Efficacy and safety of subgroup analysis stratified by baseline HbA1c in a Japanese phase 3 study of dulaglutide 0.75 mg compared with insulin glargine in patients with type 2 diabetes

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Abstract. The efficacy and safety of once-weekly dulaglutide 0.75 mg (dulaglutide) compared with once-daily insulin glargine (glargine) in Japanese patients with type 2 diabetes were evaluated according to subgroups stratified by baseline glycated hemoglobin (HbA1c) (≤8.5% or >8.5%). This exploratory analysis of a randomized, open-label, phase 3 study included 361 patients. In both HbA1c subgroups (patients with baseline HbA1c ≤8.5% or >8.5%), a statistically significantly greater reduction in HbA1c was observed in dulaglutide-treated patients compared with glargine-treated patients after 26 weeks of treatment (HbA1c ≤8.5%: dulaglutide, -1.27%; glargine, -0.72%; HbA1c >8.5%: dulaglutide, -2.04%; glargine, -1.47%; \( p < 0.001 \) for both). Mean body weight was decreased from baseline in both subgroups of the dulaglutide group and increased in both subgroups of the glargine group; there were statistically significant differences between the treatment groups in both subgroups (\( p < 0.05 \) for both). In both subgroups, similar reductions in fasting blood glucose were observed for dulaglutide- and glargine-treated patients, and a greater reduction in postprandial blood glucose was observed for dulaglutide-treated patients compared with glargine-treated patients. Although dulaglutide increased gastrointestinal adverse events compared with glargine in both subgroups, all gastrointestinal events of diarrhea, nausea, constipation, and vomiting in dulaglutide-treated patients were mild in intensity and well tolerated. In both subgroups, there was a lower incidence of hypoglycemia with dulaglutide than with glargine. Dulaglutide demonstrated significantly greater HbA1c reduction compared with glargine, with an acceptable safety profile, regardless of baseline HbA1c.

Key words: Dulaglutide, GLP-1 receptor agonist, HbA1c subgroup analysis, Type 2 diabetes

DULAGLUTIDE, a long-acting injectable glucagon-like peptide-1 (GLP-1) receptor agonist, is a recombinant GLP-1 immunoglobulin G4 (IgG4) Fc fusion protein consisting of 2 identical chains, and it mimics some of the effects of endogenous GLP-1 [1]. It has been approved and launched in the United States, the European Union [2, 3], and Japan [4]. In phase 3 studies in Japanese and non-Japanese patients with type 2 diabetes (T2D), once-weekly dulaglutide 0.75 mg and/or 1.5 mg showed superiority to insulin glargine (glargine) [5-7], sitagliptin [8], and twice-daily exenatide [9] and noninferiority to once-daily liraglutide in glycated hemoglobin (HbA1c) changes [10, 11].

Subgroup analyses using pooled data from the 3 Japanese phase 3 studies of dulaglutide 0.75 mg (dulaglutide) in patients with T2D stratified by several patient characteristics, including baseline HbA1c, were previously reported [12]. However, because these analyses did not include comparator treatments, further studies are needed to assess the benefits and risks (efficacy and safety based on baseline HbA1c levels) of dulaglutide compared with basal insulin (such as glargine) as a treatment option for patients. In this study, to compare efficacy and safety between dulaglutide and glargine based on HbA1c levels, we conducted further exploratory subgroup analyses of...
the randomized, glargine-controlled study in Japanese patients with T2D [5].

Materials and Methods

Study design and patient population

The study was a 26-week, randomized, open-label, noninferiority phase 3 study that compared the efficacy and safety of once-weekly dulaglutide 0.75 mg with once-daily glargine in Japanese patients with T2D inadequately controlled with sulfonylureas (SUs) and/or biguanides (BGs) [5]. Japanese men and women with T2D, aged ≥20 years, with HbA1c at screening ≥7.0 and ≤10.0%, who were taking stable doses of SUs (2.5-5 mg of glibenclamide, 60-80 mg of gliclazide, or 2-3 mg of glimepiride) and/or BGs (750-1,500 mg of metformin or 100-150 mg of buformin) were randomized. Randomization was stratified by concomitant oral hypoglycemic agent (OHA) regimen (SU only, BG only, or SU and BG), body mass index (BMI) group at baseline (<25 and ≥25 kg/m²), and screening HbA1c (≤8.5 and >8.5%).

The study protocol was approved at each site by an institutional review board, and the study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participation. The study was registered at ClinicalTrials.gov (NCT01584232).

Analysis methods

To evaluate the effects of baseline HbA1c, patients were classified into 2 subgroups based on baseline HbA1c (≤8.5% or >8.5%). Subgroup analyses to evaluate changes in HbA1c and body weight by baseline HbA1c subgroup were conducted using a mixed-effects model for repeated measurements (MMRM) similar to the primary efficacy analysis [5] in the study that included treatment, OHA regimen (SU only, BG only, or SU and BG), baseline BMI group (<25 or ≥25 kg/m²), visit, treatment by visit, baseline HbA1c group, treatment-by-baseline HbA1c, visit-by-baseline HbA1c, and treatment-by-visit-by-baseline HbA1c interaction as fixed effects; baseline weight as a covariate (for weight); and patient as a random effect. Based on this MMRM, p values for changes in HbA1c and body weight were calculated from pairwise comparisons of least-squares (LS) means at week 26 from restricted maximum likelihood. For the 8-point self-monitored blood glucose (SMBG) profiles, summary statistics of measurements and changes from baseline were reported for baseline and the 26-week endpoint. P values were calculated from t-tests. Incidences (%) of patients experiencing adverse events or hypoglycemia were summarized by treatment and baseline HbA1c subgroup. P values for incidence of treatment-emergent adverse events were calculated from Fisher’s exact test. P values for incidence of hypoglycemia were computed by chi-square test if at least 80% of cells had an expected value ≥5; otherwise Fisher’s exact test was used. Some demographic characteristics at baseline were also summarized descriptively by treatment and baseline HbA1c subgroup.

The subgroup analyses of changes in HbA1c and body weight and of incidences of adverse events, and total and nocturnal hypoglycemia were prespecified in the study analysis plan, whereas the analyses of demographic characteristics, insulin dose, SMBG profiles, and documented symptomatic, asymptomatic, and probable symptomatic hypoglycemia were all post hoc.

Results

Patient characteristics

Demographics for all 361 patients stratified by treatment and baseline HbA1c subgroup are presented in Table 1. Overall, 275/361 (76%) of patients had baseline HbA1c ≤8.5%, and 86/361 (24%) had baseline HbA1c >8.5%. Baseline patient characteristics were similar between the treatment groups in each subgroup. For both the dulaglutide and glargine treatment groups at baseline, patients with higher baseline HbA1c (>8.5%) had higher mean fasting serum glucose levels and greater mean body weights (186 mg/dL for both; 72.5 and 72.0 kg, respectively) than patients with lower baseline HbA1c (≤8.5%) (151 and 146 mg/dL; 70.4 and 70.8 kg, respectively). There were no meaningful differences in other factors between the 2 subgroups for either treatment.

At endpoint (26 weeks), the mean glargine dose was 11.2 and 16.8 IU/day in patients with baseline HbA1c ≤8.5% and >8.5%, respectively.

Efficacy

In both subgroups, dulaglutide-treated patients had a statistically significantly greater reduction from baseline in HbA1c (LS mean) than glargine-treated patients after 26 weeks (HbA1c ≤8.5%; dulaglutide, -1.27%; glargine, -0.72%; HbA1c >8.5%; dulaglutide, -2.04%; glargine, -1.47%; p < 0.001 for both subgroups) (Fig. 1A). There
Table 1  Demographic and baseline characteristics by treatment and baseline HbA1c subgroup

<table>
<thead>
<tr>
<th>HbA1c Subgroup</th>
<th>≤8.5%</th>
<th>&gt;8.5%</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>Dulaglutide 0.75 mg (n = 137)</td>
<td>Insulin Glargine (n = 138)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (67)</td>
<td>98 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>45 (33)</td>
<td>40 (29)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.6 ± 10.4</td>
<td>56.7 ± 11.1</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>8.9 ± 6.9</td>
<td>8.7 ± 6.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.4 ± 13.4</td>
<td>70.8 ± 13.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9 ± 3.4</td>
<td>26.0 ± 3.9</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.7 ± 0.5</td>
<td>7.6 ± 0.5</td>
</tr>
<tr>
<td>Fasting serum glucose, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>150.9 ± 33.1</td>
<td>145.9 ± 29.9</td>
</tr>
</tbody>
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Baseline OHA therapy, n (%)

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<tr>
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</thead>
<tbody>
<tr>
<td>SU only</td>
<td>22 (16)</td>
<td>24 (17)</td>
<td>12 (27)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>BG only</td>
<td>54 (39)</td>
<td>52 (38)</td>
<td>10 (23)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>SU and BG</td>
<td>61 (45)</td>
<td>62 (45)</td>
<td>22 (50)</td>
<td>19 (45)</td>
</tr>
</tbody>
</table>

Data are mean ± SD, unless indicated. Dulaglutide administered once weekly. Insulin glargine administered once daily. BG, biguanide; BMI, body mass index; HbA1c, glycated hemoglobin; n, number of patients; OHA, oral hypoglycemic agent; SD, standard deviation; SU, sulfonylurea. <sup>a</sup>Fasting serum glucose was measured at the central laboratory.

![Fig. 1](image-url)  
(A) LS mean (SE) changes from baseline to Week 26 in HbA1c (%) by treatment and baseline HbA1c subgroup.  
(B) LS mean (SE) changes from baseline to Week 26 in body weight (kg) by treatment and baseline HbA1c subgroup

<sup>*</sup>p < 0.05, <sup>**</sup>p < 0.001 for dulaglutide vs. insulin glargine within subgroup. HbA1c, glycated hemoglobin; LS, least-squares; SE, standard error.
was no significant treatment-by-baseline HbA1c interaction effect on the change from baseline in HbA1c (p = 0.503). In both the dulaglutide and glargine treatment groups, patients with baseline HbA1c >8.5% experienced statistically greater reductions in HbA1c than patients with baseline HbA1c ≤8.5% (p < 0.001, respectively).

In both subgroups, LS mean body weight was decreased from baseline in dulaglutide-treated patients and increased from baseline in glargine-treated patients after 26 weeks (HbA1c ≤8.5%: dulaglutide, -0.57 kg; glargine, 0.80 kg; HbA1c >8.5%: dulaglutide, -0.20 kg; glargine, 1.38 kg). For both subgroups, the differences in change in body weight between the treatment groups were statistically significant (p < 0.05) (Fig. 1B). There was no significant treatment-by-baseline HbA1c interaction effect on the change from baseline in body weight (p = 0.595). There were no statistically significant differences between the subgroups in changes in body weight for either treatment group (dulaglutide: p = 0.344; glargine: p = 0.148).

Mean 8-point SMBG profiles by treatment groups at baseline and week 26 (last observation carried forward) and the changes from baseline are shown in Fig. 2 and Fig. 3 for patients with baseline HbA1c ≤8.5% and HbA1c >8.5%, respectively. In patients with baseline HbA1c ≤8.5%, dulaglutide significantly reduced SMBG values from baseline after 26 weeks compared with glargine for all time points (p < 0.05 for all), except for before breakfast and before breakfast the following day (second before breakfast) (Fig. 2). In patients with baseline HbA1c >8.5%, dulaglutide significantly reduced SMBG values from baseline after 26 weeks compared with glargine for the after lunch, before dinner, and after dinner time points (p < 0.05 for all) (Fig. 3). Furthermore, patients with baseline HbA1c >8.5% in both the dulaglutide and glargine treatment groups experienced greater reductions from baseline at all 8 points of their SMBG profiles compared with patients with baseline HbA1c ≤8.5% (Fig. 2C and Fig. 3C).

**Safety**

Table 2 shows the incidences of frequent adverse events (those occurring in >5% of dulaglutide- or glargine-treated patients) and hypoglycemia (defined by blood glucose ≤70 mg/dL and/or symptoms/signs attributable to hypoglycemia) through week 26 by treatment and HbA1c subgroup. In both subgroups, gastrointestinal disorders occurred more frequently with dulaglutide than glargine (p = 0.002 for HbA1c ≤8.5%; p < 0.001 for HbA1c >8.5%). Dulaglutide-treated patients with baseline HbA1c ≤8.5% had statistically significantly higher incidences of diarrhea, nausea, and lipase-level increase than glargine-treated patients (p < 0.05 for all). Although 1 patient discontinued dulaglutide treatment because of an adverse event of vomiting, all observed gastrointestinal adverse events (diarrhea, nausea, constipation, and vomiting) in dulaglutide-treated patients were reported as mild in intensity. The incidences of total, asymptomatic, and nocturnal hypoglycemia were statistically significantly lower with dulaglutide compared with glargine in both subgroups (p < 0.05 for all). The incidence of probable symptomatic hypoglycemia was statistically significantly lower with dulaglutide compared with glargine in patients with baseline HbA1c >8.5% (p < 0.05). There were no meaningful differences in the incidences of frequent adverse events or hypoglycemia between the subgroups for either treatment group.

**Discussion**

This analysis was an exploratory evaluation of the efficacy and safety of once-weekly dulaglutide 0.75 mg compared with once-daily glargine by subgroups of baseline HbA1c (≤8.5% or >8.5%) in Japanese patients with T2D treated for up to 26 weeks in a randomized, controlled study [5].

In this subgroup analysis, in both the dulaglutide and glargine groups, greater HbA1c reductions were observed in patients with higher baseline HbA1c (>8.5%) compared with patients with lower baseline HbA1c (≤8.5%). This is because there is a greater potential for improvement in glycemic control in patients with higher baseline HbA1c. Similar relationships between baseline HbA1c levels and improvements in glycemic control have also been seen in previous reports of meta-analyses of various glucose-lowering therapies [13], meta-analyses of GLP-1 receptor agonists other than dulaglutide [14, 15], and global phase 3 studies of dulaglutide [16].

Because it has been reported that the relative contribution of fasting hyperglycemia to glycemic control increases gradually with worsening of T2D [17], it was anticipated that glargine, which is considered to have a robust effect on fasting hyperglycemia, would have an advantage for HbA1c reductions in patients with higher baseline HbA1c. However, the treatment differences (dulaglutide – glargine) in HbA1c reduction at week
Dulaglutide analysis by HbA1c in Japan

Fig. 2 Mean 8-point SMBG profiles (mg/dL) in patients with baseline HbA1c ≤8.5% by treatment. (A) At baseline, (B) At Week 26 (LOCF), (C) Changes from baseline

*, **: SMBG significantly lower, or reduction in SMBG significantly greater in dulaglutide group compared with insulin glargine group (*p < 0.05, **p < 0.001). +, ++: SMBG significantly lower, or reduction in SMBG significantly greater in insulin glargine group compared with dulaglutide group (+p < 0.05, ++p < 0.001). AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BB#, before breakfast next day; BD, before dinner; BL, before lunch; BT, bedtime; LOCF, last observation carried forward; SD, standard deviation; SE, standard error; SMBG, self-monitored blood glucose.

Fig. 3 Mean 8-point SMBG profiles (mg/dL) in patients with baseline HbA1c >8.5% by treatment. (A) At baseline, (B) At Week 26 (LOCF), (C) Changes from baseline

*, **: SMBG significantly lower, or reduction in SMBG significantly greater in dulaglutide group compared with insulin glargine group (*p < 0.05). AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BB#, before breakfast next day; BD, before dinner; BL, before lunch; BT, bedtime; LOCF, last observation carried forward; SD, standard deviation; SE, standard error; SMBG, self-monitored blood glucose.
26 were nearly the same for both HbA1c subgroups (-0.54% and -0.57% for HbA1c ≤8.5% and HbA1c >8.5%, respectively). This was supported by the SMBG results, which showed that, in both HbA1c subgroups, 1) similar reductions in fasting blood glucose were observed for dulaglutide- and glargine-treated patients, and 2) a greater reduction in postprandial blood glucose was observed for dulaglutide-treated patients compared with glargine-treated patients. In addition, it is thought that long-acting GLP-1 receptor agonists might have stronger effects on both postprandial and fasting blood glucose than short-acting GLP-1 receptor agonists [9].

In this study, the investigator adjusted glargine dosing based on the dosing algorithm, which was modified from the ATLAS study [5], with a fasting serum glucose target of ≤110 mg/dL. Consistent with the overall results of the original study [5], the mean fasting blood glucose at week 26 in the glargine-treated patients with baseline HbA1c ≤8.5% and HbA1c >8.5% (Fig. 2 and Fig. 3, respectively) was higher than the target glucose levels in this study. Therefore, there remained the possibility that this dosing method might not sufficiently suppress increases of postprandial blood glucose at daytime. However, the mean glargine doses at endpoint (11.2 and 16.8 IU/day in patients with baseline HbA1c ≤8.5% and >8.5%, respectively) in this study were similar to the average dose in Japanese patients (10–15 IU/day) reported in clinical studies and post-marketing surveillance for glargine [18-20]. Also, both the mean fasting blood glucose and HbA1c at endpoint as well as the incidence of hypoglycemia in this study were similar to the mean fasting blood glucose and HbA1c (121 mg/dL and 7.1%, respectively) reported in a review article in a treat-to-target study of insulin glargine [21, 22].

Treatment differences (dulaglutide − glargine) in changes at week 26 in body weight were also

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### Table 2 Incidence (percentage of patients) of frequent treatment-emergent adverse events and hypoglycemia through 26 weeks by treatment and baseline HbA1c subgroup

<table>
<thead>
<tr>
<th>HbA1c Subgroup</th>
<th>≤ 8.5%</th>
<th>&gt; 8.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
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<tr>
<td>Dulaglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75 mg (n = 137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Glargine (n = 138)</td>
<td></td>
<td></td>
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<tr>
<td>P Value Between Treatments&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥1 TEAE</td>
<td>74.5</td>
<td>60.1</td>
</tr>
<tr>
<td>TEAEs occurring in ≥5% of patients in either treatment group overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>24.8</td>
<td>26.8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>29.9</td>
<td>14.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>5.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypoglycemia&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Total</td>
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<td>Documented symptomatic&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8.0</td>
<td>14.5</td>
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<td>Asymptomatic&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>37.0</td>
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<tr>
<td>Probable symptomatic&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>8.8</td>
<td>23.9</td>
</tr>
</tbody>
</table>

Data are percentages of patients. Medical Dictionary for Regulatory Activities version 16.1. Dulaglutide administered once weekly. Insulin glargine administered once daily. HbA1c, glycated hemoglobin; n, number of patients; TEAE, treatment-emergent adverse event.  
<sup>a</sup> P values for TEAEs were calculated from Fisher’s exact test.  
<sup>b</sup> P values for hypoglycemia were computed by chi-square test if at least 80% of cells had an expected value ≥5; otherwise Fisher’s exact test was used.  
<sup>c</sup> Hypoglycemia was defined as a blood glucose concentration of ≤70 mg/dL and/or symptoms/signs attributable to hypoglycemia.  
<sup>d</sup> Documented symptomatic hypoglycemia was defined as a blood glucose concentration of ≤70 mg/dL and symptoms/signs attributable to hypoglycemia.  
<sup>e</sup> Asymptomatic hypoglycemia was defined as a blood glucose concentration of ≤70 mg/dL without typical symptoms/signs attributable to hypoglycemia.  
<sup>f</sup> Probable symptomatic hypoglycemia was defined as symptoms/signs attributable to hypoglycemia without any record of a blood glucose concentration of ≤70 mg/dL.
similar for both HbA1c subgroups (-1.38 kg and -1.58 kg for HbA1c ≤8.5% and HbA1c >8.5%, respectively). However, patients with lower baseline HbA1c tended to have numerically greater weight loss (dulaglutide) or less weight gain (glargine) than patients with higher baseline HbA1c. The mean glargine dose at endpoint was higher in patients with higher baseline HbA1c than in patients with lower baseline HbA1c (16.8 and 11.2 IU/day for HbA1c >8.5% and HbA1c ≤8.5%, respectively). Similarly, for dulaglutide-treated patients, greater insulin secretion might be required in patients with higher baseline HbA1c compared with patients with lower baseline HbA1c to incorporate excess blood glucose into peripheral tissues. The glucose-dependent insulinotropic effect of incretin-based therapies can also explain greater insulin secretion in patients with higher baseline HbA1c.

Results from these subgroup analyses showed that in both HbA1c subgroups, dulaglutide-treated patients experienced gastrointestinal adverse events more frequently than glargine-treated patients; however, all observed gastrointestinal adverse events (diarrhea, nausea, constipation, and vomiting) in dulaglutide-treated patients were reported as mild in intensity and well tolerated. The incidences of total, asymptomatic, and nocturnal hypoglycemia were statistically significantly lower with dulaglutide compared with glargine in both subgroups. The incidences of hypoglycemia tended to be lower with dulaglutide than with glargine in all subcategories in both subgroups. Contrary to expectations, in the glargine group, incidences of hypoglycemia were higher in patients with higher baseline HbA1c than in patients with lower baseline HbA1c; this may have been due to larger circadian variation observed in patients with higher baseline HbA1c [23].

The subgroup analyses reported here had some limitations. First, some of these analyses were post hoc, and all were exploratory. Second, this study included a relatively small number of patients with HbA1c >8.5% in both the dulaglutide and glargine treatment groups.

Finally, only patients with HbA1c ≥7.0 and ≤10.0% at screening participated in this clinical study; therefore, the conclusions drawn may not be applicable for patients with HbA1c >10.0%.

In conclusion, in this subgroup analysis of a randomized study of once-weekly dulaglutide 0.75 mg in Japanese patients with T2D, reductions in both HbA1c and body weight observed with dulaglutide were preferable to the changes with glargine regardless of baseline HbA1c (≤8.5% or >8.5%). Although dulaglutide increased gastrointestinal symptoms compared with glargine in both subgroups, it was well tolerated, with lower rates of hypoglycemia. Dulaglutide can be a first injection treatment option for patients with T2D inadequately controlled with OHAs in Japanese patients with T2D.

Declaration of Interest

S.K. has received honoraria for lectures from Novo Nordisk Pharma Ltd.. T.O., A.M., T.S., and M.T. are employees of Eli Lilly Japan K.K, and M.T. has the company stock option.

Funding Source

This study was funded by Eli Lilly K.K. (Kobe, Japan).

Author Contributions

S.K. was a trial investigator and participated in data collection. T.O., A.M., T.S., and M.T. prepared the first draft of the manuscript. T.O. was responsible for statistical considerations. M.T. was responsible for trial design and medical oversight during the trial. All authors participated in reviewing and interpreting the data and providing comments and revisions to the manuscript. All authors participated in the final version of the manuscript and take full responsibility for the content.

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