2. GBDN Synopsis

Clinical Study Report Synopsis: Study H9X-MC-GBDN

Title of Study: The Effect of LY2189265 on Blood Pressure and Heart Rate, as Assessed by Ambulatory Blood Pressure Monitoring, in Patients with Type 2 Diabetes Mellitus

Number of Investigator(s): This multicenter study included 76 principal investigators.

Study Center(s): This study was conducted at 76 study centers in 7 countries.

Publication(s) Based on the Study:

(Abstract) Ferdinand KC, White WB, Calhoun DA, Lonn EM, Jiang H, Threlkeld RJ, Robertson KE, Geiger MJ. Effects of dulaglutide, a GLP-1 receptor agonist, on ambulatory diurnal and nocturnal blood pressure in patients with type 2 diabetes. *J Clin Hypertens* 2013;15 (suppl); A20.

(Abstract) Ferdinand KC, Calhoun DA, Lonn EM, White WB, Jiang H, Threlkeld RJ, Robertson KE, Geiger MJ. Long-term effects of dulaglutide, a novel GLP-1 agonist, on ambulatory blood pressure and heart rate in patients with type 2 diabetes *J Clin Hypertens.* 2012;14:488.

Length of Study:	**Phase of Development:** 2
Date first patient enrolled: 08 June 2010 Date last patient visit: 04 January 2012	

Objectives: The primary objective of this study was to demonstrate that the change from baseline in mean 24-hour systolic blood pressure (SBP) of the 1.5- and 0.75-mg doses of dulaglutide were noninferior to placebo at Week 16, as measured by ambulatory blood pressure monitoring (ABPM), in patients with type 2 diabetes mellitus (T2DM).

The secondary objectives of this study were:

- To assess the effects of the 1.5- and 0.75-mg doses of dulaglutide compared to placebo (change from baseline) at 16 and 26 weeks on:
  - daytime and nighttime SBP, as measured by ABPM
  - mean 24-hour, daytime, and nighttime diastolic blood pressure (DBP), as measured by ABPM
  - mean 24-hour, daytime, and nighttime heart rate (HR), as measured by ABPM
  - mean 24-hour, daytime, and nighttime pulse pressure, as measured by ABPM
  - mean 24-hour, daytime, and nighttime mean arterial pressure (MAP), as measured by ABPM
- To demonstrate that the change from baseline in mean 24-hour SBP of the 1.5- and 0.75-mg doses of dulaglutide are noninferior to placebo at 26 weeks, as measured by ABPM.
- To assess the effects of the 1.5- and 0.75-mg doses of dulaglutide compared to placebo on vital signs (HR, SBP, and DBP).
- To assess the effects of the 1.5- and 0.75-mg doses of dulaglutide compared to placebo on glycemic control (HbA1c, fasting blood glucose [FBG], proportion of patients achieving an HbA1c <7% and ≤6.5%).
- To assess the effect of dulaglutide on other safety measures (treatment-emergent adverse events [TEAEs], laboratory analytes, cardiovascular [CV] analytes, electrocardiogram [ECG] parameters, dulaglutide anti-drug antibodies (ADAs), hypoglycemic events, and body weight).
- To characterize the pharmacokinetics (PK) of dulaglutide, and the relationship between dulaglutide concentration and primary and secondary measures.

Study Design: This was a multicenter, randomized, double-blind, parallel-arm, 26-week treatment, placebo-controlled study to evaluate the effects of 1.5- and 0.75-mg doses of dulaglutide on blood pressure (BP) and HR, using ABPM, in patients with T2DM receiving oral antihyperglycemic medications (OAMs). The study included a 2-week screening and lead-in period, followed by a 26-week treatment period, and a 4-week safety follow-up period.

Number of Patients:
Planned: 693 randomized
Randomized: 755 (placebo: 250; dulaglutide 1.5 mg: 251, dulaglutide 0.75 mg: 254)
Treated (at least 1 dose): 755 (placebo: 250; dulaglutide 1.5 mg: 251; dulaglutide 0.75 mg: 254)
Completed: 630 patients completed the treatment period (placebo: 206; dulaglutide 1.5 mg: 199; dulaglutide 0.75 mg: 225); 719 patients completed the 30-day safety follow-up visit.

Diagnosis and Main Criteria for Inclusion: Patients included men and non-pregnant women aged ≥18 years with T2DM, treated with a stable regimen of 1 or more OAMs, and an HbA1c ≥7.0% and ≤9.5%. All patients had to have a mean seated clinic BP >90/60 mmHg and <140/90 mmHg, and if the patient was being treated for hypertension, had to be taking ≤3 antihypertensive medications (same regimen for at least 1 month). Weight had to be stable for at least 3 months, and patients had to have a body mass index ≥23 kg/m^2.

Study Drug, Dose, and Mode of Administration: Dulaglutide 1.5 mg or dulaglutide 0.75 mg was administered by subcutaneous injection once weekly. Dulaglutide 1.5 mg was administered as a 0.5-mL injection of a 3.00-mg/mL solution. Dulaglutide 0.75 mg was administered as a 0.5-mL injection of a 1.50-mg/mL solution.

Reference Therapy, Dose, and Mode of Administration: Placebo was administered as a 0.5-mL subcutaneous injection solution once weekly.

Duration of Treatment: 26 weeks
Dulaglutide (1.5 mg or 0.75 mg): once weekly for 26 weeks
Placebo: once weekly during the lead-in period and once weekly for 26 weeks

Variables:
Efficacy: Study GBDN was a Phase 2 (hemodynamic) safety study. Dulaglutide is being developed as an antihyperglycemic drug; therefore, traditional efficacy measures such as HbA1c and FBG were assessed and are reported in the safety section of this report.
Safety: Mean 24-hour ABPM, daytime and nighttime SBP, DBP, HR, pulse pressure, and MAP; vital signs (seated clinic-measured SBP, DBP, HR); glycemic response (HbA1c, FBG, hypoglycemic events); laboratory analytes; exploratory CV analytes; ECGs; TEAEs; dulaglutide ADAs; and CV, pancreatic, and thyroid adverse events (AEs) of interest
Pharmacokinetic/Pharmacodynamic: Plasma concentrations of dulaglutide and ABPM measurements

Statistical Evaluation Methods

The majority of analyses were conducted using the Intent-to-Treat (ITT) population. The 24-hour ABPM analyses for SBP, DBP, and HR were also conducted using the Per-Protocol population. Unless otherwise noted, all tests of treatment effects were conducted at a 2-sided alpha level of 0.05 and 2-sided 95% confidence intervals (CI) were calculated. Two analysis models were used for the primary efficacy measurement. The primary analysis for the primary endpoint was a mixed-model repeated-measure (MMRM) analysis. The secondary analysis model was analysis of covariance (ANCOVA). The primary comparison of ABPM mean 24-hour SBP change from baseline at 16 weeks (Visit 7) was the comparison of both dulaglutide 1.5- and 0.75-mg doses versus placebo for noninferiority with a margin of 3 mmHg. If the upper limit of the 95% CI (adjusted for multiplicity, ie, a 2-sided 97.3% CI) of the difference between dulaglutide 1.5- or 0.75-mg dose and placebo was below 3 mmHg, the respective dulaglutide dose was declared noninferior to placebo. If the upper limit of the CI was below zero, the dulaglutide dose was declared superior to placebo.

Both MMRM and ANCOVA models were used to analyze the change from baseline for the ABPM summary measurements of mean 24-hour mean SBP, DBP, and HR. Only MMRM was used for the analyses of the other ABPM-derived parameters, the daytime and nighttime ABPM parameters, as well as the other safety measurements, unless otherwise noted.

For continuous measures, summary statistics included sample size, mean, standard deviation, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-squares mean (LSM) and standard error (SE) derived from the model were displayed for the change from baseline. Treatment comparisons were displayed showing the treatment difference LSM and the 95% CIs of the treatment differences along with the p-value for the treatment comparison.

For continuous laboratory measurements, an ANOVA on ranks was used and p-values for the difference between the dulaglutide doses and the placebo were reported.
For categorical measures, summary statistics included sample size, frequency, and percentages. Unless otherwise noted, a chi-squared test was used if at least 80% of cells had an expected number of events no less than 5, otherwise a Fisher's exact test was used.

Bioanalytical Methods:
Human plasma samples obtained during this study were analyzed for dulaglutide using a validated radioimmunoassay method.

Pharmacokinetic/Pharmacodynamic: A population PK model was developed using NONMEM® Version 7.2 to describe dulaglutide plasma concentrations over time. Population PK/pharmacodynamic (PD) models were developed for ambulatory SBP, DBP, and HR measurements. Finally, a linked PK/PD model was developed for ambulatory measurements of systolic and diastolic BP.

Summary:

- The treatment groups were balanced with respect to baseline characteristics (with the exception of duration of diabetes), other CV risk-assessment characteristics (with the exception of prior history of myocardial infarction [MI]), concomitant medication use, ABPM measurements (mean 24-hour, daytime and nighttime), and LSM seated clinic BP and HR measurements. A total of 67% of patients had hypertension at baseline; of these, the majority was taking 1 or 2 antihypertensive therapies. All patients were taking OAMs (93% on metformin, 60% on a sulfonylurea).
- A total of 86.9% of patients completed the treatment period though 16 weeks, and 83.4% completed the entire treatment period of 26 weeks. Fewer patients in the dulaglutide 1.5 mg arm completed 26 weeks

(79.3%) compared with the other treatment groups. More than 95% of patients completed the 30-day safety follow-up visit.

- The primary objective of the study was met. Both doses of dulaglutide were noninferior to placebo for mean 24-hour SBP at 16 weeks, using a noninferiority margin of 3 mmHg The dulaglutide 1.5 mg dose was shown to significantly reduce mean 24-hour SBP compared with placebo at 16 weeks (-2.8 mmHg; p<.001) and at 26 weeks (-2.7 mmHg; p=.002).
- Both doses of dulaglutide were shown to be noninferior to placebo for mean 24-hour DBP at 16 and 26 weeks, using a noninferiority margin of 2.5 mmHg.
- Dulaglutide 0.75 mg was shown to be noninferior to placebo for mean 24-hour HR at 16 and 26 weeks, using a noninferiority margin of 3 bpm. Dulaglutide 1.5 mg compared with placebo did not satisfy the noninferiority criteria, and small increases in HR were observed at 16 weeks (2.84 bpm) and at 26 weeks (3.50 bpm).
- Dulaglutide was associated with reductions in clinic-measured SBP; however, treatment comparisons with placebo were often not statistically significant. Dulaglutide was not observed to have any effect on LSM seated clinic DBP. Therefore, the effects of dulaglutide on LSM seated clinic BP measurements were consistent with the ambulatory BP findings. The effect of dulaglutide on LSM seated clinic-measured HR was similar to the ambulatory HR findings, and a dose-dependent increase in HR was observed with dulaglutide.
- The TEAE profile for dulaglutide in this study was similar to that previously observed in other studies. Gastrointestinal (GI) disorders, in particular, nausea, diarrhea, and vomiting, were the most commonly reported TEAEs associated with dulaglutide. The incidence of GI TEAEs in the 2 dulaglutide groups was 32% (each) compared with the placebo group (21%). There were no deaths during the study, and 28 patients reported 33 serious adverse events (SAEs). More patients in the dulaglutide 1.5 mg group discontinued from the study due to an AE compared with the other 2 treatment groups.
- Small but significant increases from baseline in mean total amylase, p-amylase, and lipase were observed in both dulaglutide groups at Week 4 and at all subsequent time points through 26 weeks (compared with negligible changes in the placebo group). There were no reported TEAEs or SAEs of pancreatitis. Seventeen patients (21 events) required additional pancreatic follow-up assessments. Nineteen of these 21 events were submitted for adjudication, but none were adjudicated as pancreatitis.
- Small but statistically significant decreases from baseline in mean calcitonin levels were observed within the placebo and dulaglutide 1.5 mg groups (<0.5 pg/mL). Mean calcitonin levels in the dulaglutide 0.75 mg group were essentially unchanged. Five patients had elevations in calcitonin levels that warranted further assessment per the calcitonin-monitoring algorithm. No thyroid neoplasms, including c-cell hyperplasia or medullary thyroid cancer, were reported in this study.
- The overall prevalence of prior CV disease in the study population was low (8.1%), though a higher proportion of patients in the dulaglutide 1.5 mg group had a prior MI at baseline. Nine patients reported a total of 9 CV events; all were submitted for adjudication. Of these 9 events, 4 events in the placebo group met the prespecified CV-event definitions (1 MI, 1 ischemic stroke, 1 TIA, and 1 PCI) compared with 2 events in the 2 dulaglutide groups (1 stroke, 1 coronary revascularization).

- Significant reductions in HbA1c were observed with both dulaglutide doses at 16 weeks (dulaglutide 1.5 mg: -1.18%); dulaglutide 0.75 mg: -1.04%) and 26 weeks (dulaglutide 1.5 mg: -1.01%); dulaglutide 0.75 mg: -0.89%) when added to a patient's existing antihyperglycemic regimen.
- No severe hypoglycemic episodes were reported. The incidence of total hypoglycemic events was 29% overall and was higher in both dulaglutide groups (34% with dulaglutide 1.5 mg and 32% with dulaglutide 0.75 mg) compared with the placebo group (21%), especially at 4 to 8 weeks following initiation of therapy. Overall, similar findings were observed for documented symptomatic and asymptomatic hypoglycemic episodes. Most episodes occurred during the daytime. The overall rate of total hypoglycemic episodes (adjusted for 30 days) in the 2 dulaglutide groups was nearly double the rate observed in the placebo group.
- Both dulaglutide doses were associated with significant reductions in mean body weight compared with placebo (dulaglutide 1.5 mg: -1.85 kg; dulaglutide 0.75 mg: -0.86 kg at 26 weeks). Significant weight reduction was observed as early as 4 weeks after initiation of therapy and plateaued around 16 weeks. This change in body weight did not affect the primary ambulatory BP results.
- Overall, the quantitative ECG findings for dulaglutide were consistent with what has been observed previously in other trials. A small (2% to 3%) prolongation of the PR interval was observed with use of dulaglutide, along with an increase in the incidence of arterioventricular block (AVB), primarily first-degree AVB. These findings were contrary to what would be expected given that dulaglutide increases HR. The clinical significance of these observations remains to be determined.
- In 97% of patients, dulaglutide anti-drug antibodies (ADA) were not detected at baseline, during treatment, or at follow-up. Seven patients exposed to dulaglutide (with no prior exposure to a GLP-1 receptor agonist) developed ADAs defined as treatment emergent (4-fold greater change in titer from baseline). Neutralization of dulaglutide was detected in all 7 patients. Two patients had nsGLP-1 neutralizing antibodies. Glycemic control was not affected by TE ADAs in any of these 7 patients. The pharmacokinetics of dulaglutide were well described by a 2-compartment population PK model with first-order absorption. PK parameter estimates were consistent with previous population analyses of dulaglutide pharmacokinetics.
- Based on PK/PD model simulations using the final linked model for ambulatory BP, a dose of 1.5 mg dulaglutide was predicted to cause a median reduction in SBP of approximately 2 mmHg. No relationship was found between dulaglutide concentration and ambulatory DBP.
- Ambulatory HR was found to increase with increasing dulaglutide concentration; a dose of 1.5 mg dulaglutide was predicted to cause a median increase in HR of approximately 3.2 bpm.

Conclusions:

Study GBDN was a large (N=755), randomized, prospective, placebo-controlled study to assess the effects of a long-acting GLP-1 receptor agonist (dulaglutide) on BP and HR using ABPM in patients with T2DM on OAMs. The doses of dulaglutide, 1.5 mg and 0.75 mg, investigated in GBDN were the same doses being assessed in Phase 3 clinical trials. Both doses of dulaglutide were shown to be noninferior to placebo for mean 24-hour SBP (using a noninferiority margin of 3 mmHg); thus, the primary objective of the study was met. In addition, dulaglutide 1.5 mg significantly reduced mean 24-hour SBP compared with placebo at 16 weeks (-2.8 mmHg) and 26 weeks (-2.7 mmHg). These findings were not influenced by the reduction in weight observed in the dulaglutide-treated groups. Although these reductions in SBP were small, they are likely to be clinically meaningful. This interpretation was

based on a population approach to prevent hypertension that suggests even modest decreases in SBP (e.g., 2 mmHg) have the potential to result in substantial reductions in BP-related illnesses, namely stroke, coronary heart disease, and total mortality. The mechanism of action by which dulaglutide lowers SBP is not known. However, dulaglutide did not appear to be acting through the renin-angiotensin-aldosterone system or influencing serum catecholamine levels.

Previous studies with dulaglutide showed varying findings with regards to DBP; in some studies dose-dependent increases in clinic DBP were observed, and in other studies, no effects were evidenced. In Study GBDN, DBP was a prespecified secondary objective and the study was appropriately powered to test this objective, unlike the prior studies. Both doses of dulaglutide were shown to be noninferior to placebo for mean 24-hour DBP, using a noninferiority margin of 2.5 mmHg. Thus ,GBDN provides the best evidence that dulaglutide has no effect on DBP in the population intended to use the drug.

Small dose-dependent increases in HR have been observed in previous studies with dulaglutide. Similar observations have been reported with other GLP-1 analogs. In Study GBDN, dulaglutide 0.75 mg was noninferior to placebo for mean 24-hour HR, using a noninferiority margin of 3 bpm. However, the noninferiority criteria were not satisfied when dulaglutide 1.5 mg was compared with placebo and small increases in HR (3 to 4 bpm) were observed with this dose. Assessment of day- and nighttime ambulatory HR supports the notion of dose-dependent increases in HR with dulaglutide. The mechanism of action and clinical significance of these small increases in HR remains to be determined.

Since dulaglutide is in development for the treatment of T2DM, glycemic response was analyzed. Significant and clinically meaningful reductions in HbA1c (0.89% to 1.18%) were observed in patients treated dulaglutide, when added to a patient's existing antihyperglycemic regimen. The majority of patients treated with dulaglutide achieved an HbA1c goal of <7% at study end. There were no severe hypoglycemic events. The overall incidence and rate of hypoglycemic episodes was low in the population; however, they were greater in the dulaglutide groups compared with the placebo group. These findings are consistent with what has been observed in prior dulaglutide clinical trials in which glycemic response was the primary efficacy measure. In addition, significant and clinically meaningful reductions in body weight were associated with use of dulaglutide.

In summary, dulaglutide 1.5 mg reduced the mean 24-hour ambulatory SBP, approximately 2.8 mmHg and increased the mean 24-hour HR about 3 to 4 bpm, but had no effect on DBP (compared with placebo). Dulaglutide 0.75 mg was noninferior to placebo with respect to mean 24-hour ambulatory SBP, DBP, and HR. Both dulaglutide doses significantly lowered HbA1c and reduced body weight. Other safety findings were consistent overall with what has been reported in previous dulaglutide studies.