2. GBDD Synopsis

Clinical Study Report Synopsis: Study H9X-MC-GBDD

Title of Study: 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)	
Number of Investigators: This multicenter study included 109 investigators.	
Study Centers: This study was conducted at 105 study centers in 16 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 27 October 2010 Date of last patient completed: 21 September 2012	**Phase of Development:** 3

Objectives: The primary objective was to compare effects of once-weekly 1.5-mg dulaglutide (LY2189265), injected subcutaneously, to insulin glargine (treated-to-target) on hemoglobin A1c (HbA1c) at 26 weeks (change from baseline) in patients with type 2 diabetes mellitus (T2DM), both in combination with prandial insulin lispro. Noninferiority of 1.5-mg dulaglutide to insulin glargine for HbA1c was to be declared if the upper bound of the 2-sided 95% confidence interval (CI) for the difference between dulaglutide 1.5-mg and insulin glargine was below the margin of noninferiority (0.4%).

Key secondary objectives compared glycemic control (change in HbA1c from baseline) between dulaglutide (1.5-mg and 0.75-mg) and insulin glargine using a tree-gatekeeping method:

- To demonstrate that 0.75-mg dulaglutide is noninferior to insulin glargine at 26 weeks.
- To demonstrate that 1.5-mg dulaglutide is superior to insulin glargine at 26 weeks.
- To demonstrate that 0.75-mg dulaglutide is superior to insulin glargine at 26 weeks.

Additional secondary objectives compared glycemic control (change in HbA1c from baseline to 52 weeks) between dulaglutide (1.5-mg and 0.75-mg) and insulin glargine using a tree-gatekeeping method:

- To demonstrate that 1.5-mg dulaglutide is noninferior to insulin glargine at 52 weeks.
- To demonstrate that 0.75-mg dulaglutide is noninferior to insulin glargine at 52 weeks.
- To demonstrate that 1.5-mg dulaglutide is superior to insulin glargine at 52 weeks.
- To demonstrate that 0.75-mg dulaglutide is superior to insulin glargine at 52 weeks.

The efficacy of dulaglutide (1.5-mg and 0.75-mg) and insulin glargine was compared at 26 and 52 weeks for:

- plasma glucose (PG) values from the 8-point self-monitored PG (SMPG) profiles (actual values and change from baseline) and percent of patients attaining HbA1c <7%; and ≤6.5%
- fasting serum glucose (FSG) as measured by the central laboratory
- total daily insulin lispro dose
- percentage of patients achieving HbA1c <7.0% without a single instance of symptomatic nocturnal hypoglycemia, confirmed by plasma-referenced glucose ≤70 mg/dL (3.9 mmol/L), or meeting the criteria for severe hypoglycemia
- patient-reported outcomes (PRO): European Quality of Life – 5 dimensions (EQ-5D), Impact of Weight on Activities of Daily Living (IW-ADL), Impact of Weight on Self-Perception (IW-SP), The Low Blood Sugar Survey (LBSS)

The safety of dulaglutide (1.5-mg and 0.75-mg) and insulin glargine was compared at 26 weeks, 52 weeks, and at the end of the safety follow-up period for:

- change in body weight and body mass index (BMI) from baseline
- cardiovascular (CV) system-related safety: reported and adjudicated CV events, electrocardiogram (ECG) parameters, pulse rate (PR), and blood pressure (BP)
- pancreas and thyroid gland-related safety: adjudicated events of acute pancreatitis and reported elevations in pancreatic enzymes or serum calcitonin, an indicator of thyroid C-cell abnormalities
- glycemia-related safety: self-reported hypoglycemic events (rate and incidence of documented symptomatic, asymptomatic, severe, nocturnal, or probable symptomatic hypoglycemia)
- immune system-related safety: dulaglutide anti-drug antibody (ADA) titer and immune system-related adverse events (AEs)
- general safety: treatment-emergent adverse events (TEAEs) and laboratory analytes

Study Design: A 52-week, Phase 3, parallel, active comparator, outpatient trial to assess the safety and efficacy of dulaglutide compared with insulin glargine both in combination with prandial insulin lispro (with or without metformin). The insulin glargine arm was open-label while dulaglutide dose assignment was double-blinded.

Number of Patients:

Planned: 837 total randomized patients (279 per treatment arm)
Randomized: Total: 884; dulaglutide 1.5 mg: 295; dulaglutide 0.75 mg: 293; glargine: 296
Treated (at least 1 dose): Total: 884; dulaglutide 1.5 mg: 295; dulaglutide 0.75 mg: 293; glargine: 296
Completed 26 Weeks: Total: 759; dulaglutide 1.5 mg: 248; dulaglutide 0.75 mg: 255; glargine: 256
Completed 52 Weeks: Total: 719; dulaglutide 1.5 mg: 237; dulaglutide 0.75 mg: 238; glargine: 244
Completed LV30: Total: 833; dulaglutide 1.5 mg: 278; dulaglutide 0.75 mg: 276; glargine: 279

Diagnosis and Main Criteria for Inclusion: Patients who were diagnosed with T2DM with a screening HbA1c ≥7% and ≤11%, after being treated for ≥3 months with a conventional insulin regimen (≤2 doses of insulin per day including any combination of basal, basal with prandial, or premixed insulin [excluding any prandial only regimen]), alone or in combination with oral antihyperglycemic medications (OAMs). If the most commonly administered total daily dose during the prior 3 months was ≥40 units, then all total daily doses were to be within ±10% of that dose to confirm that intensification of therapy was needed. If the most commonly administered total daily dose during the prior 3 months was <40 units, then all total daily doses were to be within ±4 units of that dose.

Study Drug, Dose, and Mode of Administration: Once-weekly 0.75- or 1.5-mg dulaglutide subcutaneous injection.

Comparator, Dose, and Mode of Administration: Insulin glargine initiated at 50% of prerandomization total daily insulin dose; dose adjusted using the treat-to-target algorithm; administered in the Solostar™ device.

Combination Therapy, Dose and Mode of Administration: Insulin lispro prior to meals started at 50% of prerandomization total daily insulin dose; dose adjusted using an algorithm; administered by Kwikpen™ device.

Duration of Treatment:

Lead-in period: 9 weeks
Treatment period: 52 weeks
Follow-up safety period: 4 weeks

Variables:

Efficacy:

Change in HbA1c; proportion of patients achieving HbA1c <7% and ≤6.5%; and percentage of patients achieving HbA1c <7.0% without a single instance of symptomatic nocturnal hypoglycemia (confirmed by plasma-referenced glucose ≤70 mg/dL [3.9 mmol/L]) or meeting the criteria for severe hypoglycemia; 8-point SMPG profile and FSG measured in the central laboratory (actual values and change from baseline); and insulin daily doses and insulin algorithms.

Safety:

TEAEs; deaths and other serious adverse events; study drug and study discontinuations; laboratory analytes; change in body weight and body mass index (BMI) from baseline; vital signs; ECG parameters; safety topics of special interest which included analysis of pancreatic events, thyroid events, immunogenicity of dulaglutide assessed by dulaglutide anti-drug antibodies (ADA), gastrointestinal safety, cardiovascular events, and hypoglycemia; overdose; and pregnancies.

Health Outcomes:

PROs: EQ-5D, IW-ADL, IW-SP, LBSS.

Statistical Evaluation Methods:

Efficacy and Safety:

Both efficacy and safety analyses were performed in the intent-to-treat (ITT) population. In addition, analyses for primary and key secondary objectives were repeated in the per-protocol (PP) population.

The primary efficacy measurement was HbA1c change from baseline at 26 weeks (Visit 11) for the ITT population. The primary analysis model was analysis of covariance (ANCOVA) for the change from baseline to endpoint in HbA1c. Missing endpoints were imputed with the last postbaseline observation carried forward (LOCF). The model included treatment, country, and metformin as fixed effects and baseline HbA1c as a covariate. The primary analysis model was used to examine both noninferiority and superiority of 1.5-mg dulaglutide to insulin glargine and 0.75-mg dulaglutide to insulin glargine using a gatekeeping strategy to control the family-wise Type 1 error rate. In addition, the mixed-effects model repeated-measures (MMRM) approach based on the ITT population using restricted maximum likelihood (REML) with baseline as a covariate, which implicitly adjusts for missing data through a variance-covariance structure, was also conducted for the primary and key secondary objectives.

The noninferiority margin was defined as 0.4%. If the upper limit of the 95% CI of 1.5-mg dulaglutide versus insulin glargine was below 0.4%, then 1.5-mg dulaglutide could be declared noninferior to insulin glargine. If the upper limit of the CI was below zero, then 1.5-mg dulaglutide could be declared superior to insulin glargine. The primary analysis for the primary endpoint was conducted based upon the intent-to-treat (ITT) population prior to taking rescue therapy.

To show noninferiority of the 1.5-mg dulaglutide arm to insulin glargine with 90% power, 669 total completers (223 per arm) at 52 weeks or 744 total completers (248 per arm) at 26 weeks were required. This calculation assumed a zero difference in HbA1c between the 1.5-mg dulaglutide and insulin glargine, 0.4% margin of noninferiority, common standard deviation (SD) of 1.3% for change from baseline in HbA1c, 0.05 2-sided significance level, and 20% dropout rate at 52 weeks.

For other continuous measures, treatment comparisons were performed for the LS means and 95% CI of the treatment differences, along with the p-value for the comparison. For categorical measures, unless otherwise noted, a Chi-square test was used for the treatment comparisons. If the total measure count was < 10, then Fisher's exact test was used.

The health outcomes analyses consisted of 4 PRO instruments that were analyzed in a manner broadly consistent with the overall statistical analysis plan (SAP), including fixed effects for treatment, country, and baseline score as a covariate. The LOCF approach was used to impute missing postbaseline values, and treatment contrasts at 26 weeks (Visit 11) and 52 weeks (Visit 13) were used to assess response.

Summary:

Demographics, Disease Characteristics, Populations, Treatment Compliance and Protocol Violations

A total of 884 patients with T2DM requiring intensive (basal-bolus) insulin therapy were randomized into 3 treatment arms (dulaglutide 1.5 mg: 295; dulaglutide 0.75 mg: 293; glargine: 296). The mean age for all patients was 59.4 years; 72.5% were <65 years old; 53.5% were male. Approximately 79% were White and 35% patients were Hispanic or Latino. The mean duration of diabetes was 12.7 years and mean HbA1c 8.5%. The groups were balanced for these characteristics. The mean BMI was 32.5 kg/m^2, with significant differences between the groups (dulaglutide 1.5 mg: 31.99 kg/m^2; dulaglutide 0.75 mg: 33.08 kg/m^2; insulin glargine: 32.41 kg/m^2; p=0.013).

Summary of Efficacy Results

Primary and Key Secondary Objectives

The dulaglutide 1.5 mg arm met criteria for both noninferiority (primary objective) and superiority to insulin glargine at 26 weeks (adjusted one-sided p-value <.001) on HbA1c change from baseline. The LS mean and nominal 95% CI for the difference of the dulaglutide 1.5 mg arm relative to insulin glargine at 26 weeks was: -0.22% (-0.38, -0.07). Results of the sensitivity analyses using the MMRM model for the ITT population and ANCOVA model for the PP population were similar to the primary analysis. The dulaglutide 0.75 mg group also met criteria for both noninferiority and superiority to insulin glargine at 26 weeks. The LS mean and nominal 95% CI for the difference between dulaglutide 0.75 mg and insulin glargine at 26 weeks was: -0.17% (-0.33, -0.02).

Additional Secondary Objectives

Noninferiority/Superiority Comparison at 52 Weeks

The dulaglutide 1.5 mg and dulaglutide 0.75 mg groups were superior to insulin glargine at 52 weeks on HbA1c change from baseline. The LS mean and nominal 95% CI for the difference of the dulaglutide 1.5 mg arm relative to insulin glargine at 52 weeks was: -0.25% (-0.42, -0.07). The LS mean and nominal 95% CI for the difference of the dulaglutide 0.75 mg arm relative to insulin glargine at 52 weeks was: -0.19% (-0.37, -0.02).

Percentage of Patients Attaining Target Thresholds of HbA1c

HbA1c <7% or ≤6.5%:

At 26 weeks, significantly higher proportions of patients in the dulaglutide treatment groups had HbA1c levels <7% compared with insulin glargine. The proportion of patients with HbA1c levels ≤6.5% was higher in the dulaglutide 1.5 mg group compared with insulin glargine. At 52 weeks, a significant difference between the dulaglutide 1.5 mg and insulin glargine groups was noted for patients with HbA1c levels <7%.

Self-monitored Glucose Profiles and Fasting Serum Glucose

At 26 weeks, the mean SMPG values (8-point daily profile) were lower at all-time points compared with the corresponding baseline values for all treatment groups. The decrease from baseline was significantly greater with glargine compared to dulaglutide at 3AM (or 5 hours after bedtime), pre-morning meal, and 2-hour post-morning meal measurements. On the other hand, the changes were generally significantly greater (decreased) with dulaglutide compared to glargine at the 2-hour post midday meal, pre-evening meal, 2 hour post-evening meal, and at bedtime. The results were similar at 52 weeks.

At 26 weeks and 52 weeks, the change from baseline in FSG (central laboratory) was significantly greater with glargine compared to the dulaglutide groups.

Insulin Daily Doses

At 26 weeks, the mean TDI dose was approximately 30% lower in the dulaglutide groups compared with glargine. The mean daily dose of lispro was approximately 30% higher in the dulaglutide groups compared with glargine. The assessment of daily insulin doses indicated that stable mean insulin doses (defined as the dose that >90% of the highest mean visit dose) were reached by Visit 10 (13 weeks) in all 3 treatment groups.

Continuous Glucose Monitoring Substudy Results

Overall, aspects of glucose control as assessed by CGMS were similar in the 3 treatment groups. The CGMS findings were consistent with findings of the SMPG analyses for most of the outcomes.

Assessment of Hyperglycemia in CGMS:

At 26 weeks (but not at 52 weeks), the change from baseline in percent of time points (LSM) with glucose values (LOCF) within the 71 to 180 mg/dL range was significantly greater in the dulaglutide 1.5 mg group compared with the corresponding increase in the glargine group (p=0.014).

Assessment of Hypoglycemia in CGMS:
The overall incidence of total hypoglycemia (LOCF) was similar in the 3 treatment groups at baseline and at postbaseline assessments. The overall incidence of nocturnal hypoglycemia at 26 weeks (LOCF) was significantly higher with glargine compared to dulaglutide 0.75 mg. At 52 weeks, the percent of time points with glucose values in this range was significantly fewer in the dulaglutide groups compared with glargine.

Change in Body Weight and BMI
At 26 weeks, there was a significant difference in LSM for change from baseline in body weight between dulaglutide 1.5 mg and glargine groups (-3.20 kg) and between dulaglutide 0.75 mg and glargine groups (-2.15 kg). At 26 weeks, the BMI was significantly lower in the dulaglutide groups compared with glargine; the LSM difference between the dulaglutide 1.5 mg and glargine groups was -1.20 kg/ m^2; and between dulaglutide 0.75 mg and glargine: -0.79 kg/ m^2. At 52 weeks, the body weight and BMI results for between-group differences were similar.

Subgroup Analyses
Subgroup analyses, using the similar statistical model described for the primary analysis, were performed for HbA1c. Significant treatment by factor interactions for the effect on HbA1c were observed for race at 52 weeks; ethnicity at 52 weeks; for duration of diabetes at 26 and 52 weeks; for BMI at 26 and 52 weeks. The results of body weight by subgroup analysis did not reveal interaction between any of the factors analyzed.

Patient Reported Outcomes Conclusion
Patients' health status and ability to perform physical activities of daily living on average decreased in the study, and patients indicated more worries about hypoglycemia and increased their hypoglycemia-avoidance behaviors. However, dulaglutide 1.5-mg groups demonstrated a reduced impact of weight on self-perception.

Summary of Safety Results

Treatment Emergent Adverse Events
A significantly higher proportion of patients in the two dulaglutide treatment groups experienced at least 1 TEAE compared with the glargine group (dulaglutide 1.5 mg: 73.6%; dulaglutide 0.75 mg: 78.5%; glargine: 69.6%; overall p=0.048). At the preferred term level, nausea (dulaglutide 1.5 mg: 25.8%; dulaglutide 0.75 mg: 17.7%; glargine: 3.4%; p<.001), diarrhea (dulaglutide 1.5 mg: 16.6%; dulaglutide 0.75 mg: 15.7%; glargine: 6.1%; p<.001), and nasopharyngitis (dulaglutide 1.5 mg: 6.8%; dulaglutide 0.75 mg: 10.9%; glargine: 10.8%; p=.148) were the 3 most frequent TEAEs.

Deaths
Five patient deaths (dulaglutide 1.5 mg: 1; dulaglutide 0.75 mg: 1; glargine: 3) occurred postbaseline; causes of death were pneumonia (dulaglutide 0.75 mg), septicemia (dulaglutide 1.5 mg; this death was post-treatment discontinuation), cardiogenic shock (glargine), ventricular fibrillation (glargine), and unknown causes (glargine).

Serious Adverse Events
The incidence of SAEs was significantly different among the treatment groups (dulaglutide 1.5 mg: 9.2%; dulaglutide 0.75 mg: 15%; glargine: 18.2%; p<.001). The most frequent SAE, reported in >1% of patients, was hypoglycemia (total 3.7%; dulaglutide 1.5 mg: 3.4%; dulaglutide 0.75 mg: 2.7%; glargine: 5.1%).

Study Discontinuation due to Adverse Events or Death
A total of 46 (5.2%) patients discontinued from the study due to AEs (dulaglutide 1.5 mg: 21 [7.1%]; dulaglutide 0.75 mg: 14 [4.8%], glargine: 11 [3.7%]). Nausea was the most frequent AE leading to discontinuation with a significant difference among the treatment groups (n=10; dulaglutide 1.5 mg: 5; dulaglutide 0.75 mg: 5; glargine: 0).

Treatment Discontinuation due to Adverse Events or Death
A total of 64 (7.2%) patients in the study discontinued study treatment due to an AE or death (dulaglutide 1.5 mg: 10.5%; dulaglutide 0.75 mg: 7.2%; glargine: 4.1%). Nausea was the most frequent AE leading to treatment discontinuation (n=13; dulaglutide 1.5 mg: 8; dulaglutide 0.75 mg: 5; glargine: 0).

Laboratory Measures
There were no clinically relevant differences between the groups in the hepatic or renal laboratory analytes. Analysis of the time course for pancreatic enzyme values indicated greater median increases in lipase, p-amylase, and total amylase at 52 weeks for dulaglutide 1.5 mg and dulaglutide 0.75 mg compared with glargine. Categorical shift assessments indicated that significantly higher proportion of patients receiving dulaglutide 1.5 mg and dulaglutide 0.75 mg, compared with glargine, shifted to a higher category relative to baseline for lipase and p-amylase. There were no changes in median calcitonin levels in any of the study groups and no differences between the groups were observed at 26 or 52 weeks. Treatment-emergent abnormal (>ULN) calcitonin values were rare; no significant differences between the groups were reported.

Vital Signs
LSM changes from baseline (decreases) in seated SBP were significantly greater in each dulaglutide group compared to glargine at 26 weeks (LSM difference at 26 weeks for dulaglutide 1.5 mg vs glargine: -3.20 mm Hg, p=0.005; dulaglutide 0.75 mg vs glargine: -2.88 mm Hg). At 52 weeks, there was no significant difference between either dulaglutide arm and insulin glargine. There were no significant differences between the dulaglutide groups and glargine for change from baseline in seated DBP at any postbaseline time point.

LSM changes from baseline (increases) in seated HR were significantly greater in both dulaglutide groups compared with glargine up to 26 weeks; at this time point, the LSM difference between dulaglutide 1.5 mg and glargine was 2.8 bpm and between dulaglutide 0.75 mg and glargine was 2.8 bpm. At 52 weeks, the LSM difference between dulaglutide 1.5 mg and glargine was 1.45 bpm and between dulaglutide 0.75 mg and glargine was 1.3 bpm.

Electrocardiograms
Results of ECG-based HR analysis were similar to seated measurements, showing significantly greater increases in dulaglutide treatment groups compared to glargine. There were no other clinically relevant findings for any of the ECG variables.

Safety of Exocrine Pancreas
There were no cases of investigator-reported pancreatitis or cases of pancreatitis confirmed by adjudication in this trial.

Thyroid safety
There were no reports of thyroid malignancies during the trial.

Immunogenicity and Potentially Immune-mediated Events
Of the 562 patients in the two dulaglutide arms, 9 (1.6%) developed TE dulaglutide ADAs. No patient with TE dulaglutide ADAs presented with systemic or local injection site TEAEs indicative of hypersensitivity reaction.

Cardiovascular safety
A total of 23 (2.6%) patients in the study experienced at least 1 CV event (dulaglutide 1.5 mg: 5; dulaglutide 0.75 mg: 6; glargine: 12).

Gastrointestinal events
During the entire 52-week treatment period, the incidence of GI AEs (at the SOC level) was significantly higher in the dulaglutide treatment groups compared with insulin glargine (dulaglutide 1.5 mg: 47.5%; dulaglutide 0.75 mg: 37.9%; insulin glargine: 17.6%). Nausea, diarrhea, and vomiting were the 3 most frequent gastrointestinal events. The majority of the gastrointestinal events were mild to moderate in severity, and none of the events reported were more severe than at the baseline.

Injection site reactions
A total of 5 patients in the study reported injection site reactions from baseline to 52 weeks (dulaglutide 1.5 mg: 1; dulaglutide 0.75 mg: 4; insulin glargine: 0). None of these events were serious.

Hypoglycemia
Total hypoglycemia:
The overall incidences of total hypoglycemia (≤70 mg/dL) were similar in the 3 treatment groups at 26 weeks (85.9%, 88.4% and 89.5%). Results were similar at 52 weeks. The overall 1-year adjusted rate of total hypoglycemia during the first 26 weeks (dulaglutide 1.5 mg: 43.8; dulaglutide 0.75 mg: 52.3 insulin glargine: 63.2 events/patient/year) was significantly lower in the dulaglutide 1.5 mg group compared with the insulin glargine. The difference in overall 1-year adjusted rates between these two groups was similar at 52 weeks.

Documented symptomatic hypoglycemia:
The overall incidences of documented symptomatic hypoglycemia (≤70 mg/dL) were similar in the 3 treatment groups at 26 weeks (78.4%, 82.9%, and 82.4%). Results were similar at 52 weeks.
The mean 1-year adjusted rates at baseline were similar in the 3 treatment groups (range: 11 to 12 events/patient/year; the overall 1-year adjusted rate during the initial 26 weeks (dulaglutide 1.5 mg: 32.3; dulaglutide 0.75 mg: 38.7; insulin glargine: 44.4 events/patient/year) was significantly lower in the dulaglutide 1.5 mg group compared with insulin glargine. The difference in overall 1-year adjusted rates between these two groups was similar at 52 weeks.

Nocturnal hypoglycemia:
The overall incidences of nocturnal hypoglycemia (≤70 mg/dL) during the entire 26 week period were significantly different among the 3 treatment groups (dulaglutide 1.5 mg: 46.7%; dulaglutide 0.75 mg: 45.2%; insulin glargine: 61.4%). The overall incidences during the entire 52 weeks were also significantly different and were 54.3%, 53.8%, and 67.5%, respectively.

The overall 1-year adjusted rate at 26 weeks (dulaglutide 1.5 mg: 3.7; dulaglutide 0.75 mg: 4.7; insulin glargine: 9.2 events/patient/year) was significantly lower in each dulaglutide group compared with insulin glargine. The overall 1-year adjusted rates were similar at 52 weeks.

Severe hypoglycemia:
Overall, 48 events of severe hypoglycemia were reported during the study, and 7 additional events occurred after discontinuation of the study drug (post-rescue) (dulaglutide 1.5 mg: 11 events in 10 [3.4%] patients; dulaglutide 0.75 mg: 15 events in 7 [2.4%] patients; insulin glargine: 22 events in 15 [5.1%] patients); 32 of these events were recorded during the first 26 weeks (dulaglutide 1.5 mg: 2.1%; dulaglutide 0.75 mg: 1.7%; insulin glargine: 3.7%). At 26 weeks and 52 weeks, the incidences of severe hypoglycemia were similar between the treatment groups.

Overall Conclusion:

The combination of dulaglutide 1.5 mg dose with insulin lispro provides an effective and safe treatment option for patients with T2DM unable to attain their glycemic targets with conventional insulin regimens, with greater effect on HbA1c reduction than basal-bolus therapy with insulin glargine and insulin lispro. Treatment with dulaglutide 1.5 mg was also associated with lower risk of hypoglycemia and significant weight loss compared with insulin glargine. The dulaglutide 0.75 mg plus lispro combination provided similar reduction in HbA1c compared with insulin glargine plus insulin lispro, but smaller difference in body weight changes and no difference in hypoglycemia risk.