

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Lab Test (unit) = LIPASE (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Dula_1.5 (N=821)	<=1x ULN	426 (51.9)	216 (26.3)	19 (2.3)	3 (0.4)	1 (0.1)	665 (81.0)
	>1 to <3x ULN	20 (2.4)	101 (12.3)	18 (2.2)	4 (0.5)	3 (0.4)	146 (17.8)
	>=3 to <5x ULN	1 (0.1)	4 (0.5)	0 (0.0)	2 (0.2)	1 (0.1)	8 (1.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	>=10x ULN	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	Total	447 (54.4)	321 (39.1)	38 (4.6)	10 (1.2)	5 (0.6)	821 (100.0)
All_Dula (N=1641)	<=1x ULN	859 (52.3)	407 (24.8)	37 (2.3)	7 (0.4)	1 (<0.1)	1311 (79.9)
	>1 to <3x ULN	45 (2.7)	213 (13.0)	36 (2.2)	11 (0.7)	3 (0.2)	308 (18.8)
	>=3 to <5x ULN	1 (<0.1)	7 (0.4)	1 (<0.1)	4 (0.2)	1 (<0.1)	14 (0.9)
	>=5 to <10x ULN	0 (0.0)	3 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)	6 (0.4)
	>=10x ULN	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	2 (0.1)
	Total	905 (55.1)	631 (38.5)	75 (4.6)	25 (1.5)	5 (0.3)	1641 (100.0)

Lab Test (unit) = AMYLASE, PANCREAS DERIVED (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Placebo (N=557)	<=1x ULN	467 (83.8)	45 (8.1)	1 (0.2)	0 (0.0)	0 (0.0)	513 (92.1)
	>1 to <3x ULN	11 (2.0)	30 (5.4)	1 (0.2)	0 (0.0)	0 (0.0)	42 (7.5)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	478 (85.8)	76 (13.6)	3 (0.5)	0 (0.0)	0 (0.0)	557 (100.0)
Dula_0.75 (N=812)	<=1x ULN	622 (76.6)	123 (15.1)	1 (0.1)	0 (0.0)	0 (0.0)	746 (91.9)
	>1 to <3x ULN	14 (1.7)	43 (5.3)	5 (0.6)	0 (0.0)	0 (0.0)	62 (7.6)
	>=3 to <5x ULN	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.5)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	637 (78.4)	169 (20.8)	6 (0.7)	0 (0.0)	0 (0.0)	812 (100.0)

Lab Test (unit) = AMYLASE, PANCREAS DERIVED (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Dula_1.5 (N=817)	<=1x ULN	616 (75.4)	136 (16.6)	3 (0.4)	0 (0.0)	0 (0.0)	755 (92.4)
	>1 to <3x ULN	18 (2.2)	36 (4.4)	5 (0.6)	1 (0.1)	0 (0.0)	60 (7.3)
	>=3 to <5x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	634 (77.6)	173 (21.2)	8 (1.0)	2 (0.2)	0 (0.0)	817 (100.0)
All_Dula (N=1629)	<=1x ULN	1238 (76.0)	259 (15.9)	4 (0.2)	0 (0.0)	0 (0.0)	1501 (92.1)
	>1 to <3x ULN	32 (2.0)	79 (4.8)	10 (0.6)	1 (<0.1)	0 (0.0)	122 (7.5)
	>=3 to <5x ULN	1 (<0.1)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1271 (78.0)	342 (21.0)	14 (0.9)	2 (0.1)	0 (0.0)	1629 (100.0)

Lab Test (unit) = AMYLASE, TOTAL (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Placebo (N=537)	<=1x ULN	469 (87.3)	38 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	507 (94.4)
	>1 to <3x ULN	12 (2.2)	15 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	27 (5.0)
	>=3 to <5x ULN	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	482 (89.8)	55 (10.2)	0 (0.0)	0 (0.0)	0 (0.0)	537 (100.0)
Dula_0.75 (N=800)	<=1x ULN	655 (81.9)	94 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	749 (93.6)
	>1 to <3x ULN	8 (1.0)	42 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	50 (6.3)
	>=3 to <5x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	663 (82.9)	137 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)	800 (100.0)

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Lab Test (unit) = AMYLASE, TOTAL (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Dula_1.5 (N=801)	<=1x ULN	667 (83.3)	83 (10.4)	1 (0.1)	0 (0.0)	0 (0.0)	751 (93.8)
	>1 to <3x ULN	9 (1.1)	40 (5.0)	1 (0.1)	0 (0.0)	0 (0.0)	50 (6.2)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	676 (84.4)	123 (15.4)	2 (0.2)	0 (0.0)	0 (0.0)	801 (100.0)
All_Dula (N=1601)	<=1x ULN	1322 (82.6)	177 (11.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1500 (93.7)
	>1 to <3x ULN	17 (1.1)	82 (5.1)	1 (<0.1)	0 (0.0)	0 (0.0)	100 (6.2)
	>=3 to <5x ULN	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1339 (83.6)	260 (16.2)	2 (0.1)	0 (0.0)	0 (0.0)	1601 (100.0)

Abbreviations: N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in the specified category; ULN = upper limit of normal range.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.

Source: ISS page 4792-4797

Table ISS.6.45. Summary of Maximum Postbaseline Pancreatic Enzymes - Comparison by Concomitant Antihyperglycemic Medication Postbaseline in Phase 2 and 3 Studies with Dulaglutide 0.75 mg and 1.5 mg – Observations through 26 Weeks (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN)

Study (Concomitant Antihyperglycemic Medication)	Dula 0.75 N[a]	Dula 0.75 Max-to-Max Median Change (U/L)	Dula 0.75 PBL Max[b] >1x ULN (%)	Dula 0.75 PBL Max[b] ≥3x ULN (%)	Dula 1.5 N[a]	Dula 1.5 Max-to-Max Median Change (U/L)	Dula 1.5 PBL Max[b] >1x ULN (%)	Dula 1.5 PBL Max[b] ≥3x ULN (%)
Lipase								
GBDC (Diet/Exercise)	267	8.0	28.8%	2.6%	266	10.0	34.6%	4.9%
GBCF (Met)	299	12.0	46.2%	7.0%	302	16.5	50.0%	6.3%
GBDA (Met+TZD)	277	5.0	37.5%	5.1%	275	7.0	38.2%	6.2%
GBDB (Met+glimepiride)	269	10.0	42.8%	5.9%	271	12.0	48.0%	11.4%
GBDN (≥1 OAM)	249	16.5	49.8%	7.2%	245	17.0	48.6%	7.3%
GBDD (Insulin lispro±Met)	282	4.0	26.6%	2.5%	284	7.0	30.3%	2.5%
Pancreatic Amylase								
GBDC (Diet/Exercise)	267	4.0	14.2%	0	266	6.0	12.4%	1.5%
GBCF (Met)	299	7.0	22.7%	0.3%	302	8.0	22.2%	0.7%
GBDA (Met+TZD)	277	4.0	19.5%	0.7%	275	4.0	18.9%	1.5%
GBDB (Met+glimepiride)	269	6.0	23.4%	2.2%	271	6.0	24.7%	4.1%
GBDN (≥1OAM)	249	10.0	22.9%	1.2%	245	10.0	26.9%	1.6%
GBDD (Insulin lispro±Met)	282	2.0	12.8%	1.1%	284	4.0	16.9%	0.4%
Total Amylase								
GBDC (Diet/Exercise)	267	6.0	9.7%	0.4%	266	8.0	10.5%	0.4%
GBCF (Met)	298	10.0	15.8%	0	301	10.0	15.6%	0
GBDA (Met+TZD)	277	6.0	15.2%	0	275	8.0	13.1%	0.4%
GBDB (Met+glimepiride)	269	9.0	15.6%	0.4%	271	10.0	22.5%	1.5%
GBDN (≥1 OAM)	249	16.0	21.3%	0	245	16.0	18.4%	0.4%
GBDD (Insulin lispro±Met)	282	4.0	8.2%	0	284	5.5	13.0%	0

Abbreviations: Dula = dulaglutide; Max = maximum; Met = metformin; N = number of patients assigned to this treatment group who received at least 1 dose of study drug and had PBL data; OAM = oral antihyperglycemic medication; PBL = postbaseline; TZD = thiazolidinedione; ULN = upper limit of normal.

a N used to calculate max-to-max median change in analytes for GBCF and GBDN may have differed from N used to calculate PBL max relative to ULN.

b PBL Max value is for all patients PBL, irrespective of baseline Max. N was used a denominator to calculate percentages.

Source: Table ISS.APP.248 (co_pancenz-posbsl_max_26w.rtf).

ISS page 329.

Table ISS.6.46. Summary of Maximum Postbaseline Pancreatic Enzymes - Dulaglutide and Active Comparators in Phase 3 Studies – Observations through 26 Weeks (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD)

	Active Comparator				Dula_0.75				Dula_1.5			
Study (Comparator)	N[a]	Max-to-Max Median Change (U/L)	PBL Max[b] >1x ULN (%)	PBL Max[b] ≥3x ULN (%)	N[a]	Max-to-Max Median Change U/L)	PBL Max[b] >1x ULN (%)	PBL Max[b] ≥3x ULN (%)	N[a]	Max-to-Max Median Change U/L)	PBL Max[b] >1x ULN (%)	PBL Max[b] ≥3x ULN (%)
Lipase												
GBDC (Metformin)	267	5.0	23.6%	1.9%	267	8.0	28.8%	2.6%	266	10.0	34.6%	4.9%
GBCF (Sitagliptin)	314	11.0	43.3%	6.4%	299	12.0	46.2%	7.0%	302	16.5	50.0%	6.3%
GBDA (Exenatide BID)	272	4.0	30.1%	4.4%	277	5.0	37.5%	5.1%	275	7.0	38.2%	6.2%
GBDB (Insulin Glargine)	259	2.0	29.7%	4.2%	269	10.0	42.8%	5.9%	271	12.0	48.0%	11.4%
GBDD (Insulin Glargine)	287	-1.0	19.5%	1.7%	282	4.0	26.6%	2.5%	284	7.0	30.3%	2.5%
Pancreatic Amylase												
GBDC (Metformin)	267	2.0	9.0%	0.7%	267	4.0	14.2%	0	266	6.0	12.4%	1.5%
GBCF (Sitagliptin)	314	5.0	15.3%	0.3%	299	7.0	22.7%	0.3%	302	8.0	22.2%	0.7%
GBDA (Exenatide BID)	272	2.0	13.2%	0.4%	277	4.0	19.5%	0.7%	275	4.0	18.9%	1.5%
GBDB (Insulin Glargine)	259	3.0	15.1%	1.5%	269	6.0	23.4%	2.2%	271	6.0	24.7%	4.1%
GBDD (Insulin Glargine)	287	1.0	7.7%	0.3%	282	2.0	12.8%	1.1%	284	4.0	16.9%	0.4%
Total Amylase												
GBDC (Metformin)	267	4.0	5.2%	0	267	6.0	9.7%	0.4%	266	8.0	10.5%	0.4%
GBCF (Sitagliptin)	314	8.0	10.5%	0	298	10.0	15.8%	0	301	10.0	15.6%	0
GBDA (Exenatide BID)	272	3.0	10.7%	0	277	6.0	15.2%	0	275	8.0	13.1%	0.4%
GBDB (Insulin Glargine)	259	5.0	12.0%	0	269	9.0	15.6%	0.4%	271	10.0	22.5%	1.5%
GBDD (Insulin Glargine)	287	2.0	7.3%	0.7%	282	4.0	8.2%	0	284	5.5	13.0%	0

Abbreviations: BID = twice daily; Dula = dulaglutide; Max = maximum; N = number of patients assigned to this treatment group who received at least 1 dose of study medication and had postbaseline data; PBL = postbaseline; ULN = upper limit of normal.

[a] N used to calculate max-to-max median change in analytes for GBCF and GBDN may have differed from N used to calculate PBL max relative to ULN.

[b] PBL Max value is for all patients PBL, irrespective of baseline Max. N was used a denominator to calculate percentages.

Source: Table ISS.APP.248 (co_pancenz-posbsl_max_26w.rtf).

Source: ISS page 332

Table ISS.6.144. Change Analysis of Renal Markers (Creatinine: Max-to-Max; eGFR: Min-to-Min), Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Renal Subpopulations 1, 2, 3 Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS3)

	Dula_0.75	Dula_1.5	
Value	Mean	Mean	
Creatinine (mg/dL)			
Renal Subpopulation 1	(N=69)	(N=76)	p-value[a]
Baseline Maximum	1.35	1.35	
Postbaseline Maximum	1.41	1.36	
Change Max-to-Max	0.06	0.01	0.49
Renal Subpopulation 2	(N=46)	(N=55)	
Baseline Maximum	0.97	1.01	
Postbaseline Maximum	1.05	1.10	
Change Max-to-Max	0.08	0.09	0.96
Renal Impairment (Renal Subpopulation 3)	(N=111)	(N=124)	
Baseline Maximum	1.18	1.18	
Postbaseline Maximum	1.25	1.23	
Change Max-to-Max	0.07	0.04	0.76
Estimated Glomerular Filtration Rate -- CKD-EPI (mL/min/1.73 m²)			
Renal Subpopulation 1	(N=69)	(N=76)	p-value[b]
Baseline Minimum	49.11	48.33	
Postbaseline Minimum	46.92	48.49	
Change Min-to-Min	-2.13	0.24	0.50
Renal Subpopulation 2	(N=46)	(N=55)	
Baseline Minimum	81.21	80.41	
Postbaseline Minimum	75.53	74.70	
Change Min-to-Min	-5.80	-5.95	0.98
Renal Impairment (Renal Subpopulation 3)	(N=111)	(N=124)	
Baseline Minimum	62.68	63.08	
Postbaseline Minimum	58.96	60.70	
Change Min-to-Min	-3.64	-2.52	0.67

Change Analysis of Renal Markers (Creatinine: Max-to-Max; eGFR: Min-to-Min), Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Renal Subpopulations 1, 2, 3 Studies GBCF, GBDA, GBDN) (AS3)

Abbreviations: Dula = dulaglutide; eGFR = estimated glomerular filtration rate; max = maximum; min = minimum; N = total number of patients with non-missing value at baseline and at specified anchor timepoint in specified treatment group.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined

*Renal subpopulation 1= eGFR <60 mL/min/1.73 m2 at baseline; Renal subpopulation 2=UACR>300 mg/g at baseline; Renal impairment (renal subpopulation 3)=eGFR <60 mL/min/1.73 m2 and/or UACR>300 mg/g at baseline

[a] p-values are based on Type III sums of squares for Treatment from a General Linear Model (GLM) on ranks of change from baseline maximum to postbaseline maximum, comparing Dula_1.5 to Dula_0.75 with model Ranked Change = Treatment + Study

[b] p-values are based on Type III sums of squares for Treatment from a General Linear Model (GLM) on ranks of change from baseline minimum to postbaseline minimum, comparing Dula_1.5 to Dula_0.75 with model Ranked Change = Treatment + Study

Sources: Table ISS.APP.545, Table ISS.APP.550, Table ISS.APP.555, Table ISS.APP.560, Table ISS.APP.565, and Table ISS.APP.570

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Table ISS.6.142. Shift of Urine Albumin to Creatinine Ratio from Maximum Baseline to Maximum Postbaseline, Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population with eGFR (CKD-EPI) <60 mL/min/1.73 m² or Macroalbuminuria (UACR >300 mg/g) at Baseline, Studies GBCF, GBDA, GBDN) (AS1)

Shift of Urine Albumin to Creatinine Ratio from Maximum Baseline to Maximum Postbaseline
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population with eGFR (CKD-EPI) <60 mL/min/1.73 m² or Macroalbuminuria (UACR >300 mg/g) at Baseline
Studies GBCF, GBDA, GBDN

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Lab Test (unit) = URINE ALBUMIN to CREATININE RATIO (milligram/gram)

		Maximum Postbaseline			
Treatment	Maximum Baseline	< 30 mg/g n (%)	>= 30 to <= 300 mg/g n (%)	> 300 mg/g n (%)	Total n (%)
Placebo (N=38)	< 30 mg/g	17 (44.7)	1 (2.6)	0 (0.0)	18 (47.4)
	>= 30 to <= 300 mg/g	2 (5.3)	4 (10.5)	0 (0.0)	6 (15.8)
	> 300 mg/g	0 (0.0)	1 (2.6)	13 (34.2)	14 (36.8)
	Total	19 (50.0)	6 (15.8)	13 (34.2)	38 (100.0)
Dula_0.75 (N=50)	< 30 mg/g	17 (34.0)	2 (4.0)	0 (0.0)	19 (38.0)
	>= 30 to <= 300 mg/g	2 (4.0)	9 (18.0)	0 (0.0)	11 (22.0)
	> 300 mg/g	1 (2.0)	7 (14.0)	12 (24.0)	20 (40.0)
	Total	20 (40.0)	18 (36.0)	12 (24.0)	50 (100.0)

Lab Test (unit) = URINE ALBUMIN to CREATININE RATIO (milligram/gram)

		Maximum Postbaseline			
Treatment	Maximum Baseline	< 30 mg/g n (%)	>= 30 to <= 300 mg/g n (%)	> 300 mg/g n (%)	Total n (%)
Dula_1.5 (N=45)	< 30 mg/g	17 (37.8)	0 (0.0)	0 (0.0)	17 (37.8)
	>= 30 to <= 300 mg/g	1 (2.2)	6 (13.3)	0 (0.0)	7 (15.6)
	> 300 mg/g	0 (0.0)	6 (13.3)	15 (33.3)	21 (46.7)
	Total	18 (40.0)	12 (26.7)	15 (33.3)	45 (100.0)
All_Dula (N=95)	< 30 mg/g	34 (35.8)	2 (2.1)	0 (0.0)	36 (37.9)
	>= 30 to <= 300 mg/g	3 (3.2)	15 (15.8)	0 (0.0)	18 (18.9)
	> 300 mg/g	1 (1.1)	13 (13.7)	27 (28.4)	41 (43.2)
	Total	38 (40.0)	30 (31.6)	27 (28.4)	95 (100.0)

Abbreviations: eGFR (CKD-EPI) = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); mg/g = milligram per gram; mL/min/1.73 m² = milliliter per minute per 1.73 square meters of body surface area; N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in a specified category; UACR = urine albumin-to-creatinine ratio.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.

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Table ISS.APP.298. Collage of Hypoglycemia Episode Incidence, Estimated Rates, and Odds Ratios by Treatment, Total, Documented Symptomatic, Asymptomatic, and Severe Hypoglycemia, Plasma Glucose less than or equal to 70 mg/dL, Including Post-Rescue Visits – Placebo Comparison, Observations Through 26 Weeks of the Planned Treatment Period (Safety Population, Studies GBCF, GBDA)

Collage of Hypoglycemia Episode Incidence, Estimated Rates, and Odds Ratios By Treatment 08MAY2013 14:15
Total, Documented Symptomatic, Asymptomatic, and Severe Hypoglycemia, Plasma Glucose <=70 mg/dL, Including Post-Rescue Visits

Study (Background) Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBCF (MET)								
Total Hypo (PG <=70 mg/dL)								
Placebo	177	2	(1.1)	7	0.01	0.08		
Dula_0.75	302	12	(4.0)	27	0.01	0.18	Dula_0.75 vs Pla	3.62
Dula_1.5	304	24	(7.9)	59	0.03	0.39	Dula_1.5 vs Pla	7.50
All_Dula	606	36	(5.9)	86	0.02	0.28	All_Dula vs Pla	5.53
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Placebo	177	2	(1.1)	7	0.01	0.08		
Dula_0.75	302	8	(2.6)	19	0.01	0.13	Dula_0.75 vs Pla	2.38
Dula_1.5	304	17	(5.6)	40	0.02	0.26	Dula_1.5 vs Pla	5.18
All_Dula	606	25	(4.1)	59	0.02	0.19	All_Dula vs Pla	3.77
Asymptomatic Hypo (PG <=70 mg/dL)								
Placebo	177	0	(0.0)	0	0.00	0.00		
Dula_0.75	302	5	(1.7)	8	0.00	0.05	Dula_0.75 vs Pla	
Dula_1.5	304	5	(1.6)	12	0.01	0.08	Dula_1.5 vs Pla	
All_Dula	606	10	(1.7)	20	0.01	0.07	All_Dula vs Pla	
Severe Hypo								
Placebo	177	0	(0.0)	0	0.00	0.00		
Dula_0.75	302	0	(0.0)	0	0.00	0.00	Dula_0.75 vs Pla	
Dula_1.5	304	0	(0.0)	0	0.00	0.00	Dula_1.5 vs Pla	
All_Dula	606	0	(0.0)	0	0.00	0.00	All_Dula vs Pla	

Study (Background) Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBDA (MET+TZD)								
Total Hypo (PG <=70 mg/dL)								
Placebo	141	13	(9.2)	45	0.07	0.81		
Dula_0.75	280	33	(11.8)	147	0.09	1.06	Dula_0.75 vs Pla	1.32
Dula_1.5	279	29	(10.4)	62	0.04	0.44	Dula_1.5 vs Pla	1.14
All_Dula	559	62	(11.1)	209	0.06	0.75	All_Dula vs Pla	1.23
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Placebo	141	9	(6.4)	26	0.03	0.36		
Dula_0.75	280	16	(5.7)	31	0.02	0.22	Dula_0.75 vs Pla	0.89
Dula_1.5	279	14	(5.0)	31	0.02	0.22	Dula_1.5 vs Pla	0.77
All_Dula	559	30	(5.4)	62	0.02	0.22	All_Dula vs Pla	0.83
Asymptomatic Hypo (PG <=70 mg/dL)								
Placebo	141	7	(5.0)	14	0.03	0.38		
Dula_0.75	280	18	(6.4)	100	0.06	0.72	Dula_0.75 vs Pla	1.32
Dula_1.5	279	16	(5.7)	26	0.02	0.19	Dula_1.5 vs Pla	1.16
All_Dula	559	34	(6.1)	126	0.04	0.45	All_Dula vs Pla	1.24
Severe Hypo								
Placebo	141	0	(0.0)	0	0.00	0.00		
Dula_0.75	280	0	(0.0)	0	0.00	0.00	Dula_0.75 vs Pla	
Dula_1.5	279	0	(0.0)	0	0.00	0.00	Dula_1.5 vs Pla	
All_Dula	559	0	(0.0)	0	0.00	0.00	All_Dula vs Pla	

Abbreviations: d = days; Dula = dulaglutide; Hypo = hypoglycemia; MET = metformin; mg/dL = milligrams per deciliter; N = total number of patients in specified treatment group; n = number of patients with at least one hypoglycemia episode; PG = plasma glucose; Pla = placebo; TZD = thiazolidedione; vs = versus.
Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.50 treatment groups combined.
*a - Rate is estimated as mean of individual patient rates; patient rate is estimated as total number of episodes for the patient divided by patient's total time in the planned treatment period, including post-rescue participation.
*b - For comparison B vs A, the estimate for the Mantel-Haenszel odds ratio is computed with B as numerator, A as denominator. Note that the Odds Ratio reflects the number of patients with episodes (n) rather than number of episodes or episode rate.

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Table ISS.APP.299. Collage of Hypoglycemia Episode Incidence, Estimated Rates, and Odds Ratios by Treatment, Total, Documented Symptomatic, Asymptomatic, and Severe Hypoglycemia, Plasma Glucose less than or equal to 70 mg/dL, Including Post-Rescue Visits – Active Comparison, All Observations During the Planned Treatment Period (Safety Population, Studies GBCF, GBDA, GBDC, GBDB, GBDD)

Collage of Hypoglycemia Episode Incidence, Estimated Rates, and Odds Ratios By Treatment 08MAY2013 14:15
Total, Documented Symptomatic, Asymptomatic, and Severe Hypoglycemia, Plasma Glucose <=70 mg/dL, Including Post-Rescue Visits
Active Comparison, All Observations During the Planned Treatment Period
Safety Population, Studies GBDC, GBCF, GBDA, GBDB, and GBDD

Study (Background) Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBDC (Monotherapy)								
Total Hypo (PG <=70 mg/dL)								
Metformin	268	37	(13.8)	76	0.03	0.31	0.75 vs Met	0.81
Dula_0.75	270	31	(11.5)	104	0.04	0.47	1.5 vs 0.75	1.15
Dula_1.5	269	35	(13.0)	101	0.08	0.91	1.5 vs Met	0.93
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Metformin	268	14	(5.2)	23	0.01	0.09	0.75 vs Met	1.14
Dula_0.75	270	16	(5.9)	34	0.01	0.15	1.5 vs 0.75	1.14
Dula_1.5	269	18	(6.7)	25	0.05	0.63	1.5 vs Met	1.30
Asymptomatic Hypo (PG <=70 mg/dL)								
Metformin	268	24	(9.0)	50	0.02	0.20	0.75 vs Met	0.86
Dula_0.75	270	21	(7.8)	64	0.02	0.30	1.5 vs 0.75	1.11
Dula_1.5	269	23	(8.6)	68	0.02	0.25	1.5 vs Met	0.95
Severe Hypo								
Metformin	268	0	(0.0)	0	0.00	0.00	0.75 vs Met	
Dula_0.75	270	0	(0.0)	0	0.00	0.00	1.5 vs 0.75	
Dula_1.5	269	0	(0.0)	0	0.00	0.00	1.5 vs Met	

Study (Background) Hypoglycemia Episode Type / Treatment Group	N	n	(%)	Episodes	Estimated Rate *a per 30d	Estimated Rate *a per year	Odds Ratio Comparison	Odds Ratio Estimate *b
GBCF (MET)								
Total Hypo (PG <=70 mg/dL)								
Sitagliptin	315	27	(8.6)	105	0.02	0.20	0.75 vs Sita	1.00
Dula_0.75	302	26	(8.6)	125	0.02	0.21	1.5 vs 0.75	1.56
Dula_1.5	304	39	(12.8)	125	0.02	0.26	1.5 vs Sita	1.57
Documented Symptomatic Hypo (PG <=70 mg/dL)								
Sitagliptin	315	18	(5.7)	91	0.01	0.17	0.75 vs Sita	1.11
Dula_0.75	302	19	(6.3)	110	0.02	0.18	1.5 vs 0.75	1.81
Dula_1.5	304	33	(10.9)	87	0.02	0.19	1.5 vs Sita	2.01
Asymptomatic Hypo (PG <=70 mg/dL)								
Sitagliptin	315	3	(1.0)	8	0.00	0.01	0.75 vs Sita	3.19
Dula_0.75	302	9	(3.0)	13	0.00	0.02	1.5 vs 0.75	0.99
Dula_1.5	304	9	(3.0)	29	0.00	0.06	1.5 vs Sita	3.17
Severe Hypo								
Sitagliptin	315	0	(0.0)	0	0.00	0.00	0.75 vs Sita	
Dula_0.75	302	0	(0.0)	0	0.00	0.00	1.5 vs 0.75	
Dula_1.5	304	0	(0.0)	0	0.00	0.00	1.5 vs Sita	

Abbreviations: d = days; Dula = dulaglutide; Exen = Exenatide; Glar = glargine; Hypo = hypoglycemia; Met = metformin; mg/dL = milligrams per deciliter; N = total number of patients in specified treatment group; n = number of patients with at least one hypoglycemia episode; PG = plasma glucose; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione; vs = versus.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly.
Note: Patients initially treated with Placebo who switched at six months to Sitagliptin (GBCF) or Dulaglutide (GBDA) are excluded from this summary.

*a - Rate is estimated as mean of individual patient rates; patient rate is estimated as total number of episodes for the patient divided by patient's total time in the planned treatment period, including post-rescue participation.
*b - For comparison B vs A, the estimate for the Mantel-Haenszel odds ratio is computed with B as numerator, A as denominator.
Note that the Odds Ratio reflects the number of patients with episodes (n) rather than number of episodes or episode rate.

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Table ISS.6.157. Treatment-Emergent Abnormal Total Bilirubin, Phase 2 and 3 Studies, Safety Population (AS1 and AS3)

Analysis Set 1[a]								
Maximum BL	Placebo (N=568)		Dula_0.75 (N=836)		Dula_1.5 (N=834)		All_Dula (N=1670)	
Subgroup	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Patients with >1x ULN Postbaseline								
All patients at BL[b]	551	14 (2.5)	811	14 (1.7)	811	8 (1.0)#	1622	22 (1.4)
≤1x ULN at BL	536	4 (0.7)	794	5 (0.6)	797	7 (0.9)	1591	12 (0.8)
Patients with ≥2x ULN Postbaseline								
All patients at BL[b]	551	1 (0.2)	811	0	811	0	1622	0*
<2x ULN at BL	551	1 (0.2)	811	0	810	0	1621	0*

Analysis Set 3[a]						
Maximum BL	Dula_0.75 (N=1671)		Dula_1.5 (N=1671)		All_Dula (N=3342)	
Subgroup	N	n (%)	N	n (%)	N	n (%)
Patients with >1x ULN Postbaseline						
All patients at BL[b]	1620	42 (2.6)	1617	27 (1.7)	3237	69 (2.1)
≤1x ULN at BL	1585	22 (1.4)	1587	17 (1.1)	3172	39 (1.2)
Patients with ≥2x ULN Postbaseline						
All patients at BL[b]	1620	2 (0.1)	1617	2 (0.1)	3237	4 (0.1)
<2x ULN at BL	1619	1 (<0.1)	1614	2 (0.1)	3233	3 (<0.1)

Abbreviations: BL = baseline; Dula = dulaglutide; n = number of patients in specified category; N = number of patients in maximum baseline subgroup in specified treatment group; ULN = upper limit of normal.

Note: Dula_x.x refers to x.x mg dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined. No more than 1 patient per maximum BL subgroup in Analysis Set 1 and 3 patients per maximum BL subgroup in Analysis Set 3 were missing a laboratory value.

[a] AS1 = Analysis Set 1 (observations through 26 weeks of the planned treatment period; placebo-controlled studies with 0.75 mg and 1.5 dulaglutide; Safety Population, Studies GBCF, GBDA, GBDN). AS3 = Analysis Set 3 (all observations during the planned treatment period; Phase 2 and 3 studies with 0.75 mg and 1.5 mg dulaglutide; Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN).

[b] Includes patients with value missing at baseline.

*p<0.05 All_Dula compared to placebo; #p<0.05 Dula_1.5 or Dula_0.75 compared to placebo, adjusted for study.

+p<0.05 Dula_1.5 compared to Dula_0.75; Cochran-Mantel-Haenszel test, adjusted for study.

Source: Table ISS.APP.673 (sm_te_hepatic_as1.rtf), Table ISS.APP.674 (sm_te_hepatic_as1a.rtf), Table ISS.APP.675 (sm_te_hepatic_as1b.rtf), Table ISS.APP.677 (sm_te_hepatic_as3.rtf)

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Table ISS.6.155. Treatment-Emergent Abnormal Alanine Aminotransferase, Phase 2 and 3 Studies, Safety Population (AS1 and AS3)

Analysis Set 1[a]								
Maximum BL	Placebo (N=568)		Dula_0.75 (N=836)		Dula_1.5 (N=834)		All_Dula (N=1670)	
Subgroup	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Patients with >1x ULN Postbaseline								
All patients at BL[b]	550	99 (18.0)	810	111 (13.7)	812	106 (13.1)	1622	217 (13.4)*
≤1x ULN at BL	420	29 (6.9)	632	30 (4.7)	608	23 (3.8)	1240	53 (4.3)
Patients with ≥3x ULN Postbaseline								
All patients at BL[b]	550	5 (0.9)	810	2 (0.2)	812	0#	1622	2 (0.1)*
<3x ULN at BL	549	4 (0.7)	809	2 (0.2)	809	0#	1618	2 (0.1)*
Patients with ≥5x ULN Postbaseline								
All patients at BL[b]	550	0	810	1 (0.1)	812	0	1622	1 (<0.1)
<5x ULN at BL	550	0	810	1 (0.1)	810	0	1620	1 (<0.1)
Patients with ≥10x ULN Postbaseline								
All patients at BL[b]	550	0	810	0	812	0	1622	0
<10x ULN at BL	550	0	810	0	811	0	1621	0

Analysis Set 3[a]						
Maximum BL	Dula_0.75 (N=1671)		Dula_1.5 (N=1671)		All_Dula (N=3342)	
Subgroup	N	n (%)	N	n (%)	N	n (%)
Patients with >1x ULN Postbaseline						
All patients at BL[b]	1618	288 (17.8)	1617	277 (17.1)	3235	565 (17.5)
≤1x ULN at BL	1281	97 (7.6)	1242	87 (7.0)	2523	184 (7.3)
Patients with ≥3x ULN Postbaseline						
All patients at BL[b]	1618	8 (0.5)	1617	6 (0.4)	3235	14 (0.4)
<3x ULN at BL	1616	7 (0.4)	1610	5 (0.3)	3226	12 (0.4)
Patients with ≥5x ULN Postbaseline						
All patients at BL[b]	1618	3 (0.2)	1617	0	3235	3 (<0.1)
<5x ULN at BL	1618	3 (0.2)	1614	0	3232	3 (<0.1)
Patients with ≥10x ULN Postbaseline						
All patients at BL[b]	1618	1 (<0.1)	1617	0	3235	1 (<0.1)
<10x ULN at BL	1618	1 (<0.1)	1615	0	3233	1 (<0.1)

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Table ISS.6.156. Treatment-Emergent Abnormal Aspartate Aminotransferase, Phase 2 and 3 Studies, Safety Population (AS1 and AS3)

Analysis Set 1[a]								
Maximum BL	Placebo (N=568)		Dula_0.75 (N=836)		Dula_1.5 (N=834)		All_Dula (N=1670)	
Subgroup	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Patients with >1x ULN Postbaseline								
All patients at BL[b]	550	39 (7.1)	809	66 (8.2)	812	53 (6.5)	1621	119 (7.3)
≤1x ULN at BL	485	14 (2.9)	711	19 (2.7)	723	19 (2.6)	1434	38 (2.6)
Patients with ≥3x ULN Postbaseline								
All patients at BL[b]	550	3 (0.5)	809	3 (0.4)	812	0	1621	3 (0.2)
<3x ULN at BL	550	3 (0.5)	808	3 (0.4)	809	0	1617	3 (0.2)
Patients with ≥5x ULN Postbaseline								
All patients at BL[b]	550	1 (0.2)	809	0	812	0	1621	0*
<5x ULN at BL	550	1 (0.2)	809	0	811	0	1620	0*
Patients with ≥10x ULN Postbaseline								
All patients at BL[b]	550	0	809	0	812	0	1621	0
<10x ULN at BL	550	0	809	0	811	0	1620	0

Analysis Set 3[a]						
Maximum BL	Dula_0.75 (N=1671)		Dula_1.5 (N=1671)		All_Dula (N=3342)	
Subgroup	N	n (%)	N	n (%)	N	n (%)
Patients with >1x ULN Postbaseline						
All patients at BL[b]	1618	158 (9.8)	1617	137 (8.5)	3235	296 (9.1)
≤1x ULN at BL	1457	66 (4.5)	1458	67 (4.6)	2915	133 (4.6)
Patients with ≥3x ULN Postbaseline						
All patients at BL[b]	1618	7 (0.4)	1617	4 (0.2)	3235	11 (0.3)
<3x ULN at BL	1616	6 (0.4)	1611	4 (0.2)	3227	10 (0.3)
Patients with ≥5x ULN Postbaseline						
All patients at BL[b]	1618	1 (<0.1)	1617	0	3235	1 (<0.1)
<5x ULN at BL	1618	1 (<0.1)	1615	0	3233	1 (<0.1)
Patients with ≥10x ULN Postbaseline						
All patients at BL[b]	1618	0	1617	0	3235	0
<10x ULN at BL	1618	0	1615	0	3233	0

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Table ISS.APP.681. Shift of Liver Analytes from Maximum Baseline to Maximum Postbaseline, Observations Through 26 Weeks of the Planned Treatment Period – Phase 2 and 3 Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Shift of Liver Analytes from Maximum Baseline to Maximum Postbaseline
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDN

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Lab Test (unit) = BILIRUBIN, TOTAL (micromole/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <2x ULN	>=2 to <3x ULN	>=3 to <5x ULN	>=5x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo (N=551)	<=1x ULN	532 (96.6)	3 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)	536 (97.3)
	>1 to <2x ULN	5 (0.9)	10 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	15 (2.7)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	537 (97.5)	13 (2.4)	0 (0.0)	1 (0.2)	0 (0.0)	551 (100.0)
Dula_0.75 (N=811)	<=1x ULN	789 (97.3)	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	794 (97.9)
	>1 to <2x ULN	8 (1.0)	9 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	17 (2.1)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	797 (98.3)	14 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	811 (100.0)

Lab Test (unit) = BILIRUBIN, TOTAL (micromole/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <2x ULN	>=2 to <3x ULN	>=3 to <5x ULN	>=5x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dula_1.5 (N=810)	<=1x ULN	790 (97.5)	7 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	797 (98.4)
	>1 to <2x ULN	12 (1.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	13 (1.6)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	802 (99.0)	8 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	810 (100.0)
All_Dula (N=1621)	<=1x ULN	1579 (97.4)	12 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1591 (98.1)
	>1 to <2x ULN	20 (1.2)	10 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	30 (1.9)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1599 (98.6)	22 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1621 (100.0)

Lab Test (unit) = BILIRUBIN, DIRECT (micromole/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <2x ULN	>=2 to <3x ULN	>=3 to <5x ULN	>=5x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo (N=550)	<=1x ULN	541 (98.4)	4 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	546 (99.3)
	>1 to <2x ULN	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	543 (98.7)	6 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	550 (100.0)
Dula_0.75 (N=807)	<=1x ULN	796 (98.6)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	798 (98.9)
	>1 to <2x ULN	7 (0.9)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.1)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	803 (99.5)	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	807 (100.0)

Lab Test (unit) = BILIRUBIN, DIRECT (micromole/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <2x ULN	>=2 to <3x ULN	>=3 to <5x ULN	>=5x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dula_1.5 (N=805)	<=1x ULN	803 (99.8)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	805 (100.0)
	>1 to <2x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	803 (99.8)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	805 (100.0)
All_Dula (N=1612)	<=1x ULN	1599 (99.2)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1603 (99.4)
	>1 to <2x ULN	7 (0.4)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)
	>=2 to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1606 (99.6)	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1612 (100.0)

Lab Test (unit) = AST/SGOT (Units/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <3x ULN	>=3 to <5x ULN	>=5 to <10x ULN	>=10x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo (N=550)	<=1x ULN	471 (85.6)	13 (2.4)	0 (0.0)	1 (0.2)	0 (0.0)	485 (88.2)
	>1 to <3x ULN	40 (7.3)	23 (4.2)	2 (0.4)	0 (0.0)	0 (0.0)	65 (11.8)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	511 (92.9)	36 (6.5)	2 (0.4)	1 (0.2)	0 (0.0)	550 (100.0)
Dula_0.75 (N=809)	<=1x ULN	692 (85.5)	19 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	711 (87.9)
	>1 to <3x ULN	51 (6.3)	43 (5.3)	3 (0.4)	0 (0.0)	0 (0.0)	97 (12.0)
	>=3 to <5x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	743 (91.8)	63 (7.8)	3 (0.4)	0 (0.0)	0 (0.0)	809 (100.0)

Lab Test (unit) = AST/SGOT (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Dula_1.5	<=1x ULN	704 (86.8)	19 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	723 (89.1)
(N=811)	>1 to <3x ULN	55 (6.8)	31 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	86 (10.6)
	>=3 to <5x ULN	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	759 (93.6)	52 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	811 (100.0)
All_Dula	<=1x ULN	1396 (86.2)	38 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1434 (88.5)
(N=1620)	>1 to <3x ULN	106 (6.5)	74 (4.6)	3 (0.2)	0 (0.0)	0 (0.0)	183 (11.3)
	>=3 to <5x ULN	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1502 (92.7)	115 (7.1)	3 (0.2)	0 (0.0)	0 (0.0)	1620 (100.0)

Lab Test (unit) = ALT/SGPT (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Placebo	<=1x ULN	391 (71.1)	28 (5.1)	1 (0.2)	0 (0.0)	0 (0.0)	420 (76.4)
(N=550)	>1 to <3x ULN	60 (10.9)	66 (12.0)	3 (0.5)	0 (0.0)	0 (0.0)	129 (23.5)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	451 (82.0)	94 (17.1)	5 (0.9)	0 (0.0)	0 (0.0)	550 (100.0)
Dula_0.75	<=1x ULN	602 (74.3)	30 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	632 (78.0)
(N=810)	>1 to <3x ULN	97 (12.0)	78 (9.6)	1 (0.1)	1 (0.1)	0 (0.0)	177 (21.9)
	>=3 to <5x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	699 (86.3)	109 (13.5)	1 (0.1)	1 (0.1)	0 (0.0)	810 (100.0)

Lab Test (unit) = ALT/SGPT (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Dula_1.5	<=1x ULN	585 (72.1)	23 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	608 (75.0)
(N=811)	>1 to <3x ULN	121 (14.9)	80 (9.9)	0 (0.0)	0 (0.0)	0 (0.0)	201 (24.8)
	>=3 to <5x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	>=5 to <10x ULN	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	706 (87.1)	105 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)	811 (100.0)
All_Dula	<=1x ULN	1187 (73.2)	53 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1240 (76.5)
(N=1621)	>1 to <3x ULN	218 (13.4)	158 (9.7)	1 (<0.1)	1 (<0.1)	0 (0.0)	378 (23.3)
	>=3 to <5x ULN	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
	>=5 to <10x ULN	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1405 (86.7)	214 (13.2)	1 (<0.1)	1 (<0.1)	0 (0.0)	1621 (100.0)

Lab Test (unit) = GAMMA GLUTAMYLTRANSFERASE (GGT) (Units/Liter)

Treatment	Maximum Baseline	Maximum Postbaseline <=1x ULN n (%)	>1 to <3x ULN n (%)	>=3 to <5x ULN n (%)	>=5 to <10x ULN n (%)	>=10x ULN n (%)	Total n (%)
Placebo	<=1x ULN	407 (73.9)	20 (3.6)	1 (0.2)	0 (0.0)	0 (0.0)	428 (77.7)
(N=551)	>1 to <3x ULN	40 (7.3)	65 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	105 (19.1)
	>=3 to <5x ULN	0 (0.0)	4 (0.7)	7 (1.3)	1 (0.2)	1 (0.2)	13 (2.4)
	>=5 to <10x ULN	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.7)	0 (0.0)	5 (0.9)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	447 (81.1)	90 (16.3)	8 (1.5)	5 (0.9)	1 (0.2)	551 (100.0)
Dula_0.75	<=1x ULN	615 (75.8)	14 (1.7)	1 (0.1)	0 (0.0)	0 (0.0)	630 (77.7)
(N=811)	>1 to <3x ULN	65 (8.0)	96 (11.8)	4 (0.5)	1 (0.1)	0 (0.0)	166 (20.5)
	>=3 to <5x ULN	1 (0.1)	7 (0.9)	2 (0.2)	0 (0.0)	0 (0.0)	10 (1.2)
	>=5 to <10x ULN	0 (0.0)	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)	4 (0.5)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
	Total	681 (84.0)	118 (14.5)	10 (1.2)	1 (0.1)	1 (0.1)	811 (100.0)

Lab Test (unit) = GAMMA GLUTAMYLTRANSFERASE (GGT) (Units/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <3x ULN	>=3 to <5x ULN	>=5 to <10x ULN	>=10x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dula_1.5 (N=812)	<=1x ULN	610 (75.1)	12 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	622 (76.6)
	>1 to <3x ULN	79 (9.7)	87 (10.7)	3 (0.4)	1 (0.1)	0 (0.0)	170 (20.9)
	>=3 to <5x ULN	3 (0.4)	8 (1.0)	1 (0.1)	1 (0.1)	0 (0.0)	13 (1.6)
	>=5 to <10x ULN	0 (0.0)	2 (0.2)	3 (0.4)	2 (0.2)	0 (0.0)	7 (0.9)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	692 (85.2)	109 (13.4)	7 (0.9)	4 (0.5)	0 (0.0)	812 (100.0)
All_Dula (N=1623)	<=1x ULN	1225 (75.5)	26 (1.6)	1 (<0.1)	0 (0.0)	0 (0.0)	1252 (77.1)
	>1 to <3x ULN	144 (8.9)	183 (11.3)	7 (0.4)	2 (0.1)	0 (0.0)	336 (20.7)
	>=3 to <5x ULN	4 (0.2)	15 (0.9)	3 (0.2)	1 (<0.1)	0 (0.0)	23 (1.4)
	>=5 to <10x ULN	0 (0.0)	3 (0.2)	6 (0.4)	2 (0.1)	0 (0.0)	11 (0.7)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
	Total	1373 (84.6)	227 (14.0)	17 (1.0)	5 (0.3)	1 (<0.1)	1623 (100.0)

Lab Test (unit) = ALKALINE PHOSPHATASE (Units/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <3x ULN	>=3 to <5x ULN	>=5 to <10x ULN	>=10x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo (N=551)	<=1x ULN	501 (90.9)	9 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	510 (92.6)
	>1 to <3x ULN	14 (2.5)	27 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	41 (7.4)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	515 (93.5)	36 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	551 (100.0)
Dula_0.75 (N=811)	<=1x ULN	719 (88.7)	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	724 (89.3)
	>1 to <3x ULN	44 (5.4)	43 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	87 (10.7)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	763 (94.1)	48 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	811 (100.0)

Lab Test (unit) = ALKALINE PHOSPHATASE (Units/Liter)

		Maximum Postbaseline					
		<=1x ULN	>1 to <3x ULN	>=3 to <5x ULN	>=5 to <10x ULN	>=10x ULN	Total
Treatment	Maximum Baseline	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dula_1.5 (N=811)	<=1x ULN	705 (86.9)	16 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	721 (88.9)
	>1 to <3x ULN	50 (6.2)	40 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	90 (11.1)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	755 (93.1)	56 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	811 (100.0)
All_Dula (N=1622)	<=1x ULN	1424 (87.8)	21 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1445 (89.1)
	>1 to <3x ULN	94 (5.8)	83 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	177 (10.9)
	>=3 to <5x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=5 to <10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>=10x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1518 (93.6)	104 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	1622 (100.0)

Abbreviations: N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in the specified category; ULN = upper limit of normal range.

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Table ISS.APP.731. Listing for Medical Query: Any Malignant or Unspecified Tumour, All Postbaseline Observations including Safety Follow-Up – All Treatment-Emergent Adverse Events Satisfying the Medical Query (Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN)

Listing for Medical Query: Any Malignant or Unspecified Tumour
All Postbaseline Observations Including Safety Follow-Up
All Treatment-Emergent Adverse Events Satisfying the Medical Query
Safety Population, Studies GBCF, GBCJ, GBCK, GBCZ, GBDA, GBDB, GBDC, GBDD, GBDN

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Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBCF	3	215	Placebo/Sitagliptin*	66	Male	Basal cell carcinoma /basal cell cancer, face	04MAY2011	170	170	ongoing
		217	Dula 1.5	29	Female	Thyroid neoplasm /thyroid nodule, right upper lobe	13JUN2011	368	368	ongoing
	10	573	Dula 0.75	52	Female	Breast cancer /newly diagnosed breast cancer	28JUN2010	144	144	ongoing
	13	701	Dula 2.0	56	Female	Thyroid cancer /Medullary Thyroid Cancer	11DEC2009	170	360	190
		715	Dula 1.5	37	Female	Tongue neoplasm /Tongue Lesion	19OCT2011	713	713	ongoing
	26	1352	Dula 0.75	60	Female	Basal cell carcinoma /Basal cell skin carcinoma	21JAN2009	62	62	ongoing
	27	1403	Placebo*/Sitagliptin	58	Female	Non-secretory adenoma of pituitary /Non Secreting Macroadenoma	12MAY2009	70	77	7
	34	1750	Placebo/Sitagliptin*	38	Female	Thyroid neoplasm /Left thyroid (2) nodules	02FEB2011	524	524	ongoing
	201	105	Placebo*/Sitagliptin	52	Male	Oesophageal adenocarcinoma /Distal Esophagus Adenocarcinoma	01DEC2009	15	15	ongoing
	203	4108	Dula 0.75	65	Male	Thyroid neoplasm /thyroid nodule	27JAN2011	605	605	ongoing

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBCF	205	4225	Sitagliptin	52	Female	Laryngeal cancer stage III /Epidermoid Carcinoma of Larynx Stage III	12FEB2010	262	262	ongoing
	501	6015	Dula 1.5	57	Male	Gastric cancer /gastric adenocarcinoma	14NOV2011	603	603	ongoing
	502	6056	Dula 1.5	66	Female	Vocal cord neoplasm /vocal cords lesio	21JUN2011	653	653	ongoing
	503	6125	Placebo/Sitagliptin*	60	Female	Lung neoplasm /Small change nodules of lungs.	31AUG2011	325	325	ongoing
	507	6252	Dula 0.75	65	Male	Chronic lymphocytic leukaemia /chronic lymphatic leucemia	27NOV2010	186	186	ongoing
	601	6313	Sitagliptin	61	Male	Gastric cancer /gastric cancer diagnosis	28JUL2011	575	575	ongoing
	603	6413	Sitagliptin	56	Female	Lung neoplasm /small nodule in left apical lung	22JUL2011	473	473	ongoing
	608	6653	Dula 1.5	44	Female	Thyroid cancer /Papillary Thyroid Cacinoma	06FEB2012	739	743	4
	852	7401	Sitagliptin	65	Male	Prostate cancer /prostate cancer	20OCT2011	696	696	ongoing
		7405	Dula 1.5	73	Male	Colon cancer /adecarcinoma of colon	03NOV2011	596	606	10

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBCF	878	8406	Dula 0.75	61	Female	Breast cancer /infiltrativ galadic canal carcinoma (right breast)	02SEP2011	652	652	ongoing
	924	9700	Sitagliptin	58	Female	Uterine cancer /uterine cancer	24SEP2010	196	213	17
	940	3035	Sitagliptin	43	Female	Breast cancer /Carcinoma(right breast)	04MAY2010	54	60	6
GBCJ	40	4018	Dula 1.0/1.0	39	Male	Colon cancer /Colon Cancer	02JUL2008	15	24	9
	41	4115	Placebo	51	Male	Neoplasm skin /Neoplasm chest / face	17NOV2008	107	110	3
GBCK	105	513	Dula 0.5	69	Female	Breast cancer /Breast Cancer	23JUL2009	21	21	ongoing
	107	702	Dula 0.5	65	Female	Basal cell carcinoma /basal cell carcinoma	16JUN2009	62	62	ongoing
GBCZ	117	1712	Dula 0.75	61	Male	Pancreatic carcinoma /PANCREATIC CANCER	31MAY2010	1	11	10
GBDA	7	302	Exenatide	76	Male	Prostate cancer /prostate cancer	21JUL2010	48	48	ongoing
		329	Dula 0.75	53	Male	Lung neoplasm /lung nodule	20AUG2011	167	167	ongoing
	12	555	Dula 1.5	56	Female	Pancreatic carcinoma /Pancreatic cancer	14DEC2010	162	166	4

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDA	12	559	Exenatide	60	Male	Thyroid neoplasm /Thyroid nodule	20SEP2010	62	62	ongoing
	28	1380	Placebo	58	Male	Malignant melanoma /Melanoma	12JUL2011	167	167	ongoing
	33	1609	Dula 0.75	72	Male	Basal cell carcinoma /BASAL CELL CARCINOMA (NOSE)	15SEP2010	44	44	ongoing
						Liposarcoma /LIPOSARCOMA RIGHT SARTORIUS MUSCLE	19JAN2011	170	170	ongoing
	41	2008	Placebo/Dula 0.75*	65	Male	Renal neoplasm /17mm nodule lower pole left kidney	24AUG2011	121	121	ongoing
	49	2439	Dula 0.75	65	Female	Breast cancer in situ /Carcinoma in situ right breast	21MAR2012	351	372	21
	54	2652	Exenatide	49	Male	Colon cancer /Colon Cancer	01MAY2011	254	254	ongoing
	59	2933	Dula 0.75	76	Male	Prostate cancer stage 0 /Prostate Cancer in situ	03MAY2011	187	187	ongoing
	68	3356	Dula 0.75	59	Female	Skin cancer /SKIN CANCER - LEFT EAR	06JUL2011	330	330	ongoing
	71	3507	Placebo	61	Male	Prostate cancer /Prostate cancer	05NOV2010	87	87	ongoing

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDA	74	3654	Dula 0.75	61	Female	Gastrointestinal stromal tumour /Gastrointestinal Stromal Tumor	26JAN2011	135	135	ongoing
	91	4518	Dula 0.75	58	Male	Squamous cell carcinoma of skin /Left arm lesion squamous cell Carcinoma	15JAN2011	185	185	ongoing
GBDB	6	274	Dula 0.75	61	Female	Breast cancer metastatic /metastatic breast cancer	25APR2011	183	183	ongoing
	53	654	Dula 0.75	58	Female	Squamous cell carcinoma /squamous cell carcinoma Left Wrist	27OCT2010	73	73	ongoing
	202	2102	Dula 1.5	46	Female	Thyroid cancer /Papillary thyroid carcinoma of follicular variant	27MAY2011	246	253	7
						Thyroid neoplasm /Bilateral Thyroid Nodules	09DEC2010	84	84	ongoing
		2107	Dula 0.75	64	Female	Adenocarcinoma /Adenocarcinoma	09AUG2011	267	267	ongoing
	206	2303	Dula 0.75	76	Female	Bowen's disease /Bowen's Disease (right neck basal cell carcinoma)	15JUL2010	8	8	ongoing
	253	2652	Insulin Glargine	54	Female	Breast cancer /Adenocarcinoma mamae (right)	26MAY2011	53	53	ongoing

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDB	351	3550	Dula 1.5	68	Male	Prostate cancer stage 0 /prostatic cancer "in situ"	09NOV2011	330	330	ongoing
	452	4608	Dula 0.75	69	Male	Basal cell carcinoma /Basalioma on the left shoulder	15JUN2012	439	439	ongoing
						Basal cell carcinoma /Basalioma on the right shoulder.	14NOV2011	225	225	ongoing
	453	4658	Insulin Glargine	59	Male	Lung neoplasm /Tumor pulmonary on the left side	27FEB2012	382	382	ongoing
	454	4705	Insulin Glargine	65	Female	Breast cancer /breast cancer	11NOV2011	297	297	ongoing
	507	5353	Dula 0.75	39	Male	Testicular seminoma (pure) /Testicular seminoma	18JAN2012	477	477	ongoing
	551	5550	Dula 0.75	65	Male	Transitional cell carcinoma /hospitalization for papillary urothelial carcinoma	28JUN2011	136	155	19
	951	9353	Dula 0.75	56	Female	Multiple myeloma /multiple myeloma	15OCT2011	424	431	7
	954	9517	Insulin Glargine	65	Male	Thyroid neoplasm /left thyroid nodule	09APR2012	365	365	ongoing
GBDC	106	600	Dula 1.5	51	Male	Gastric neoplasm /gastric nodules	28OCT2010	154	154	ongoing

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDC	505	6404	Dula 1.5	59	Female	Non-Hodgkin's lymphoma /NON HODGKIN LYMPHOMA	08APR2011	120	122	2
	867	8853	Dula 0.75	63	Female	Tongue carcinoma stage I /Stage I Tongue carcinoma	29AUG2011	176	176	ongoing
GBDD	2	159	Insulin Glargine	66	Female	Vaginal neoplasm /Suspicious vaginal growth	27JUN2011	6	6	ongoing
	7	402	Dula 0.75	56	Male	Lung neoplasm /pulmonary nodual	03JAN2012	237	237	ongoing
		403	Dula 0.75	65	Female	Breast cancer /Infiltrating ductal carcinoma - left breast	15SEP2011	126	126	ongoing
	8	452	Insulin Glargine	74	Male	Skin cancer /Benign Skin cancer on left ear	14MAR2011	90	90	ongoing
	10	555	Dula 0.75	65	Male	Prostate cancer /Prostate Cancer	27JUN2012	342	342	ongoing
	12	651	Insulin Glargine	70	Male	B-cell small lymphocytic lymphoma /Diagnosis of B cell small lymphocytic lymphoma	10MAY2011	47	47	ongoing
	29	1526	Insulin Glargine	68	Male	Prostate cancer /prostate cancer	14FEB2012	320	320	ongoing
	33	1700	Insulin Glargine	51	Female	Rectal cancer /Adenocarcinoma rectum	02SEP2011	212	212	ongoing

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDD	36	1854	Insulin Glargine	64	Male	Thyroid neoplasm /two 2mm left thyroid nodules	11APR2011	47	47	ongoing
	51	2745	Dula 0.75	72	Female	Gallbladder cancer /gallbladder adenocarcinoma	02NOV2011	188	188	ongoing
	150	3414	Dula 1.5	73	Female	Basal cell carcinoma /Posterior neck Basal Cell Carcinoma	28DEC2011	203	203	ongoing
	251	4033	Insulin Glargine	55	Male	Non-small cell lung cancer /Pulmonary bronchogenic malignant neoplasia (non-small type cell).	10AUG2011	133	133	ongoing
	254	4126	Dula 1.5	64	Female	Thyroid neoplasm /left thyroid nodule	24APR2012	300	300	ongoing
	551	6076	Insulin Glargine	61	Male	Rectal cancer /rectal cancer	18JUL2011	74	75	1
	702	7103	Dula 0.75	61	Male	Thyroid neoplasm /thyroid nodule	04MAY2011	2	2	ongoing
		7104	Dula 0.75	60	Male	Rectal neoplasm /Rectum neoplasm	29JUL2011	85	123	38
GBDN	13	705	Dula 0.75	42	Female	Basal cell carcinoma /basal cell carcinoma right forehead	14SEP2010	15	15	ongoing

Study	Inv	Pat	Treatment	Age	Sex	Preferred Term /Actual Term	Date of AE	Days on Therapy	Days Since First Dose	Days Since Final Dose
GBDN	47	2417	Placebo	55	Female	Neoplasm skin /Skin neoplasm uncertain behavior	13JAN2011	31	31	ongoing
	701	7064	Placebo	75	Male	Malignant melanoma /Malignant melanoma	28JUL2011	144	144	ongoing
	902	8365	Dula 0.75	70	Male	Basal cell carcinoma /A-BASAL CELL CARCINOMA,NODULAR(BIOPSY)	03MAR2011	141	141	ongoing

Abbreviations: AE = adverse event; Inv = investigator; NA = not applicable; Pat = patient.

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Table ISS.6.142. Shift of Urine Albumin to Creatinine Ratio from Maximum Baseline to Maximum Postbaseline, Observations Through 26 Weeks of the Planned Treatment Period - Placebo-Controlled Studies with 0.75 mg and 1.5 mg Dulaglutide (Safety Population with eGFR (CKD-EPI) <60 mL/min/1.73 m² or Macroalbuminuria (UACR >300 mg/g) at Baseline, Studies GBCF, GBDA, GBDN) (AS1)

Shift of Urine Albumin to Creatinine Ratio from Maximum Baseline to Maximum Postbaseline
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population with eGFR (CKD-EPI) <60 mL/min/1.73 m² or Macroalbuminuria (UACR >300 mg/g) at Baseline
Studies GBCF, GBDA, GBDN

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Lab Test (unit) = URINE ALBUMIN to CREATININE RATIO (milligram/gram)

		Maximum Postbaseline			
Treatment	Maximum Baseline	< 30 mg/g n (%)	>= 30 to <= 300 mg/g n (%)	> 300 mg/g n (%)	Total n (%)
Placebo (N=38)	< 30 mg/g	17 (44.7)	1 (2.6)	0 (0.0)	18 (47.4)
	>= 30 to <= 300 mg/g	2 (5.3)	4 (10.5)	0 (0.0)	6 (15.8)
	> 300 mg/g	0 (0.0)	1 (2.6)	13 (34.2)	14 (36.8)
	Total	19 (50.0)	6 (15.8)	13 (34.2)	38 (100.0)
Dula_0.75 (N=50)	< 30 mg/g	17 (34.0)	2 (4.0)	0 (0.0)	19 (38.0)
	>= 30 to <= 300 mg/g	2 (4.0)	9 (18.0)	0 (0.0)	11 (22.0)
	> 300 mg/g	1 (2.0)	7 (14.0)	12 (24.0)	20 (40.0)
	Total	20 (40.0)	18 (36.0)	12 (24.0)	50 (100.0)

Lab Test (unit) = URINE ALBUMIN to CREATININE RATIO (milligram/gram)

		Maximum Postbaseline			
Treatment	Maximum Baseline	< 30 mg/g n (%)	>= 30 to <= 300 mg/g n (%)	> 300 mg/g n (%)	Total n (%)
Dula_1.5 (N=45)	< 30 mg/g	17 (37.8)	0 (0.0)	0 (0.0)	17 (37.8)
	>= 30 to <= 300 mg/g	1 (2.2)	6 (13.3)	0 (0.0)	7 (15.6)
	> 300 mg/g	0 (0.0)	6 (13.3)	15 (33.3)	21 (46.7)
	Total	18 (40.0)	12 (26.7)	15 (33.3)	45 (100.0)
All_Dula (N=95)	< 30 mg/g	34 (35.8)	2 (2.1)	0 (0.0)	36 (37.9)
	>= 30 to <= 300 mg/g	3 (3.2)	15 (15.8)	0 (0.0)	18 (18.9)
	> 300 mg/g	1 (1.1)	13 (13.7)	27 (28.4)	41 (43.2)
	Total	38 (40.0)	30 (31.6)	27 (28.4)	95 (100.0)

Abbreviations: eGFR (CKD-EPI) = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); mg/g = milligram per gram; mL/min/1.73 m² = milliliter per minute per 1.73 square meters of body surface area; N = number of patients with baseline and at least one postbaseline result in specified treatment arm; n = number of patients in a specified category; UACR = urine albumin-to-creatinine ratio.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.

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Table ISS.APP.459. Summary and Analysis of Treatment-Emergent Abnormal Values of Lipids, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with Dulaglutide 0.75 and 1.5 mg (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Summary and Analysis of Treatment-Emergent Abnormal Values of Lipids 07MAY2013 12:37
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDN

Lipid Parameter / Treatment-emergent Abnormality	Placebo (N=568) m	M	(%)	Dula_0.75 (N=836) m	M	(%)	Dula_1.5 (N=834) m	M	(%)	All_Dula (N=1670) m	M	(%)	p-value *a
CHOLESTEROL (millimole/Liter)													
<1X LLN	34	408	(8.3)	38	640	(5.9)	47	629	(7.5)	85	1269	(6.7)	0.318
>1X ULN	37	355	(10.4)	64	547	(11.7)	55	545	(10.1)	119	1092	(10.9)	0.958
HDL CHOLESTEROL (millimole/Liter)													
<1X LLN	29	317	(9.1)	37	506	(7.3)	36	488	(7.4)	73	994	(7.3)	0.443
>1X ULN	2	445	(0.4)	3	696	(0.4)	3	696	(0.4)	6	1392	(0.4)	0.793
TRIGLYCERIDES (millimole/Liter)													
<1X LLN	1	451	(0.2)	3	706	(0.4)	2	704	(0.3)	5	1410	(0.4)	0.498
>1X ULN	26	384	(6.8)	41	608	(6.7)	25	596	(4.2)	66	1204	(5.5)	0.494
LDL CHOLESTEROL (millimole/Liter)													
>1X ULN	25	382	(6.5)	34	590	(5.8)	43	595	(7.2)	77	1185	(6.5)	0.684
TOTAL CHOLESTEROL/HDL (Proportion of 1.0)													
>1X ULN	26	375	(6.9)	28	575	(4.9)	31	570	(5.4)	59	1145	(5.2)	0.294

Abbreviations: Dula = dulaglutide; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LLN = Lower Limit of Normal; M = number of patients with baseline not in specified direction of treatment-emergent abnormality and at least one post-baseline result; m = number of patients in specified category; N = number of patients in specified treatment group; ULN = Upper Limit of Normal.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.
Note: For TOTAL CHOLESTEROL/HDL an upper limit of 5.0 was used.

**a - p-values are from Cochran-Mantel-Haenszel (CMH) test comparing All_Dula to Placebo adjusted for study.

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Table ISS.APP.462. Minimum to Minimum Change Analysis of Lipids, All Observations During the Planned Treatment Period – Phase 2 and 3 Studies With 0.75 mg and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN) (AS3)

Summary and Analysis of Treatment-Emergent Abnormal Values of Lipids 07MAY2013 12:37
All Observations During the Planned Treatment Period
Phase 2 and 3 Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN

Lipid Parameter / Treatment Emergent Abnormality	Dula_0.75 (N=1671) m	M	(%)	Dula_1.5 (N=1671) m	M	(%)	All_Dula (N=3342) m	M	(%)	p-value *a
CHOLESTEROL (millimole/Liter)										
<1X LLN	134	1358	(9.9)	134	1333	(10.1)	268	2691	(10.0)	0.872
>1X ULN	200	1119	(17.9)	202	1116	(18.1)	402	2235	(18.0)	0.850
HDL CHOLESTEROL (millimole/Liter)										
<1X LLN	140	1068	(13.1)	136	1040	(13.1)	276	2108	(13.1)	0.910
>1X ULN	17	1490	(1.1)	12	1479	(0.8)	29	2969	(1.0)	0.352
TRIGLYCERIDES (millimole/Liter)										
<1X LLN	9	1510	(0.6)	12	1499	(0.8)	21	3009	(0.7)	0.513
>1X ULN	165	1294	(12.8)	136	1273	(10.7)	301	2567	(11.7)	0.104
LDL CHOLESTEROL (millimole/Liter)										
>1X ULN	149	1245	(12.0)	154	1241	(12.4)	303	2486	(12.2)	0.673
TOTAL CHOLESTEROL/HDL (Proportion of 1.0)										
>1X ULN	117	1222	(9.6)	128	1203	(10.6)	245	2425	(10.1)	0.335

Abbreviations: Dula = dulaglutide; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LLN = Lower Limit of Normal; M = number of patients with baseline not in specified direction of treatment-emergent abnormality and at least one post-baseline result; m = number of patients in specified category; N = number of patients in specified treatment group; ULN = Upper Limit of Normal.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.
Note: For TOTAL CHOLESTEROL/HDL an upper limit of 5.0 was used.

*a - p-values are from Cochran-Mantel-Haenszel (CMH) test comparing Dula_0.75 to Dula_1.5 adjusted for study.

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Table ISS.6.91. Summary of Treatment-Emergent Abnormal Low and High of Vital Signs, Observations Through 26 Weeks of the Planned Treatment Period – Placebo-Controlled Studies with 0.75 and 1.5 mg Dulaglutide (Safety Population, Studies GBCF, GBDA, GBDN) (AS1)

Summary of Treatment-Emergent Abnormal Low and High of Vital Signs 07MAY2013 12:31
Observations Through 26 Weeks of the Planned Treatment Period
Placebo-Controlled Studies With 0.75 mg and 1.5 mg Dulaglutide Groups
Safety Population, Studies GBCF, GBDA, GBDN

Vital Sign Abnormal Low/High	Placebo (N=568) m	M	(%)	Dula_0.75 (N=836) m	M	(%)	Dula_1.5 (N=834) m	M	(%)	All_Dula (N=1670) m	M	(%)	p-value *a
Office-Measured Sitting Systolic BP (mm Hg)													
<= 90 and Decr >= 20	0	566	(0.0)	3	823	(0.4)	1	819	(0.1)	4	1642	(0.2)	.247
>= 160 and Incr >= 20	10	549	(1.8)	11	790	(1.4)	9	796	(1.1)	20	1586	(1.3)	.438
Office-Measured Sitting Diastolic BP (mm Hg)													
<= 50 and Decr >= 10	2	565	(0.4)	1	823	(0.1)	0	820	(0.0)	1	1643	(<0.1)	.162
>= 100 and Incr >= 10	10	557	(1.8)	8	814	(1.0)	12	807	(1.5)	20	1621	(1.2)	.430
Office-Measured Sitting Heart Rate (bpm)													
< 50 and Decr >= 15	2	564	(0.4)	0	819	(0.0)	0	816	(0.0)	0	1635	(0.0)	.007
> 100 and Incr >= 15	4	554	(0.7)	11	815	(1.3)	18	804	(2.2)	29	1619	(1.8)	.060

Abbreviations: BP = blood pressure; bpm = beats per minute; Decr = decrease from baseline; Incr = increase from baseline; M = number of patients with baseline not in the specified direction of treatment-emergent abnormality and at least one post-baseline result; m =number of patients in specified category; mm Hg = millimeters of mercury; N = total number of patients in specified treatment group.

Note: Dula_0.75 refers to 0.75 milligrams dulaglutide once weekly and Dula_1.5 refers to 1.5 milligrams dulaglutide once weekly. All_Dula refers to Dula_0.75 and Dula_1.5 treatment groups combined.

*a - p-values are from Cochran-Mantel-Haenszel (CMH) test comparing All_Dula to Placebo adjusted for study.

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/s/

SUCHITRA M BALAKRISHNAN
08/12/2014

WILLIAM H CHONG
08/13/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125,469 **Applicant:** Eli Lilly **Stamp Date:** 9/18/2013

Drug Name: Dulaglutide Injection **BLA Type:** NME 351(a)
[(b) (4)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The PI is too long and has extraneous information. The adverse reaction data will be examined closely to determine whether all data from the 0.75 mg dosage arms should be presented in the label. We will communicate deficiencies to the Applicant early in the review cycle.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA 351(a)
DOSE					

Reference ID: 3401616

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	X			All Phase 3 studies were conducted in subjects with T2DM and are deemed equally pivotal by the Applicant. The studies compare dulaglutide with metformin as monotherpay or with various add-on combinations including oral antidiabetic agents, insulin, or exenatide.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The primary efficacy endpoint for the dulaglutide Phase III studies was a change from baseline in HbA1c.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

Reference ID: 3401616

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3401616

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

If the Application is not fileable from the clinical 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.

Karim A. Calis, Pharm.D., MPH 11/4/2013

Reviewing Medical Officer Date

Ali Mohamadi, M.D.

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3401616

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/s/

KARIM A CALIS
11/05/2013

ALI MOHAMADI
11/05/2013