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Efficacy and safety analyses across 4 subgroups combining low and high age and body mass index groups in Japanese phase 3 studies of dulaglutide 0.75 mg after 26 weeks of treatment

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Abstract. In 855 Japanese patients with type 2 diabetes receiving once weekly dulaglutide 0.75 mg in 3 phase 3 studies, the effects on efficacy and safety at week 26 (last observation carried forward) were investigated in a *post hoc* descriptive analysis of subgroups of age (<65 years [young], ≥65 years [elderly]) and body mass index (BMI [<25 kg/m², ≥25 kg/m²]). The 4 subgroups were as follows: 1) the young/low-BMI subgroup (Y/L) (n = 255); 2) the young/high-BMI subgroup (Y/H) (n = 386), 3) the elderly/low-BMI subgroup (E/L) (n = 137), and 4) the elderly/high-BMI subgroup (E/H) (n = 77). The mean changes from baseline in glycated hemoglobin (HbA1c) and body weight, respectively, were -1.69% and -0.29 kg in the Y/L subgroup; -1.48% and -0.09 kg in the Y/H subgroup; -1.68% and -0.20 kg in the E/L subgroup; and -1.72% and -0.26 kg in the E/H subgroup. The incidences of nausea and hypoglycemia, respectively, were 6.7% and 11.0% in the Y/L subgroup; 7.0% and 8.0% in the Y/H subgroup; 10.2% and 18.2% in the E/L subgroup; and 3.9% and 22.1% in the E/H subgroup. Dulaglutide improved HbA1c regardless of age or BMI; a higher incidence of hypoglycemia was observed in elderly patients compared to younger patients.

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

IN JAPAN, the mean age of patients with diabetes seems to be increasing over time. The prevalence of diabetes has most likely increased primarily as a result of the general aging of the population of Japan [1]. The treatment of diabetes in the elderly is often complicated by the presence of multiple other concomitant conditions [2]. The Japan Diabetes Society (JDS) recommends a careful approach to the treatment of older patients with diabetes to avoid adverse events such as hypoglycemia (induced by sulfonylureas [SU]), lactic acidosis (due to biguanides [BG]), and edema and heart failure (caused by thiazolidinediones), among other issues [3]. Body mass is also of clinical interest in the treatment of patients with type 2 diabetes (T2D) since drug concentrations tend to be increased in patients with lower body mass. In addition, age and

body mass index (BMI) are always collected during treatment of patients with T2D, and these factors when combined allow clinicians a convenient way to obtain clear patient profiles and predict treatment outcomes.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, which are incretin-based therapies for T2D, are well-tolerated overall and have a low risk of hypoglycemia [4-5]. Thus, they have become important treatment options for patients in Japan, including the elderly, often as first-line therapy [6-8]. Glucagon-like peptide-1 (GLP-1) receptor agonists are also incretin-based and have similar safety and better efficacy profiles in patients with T2D compared to DPP-4 inhibitors [4-5]. However, they are not yet used as frequently in Japan. One of the reasons for this has been that GLP-1 receptor agonist therapy required daily injections, but with

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Abbreviations: BG, biguanide; BMI, body mass index; E, elderly; FSG, fasting serum glucose; GLP-1, glucagon-like peptide-1; H, high BMI; HbA1c, glycated hemoglobin; L, low BMI; SD, standard deviation; SE, standard error; SMBG, self-monitored blood glucose; SU, sulfonylurea; T2D, type 2 diabetes; Y, young

the recent approvals of medications such as exenatide once weekly and dulaglutide, which require only once weekly injection, it is expected that their use will increase. Dulaglutide is a once weekly GLP-1 receptor agonist [9] approved in Japan at a dose of 0.75 mg (hereafter “dulaglutide”) [10]. In phase 3 studies in Japanese patients with T2D, after 26 weeks of treatment dulaglutide has shown non-inferiority to liraglutide in changes in glycated hemoglobin (HbA1c) [11] as well as superiority to insulin glargine in changes in HbA1c along with a lower incidence of hypoglycemia [12]. In the third phase 3 study in Japan, dulaglutide in combination with a single oral hypoglycemic agent from among 5 classes was overall safe and effective through 52 weeks of treatment [13]. The most frequent adverse events during the 3 phase 3 studies were gastrointestinal events such as nausea, constipation, and diarrhea, but most of the adverse events were mild to moderate in intensity.

In this *post hoc* subgroup analysis, we analyzed efficacy and safety of dulaglutide across 4 subgroups: 1) young (nonelderly) patients with lower BMI; 2) young (nonelderly) patients with higher BMI; 3) elderly patients with lower BMI, and 4) elderly patients with higher BMI.

Materials and Methods

Study design and patient population

This analysis combines data from dulaglutide-treated patients in the 3 phase 3 studies of dulaglutide in Japanese patients with T2D: 1) “the monotherapy study” [11, 14], a randomized, double-blind and open-label 52-week study which had the primary endpoint at 26 weeks; 2) “the combination study” [12], a randomized, open-label 26-week study; and 3) “the safety study” [13], a nonrandomized and open-label 52-week study.

For each of the studies a common protocol was approved at each site by an institutional review board, and the studies were performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participation. All 3 studies were registered with ClinicalTrials.gov (NCT01558271, NCT01584232, and NCT01468181).

Analysis methods

For this exploratory analysis, patients were classified into 4 subgroups based on age (<65 years [young],

≥65 years [elderly]) and BMI (<25 kg/m² [low], ≥25 kg/m² [high]): 1) the “young/low BMI” (Y/L) subgroup, age <65 years and BMI <25 kg/m²; 2) the “young/high BMI” (Y/H) subgroup, age <65 years and BMI ≥25 kg/m²; 3) the “elderly/low BMI” (E/L) subgroup, age ≥65 years and BMI <25 kg/m²; and 4) the “elderly/high BMI” (E/H) subgroup, age ≥65 years and BMI ≥25 kg/m².

Efficacy (changes from baseline in HbA1c, fasting serum glucose [FSG] from the central laboratory, and body weight; and 7-point self-monitored blood glucose [SMBG] profiles) and safety outcomes (incidences of adverse events [in particular gastrointestinal effects such as nausea] and hypoglycemia [defined as a blood glucose concentration of ≤70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia], and changes from baseline in blood pressure and pulse rate) were summarized descriptively by subgroup through 26 weeks of treatment.

For continuous variables, missing data at week 26 were imputed with an available last observation carried forward (LOCF) value if necessary. Comparisons between the 4 subgroups were performed with an analysis of covariance with the baseline value as a covariate. For categorical (incidence) variables, 2-sided *p*-values were computed by Chi-square test if at least 80% of cells had an expected value ≥5 (otherwise by Fisher’s exact test) to test the independence of the incidence and the subgroup categories.

Results

Patient characteristics

A total of 855 Japanese patients with T2D who received dulaglutide in the 3 studies were included in this analysis (Table 1). The majority (76%) were male. Mean age and duration of diabetes were 57.3 and 7.6 years, respectively. While some baseline characteristics varied across the 4 subgroups, glycemic control was similar (mean HbA1c was 8.3% in all 4 subgroups, and mean FSG ranged from 162 to 170 mg/dL). Approximately 29% of patients overall were receiving SU (range 26% to 36% across the 4 subgroups, higher among elderly patients compared to younger patients), and approximately 24% of patients were receiving BG (range 15% to 29% across the 4 subgroups). Overall, approximately 8% of patients were receiving alpha-glucosidase inhibitors (AGI).

Table 1 Demographic and baseline characteristics overall and by 4 subgroups of low and high age and BMI

	Y/L age <65 years BMI <25 kg/m ² (n=255)	Y/H age <65 years BMI ≥25 kg/m ² (n=386)	E/L age ≥65 years BMI <25 kg/m ² (n=137)	E/H age ≥65 years BMI ≥25 kg/m ² (n=77)	All patients (N=855)
Sex, n (%)					
Males	197 (77)	300 (78)	102 (74)	50 (65)	649 (76)
Females	58 (23)	86 (22)	35 (26)	27 (35)	206 (24)
Age, years	55.7 ± 7.2	51.4 ± 8.4	70.3 ± 3.8	69.5 ± 3.9	57.3 ± 10.4
Diabetes duration, years	7.8 ± 6.1	6.0 ± 5.1	11.6 ± 7.7	8.6 ± 5.3	7.6 ± 6.2
Weight, kg	63.5 ± 7.8	80.8 ± 10.8	58.8 ± 7.2	71.6 ± 9.5	71.3 ± 13.1
BMI, kg/m ²	22.9 ± 1.6	28.7 ± 2.7	22.5 ± 1.7	27.6 ± 2.3	25.9 ± 3.6
HbA1c					
%	8.3 ± 1.0	8.3 ± 0.9	8.3 ± 1.0	8.3 ± 1.0	8.3 ± 1.0
mmol/mol	67 ± 10.9	67 ± 9.8	67 ± 10.9	67 ± 10.9	67 ± 10.9
FSG					
mg/dL	170 ± 37	169 ± 41	169 ± 35	162 ± 37	169 ± 39
mmol/L	9.4 ± 2.1	9.4 ± 2.3	9.4 ± 1.9	9.0 ± 2.1	9.4 ± 2.2
Therapy, n (%)					
Monotherapy	84 (33)	128 (33)	46 (34)	22 (29)	280 (33)
Comb with SU ^a	71 (28)	100 (26)	50 (36)	27 (35)	248 (29)
Comb with BG ^b	57 (22)	113 (29)	21 (15)	17 (22)	208 (24)

Data are mean±SD, unless indicated. Y, young; E, elderly; L, low BMI; H, high BMI; SU, sulfonylurea; BG, biguanide; Comb, combination; BMI, body mass index; FSG, fasting serum glucose; HbA1c, glycated hemoglobin; n/N, number of patients; SD, standard deviation. ^a Includes patients taking SU with or without BG. ^b Includes patients taking BG with or without SU.

Efficacy

Clinically meaningful reductions from baseline in HbA1c and FSG were observed in all 4 subgroups after 26 weeks of treatment (LOCF), and there were statistically significant differences among the 4 subgroups for both measures ($p \leq 0.009$, both; Fig. 1). Mean reductions from baseline in HbA1c and FSG were smallest in the Y/H subgroup: mean±standard deviation (SD) changes in HbA1c ranged from $-1.48 \pm 0.91\%$ (Y/H subgroup) to $-1.72 \pm 0.93\%$ (E/H subgroup), and mean±SD changes in FSG ranged from -37.6 ± 40.0 mg/dL (Y/H subgroup) to -44.0 ± 34.1 mg/dL (Y/L subgroup). Mean±SD changes from baseline in body weight ranged from -0.09 ± 2.67 kg (Y/H subgroup) to -0.29 ± 2.43 kg (Y/L subgroup) (Fig. 1); the changes from baseline were not statistically significantly different across the 4 subgroups. Mean 7-point SMBG profiles were similar across the 4 subgroups at baseline and at week 26 (LOCF) (Fig. 2).

Safety

The overall profile of treatment-emergent adverse events through 26 weeks was similar across the 4 subgroups (Table 2). After 26 weeks of treatment, the E/L subgroup had the highest percentage of patients who experienced at least 1 treatment-emergent adverse event (73.0%); percentages in the other 3 subgroups

ranged from 63.1% (Y/L subgroup) to 65.0% (Y/H subgroup). The difference in overall incidence of treatment-emergent adverse events across the subgroups largely paralleled the differences in the incidence of nasopharyngitis (range 11.7% [E/H subgroup] to 19.7% [E/L subgroup]), which was the most frequently occurring treatment-emergent adverse event overall. Of the 7 most frequently reported treatment-emergent adverse events (those occurring in more than 2.5% of dulaglutide-treated patients), 5 of them occurred most frequently in the E/L subgroup. Nausea occurred in 7.1% of patients overall, with no particular pattern of incidence across the 4 subgroups: 6.7% and 7.0% in the Y/L and Y/H subgroups, respectively, and 10.2% and 3.9% in the E/L and E/H subgroups, respectively. There were statistically significant differences in the incidence of constipation (overall incidence 7.8%) and decreased appetite (overall incidence 2.9%) across the 4 subgroups ($p \leq 0.019$, both): the incidence of both was highest in the E/L subgroup (13.9% and 7.3%, respectively; Table 2).

Among all patients, there were statistically significant differences in incidences of both total and nocturnal hypoglycemia through week 26 (LOCF) between the 4 subgroups ($p \leq 0.009$, both), with higher incidence of both among elderly patients compared to younger patients (Table 3). The incidences of total and

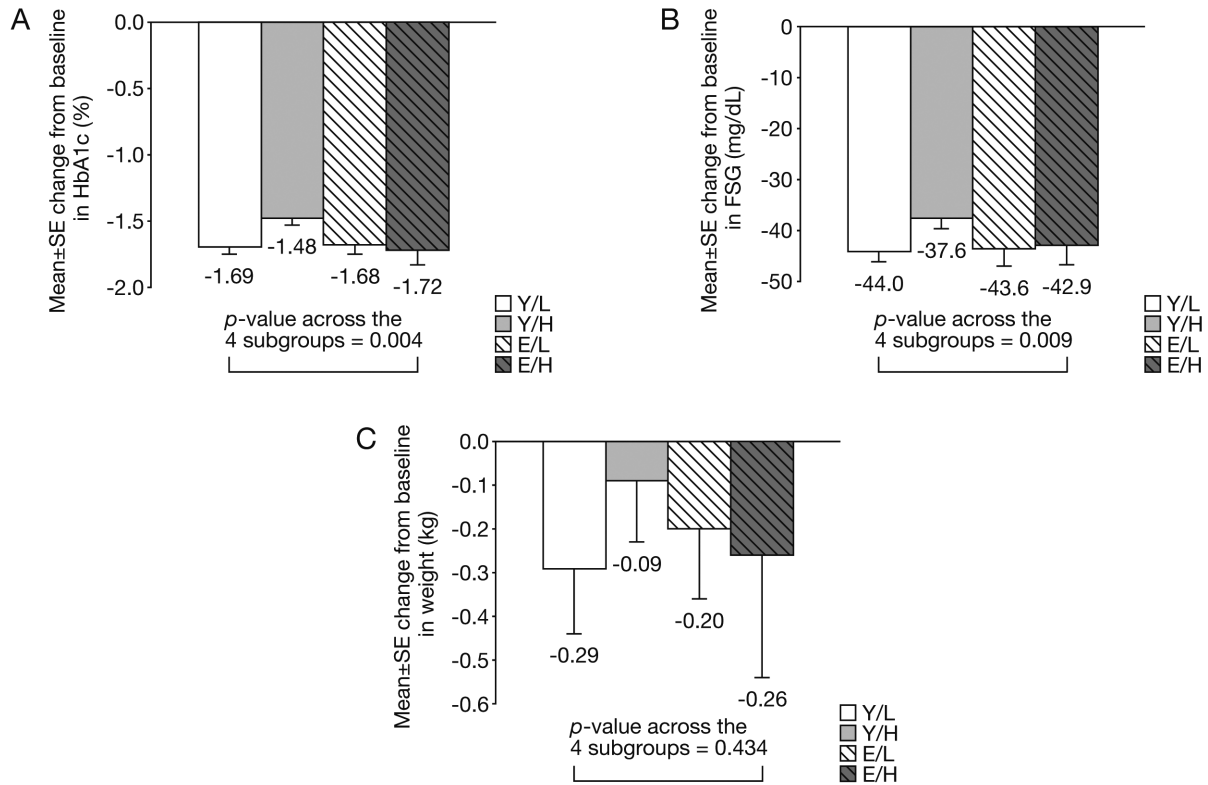


Fig. 1 Mean \pm SE changes from baseline to week 26 (LOCF) in efficacy outcomes by 4 subgroups of low and high age and BMI

A, HbA1c (%). **B**, FSG (mg/dL). **C**, Body weight (kg). p -values based on analysis of covariance with the baseline value as a covariate. Y, young; E, elderly; L, low BMI; H, high BMI; BMI, body mass index; FSG, fasting serum glucose; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; n, number of patients; SE, standard error. Y/L: age <65 years, BMI <25 kg/m² (n=255); Y/H: age <65 years, BMI \geq 25 kg/m² (n=386); E/L: age \geq 65 years, BMI <25 kg/m² (n=137); E/H: age \geq 65 years; BMI \geq 25 kg/m² (n=77).

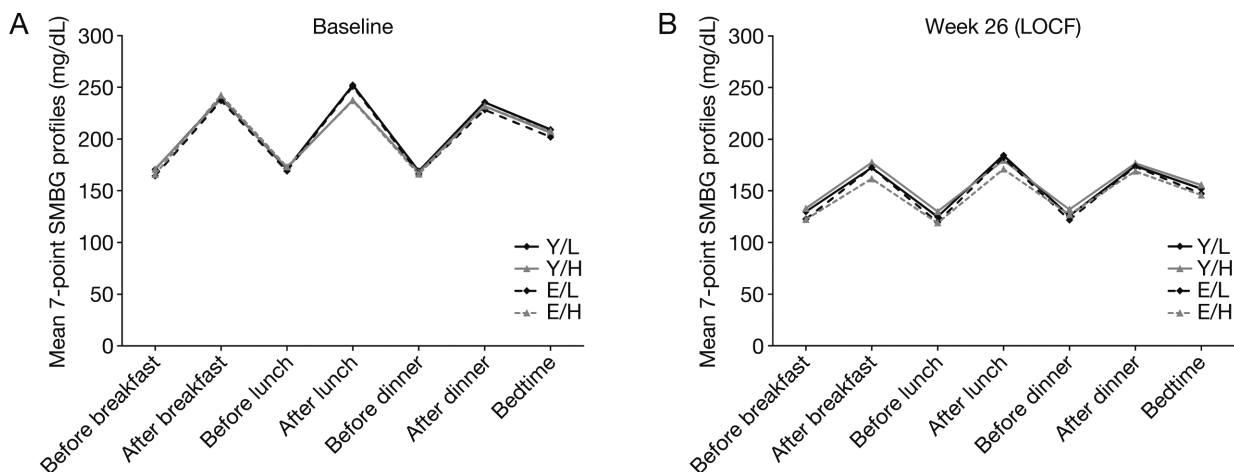


Fig. 2 Mean 7-point SMBG profiles (mg/dL) at baseline and week 26 (LOCF) by 4 subgroups of low and high age and BMI

A, At baseline. **B**, At week 26 (LOCF). Y, young; E, elderly; L, low BMI; H, high BMI; BMI, body mass index; LOCF, last observation carried forward; n, number of patients; SMBG, self-monitored blood glucose. Y/L: age <65 years, BMI <25 kg/m² (n=255); Y/H: age <65 years, BMI \geq 25 kg/m² (n=386); E/L: age \geq 65 years, BMI <25 kg/m² (n=137); E/H: age \geq 65 years; BMI \geq 25 kg/m² (n=77).

nocturnal hypoglycemia across the 4 subgroups were also compared among patients receiving SU and those not receiving SU. Overall, incidences of hypoglycemia were higher in patients receiving SU, but there were no statistically significant differences among the 4 subgroups except for the incidence of total hypoglycemia in patients not receiving SU ($p = 0.004$).

The changes from baseline in seated pulse rate and systolic blood pressure at week 26 (LOCF) were not clinically meaningful, and the comparisons across the subgroups were not statistically significant (Table 4). The comparison of changes in seated diastolic blood pressure across the 4 subgroups was statistically significant ($p = 0.013$), but the changes were not clinically meaningful.

Table 2 Treatment-emergent adverse events through 26 weeks overall and by 4 subgroups of low and high age and BMI

	Y/L age <65 years BMI <25 kg/m ² (n=255)	Y/H age <65 years BMI ≥25 kg/m ² (n=386)	E/L age ≥65 years BMI <25 kg/m ² (n=137)	E/H age ≥65 years BMI ≥25 kg/m ² (n=77)	All patients (N=855)	<i>p</i> -value
Patients with ≥1TEAE	63.1	65.0	73.0	64.9	65.7	0.253
TEAEs occurring in >2.5% of dulaglutide-treated patients overall						
Nasopharyngitis	14.5	17.9	19.7	11.7	16.6	0.314
Gastrointestinal disorders						
Diarrhea	7.5	9.3	7.3	6.5	8.2	0.732
Nausea	6.7	7.0	10.2	3.9	7.1	0.350
Constipation	6.7	6.0	13.9	10.4	7.8	0.019
Vomiting	3.9	2.3	5.8	1.3	3.3	0.176
Lipase increased	4.7	5.7	5.1	3.9	5.1	0.899
Decreased appetite	2.4	1.6	7.3	3.9	2.9	0.009

Data are percentages of patients. MedDRA version 16.1. *p*-values computed by Chi-square test if at least 80% of cells had an expected value ≥5, otherwise by Fisher's exact test. Y, young; E, elderly; L, low BMI; H, high BMI; BMI, body mass index; MedDRA, Medical Dictionary for Regulatory Activities; n/N, number of patients; TEAE, treatment-emergent adverse event.

Table 3 Incidence of hypoglycemia through 26 weeks overall and by 4 subgroups of low and high age and BMI

	Y/L age <65 years BMI <25 kg/m ² n=255	Y/H age <65 years BMI ≥25 kg/m ² n=386	E/L age ≥65 years BMI <25 kg/m ² n=137	E/H age ≥65 years BMI ≥25 kg/m ² n=77	All patients N=855	<i>p</i> -value
All patients	n=255	n=386	n=137	n=77	N=855	
Total	11.0	8.0	18.2	22.1	11.8	<0.001
Nocturnal	2.0	1.8	6.6	6.5	3.0	0.009
Patients receiving SU	n=71	n=100	n=50	n=27	N=248	
Total	28.2	25.0	42.0	37.0	30.6	0.154
Nocturnal	5.6	6.0	18.0	11.1	8.9	0.071
Patients not receiving SU	n=184	n=286	n=87	n=50	N=607	
Total	4.3	2.1	4.6	14.0	4.1	0.004
Nocturnal	0.5	0.3	0.0	4.0	0.7	0.090

Data are percentages of patients. *p*-values computed by Chi-square test if at least 80% of cells had an expected value ≥5, otherwise by Fisher's exact test. Y, young; E, elderly; L, low BMI; H, high BMI; BMI, body mass index; n/N, number of patients; SU, sulfonylurea.

Table 4 Mean±SD changes from baseline in seated blood pressure and pulse rate at week 26 (LOCF) overall and by 4 subgroups of low and high age and BMI

	Y/L age <65 years BMI <25 kg/m ² (n=255)	Y/H age <65 years BMI ≥25 kg/m ² (n=386)	E/L age ≥65 years BMI <25 kg/m ² (n=137)	E/H age ≥65 years BMI ≥25 kg/m ² (n=77)	All patients (N=855)	<i>p</i> -value
Systolic BP (mmHg)	-0.5 ± 11.1	-0.5 ± 11.3	-1.4 ± 13.8	0.1 ± 14.2	-0.6 ± 11.9	0.238
Diastolic BP (mmHg)	0.7 ± 7.5	-0.0 ± 7.6	0.3 ± 7.2	-0.0 ± 7.3	0.3 ± 7.5	0.013
Pulse rate (bpm)	2.9 ± 8.0	3.0 ± 7.2	3.5 ± 8.0	2.0 ± 8.2	2.9 ± 7.6	0.073

p-values based on analysis of covariance with baseline value as covariate. Y, young; E, elderly; L, low BMI; H, high BMI; BMI, body mass index; BP, blood pressure; bpm, beats per minute; n/N, number of patients; LOCF, last observation carried forward; SD, standard deviation.

Discussion

In this subgroup analysis, efficacy and safety were analyzed using pooled data from 3 phase 3 studies of dulaglutide in Japanese patients with T2D. Subgroup analyses using the same data stratified by several patient characteristics (gender, age, duration of diabetes, body weight, BMI, baseline HbA1c, use of concomitant SU, and use of concomitant BG) were previously reported [15]. In the previous analysis, baseline HbA1c was confirmed as the most influential factor affecting HbA1c and weight (patients with higher baseline HbA1c had more favorable outcomes with respect to HbA1c and less favorable outcomes with respect to weight compared to patients with lower baseline HbA1c), and concomitant SU increased incidences of nausea and hypoglycemia [15]. However, clinicians expect to use demographic factors other than baseline HbA1c to predict efficacy and safety results of new therapies. Therefore, to gain further insight from these data, for this analysis we selected 2 patient characteristics which are always collected during treatment of patients with T2D: age (<65 [young] or ≥65 years [elderly]) and BMI (<25 [low] or ≥25 kg/m² [high]). These characteristics have previously been used for subgroup analyses of patients treated with liraglutide, exenatide twice daily, exenatide once weekly, and lixisenatide [16-19].

Overall in this *post hoc* analysis, treatment with dulaglutide resulted in clinically meaningful improvements in efficacy parameters across the 4 age/BMI subgroups. At week 26 (LOCF), mean HbA1c reductions ranged from -1.48% to -1.72% and mean FSG reductions ranged from -37.6 mg/dL to -44.0 mg/dL. These results were consistent with results of a subgroup analysis of 6 global studies of dulaglutide, in which the efficacy of dulaglutide was similar for elderly and younger patients [20]. In our analysis, weight reductions after 26 weeks in all 4 subgroups were small (mean changes ranged from -0.09 kg to -0.29 kg). Previous studies of dulaglutide in Japan have shown weight gain from baseline with dulaglutide in combination with thiazolidinediones, no change in weight with dulaglutide monotherapy or with dulaglutide in combination with SU or glinides, and weight loss with dulaglutide in combination with BG or AGI [11, 13, 14, 21]. Mean weight reduction was likely small in this population because only 24% of patients were receiving BG and 8% were receiving AGI.

It has been reported that hypoglycemia is a frequently observed adverse event in older patients with T2D [22]. Concomitant use of SU is also a known risk factor for hypoglycemia. In our analysis, incidence of total hypoglycemia among elderly patients (18.2% to 22.1%) was approximately 2 times higher than among younger patients (8.0% to 11.0%), and use of SU was higher among elderly patients (36%) than among younger patients (27%). The incidence of total hypoglycemia across the 4 subgroups for patients using SU in this analysis ranged from 25.0% to 42.0%, compared to 2.1% to 14.0% for patients not using SU; the results were similar for nocturnal hypoglycemia. The JDS Committee for proper use of incretin drugs (GLP-1 receptor agonists and DPP-4 inhibitors) recommends reducing concomitant SU doses when treatment with incretin drugs such as DPP-4 inhibitors or GLP-1 receptor agonists is begun [23].

Overall in this analysis, dulaglutide was well tolerated in all 4 age/BMI subgroups, and the incidences of adverse events were generally low: only nasopharyngitis, which is often observed in clinical studies, occurred in >10% of patients. Besides nasopharyngitis, the most frequently observed adverse events were gastrointestinal events such as diarrhea, nausea, and constipation. In elderly patients, including those with autonomic neuropathy, constipation is a frequently reported bowel symptom [24]. In our analysis, the incidence of constipation was relatively higher in elderly patients (10.4% to 13.9%) compared with younger patients (6.0% to 6.7%), but no elderly patients experienced severe constipation resulting in study discontinuation.

The subgroup analyses of the studies reported here had some potential limitations. First, these were *post hoc*, exploratory analyses using data integrated from studies with different designs (*i.e.*, randomized and non-randomized, double-blind and open-label). Second, the types of patients included were limited to some extent, as exemplified by the small numbers of females and the exclusion of patients with clinically significant medical conditions such as renal and hepatic disorders or frailty. Third, other potential confounding factors (*e.g.*, concomitant anti-diabetic medications) may have affected the results.

In conclusion, in this analysis of 3 phase 3 studies of dulaglutide in Japanese patients with T2D, dulaglutide improved blood glucose control as measured by HbA1c and FSG after 26 weeks of treatment regardless of age or BMI. For elderly patients with T2D, once

weekly dulaglutide, which comes in an easy-to-inject device and has a low incidence of hypoglycemia, may be a beneficial treatment option.

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final version of the manuscript and take full responsibility for the content.

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