Monotherapy with the once weekly GLP-1 receptor agonist dulaglutide for 12 weeks in Japanese patients with type 2 diabetes: dose-dependent effects on glycaemic control in a randomised, double-blind, placebo-controlled study

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Abstract. The aim of this study was to evaluate the dose-dependent effect of dulaglutide, a glucagon-like peptide-1 receptor agonist, on glycaemic control in Japanese patients with type 2 diabetes mellitus who were treated with diet/exercise or oral antidiabetic drug monotherapy. In this randomised, double-blind, placebo-controlled, parallel-group, 12-week study, patients received once weekly subcutaneous dulaglutide doses of 0.25, 0.5, or 0.75 mg (DU 0.25, DU 0.5, and DU 0.75, respectively) or placebo (n=36, 37, 35, and 37, respectively). The primary measure was change from baseline in glycated haemoglobin (HbA1c; %) at 12 weeks. Continuous variables were analysed using a mixed-effects model for repeated measures. Significant dose-dependent reductions in HbA1c were observed (least squares mean difference versus placebo [95% confidence interval]: DU 0.25= –0.72% (–0.95, –0.48), DU 0.5= –0.97% (–1.20, –0.73), and DU 0.75= –1.17% (–1.41, –0.93); p<0.001. Significant improvements in plasma glucose (PG), both fasting and average 7-point self-monitored blood glucose, were also observed with dulaglutide versus placebo (p<0.001). Dulaglutide was well-tolerated. Gastrointestinal adverse events (AEs) were more common in dulaglutide-treated patients, with nausea the most frequent (8 [5.5%]). Few dulaglutide-treated patients discontinued due to AEs (4 [3.7%]), and no serious AEs related to study medication occurred. Three patients (DU 0.5=1 and DU 0.75=2) reported asymptomatic hypoglycaemia (PG ≤70 mg/dL). The observed dose-dependent reduction in HbA1c and acceptable safety profile support further clinical development of dulaglutide for treatment of type 2 diabetes mellitus in Japan.

Key words: Dulaglutide, Japanese, Dose-response, Type 2 diabetes mellitus
injection for the treatment of type 2 diabetes mellitus. It consists of two GLP-1 analogs covalently linked by a small peptide to a human immunoglobulin G4 (IgG4-Fc) region specific heavy chain. The GLP-1 moieties contain amino acid substitutions that protect from inactivation by dipeptidyl peptidase-IV (DPP-4), while the linker peptide maintains the potency of the GLP-1 analog. The human IgG4-Fc is modified by substituting several amino acids to reduce interaction with high-affinity Fc receptors, cytotoxicity, and immunogenicity [8]. The half-life is approximately 5 days, and time to peak concentration after a single 0.75 mg dose is approximately 3 days (Eli Lilly, unpublished data on file).

In two phase 1 studies in Japanese patients with type 2 diabetes mellitus, dulaglutide was generally well-tolerated following single-dose (0.3, 1.0, 3.0, and 6.0 mg) and repeated dose (1.0 and 1.5 mg) administration. In these phase 1 studies, however, increased pulse rate (PR) and elevated blood pressure (BP) were observed at dulaglutide doses of 1.0 mg and higher, which suggested that doses less than 1.0 mg would be appropriate in future studies of Japanese patients with type 2 diabetes mellitus.

The aim of this 12-week, phase 2, double-blind, placebo-controlled study was to assess the dose response to three doses of dulaglutide (0.25, 0.5, and 0.75 mg) in Japanese patients with type 2 diabetes mellitus who were treated with diet/exercise only or oral antidiabetic drug (OAD) monotherapy.

Materials and Methods

Subjects

The study was conducted from December 2009 to December 2010 at 15 sites in Japan. The study population was comprised of male and female patients with type 2 diabetes mellitus, ≥20 and <75 years of age, who were antihyperglycaemic medication-naïve (on diet and exercise only) or who were on OAD monotherapy (N=145). Additionally, patients must have had a body mass index (BMI) ≥18.5 kg/m² and <40.0 kg/m²; stable weight for 12 weeks before screening; and glycated haemoglobin (HbA1c) at screening ≥7.0 to ≤9.5% if OAD-naïve or ≥6.0% to ≤8.5% if taking OAD. Exclusion criteria included patients using more than half the maximum approved dose of a sulfonylurea or currently taking a GLP-1 receptor agonist, DPP-4 inhibitor, or insulin within 24 weeks before screening; patients taking prescription weight loss medication; patients undergoing chronic systemic glucocorticoid therapy; and patients who had a clinically significant GI disorder, liver disease, renal disease, poorly controlled hypertension, a history of chronic pancreatitis or acute pancreatitis, obvious clinical signs or symptoms of pancreatitis, or a family history of, or obvious clinical signs or symptoms of, medullary thyroid carcinoma.

Study design

A common protocol was approved at each site by an institutional review board; the study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Before participation, all patients provided written informed consent. The trial is registered at clinicaltrials.gov (NCT01001104).

The study was made up of four periods: 2-week screening, 4- to 12-week lead-in (an 8-week washout after discontinuing OAD and a 12-week washout after discontinuing thiazolidinediones was required prior to obtaining the qualifying HbA1c), 12-week treatment, and 4-week safety follow-up. After lead-in, an HbA1c value of ≥7.0 to ≤9.5% was required for randomisation. Patients were randomised to one of four treatment arms: placebo or dulaglutide 0.25 mg, 0.5 mg, or 0.75 mg (DU 0.25, DU 0.5, and DU 0.75, respectively) in a 1:1:1:1 ratio.

Patients were stratified for randomisation by BMI at baseline (<25 kg/m², ≥25 kg/m²) and pre-study therapy (OAD yes/no). Study drug was administered once weekly by subcutaneous injection. The use of additional OADs other than GLP-1 receptor agonists, DPP-4 inhibitors, or insulin therapy was permitted only when needed for rescue therapy (according to pre-specified criteria); however, no patient received glycaemic rescue therapy in this study.

Endpoints and assessments

The primary efficacy measure was change from baseline in HbA1c (NGSP) at 12 weeks. Additional measures included changes in 7-point self-monitored blood glucose (SMBG), fasting plasma glucose (PG; central laboratory), updated homeostasis model assessment of β-cell function (HOMA2-%B) and insulin sensitivity (HOMA2-%S) [9], body weight, and proportion of patients achieving HbA1c <7.0% or <6.5% [10, 11]. Measurements for HbA1c were obtained at baseline and Weeks 4, 8, and 12, and measurements for
SMBG, fasting PG and insulin, and body weight were obtained at baseline and Weeks 2, 4, 8, and 12.

Safety assessments included AEs, cardiovascular (seated PR and BP, electrocardiogram [ECG]) and laboratory parameters, and dulaglutide anti-drug antibodies. ECGs were recorded in triplicate, and tracings were over-read by a cardiologist at a centralized vendor (Quintiles Data Processing Centre [India] Private LTD, Andheri [East], Mumbai, India); this report was used for analysis. A treatment-emergent AE (TEAE) was defined as an event that first occurred or worsened after first administration of study drug, as compared with the maximum severity at or before randomisation. Serious AEs were defined as any AE that met one of the following criteria: death; initial or prolonged inpatient hospitalisation; a lifethreatening experience; persistent or significant disability/incapacity; congenital anomaly/birth defect; or an event considered significant by the investigator for any other reason. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.0.

Per the American Diabetes Association definition, hypoglycaemia was defined as PG $\leq 70$ mg/dL and/or symptoms and/or signs attributable to hypoglycaemia. Severe hypoglycaemia was defined as an episode requiring the assistance of another person to actively administer therapy [11]. Deaths, nonfatal cardiovascular AEs, and pancreatitis were adjudicated by an external judgment committee. Plasma analytes and HbA1c were quantified by Quintiles Laboratories Limited (Marietta, GA, USA). Electrochemiluminescence immunosorbent assay was used for detection of dulaglutide anti-drug antibodies (Millipore Corporation, St. Charles, MO, USA); positive samples were titrated for antibody titres.

Sample size

The target sample size of 144 patients (36 patients per arm) was calculated to provide 84% power for detecting a dose-response for change from baseline in HbA1c with a linear contrast. The model used a linear dose-response relationship and a two-sided alpha level of 0.05; it assumed that the difference in HbA1c between placebo and DU 0.75 was 0.8%, and the common standard deviation was 1.2%.

Statistical methods

The primary and secondary analyses were performed on the intent-to-treat population (n=145), defined as all randomised patients who received study therapy and referred to as the full analysis set (FAS). The primary efficacy analysis included data from the FAS and excluded any measurements obtained after the beginning of rescue therapy. The primary analysis was also performed on the per-protocol set, defined as all randomised patients who completed the study through 12 weeks with no significant protocol violations and no glycaemic rescue therapy.

Continuous variables were analysed with a mixed-effects model for repeated measures (MMRM) in the FAS. To evaluate the dose-response relationship (linear contrast among doses) for each continuous variable, including change in HbA1c, the MMRM included dose, pre-study therapy (OAD yes/no), baseline BMI ($<25$ kg/m$^2$, $\geq 25$ kg/m$^2$), visit, and dose-by-visit interaction as the fixed effects, baseline value as a covariate, and patient as a random effect. Comparison between each dulaglutide group and placebo was also performed by pairwise test of LS means (LSMs) based on the same model. An additional sensitivity analysis for change in HbA1c at 12 weeks (FAS) was performed with an analysis of covariance (ANCOVA) model with a last observation carried forward (LOCF) approach that included dose, pre-study therapy (OAD yes/no), and baseline BMI as factors and baseline value as a covariate, and patient as a random effect. Comparison between each dulaglutide group and placebo was also performed by pairwise test of LSM means (LSMs) based on the same model. An additional sensitivity analysis for change in HbA1c at 12 weeks (FAS) was performed with an analysis of covariance (ANCOVA) model with a last observation carried forward (LOCF) approach that included dose, pre-study therapy (OAD yes/no), and baseline BMI as factors and baseline value as a covariate. Changes from baseline were reported as LSM and standard error (LSM $\pm$ SE).

A Fisher’s exact test was used to assess categorical data, along with a Cochran-Armitage trend test to assess the dose-response relationship. For laboratory data, a one-way analysis of variance (ANOVA) with treatment as a fixed effect was conducted. All statistical analyses were performed with the SAS System Version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient population

Of the 219 patients screened, 145 (placebo=37; DU 0.25=36; DU 0.5=37; and DU 0.75=35) were randomised to treatment. Of the 145 patients randomised, 138 completed the study and 7 discontinued from the study, for the following reasons: AE (DU 0.5=1; DU 0.75=2), subject decision (placebo=2), lost to follow-up (DU 0.25=1), and entry criteria not met (placebo=1). Patient characteristics at randomisation, including HbA1c, were comparable among groups (Table 1).
In response to treatment with dulaglutide, significant dose-dependent reductions in fasting PG were observed at endpoint across the groups (Fig. 1c; \( p < 0.001 \)). Fasting PG was significantly reduced for each dulaglutide group compared with placebo at Week 2, and this significant reduction was maintained throughout the treatment period (Fig. 1d; \( p < 0.01 \)). The LSM difference versus placebo (95% CI) at endpoint was: DU 0.25 = –20.2 mg/dL (–33.2, –7.2), DU 0.5 = –19.5 mg/dL (–32.5, –6.6), and DU 0.75 = –28.5 mg/dL (–41.7, –15.3). Dose-dependent effects on both fasting and post-prandial glycaemic control with dulaglutide were also confirmed by 7-point SMBG profiles (Fig. 1e: baseline and Fig. 1f: endpoint [LOCF]). Statistically significant reductions were observed in average daily PG, average of all pre-meal PG, and average of all postprandial PG from the 7-point SMBG profile. The LSM differences versus placebo (95% CI) at endpoint were: DU 0.25 = –33.2 mg/dL (–46.3, –20.1), DU 0.5 = –45.6 mg/dL (–58.6, –32.7), and DU 0.75 = –41.5 mg/dL (–55.0, –28.0) for average daily PG; DU 0.25 = –25.0 mg/dL (–35.3, –14.8), DU 0.5 = –33.7 mg/dL (–43.9, –23.6), and DU 0.75 = –35.2 mg/dL (–45.7, –24.6) for average of all pre-meal PG; and DU 0.25 = –35.9 mg/dL (–54.7, –17.2), DU 0.5 = –56.6 mg/dL (–75.2, –38.0), and DU 0.75 = –50.6 mg/dL (–69.7, –31.6) for average of all postprandial PG.

**Efficacy**

Mean baseline HbA1c ranged from 8.0% to 8.1% across the groups (Table 1). In response to treatment with dulaglutide, significant dose-dependent reductions in HbA1c were observed at endpoint (Week 12) across the groups (Fig. 1a; \( p < 0.001 \)). HbA1c was significantly reduced for each dulaglutide group compared with placebo at Week 4, and this significant reduction was maintained throughout the treatment period (Fig. 1b; \( p < 0.01 \) for all comparisons). The LSM difference versus placebo (95% confidence interval [CI]) at endpoint was: DU 0.25 = –0.72% (–0.95, –0.48), DU 0.5 = –0.97% (–1.20, –0.73), and DU 0.75 = –1.17% (–1.41, –0.93). Analyses of the per-protocol set yielded comparable results at Weeks 4, 8, and 12 (\( p < 0.001 \) for all comparisons, data not shown), as did the sensitivity analysis (ANCOVA; \( p < 0.001 \) for all comparisons, data not shown). There was an increasing trend across groups in the proportion of patients achieving HbA1c <7.0% (Table 2 [placebo=10.8%, DU 0.25=47.2%, DU 0.5=59.5%, and DU 0.75=77.1%; \( p < 0.001 \); Cochran-Armitage trend test]) and in the proportion of patients achieving HbA1c <6.5% (Table 2 [placebo=2.7%, DU 0.25=8.3%, DU 0.5=24.3%, DU 0.75=34.3%; \( p < 0.001 \))). The proportion of patients with HbA1c <7.0% was significantly larger for each dulaglutide group at endpoint compared with placebo (Table 2; \( p < 0.001 \)). Likewise, the proportion of patients with HbA1c <6.5% was significantly larger for the DU 0.5 (\( p = 0.014 \)) and DU 0.75 (\( p < 0.001 \)) groups at endpoint compared with placebo (Table 2), but not for the DU 0.25 group (\( p = 0.358 \)).

In response to treatment with dulaglutide, significant dose-dependent reductions in fasting PG were observed at endpoint across the groups (Fig. 1c; \( p < 0.001 \)). Fasting PG was significantly reduced for each dulaglutide group compared with placebo at Week 2, and this significant reduction was maintained throughout the treatment period (Fig. 1d; \( p < 0.01 \) for all comparisons). The LSM difference versus placebo (95% CI) at endpoint was: DU 0.25 = –20.2 mg/dL (–33.2, –7.2), DU 0.5 = –19.5 mg/dL (–32.5, –6.6), and DU 0.75 = –28.5 mg/dL (–41.7, –15.3).

Dose-dependent effects on both fasting and post-prandial glycaemic control with dulaglutide were also confirmed by 7-point SMBG profiles (Fig. 1e: baseline and Fig. 1f: endpoint [LOCF]). Statistically significant reductions were observed in average daily PG, average of all pre-meal PG, and average of all postprandial PG from the 7-point SMBG profile. The LSM differences versus placebo (95% CI) at endpoint were: DU 0.25 = –33.2 mg/dL (–46.3, –20.1), DU 0.5 = –45.6 mg/dL (–58.6, –32.7), and DU 0.75 = –41.5 mg/dL (–55.0, –28.0) for average daily PG; DU 0.25 = –25.0 mg/dL (–35.3, –14.8), DU 0.5 = –33.7 mg/dL (–43.9, –23.6), and DU 0.75 = –35.2 mg/dL (–45.7, –24.6) for average of all pre-meal PG; and DU 0.25 = –35.9 mg/dL (–54.7, –17.2), DU 0.5 = –56.6 mg/dL (–75.2, –38.0), and DU 0.75 = –50.6 mg/dL (–69.7, –31.6) for average of all postprandial PG.
Dose-dependent effects of dulaglutide

Fig. 1  Glycaemic control in patients with type 2 diabetes mellitus (N=145) in response to treatment with placebo (n=37), DU 0.25 (n=36), DU 0.5 (n=37), or DU 0.75 (n=35): (a) LS mean changes (95% CI) at endpoint in HbA1c; (b) LS mean changes in HbA1c across the 12-week treatment period; (c) LS mean changes (95% CI) at endpoint in FPG; (d) LS mean changes in FPG across the 12-week treatment period; (e) Mean 7-point SMBG profile for each treatment group at baseline; (f) Mean 7-point SMBG profile for each treatment group at endpoint (LOCF).

Abbreviations: AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BD, before dinner; BL, before lunch; BT, bedtime; CI, confidence interval; DU 0.25, 0.25-mg dose of dulaglutide; DU 0.5, 0.5-mg dose of dulaglutide; DU 0.75, 0.75-mg dose of dulaglutide; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; LS mean, least-squares mean; SMBG, self-monitored blood glucose.

* p<0.01 for dulaglutide dose compared to placebo.
Although dulaglutide did not have a dose-dependent effect on HOMA2-%S (\(p=0.202\)), significant dose-dependent increases in HOMA2-%B were observed at endpoint across the groups (\(p<0.001\)) (Table 2). The LSM differences versus placebo (95% CI) at endpoint were: DU 0.25=13.1 (0.9, 25.3), DU 0.5=19.7 (7.4, 32.1), and DU 0.75=31.7 (19.2, 44.2). These increases returned to baseline after 4-week safety follow-up.

Safety

Overall, 45.5% (n=66) of patients reported at least one TEAE during the treatment period, with no significant trend across groups (Table 3). Most of these events were transient, mild to moderate in severity, and resolved spontaneously. The most frequent TEAEs were nasopharyngitis, nausea, diarrhea, and seasonal allergies. There was no significant trend across groups for any individual TEAE, with the exception of nausea (\(p=0.050\); Cochran-Armitage trend test) and constipation (\(p=0.013\)). No significant differences were observed between any dulaglutide group compared with placebo for any individual TEAE except for nausea, which occurred significantly more with DU 0.5 versus placebo (\(p=0.025\)). No treatment-emergent injection site reactions were reported.

Of the 66 patients who experienced a TEAE, 19 experienced at least one considered to be possibly related to study drug by the investigator. Sixteen of these 19 patients experienced GI disorders, with the most frequently reported events (\(\geq 5\%\) in any treatment group) being nausea, constipation, and upper abdominal pain; however, no patient discontinued due to a GI-related TEAE. Two patients discontinued from the study due to a TEAE (Table 3; mild ECG abnormal without significant PR interval prolongation in a patient taking DU 0.5, and moderate peripheral vascular disorder in a patient taking DU 0.75), and both were considered by the investigator to be possibly related to study drug.

Investigators reported two serious AEs (1.4%), neither of which was considered by the investigator to be possibly related to study drug (Table 3). One was pancreatic carcinoma diagnosed by computed tomography (CT) scan fol-
Dose-dependent effects of dulaglutide

following randomisation in a patient who received one single dose of DU 0.75. This patient discontinued from the study and died approximately 5 months later. The other serious AE, VIIth nerve paralysis (i.e., Bell’s palsy), led to study discontinuation in a patient taking DU 0.25 and was diagnosed during the safety follow-up period after the last study drug administration.

During the treatment period, no severe hypoglycaemic events were reported. The overall incidence of hypoglycaemia was not different among the groups (Table 3; \( p=0.073 \), Cochran-Armitage trend test). Three patients (DU 0.5=1 and DU 0.75=2) reported five episodes (DU 0.5=3 and DU 0.75=2) of asymptomatic hypoglycaemia with PG ≤70 mg/dL during the treatment period. No patient discontinued from the study due to hypoglycaemia.

No acute pancreatitis was reported during the study. Increases in mean amylase and lipase were observed in all dulaglutide groups after randomisation, irrespective of the patients’ baseline amylase and lipase values. There were statistically significant baseline-to-endpoint (LOCF) increases in amylase (LSM difference [95% CI]: 9.6 units/L [1.3, 17.9]; \( p=0.023 \)) and lipase (17.4 units/L [3.0, 31.8]; \( p=0.018 \)) in the DU 0.75 group when compared with placebo. Only one patient experienced amylase or lipase values at least three times the ULN; this occurred at baseline in the patient who had a serious AE of pancreatic carcinoma. No other clinically significant changes were detected for any other laboratory safety assessment. In addition, no patients treated with dulaglutide tested positive for dulaglutide antibody titers at any visit.

There were no statistically significant differences in baseline-to-endpoint mean changes in systolic or diastolic BP between any dulaglutide group and placebo (data not shown). The dulaglutide groups had similar LSM increases from baseline in PR (DU 0.25=1.40 bpm, DU 0.5=1.56 bpm, and DU 0.75=1.32 bpm), while the placebo group had an LSM decrease from baseline (–3.44 bpm) that was significantly different from all three dulaglutide groups (\( p<0.005 \)). No clinically significant AEs were associated with changes in vital signs. In addition, no clinically relevant changes in ECG parameters were observed.

### Discussion

This is the first trial to assess the dose-response of dulaglutide on glycaemic control in Japanese patients with type 2 diabetes mellitus. This study extends the
findings of previous studies of dulaglutide by providing evidence of the efficacy of once weekly dulaglutide up to the 0.75 mg dose in a multicenter sample of patients from Japan with type 2 diabetes mellitus [12-15]. The results demonstrated a significant dose-dependent effect of dulaglutide on glycemic control as measured by changes from baseline to the 12-week endpoint in HbA1c, average 7-point SMBG, and fasting PG, which is consistent with results from a large global 12-week phase 2 study of dulaglutide [13] and another 16-week phase 2 study of dulaglutide in overweight/obese patients with type 2 diabetes mellitus [15].

This study met its primary endpoint of showing significant dose-dependent reductions in HbA1c at endpoint (Week 12) across the treatment groups. Furthermore, there was a statistically significant reduction in HbA1c for each dulaglutide group compared with placebo throughout the treatment period. The HbA1c-lowering effect of DU 0.75 mg at endpoint was clinically relevant (−1.17%). Approximately 77% of patients in the DU 0.75 group reached the treatment target of HbA1c <7.0% determined by the Japanese Diabetes Association. The magnitude of this effect is comparable to that reported for once daily monotherapy with liraglutide in Japanese patients with type 2 diabetes mellitus [16]: treatment with the highest dose of liraglutide (0.9 mg) resulted in 75% of patients achieving HbA1c <7.0%. GLP-1 receptor agonists appear to be particularly effective in Asian and Japanese patients with type 2 diabetes mellitus, who tend to have a pathophysiology of insulin secretion impairment rather than insulin resistance and are inclined to be less obese compared to Western populations [17-20]. This suggests that dulaglutide could be a useful option for helping the large proportion of patients in clinical practice who do not achieve recommended HbA1c goals [20], as well as for overcoming the limited therapeutic response provided by some existing therapies.

Treatment with dulaglutide was also associated with dose-dependent increases in β-cell function as measured by HOMA2-%B. At endpoint, each dulaglutide group had a statistically significant and clinically meaningful increase from baseline in HOMA2-%B compared with placebo. Because the duration of the study was relatively short, these HOMA2-%B results should be interpreted cautiously. The increase in HOMA2-%B may not translate into long-term improvement in β-cell function; rather, it may reflect a GLP-1 receptor agonist-mediated increase in insulin secretion.

In this study, observed weight changes were generally small following treatment with dulaglutide, and a dose-dependent reduction in body weight was not observed. In the DU 0.75 group, the LSM change in body weight compared with placebo was +0.3 kg. Since the lack of a treatment effect on body weight may be due to the relatively short treatment period, more comprehensive assessments will be conducted in longer phase 3 studies.

Dulaglutide was generally well-tolerated in the present study, with an AE profile similar to that observed in other phase 1 and 2 studies of dulaglutide [12-15]. Most AEs were transient, mild to moderate in severity, and resolved spontaneously. Very few AEs led to study discontinuation in the dulaglutide (4 [3.7%]) and placebo (0 [0.0%]) groups, and there were no serious AEs related to study medication. As expected and consistent with other GLP-1 receptor agonists [16, 21, 22], GI AEs were the most commonly observed AEs in patients treated with dulaglutide. The rates of GI AEs were comparable to studies of liraglutide [16] and lower than those reported for exenatide and lixisenatide [22-25]. Of the GI events observed in dulaglutide-treated patients in the current study, nausea was the most frequent, followed by diarrhea, constipation, and abdominal discomfort (data not shown). With the exception of nausea and constipation, no clear dose-dependence for any individual GI AE was observed.

Neither symptomatic nor severe hypoglycaemia occurred in this study. The incidence of asymptomatic hypoglycaemia in the dulaglutide groups was low and similar to placebo, and no dose-dependent increase in the incidence was observed. There were no injection site reactions, and no patients treated with dulaglutide tested positive for dulaglutide anti-drug antibodies. Dulaglutide was engineered to have low immunogenicity by linking to a modified human IgG4, which does not activate complement, and this engineering may have contributed to the low rate of anti-drug antibodies production.

Increases in amylase and lipase were observed in all dulaglutide groups after randomisation, irrespective of the patients’ baseline values. Statistically significant increases in amylase and lipase were observed in the DU 0.75 group in comparison to placebo at endpoint; however, no acute pancreatitis or severe abdominal pain were noted during the treatment period through the follow-up period. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have reviewed multiple nonclinical toxicology studies, clinical trial databases, and epide-
miologic data to assess a potential pancreatic safety signal, pancreatitis, or pancreatic cancer potentially associated with incretin-based drugs. A review of more than 250 toxicology studies determined that there were no findings of overt pancreatic toxic effects or pancreatitis [26]. Clinical trials in which amylase and lipase levels have been monitored in a systematic manner showed that incretin-based drugs may increase enzyme levels, but result in mean levels which are in the normal range. Furthermore, changes in enzyme levels were not associated with GI AEs [23-25]. Results from meta-analyses and database research have reported that exenatide and liraglutide did not increase pancreatic safety risks [27-30]. At this time, FDA and EMA agree that concerns regarding a causal association between incretin-based drugs and pancreatitis or pancreatic cancer are inconsistent with the current data, but they will continue to support labeling for the class stating that pancreatitis is a potential risk, and will continue to monitor for any safety signal [26].

In the current study, statistically significant increases in seated PR of 4 to 5 bpm were observed across the dulaglutide groups compared with placebo at endpoint. However, the actual magnitude of changes (1 to 2 bpm) in the dulaglutide groups were small and the increases were not dose-dependent. Also, no other clinically significant cardiovascular events possibly related to study drug occurred.

In conclusion, once weekly administration of dulaglutide for 12 weeks in Japanese patients with type 2 diabetes mellitus resulted in dose-dependent improvements in glycaemic control, with a significant increase in β-cell function. Dulaglutide displayed an acceptable safety and tolerability profile. This once weekly GLP-1 receptor agonist shows promising efficacy, safety, and tolerability in the management of type 2 diabetes mellitus. Clinical investigations are ongoing to fully characterise the effects of dulaglutide on safety and efficacy parameters.

Acknowledgements

Eli Lilly and Company contracted inVentiv Health Clinical, LLC, USA, for writing and editing support. Jeannine R. Lane, PhD, of inVentiv Health Clinical drafted the first draft of the manuscript, and Mary K. Re, MS, of inVentiv Health Clinical provided writing assistance on further drafts of the manuscript; all drafts were written and revised according to guidance of the authors. All authors approved the submitted version of the manuscript. The authors would like to thank inVentiv Health Clinical, LLC, USA, for their help with writing, editing, and formatting.

Disclosure


References


