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BRIEF REPORT

Efficacy and Safety of Once-Weekly Dulaglutide in Type 2 Diabetes Patients Using Insulin: Exploratory Subgroup Analysis by Insulin Regimen

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ABSTRACT

Purpose: In East Asian patients, type 2 diabetes mellitus (T2DM) is characterized primarily by β-cell dysfunction, with lower insulin secretion than in Caucasian individuals. Therefore, bolus insulin and premixed insulin containing a bolus insulin component are important therapeutic tools in Japan, in addition to basal insulin. This subgroup analysis is stratified by insulin regimen and uses data from a phase 4, randomized, placebo-controlled, double-blind and subsequent open-label study in Japan to assess the efficacy and safety of once-weekly dulaglutide combined with various insulin therapies.

Methods: This multicenter study enrolled Japanese patients with T2DM and inadequate glycemic control [glycated hemoglobin A1c (HbA1c) $\geq$ 7.5% to $\leq$ 10.5%] on insulin therapy [basal (B), premixed (PM), or basal bolus (BB)] in combination with or without one or two oral antidiabetic agents. Randomized participants received once-weekly dulaglutide 0.75 mg (n = 120) or placebo (n = 39) during a 16-week double-blind treatment period, and dulaglutide during a 36-week open-label extension. In this subgroup analysis, efficacy measures were changes from baseline in HbA1c, 7-point self-monitored blood glucose profiles, and body weight. Safety measures were incidence of adverse events and hypoglycemia during the first 16 weeks.

Results: At week 16, least squares mean differences (95% CI) regarding changes from baseline in HbA1c for each insulin regimen versus placebo were: B: − 1.62% (− 1.96, − 1.28), PM: − 1.78% (− 2.25, − 1.30), and BB: − 1.15% (− 1.54, − 0.77); $p < 0.001$ dulaglutide vs. placebo for each subgroup. No significant differences in body weight changes were observed between dulaglutide and placebo for any insulin regimen. Gastrointestinal symptoms were the most commonly observed adverse events in dulaglutide-treated patients. Hypoglycemia incidence rates were: B: dulaglutide 38.5% vs. placebo 23.5%; PM: dulaglutide 38.5% vs.

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placebo 44.4%; BB: dulaglutide 50.0% vs. placebo 30.8%.
Conclusions: Overall, dulaglutide was generally well tolerated and improved glycemic control significantly versus placebo, regardless of insulin regimen.
Trial Registration: ClinicalTrials.gov identifier, NCT02750410.

Keywords: Dulaglutide; Glycemic control; GLP-1 analog; Hypoglycemia; Insulin therapy; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

As a result of characteristics of type 2 diabetes mellitus that are specific to East Asian patients, bolus insulin and premixed insulin containing a bolus insulin component are important therapeutic tools in Japan, in addition to basal insulin.

This analysis assessed changes in HbA1c and body weight from baseline to treatment week 16, and evaluated the incidence of adverse events and hypoglycemia with respect to each insulin regimen during that time.

What was learned from the study?

At week 16, dulaglutide 0.75 mg produced a significantly greater reduction in HbA1c from baseline than placebo, irrespective of insulin regimen.

No significant differences in body weight changes were observed between dulaglutide and placebo for any insulin regimen.

Overall, dulaglutide was generally well tolerated and improved glycemic control significantly versus placebo, regardless of insulin regimen.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease characterized by multiple defects in glucose metabolism [1]. Glucagon-like peptide-1 (GLP-1) receptor agonists have been used for the treatment of T2DM in combination with insulin and/or oral antidiabetic agents (OADs) [2, 3]. Dulaglutide is a long-acting GLP-1 receptor agonist that mimics the effects of endogenous GLP-1 [4]. The efficacy and safety of dulaglutide have been assessed in monotherapy [5], in combination with OADs [6, 7], and in combination with insulin in Japan [8].

In a previous report, we described the efficacy and safety of once-weekly dulaglutide 0.75 mg in combination with various types of insulin therapy that were used depending on patients' individual needs, and which included basal (B), premixed (PM), and basal bolus (BB) insulin therapies [8]. It is recognized that T2DM in East Asians is characterized primarily by β-cell dysfunction, and insulin secretion is lower in East Asian than in Caucasian individuals [9]. Therefore, bolus insulin and PM insulin (which contains bolus insulin) are commonly used in Japan, as well as B insulin [10–12].

The purpose of the pre-planned exploratory subgroup analysis reported in this paper was to assess the changes in glycated hemoglobin A1c (HbA1c), 7-point self-monitored blood glucose profile (SMBG), and body weight from baseline to week 16 of treatment, as well as the incidence of adverse events and hypoglycemia in patients treated with once-weekly dulaglutide 0.75 mg or placebo in combination with each insulin regimen (B, PM, or BB). Overall results in terms of efficacy and safety for 52 weeks are shown in a previous report [8].

METHODS

Study Design and Treatment

In this phase 4, randomized, placebo-controlled study, participants were treated with dulaglutide in two treatment phases: a 16-week double-blind primary treatment period, and a

subsequent 36-week open-label extension period (Fig. 1) [8]. The treatment phases were preceded by a 4- or 14-week screening and lead-in (with or without a washout period for sulfonylurea (SU), glinide, and/or DPP-4 inhibitor), and were followed by a safety follow-up visit 4 weeks after the end of the extension period [8]. This article will focus on the 16-week primary treatment period.

Study participants were stratified by insulin regimen (B, PM, or BB) and baseline HbA1c (< 8.5%, ≥ 8.5%) [8]. Using an interactive web-response system, patients were randomized to dulaglutide and placebo in a 3:1 ratio [8].

During the 16-week primary treatment period, patients with T2DM who were already treated with insulin with or without 1 or 2 OADs were administered dulaglutide 0.75 mg or placebo once weekly as a subcutaneous injection by single-dose pen [8]. The dosage and administration schedule of insulin and OADs were not changed during the primary treatment period [8].

Ethics

The study protocol was approved at each site by an institutional review board. A full list of institutional ethics committees for the participating study sites is included (Table S1 in the Electronic supplementary material, ESM). This study was performed in accordance with the principles of the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights, and with the principles of Good Clinical Practice. All patients provided written informed consent before participating in the study, in alignment with Springer's policy concerning informed consent. The study was registered at ClinicalTrials.gov (NCT02750410).

Patient Inclusion and Exclusion Criteria

Eligible study participants were Japanese men and women aged ≥ 20 years with a diagnosis of T2DM. Prior to visit 1, all eligible patients were on stable doses of daily insulin (± 20% versus the most commonly used dose for the period) and > 10 units per day of stable insulin therapy [B (once or twice daily), PM (twice or 3 times daily), or BB (4 or 5 times daily)] with or without one or two OADs. Eligible patients also had HbA1c values ≥ 7.0% and ≤ 10.5% at visit 1 if they were washing out OADs (DPP-4 inhibitors, SU, or glinides) or ≥ 7.5% and ≤ 10.5% at visit 1 if not washing out OADs. At visit 2 (week − 2), all patients were required to have HbA1c ≥ 7.5% and ≤ 10.5%. Finally, eligible patients demonstrated a stable weight (defined as ± 5% ≥ 3 months prior to visit 1) and a body mass

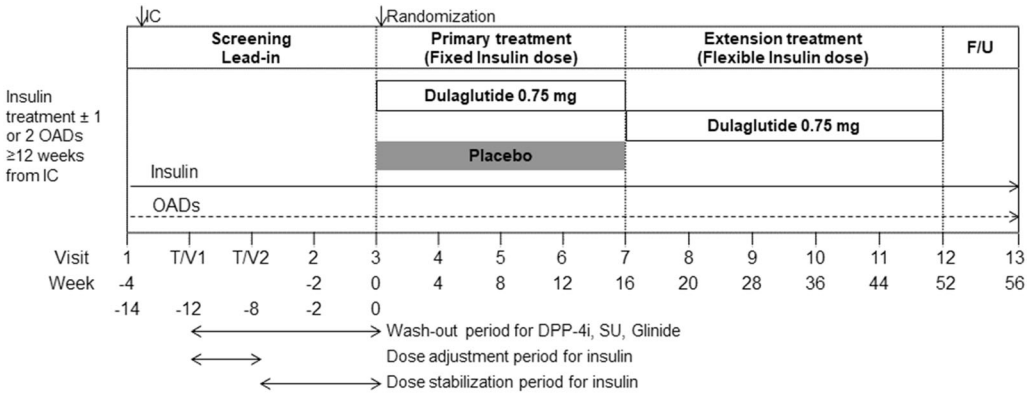

Fig. 1 H9X-JE-GBGF study design. The study featured a 16-week double-blind primary treatment period, a 36-week open-label extension treatment period, and a 4-week safety follow-up visit. Please note that a telephone visit (*T/V1*; or a site visit if preferred) was scheduled at week − 12 after screening results became available. An optional telephone visit (*T/V2*; or a site visit if preferred) could occur between weeks − 8 and 0 or at any time during the study, as needed. *DPP-4i* dipeptidyl peptidase-4 inhibitors, *F/U* follow-up, *IC* informed consent, *n* number of patients, *OAD* oral antidiabetic agent, *SU* sulfonylurea, *T/V* telephone visit

index (BMI) of 18.5–35 kg/m^2. Details of the study exclusion criteria have been published elsewhere [8]. Key exclusion criteria were a diagnosis of T1DM, treatment with a GLP-1 receptor agonist and/or weight loss-promoting drugs within 3 months before visit 1, ≥ 1 episode of severe hypoglycemia diabetic ketoacidosis within 6 months before visit 1, and a history of any other condition which, in the opinion of the investigator, could prevent the patient from following and completing the protocol [8].

Study Assessments

A complete description of the study assessments has been published previously [8]. Briefly, the primary efficacy endpoint was the change from baseline in HbA1c at week 16. Secondary efficacy endpoints included the change from baseline in body weight at week 16 and 7-point SMBG profiles. Safety measures included treatment-emergent adverse events (TEAEs) reported by patients, and both symptomatic and asymptomatic hypoglycemic episodes during the 16-week primary treatment period.

Statistical Analyses

A sample size of approximately 160 patients was needed to show that dulaglutide was superior to placebo with > 99% power, assuming a treatment difference of 1% in HbA1c reduction, a standard deviation of 1%, and a dropout rate of 15% [8].

Efficacy analyses (changes from baseline in HbA1c and body weight) were performed on the population of all patients who received ≥ 1 dose of study treatment and had ≥ 1 measurement of after-study treatment. A mixed-effects model (mixed-model repeated measures analysis) with a restricted maximum likelihood method was used for the change from baseline in HbA1c with treatment, insulin regimen group (B, PM, or BB), visit, and treatment-by-visit as fixed effects; baseline HbA1c value as a covariate; and subject as a random effect. For the change from baseline in body weight, the model includes baseline body weight as a covariate and HbA1c group (< 8.5%, ≥ 8.5%) as a fixed effect in place of baseline HbA1c as a covariate. For subgroup analyses, the following interactions were added as fixed effects to the base model described above: insulin regimen group-by-treatment, insulin regimen group-by-visit, and insulin regimen group-by-treatment-by-visit. Based on that model, the least squares (LS) mean and standard error (SE) for the change from baseline for each treatment and subgroup, *P* values for treatment comparison within insulin regimen subgroup, and *P* values for insulin regimen group-by-treatment at week 16 were provided. All tests of treatment comparison were conducted at a two-sided alpha level of 0.05. All tests of interaction were conducted at a two-sided alpha level of 0.10. For the post hoc 7-point SMBG analysis, the mean and SE for each treatment and subgroup are provided. *P* values for treatment comparison within insulin regimen subgroup regarding glucose changes from baseline were based on *t*-tests.

RESULTS

Patient Demographics and Disease Characteristics

In total, 159 patients were randomized during the primary treatment phase of this study (dulaglutide $n = 120$; placebo $n = 39$) [8]. Patient demographics and disease characteristics are detailed in Table 1. Men comprised 61.6% of patients, mean (SD) age was 59.3 (10.3) years, mean duration of T2DM was 17.0 (8.4) years, and mean HbA1c was 8.53% (0.70%) at baseline [8]. Insulin regimens were B for 69 patients (43.4%), PM for 35 patients (22.0%), and BB for 55 patients (34.6%) [8]. In general, demographics and disease characteristics were balanced across dulaglutide and placebo groups.

The OADs that were taken concomitantly by study participants are detailed in Table 1.

Change from Baseline HbA1c at Week 16

At week 16, dulaglutide produced a significantly greater reduction in HbA1c from baseline than

Table 1 Patient demographic and disease characteristics at baseline

	Dulaglutide 0.75 mg, *N* = 120			Placebo, *N* = 39		
	B *N* = 52	PM *N* = 26	BB *N* = 42	B *N* = 17	PM *N* = 9	BB *N* = 13
Age, years	57.8 (10.2)	60.1 (10.4)	60.7 (10.1)	56.8 (8.1)	64.8 (9.3)	58.2 (13.6)
Women, *n* (%)	21 (40.4)	10 (38.5)	11 (26.2)	7 (41.2)	4 (44.4)	8 (61.5)
Body weight, kg	70.0 (10.6)	67.1 (13.1)	73.1 (11.9)	71.1 (9.8)	67.8 (10.0)	72.0 (14.6)
BMI, kg/m^2	26.2 (3.6)	24.8 (3.8)	26.9 (3.5)	27.2 (4.0)	25.9 (3.5)	26.8 (3.6)
Duration of disease, years	15.6 (7.0)	17.7 (11.6)	18.5 (8.2)	13.4 (6.2)	20.7 (8.3)	18.8 (7.8)
HbA1c, %	8.6 (0.7)	8.5 (0.7)	8.4 (0.7)	8.7 (0.8)	8.6 (0.5)	8.5 (0.8)
Fasting blood glucose, mg/dL	156.7 (57.9)	159.1 (53.5)	159.7 (60.0)	151.9 (47.4)	197.2 (41.5)	182.3 (83.2)
Daily total insulin dose, U	22.7 (11.1)	33.9 (15.8)	46.0 (19.1)	20.2 (8.0)	37.2 (17.0)	43.4 (19.3)
Use of oral hypoglycemic agents, *n* (%)[a]	36 (69.2)	21 (80.8)	26 (61.9)	15 (88.2)	8 (88.9)	8 (61.5)
α-Glucosidase inhibitor	6 (11.5)	4 (15.4)	1 (2.4)	2 (11.8)	1 (11.1)	2 (15.4)
Biguanides	26 (50.0)	10 (38.5)	14 (33.3)	12 (70.6)	2 (22.2)	3 (23.1)
DPP-4 inhibitor	3 (5.8)	7 (26.9)	10 (23.8)	3 (17.6)	3 (33.3)	2 (15.4)
Glinides	2 (3.8)	0	0	0	0	0
SGLT2 inhibitor	12 (23.1)	8 (30.8)	9 (21.4)	6 (35.3)	4 (44.4)	4 (30.8)
Sulfonylurea	3 (5.8)	1 (3.8)	0	0	0	0
Thiazolidinediones	2 (3.8)	0	0	2 (11.8)	0	1 (7.7)
Formulation[b]	0	0	0	1 (5.9)	0	0

Data are presented as *n* (%) for women and use of oral hypoglycemic agents, and as mean value (standard deviation) for all other characteristics

B basal, *BB* basal bolus, *BMI* body mass index, *DPP-4* dipeptidyl peptidase 4, *PM* premixed, *SGLT2* sodium-glucose transporter 2

[a] Sulfonylurea, glinides and DPP-4 inhibitor were washed out before randomization

[b] One patient in the placebo B group had a formulation of α-glucosidase inhibitor and glinides

placebo, irrespective of insulin regimen (Fig. 2). The LS mean (SE) changes from baseline in HbA1c at week 16 for each insulin regimen versus placebo were: B: dulaglutide − 1.40% (0.08) vs. placebo 0.22% (0.15); PM: dulaglutide − 1.57% (0.12) vs. placebo 0.20% (0.21); and BB: dulaglutide − 1.42% (0.10) vs. placebo − 0.27% (0.17) ($P < 0.001$ dulaglutide vs. placebo for each subpopulation). These changes represent LS mean differences (95% CI) versus placebo of − 1.62% (− 1.96, − 1.28), − 1.78% (− 2.25, − 1.30), and − 1.15% (− 1.54, − 0.77), respectively. The interaction between insulin regimen group and treatment group at week 16 was statistically significant ($P = 0.084$).

7-Point SMBG Profile

Based on the 7-point SMBG profile, statistically significant differences in the change in blood glucose from baseline were observed at all time

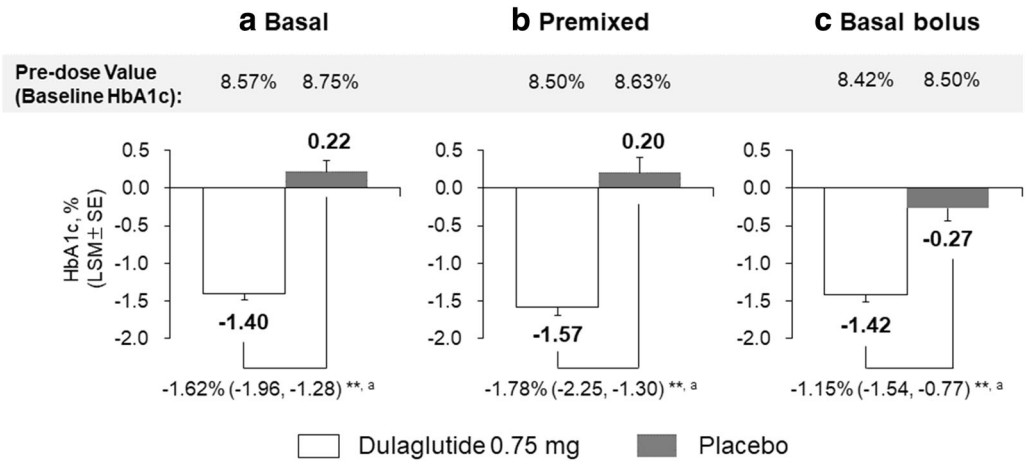

Fig. 2 At 16 weeks of administration, changes from baseline in HbA1c in patients on **a** basal, **b** premixed, and **c** basal bolus insulin regimens. Administration group, insulin therapy, visit, subpopulation, interaction between administration and visit, interaction between subpopulation and administration group, interaction between subpopulation and visit, and interaction between subpopulation and administration and visit were fixed. We used a mixed-effects model with a restricted maximum likelihood method, using the baseline parameter as the covariate and the subject as a random effect. The *P* value of the interaction between the subgroup and the treatment group was 0.084. $^{**}P < 0.001$ for dulaglutide versus placebo for each subpopulation. *CI* confidence interval, *LSM* least-squares mean, *SE* standard error. [a]LSM (95% CI)

points in the B group, at all time points except before dinner in the PM group, and before and after lunch and before dinner in the BB group (Table S2 in the ESM and Fig. 3). Overall, the increase in postprandial glucose was smaller in the BB group compared with the B and PM groups.

Change from Baseline Body Weight at Week 16

There was no change in body weight at week 16 compared to baseline (Fig. 4). The LS mean (SE) changes from baseline in body weight at week 16 versus placebo were B: dulaglutide 0.17 kg (0.26) vs. placebo − 0.30 kg (0.45); PM: dulaglutide − 0.44 kg (0.37) vs. placebo − 0.74 kg (0.65); and BB: dulaglutide − 0.53 kg (0.29) vs. placebo 0.05 kg (0.52). These changes represent LS mean differences (95% CI) in body weight versus placebo of 0.46 kg (− 0.56, 1.48), 0.30 kg (− 1.17, 1.78), and − 0.58 kg (− 1.76, 0.60), respectively. The interaction between insulin regimen group and treatment group at week 16 was not statistically significant ($P = 0.397$).

Adverse Events

The incidence of TEAEs was similar among the treatment groups: B: dulaglutide 57.7% ($n = 30$) vs. placebo 47.1% ($n = 8$); PM: dulaglutide 42.3% ($n = 11$) vs. placebo 66.7% ($n = 6$); and BB: dulaglutide 52.4% ($n = 22$) vs. placebo 53.9% ($n = 7$). The most common TEAEs were epipharyngitis, abdominal discomfort, constipation, loss of appetite, nausea, diarrhea, and vomiting. Incidences of specific TEAEs for each treatment group are summarized in Table 2.

Hypoglycemia

The incidence of symptomatic or asymptomatic hypoglycemia (defined as ≤ 70 mg/dL) for each treatment group was as follows: B: dulaglutide 38.5% ($n = 20$) vs. placebo 23.5% ($n = 4$); PM: dulaglutide 38.5% ($n = 10$) vs. placebo 44.4% ($n = 4$); and BB: dulaglutide 50.0% ($n = 21$) vs. placebo 30.8% ($n = 4$) (Table 3). The incidence of nocturnal hypoglycemia for each treatment group was as follows: B: dulaglutide 9.6% ($n = 5$) vs. placebo ($n = 0$); PM: dulaglutide ($n = 0$) vs. placebo 33.3% ($n = 3$); and BB: dulaglutide

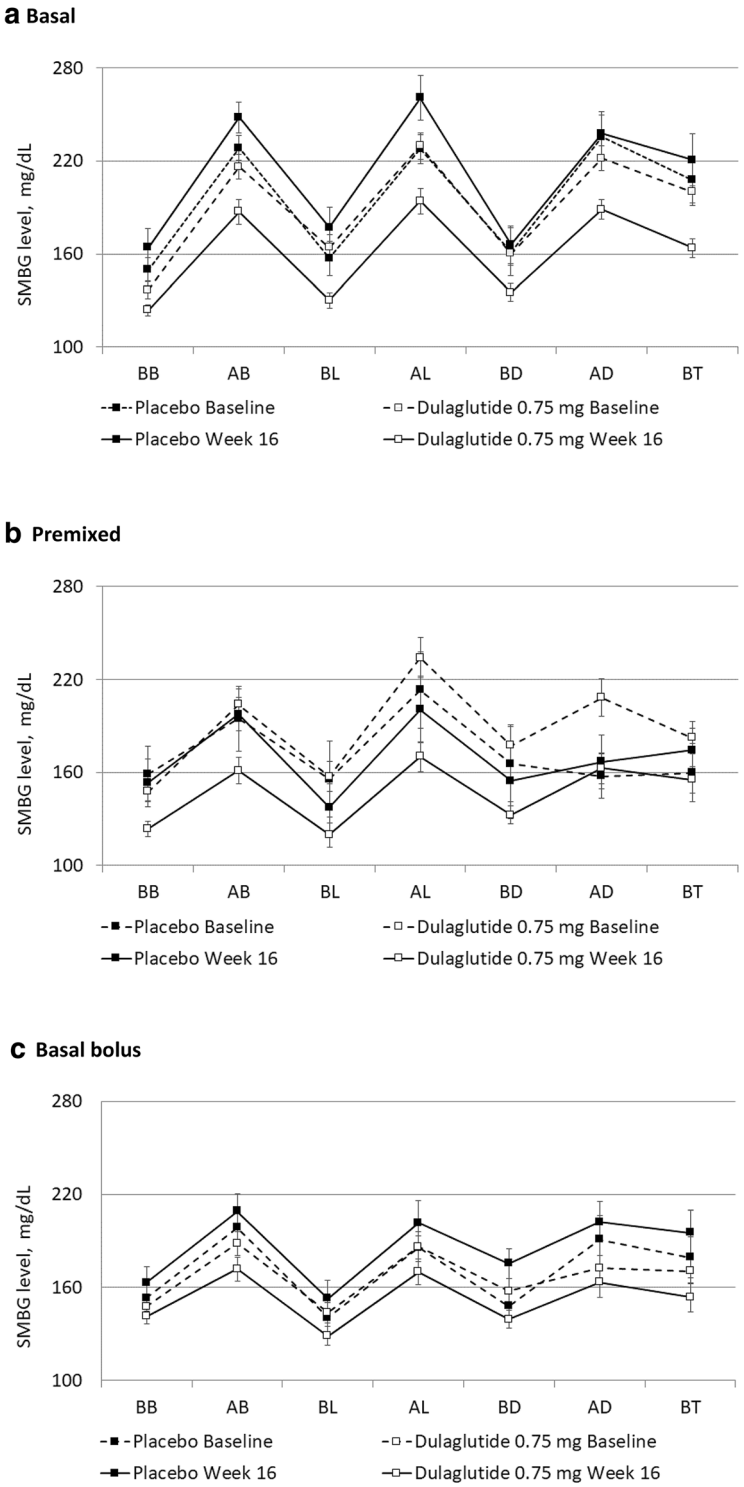

Fig. 3 7-Point SMBG profiles of patients treated with dulaglutide 0.75 mg vs. placebo at baseline and week 16 in patients on **a** basal, **b** premixed, and **c** basal bolus insulin regimens. Within-day variability of blood glucose was lower among dulaglutide-treated patients than placebo patients, and lower in the basal bolus and premixed groups than in the basal insulin group. *Error bars* represent SE. *AB* after breakfast, *AD* after dinner, *AL* after lunch, *BB* before breakfast, *BD* before dinner, *BL* before lunch, *BT* bedtime, *SE* standard error

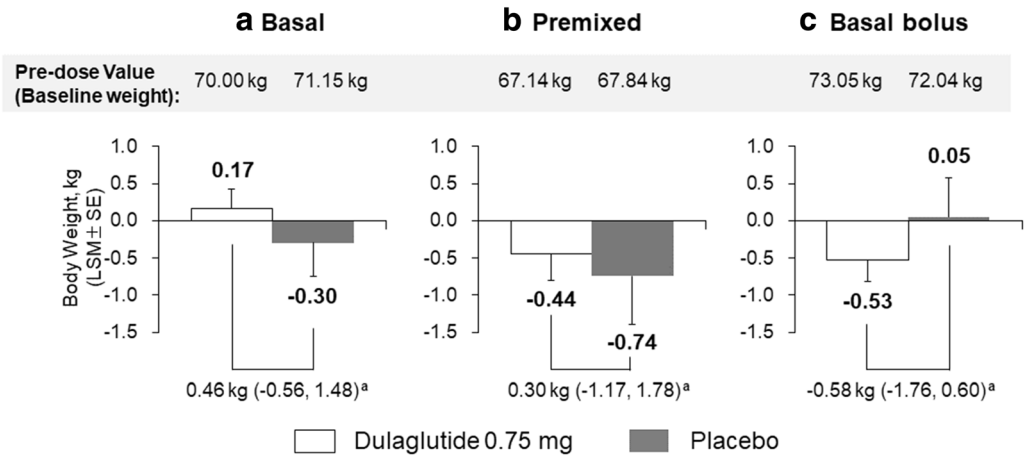

Fig. 4 At 16 weeks of administration, changes from baseline in body weight in patients on **a** basal, **b** premixed, and **c** basal bolus insulin regimens. Administration group, insulin therapy, visit, subpopulation, interaction between administration and visit, interaction between subpopulation and administration group, interaction between subpopulation and visit, and interaction between subpopulation and administration and visit were fixed. We used a mixed-effects model with a restricted maximum likelihood method, using the baseline parameter as the covariate and the subject as a random effect. The *P* value of the interaction between the subgroup and the treatment group was 0.397. *CI* confidence interval, *LSM* least-squares mean, *SE* standard error. [a]LSM (95% CI)

11.9% (*n* = 5) vs. placebo 7.7% (*n* = 1). One case of severe hypoglycemia occurred in a dulaglutide-treated patient in the PM group who missed lunch, fainted, and was hospitalized; the hypoglycemia resolved.

DISCUSSION

In this exploratory subgroup analysis, statistically significant reductions in HbA1c by dulaglutide 0.75 mg compared with placebo

Table 2 Adverse events (≥ 3 patients with any therapy), treatment weeks 0–16

Adverse event[a], *n* (%)	Dulaglutide 0.75 mg, *N* = 120			Placebo, *N* = 39		
	B *N* = 52	PM *N* = 26	BB *N* = 42	B *N* = 17	PM *N* = 9	BB *N* = 13
All adverse events	30 (57.7)	11 (42.3)	22 (52.4)	8 (47.1)	6 (66.7)	7 (53.9)
Epipharyngitis	7 (13.5)	2 (7.7)	10 (23.8)	4 (23.5)	3 (33.3)	0 (0)
Abdominal discomfort	5 (9.6)	1 (3.9)	4 (9.5)	0 (0)	1 (11.1)	0 (0)
Constipation	5 (9.6)	2 (7.7)	1 (2.4)	2 (11.8)	0 (0)	2 (15.4)
Nausea	5 (9.6)	1 (3.9)	1 (2.4)	0 (0)	0 (0)	2 (15.4)
Loss of appetite	4 (7.7)	2 (7.7)	2 (4.8)	0 (0)	0 (0)	0 (0)
Diarrhea	4 (7.7)	1 (3.9)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	3 (5.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (15.4)

B basal, *BB* basal bolus, *PM* premixed
[a] MedDRA/J version 21.0

Table 3 Hypoglycemic incidence, treatment weeks 0–16

Hypoglycemia category, *n* (%)	Dulaglutide 0.75 mg, *N* = 120			Placebo, *N* = 39		
	B *N* = 52	PM *N* = 26	BB *N* = 42	B *N* = 17	PM *N* = 9	BB *N* = 13
Total hypoglycemia	20 (38.5)	10 (38.5)	21 (50.0)	4 (23.5)	4 (44.4)	4 (30.8)
Asymptomatic hypoglycemia[a] with glucose ≤70 mg/dL	16 (30.8)	7 (26.9)	13 (31.0)	2 (11.8)	0 (0)	4 (30.8)
Documented symptomatic hypoglycemia[b] with glucose ≤70 mg/dL	7 (13.5)	6 (23.1)	13 (31.0)	3 (17.7)	3 (33.3)	4 (30.8)
Probable symptomatic hypoglycemia[c]	3 (5.8)	2 (7.7)	2 (4.8)	2 (11.8)	1 (11.1)	1 (7.7)
Relative hypoglycemia[d] with glucose > 70 mg/dL	3 (5.8)	1 (3.9)	1 (2.4)	1 (5.9)	1 (11.1)	1 (7.7)
Severe hypoglycemia[e]	0 (0)	1 (3.9)	0 (0)	0 (0)	0 (0)	0 (0)
Nocturnal hypoglycemia[f]	5 (9.6)	0 (0)	5 (11.9)	0 (0)	3 (33.3)	1 (7.7)

B, basal, *BB* basal bolus, *PM* premixed

[a] Defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose of ≤ 70 mg/dL

[b] Defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a plasma glucose level of ≤ 70 mg/dL

[c] Defined as an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but the event was presumably caused by a plasma glucose concentration of ≤ 70 mg/dL)

[d] Defined as symptomatic events during which the person reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration of > 70 mg/dL

[e] Defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

[f] Defined as any hypoglycemic event that occurs between bedtime and waking

were observed in all three evaluated insulin regimens. However, the difference between dulaglutide and placebo was smaller in the BB group (− 1.15%) compared with the B group (− 1.62%) and the PM group (− 1.78%). Seven-point SMBG profile analysis also showed greater reductions in blood glucose in the B and PM groups compared with the BB group. Baseline postprandial glucose was lower in the BB group than in the B and PM groups, and this would be one cause of the differences among insulin regimen groups. As described in the "Introduction," it is recognized that insulin secretion is lower in East Asians than in Caucasians [9]. Therefore, a higher postprandial glucose level is one feature of T2DM in Japanese patients. Adding dulaglutide to B and PM insulin may be one option to resolve the residual issue of a higher postprandial glucose level; another option is adding bolus insulin to B and PM insulin.

Regarding changes in body weight, there was no significant difference between dulaglutide and placebo at week 16 in any insulin regimen. Increasing the insulin dose in order to achieve better blood glucose control may increase body weight. Improvement of glycemic control without causing weight gain is one feature of the combination of insulin with a GLP-1 receptor agonist.

In terms of adverse events, epipharyngitis is commonly observed in clinical studies for any disease, regardless of drug type. The majority of other adverse events observed in dulaglutide-treated patients in the present study were gastrointestinal symptoms, with an incidence comparable to those previously observed in studies evaluating dulaglutide monotherapy alone [5] and in combination with OADs [6, 7].

In dulaglutide-treated groups at week 16, the incidence of symptomatic hypoglycemia with glucose ≤ 70 mg/dL was higher in the BB group

than in the B and PM groups (B: 13.5%, PM: 23.1%, BB: 31.0%). A similar tendency was observed in a clinical study of liraglutide used in combination with insulin therapy in Japanese T2DM patients; the incidence rates of confirmed hypoglycemia at week 16 were: B: 16.0%, PM: 24.0%, BB: 33.3% [13]. These results might reflect the difficulty involved in achieving glycemic control in patients receiving BB therapy.

This is the first study in Japan to assess treatment with once-weekly dulaglutide in combination with insulin therapy and to make comparisons across various insulin regimens. One limitation of this study is the small sample sizes of the individual treatment groups. In addition, because the dose of insulin was fixed during the 16-week primary treatment phase, it was not possible to assess how much the insulin dose could be reduced by adding dulaglutide.

CONCLUSIONS

In conclusion, in this study of Japanese patients with T2DM who were using insulin, dulaglutide 0.75 mg was generally well tolerated and showed a significant improvement in glycemic control compared with placebo, regardless of the type of insulin regimen.

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Compliance with Ethics Guidelines. The study protocol was approved at each site by an institutional review board. A full list of institutional ethics committees for the participating study sites is included (Table S1 in the ESM). The study was performed in accordance with the principles of the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights, and with the principles of Good Clinical Practice. All patients provided written informed consent before participating in the study, in alignment with Springer's policy concerning informed consent.

Data Availability. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date for data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after

receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at http://www.vivli.org.

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