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ORIGINAL

Analysis of efficacy and safety of dulaglutide 0.75 mg stratified by sex in patients with type 2 diabetes in 2 randomized, controlled phase 3 studies in Japan

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Abstract. We analyzed the efficacy and safety of once weekly dulaglutide 0.75 mg by sex in 2 randomized, controlled phase 3 studies in Japanese patients with type 2 diabetes (a 52-week monotherapy study [comparator liraglutide 0.9 mg] and a 26-week combination therapy study [comparator insulin glargine]). Females comprised 18% of patients in the monotherapy study and 29% of patients in the combination therapy study. Mean reductions from baseline in glycated hemoglobin (HbA1c) were similar between the sexes for dulaglutide- and liraglutide-treated patients (range -1.17% to -1.49%). Females had numerically greater weight loss or less weight gain than males across all treatment groups. The percentages of patients with reductions in both HbA1c and weight from baseline were also greater for females than for males in all treatment groups. In all treatment groups, the incidences of treatment-emergent adverse events tended to be greater among females than among males. No differences in the incidences of total or nocturnal hypoglycemia were observed between the sexes in any treatment group. Overall, in 2 studies in Japan, across all treatment groups it appeared that HbA1c lowering was unaffected by patient sex, while female patients had greater weight loss or less weight gain and greater incidence of adverse events, including nausea, compared to male patients. Incidences of patients discontinuing dulaglutide early due to adverse event were low (<10%) for both sexes, and no new safety concerns related to dulaglutide were identified for either sex. Therefore, the benefit/risk ratio for dulaglutide remains unchanged, positive for both sexes.

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

IT HAS BEEN REPORTED that there are meaningful differences between the sexes in disease course and treatment outcomes for patients with type 2 diabetes (T2D) [1, 2]. For instance, females with normal glucose tolerance have been found to have better β-cell function and to be more insulin-sensitive than males [1]. Further, efficacy and adverse events vary between the sexes for some glucose-lowering treatments [1, 2].

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone; its known functions include induction of increased insulin secretion and inhibition of gastric emptying. Administration of GLP-1 tends to result in satiation and may decrease food intake in people with and without diabetes.

Differences between the sexes have been evaluated previously in studies of some GLP-1 receptor agonist therapies in patients with T2D. In subgroup analyses using data from clinical trials of exenatide twice daily (BID) and exenatide once weekly (QW), similar changes from baseline in glycated hemoglobin (HbA1c) were observed in both males and females, and greater weight loss was observed in females compared to males [3, 4]. In another study, females treated with exenatide BID and metformin experienced greater reductions in HbA1c and weight compared to males [5]. Studies of liraglutide and albiglutide have found no meaningful differences between the sexes in glycemic control or weight changes [6, 7].

Dulaglutide is a once weekly GLP-1 receptor agonist approved in Japan at a dose of 0.75 mg. After 26

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Abbreviations: BID, twice daily; BMI, body mass index; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; T2D, type 2 diabetes; QW, once weekly

weeks of treatment in 2 randomized, controlled phase 3 studies in Japanese patients with T2D, dulaglutide 0.75 mg was shown to be noninferior to liraglutide 0.9 mg [8] for changes in HbA1c and superior to insulin glargine [9] for changes in HbA1c, with a lower incidence of hypoglycemia. In the third phase 3 study (nonrandomized, noncontrolled) in Japanese patients, dulaglutide 0.75 was overall safe and effective over 52 weeks of treatment when used in combination with a single oral hypoglycemic agent from among 5 classes (sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinedione, or glinides) [10].

In a subgroup analysis of 855 Japanese patients with T2D treated with dulaglutide 0.75 mg for up to 26 weeks in the 3 phase 3 studies, similar changes in HbA1c were observed in males and females; females had significantly greater weight loss and a significantly higher incidence of nausea than males [11]. In order to further evaluate the clinical responses in Japanese patients with T2D based on sex, we compared the efficacy and safety of dulaglutide 0.75 mg and 2 comparator drugs, another GLP-1 receptor agonist (liraglutide) and insulin glargine, between males and females using data from 2 randomized, controlled phase 3 studies.

Materials and Methods

Study design and patient population

We evaluated data from the 2 randomized, controlled phase 3 studies of once weekly dulaglutide 0.75 mg in Japanese patients with T2D: 1) "the monotherapy study" [8, 12], which was a 52-week study that had the primary endpoint at 26 weeks, and 2) "the combination study" [9], which was a 26-week study. The monotherapy study randomized patients to dulaglutide, liraglutide 0.9 mg, or placebo; after 26 weeks of treatment, patients treated with placebo were switched to dulaglutide. Only patients randomized to dulaglutide or liraglutide in the monotherapy study were included in this analysis. Study design and key patient inclusion criteria are presented in Table 1.

The protocols for both studies were approved at the study sites by an institutional review board. The studies were performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and all patients provided written informed consent. Both studies were registered with ClinicalTrials.gov (NCT01558271, NCT01584232).

Analysis methods

To evaluate changes in HbA1c and body weight by sex, subgroup analyses were conducted using the mixed model for repeated measures used for the primary efficacy analyses in the studies [8, 9], with a term for sex and terms for treatment-by-sex, visit-by-sex, and treatment-by-sex-by-visit interactions added. Least-squares mean changes for HbA1c and body weight by treatment and sex were estimated. To further explore the relationship between changes in HbA1c and body weight, changes from baseline in HbA1c and body weight at endpoint for individual patients were presented on scatter plots, and Pearson correlations between the changes

Table 1 Study designs

Study and treatment duration	Primary objective	Study design and patient population	Study drug(s) and number of patients treated
Monotherapy study Treatment duration: 52 weeks (primary endpoint after 26 weeks)	To show superiority of DU 0.75 mg *vs* placebo as measured by HbA1c change from baseline at 26 weeks.	Phase 3, multicenter, randomized, placebo- and active-controlled, parallel-group study in Japanese patients with T2D suboptimally controlled with HbA1c at randomization ≥7.0% (53 mmol/mol) to ≤10.0% (86 mmol/mol).	• DU 0.75 mg SC once weekly (double-blind) (n=280) • LIRA 0.9 mg SC once daily (open-label) (n=137) • Placebo SC once weekly (double-blind) (n=70) After 26 weeks, patients randomized to placebo received DU 0.75 mg.
Combination study Treatment duration: 26 weeks	To show non-inferiority of DU 0.75 mg to insulin glargine for HbA1c change from baseline at 26 weeks.	Phase 3, multicenter, randomized, active-controlled, parallel-group, open-label study in Japanese patients with T2D suboptimally controlled with HbA1c at screening ≥7.0% (53 mmol/mol) to ≤10.0% (86 mmol/mol).	• DU 0.75 mg SC once weekly (n=181) • Insulin glargine SC: once daily (n=180) Patients added assigned therapy to existing OHA therapy (SU, BG, or SU+BG together).

BG, biguanide; DU 0.7 mg, dulaglutide 0.75 mg; HbA1c, glycated hemoglobin; LIRA 0.9 mg, liraglutide 0.9 mg; OHA, oral hypoglycemic agent; SC, subcutaneous; SU, sulfonylurea; T2D, type 2 diabetes.

were computed by treatment and sex. For the categorical (incidence) variables, proportions were calculated by treatment and sex.

The analyses of changes in HbA1c and weight and of incidence of adverse events by sex were prespecified for both studies. The analyses of proportions of patients with reductions from baseline in HbA1c and weight and of incidence of hypoglycemia by sex were *post hoc*.

An additional *post hoc* analysis was conducted using data from the monotherapy study to evaluate the relationship between incidence of gastrointestinal events (diarrhea, constipation, nausea, vomiting) and weight changes for patients treated with dulaglutide or liraglutide. Because it appears that concomitant treatments have an effect on weight changes in dulaglutide-treated patients in Japan [13], this analysis was not conducted for the combination study.

Results

Patient characteristics

A total of 778 patients were included in the analyses: 417 from the monotherapy study and 361 from the combination study. Table 2 presents baseline characteristics by treatment and sex for each study separately. The proportion of female patients was smaller than the proportion of male patients in all treatment groups in both studies; overall, 179/778 patients (23%) were female. Patient characteristics at baseline, including HbA1c and body mass index (BMI), were generally similar across the treatments and sexes in both studies, except for body weight: mean body weight at baseline was smaller for females (range 60.1 kg to 63.5 kg) than for males (range 72.3 kg to 75.4 kg) in all treatment groups in both studies.

Efficacy

Table 3 presents least-squares mean changes from baseline in HbA1c and body weight by treatment and sex for each study separately (at week 52 for the monotherapy study; at week 26 for the combination study). Similar reductions in HbA1c were observed for males and females in the dulaglutide and liraglutide groups (range -1.17% to -1.49%); insulin glargine-treated males and females had mean changes of -0.98% and -0.69%, respectively. Females had numerically greater weight loss or less weight gain than males across all treatment groups in both studies. Dulaglutide-treated females had the greatest mean weight loss across the treatments and sexes (reductions of 1.32 and 1.13 kg in the monotherapy and combination studies, respectively). Dulaglutide-treated males in the combination study had mean weight loss of 0.21 kg, and dulaglutide-treated males in the monotherapy study had mean weight gain of 0.09 kg. Liraglutide-treated females and males had mean weight loss of 0.51 and 0.03 kg, respectively. Insulin glargine-treated females and males had mean weight gain of 0.53 and 1.07 kg, respectively.

Table 2 Demographic characteristics by study, treatment, and sex

	Monotherapy study				Combination study			
	DU 0.75 mg (N=280)		LIRA 0.9 mg (N=137)		DU 0.75 mg (N=181)		GL (N=180)	
	Female (n=52)	Male (n=228)	Female (n=24)	Male (n=113)	Female (n=56)	Male (n=125)	Female (n=47)	Male (n=133)
Age, years	56.2	57.4	58.7	57.7	60.7	56.1	58.1	55.5
Duration of T2D, years	5.9	7.0	6.1	6.4	9.5	8.7	10.0	8.3
Body weight, kg	63.5	73.1	60.1	72.3	60.9	75.4	62.8	74.0
BMI, kg/m^2	26.0	25.5	25.5	25.5	25.6	26.3	26.0	25.8
HbA1c, %	8.03	8.18	8.09	8.08	8.01	8.08	7.82	8.05
FSG, mg/dL	160	171	160	163	157	160	149	158
Combination therapy, n (%)								
BG only	N/A	N/A	N/A	N/A	21 (38)	43 (34)	18 (38)	48 (36)
SU only	N/A	N/A	N/A	N/A	13 (23)	21 (17)	4 (9)	29 (22)
SU and BG	N/A	N/A	N/A	N/A	22 (39)	61 (49)	25 (53)	56 (42)

Data presented are means except where noted. BG, biguanide; BMI, body mass index; DU 0.75 mg, dulaglutide 0.75 mg once weekly; FSG, fasting serum glucose; GL, insulin glargine; HbA1c, glycated hemoglobin; LIRA 0.9 mg, liraglutide 0.9 mg once daily; n, number of patients; N, number of patients randomized and treated; N/A, not applicable; SU, sulfonylurea; T2D, type 2 diabetes.

Table 3 Analysis of changes from baseline in HbA1c (%) and body weight (kg) by study, treatment, and sex

	Monotherapy study (52 weeks)				Combination study (26 weeks)			
	DU 0.75 mg (N=280)		LIRA 0.9 mg (N=137)		DU 0.75 mg (N=181)		GL (N=180)	
	Female (n=52)	Male (n=228)	Female (n=24)	Male (n=113)	Female (n=56)	Male (n=125)	Female (n=47)	Male (n=133)
HbA1c changes [§], %	-1.49	-1.37	-1.36	-1.17	-1.46	-1.43	-0.69	-0.98
Body weight changes [+], kg	-1.32	0.09	-0.51	-0.03	-1.13	-0.21	0.53	1.07

Data presented are least-squares means. BG, biguanide; BMI, body mass index; DU 0.75 mg, dulaglutide 0.75 mg once weekly; GL, insulin glargine; HbA1c, glycated hemoglobin A1c; LIRA 0.9 mg, liraglutide 0.9 mg once daily; n, number of patients; N, number of patients randomized and treated; OHA, oral hypoglycemic agent; SU, sulfonylurea. [§] For monotherapy study: Mixed model for repeated measures: change from baseline = baseline HbA1c + treatment + pre-study OHA (yes/no) + baseline BMI group (<25 / ≥25 kg/m^2) + visit + treatment×visit + sex + treatment×sex + visit×sex + treatment×visit×sex; for combination study: Mixed model for repeated measures: change from baseline = baseline HbA1c + treatment + OHA regimen (SU only, BG only, or SU and BG) + baseline BMI group (<25 / ≥25 kg/m^2) + visit + treatment×visit + sex + treatment×sex + visit×sex + treatment×visit×sex. [+] For monotherapy study: Mixed model for repeated measures: change from baseline = baseline weight + treatment + pre-study OHA (yes/no) + baseline BMI group (<25 / ≥25 kg/m^2) + visit + treatment×visit + sex + treatment×sex + visit×sex + treatment×visit×sex; for combination study: Mixed model for repeated measures: change from baseline = baseline weight + treatment + OHA regimen (SU only, BG only, or SU and BG) + baseline BMI group (<25 / ≥25 kg/m^2) + visit + treatment×visit + sex + treatment×sex + visit×sex + treatment×visit×sex.

Fig. 1 and Fig. 2 present scatterplots of changes from baseline in HbA1c (%) and body weight (kg) for individual patients by treatment and sex for the monotherapy study and the combination study, respectively. In both studies, greater proportions of females than males experienced reductions from baseline in both HbA1c and weight across all treatment groups: 55.8% to 58.3% of females and 45.2% to 46.4% of males in the monotherapy study after 52 weeks, and 38.3% to 68.5% of females and 26.5% to 54.0% of males in the combination study after 26 weeks.

Safety

Table 4 presents the incidence of treatment-emergent adverse events (overall and those occurring in ≥5% of patients in any treatment group in either study) by treatment and sex for each study separately. In both studies, greater proportions of females compared to males in the dulaglutide (86.5% *vs*. 61.4% in the monotherapy study and 80.4% *vs*. 72.8% in the combination study), liraglutide (83.3% *vs*. 65.5%), and insulin glargine (72.3% *vs*. 57.9%) treatment groups experienced treatment-emergent adverse events. Gastrointestinal adverse events such as nausea, constipation, and diarrhea also generally occurred more frequently among females than among males in all treatment groups. Incidence of early discontinuation of study drug due to adverse events was low (<10%) in both studies regardless of sex or treatment. Through 52 weeks of treatment in the monotherapy study, similar percentages of patients in both the dulaglutide and liraglutide groups experienced at least 1 of the 4 key gastrointestinal adverse events (18% and 17% of patients, respectively) (Table 5). In both groups, these patients experienced greater mean weight loss than patients who did not experience any of the events.

There were no differences in the incidences of total or nocturnal hypoglycemia between the sexes in any treatment group in either study (Table 4).

Discussion

This analysis was a *post hoc* evaluation of differences between the sexes in Japanese patients with T2D treated with dulaglutide 0.75 mg, liraglutide 0.9 mg, or insulin glargine for up to 52 weeks in 2 randomized, controlled studies.

Reductions from baseline in HbA1c in dulaglutide- and liraglutide-treated patients were clinically meaningful and similar for both sexes. These findings (similar improvements in HbA1c for both sexes) were consistent with results observed in studies of exenatide BID and QW [3, 4].

Females had numerically greater weight loss or less weight gain than males across all treatment groups. In a retrospective study in Ireland, it was observed that females with T2D receiving glucose-lowering therapy were more successful in losing weight than males [14],

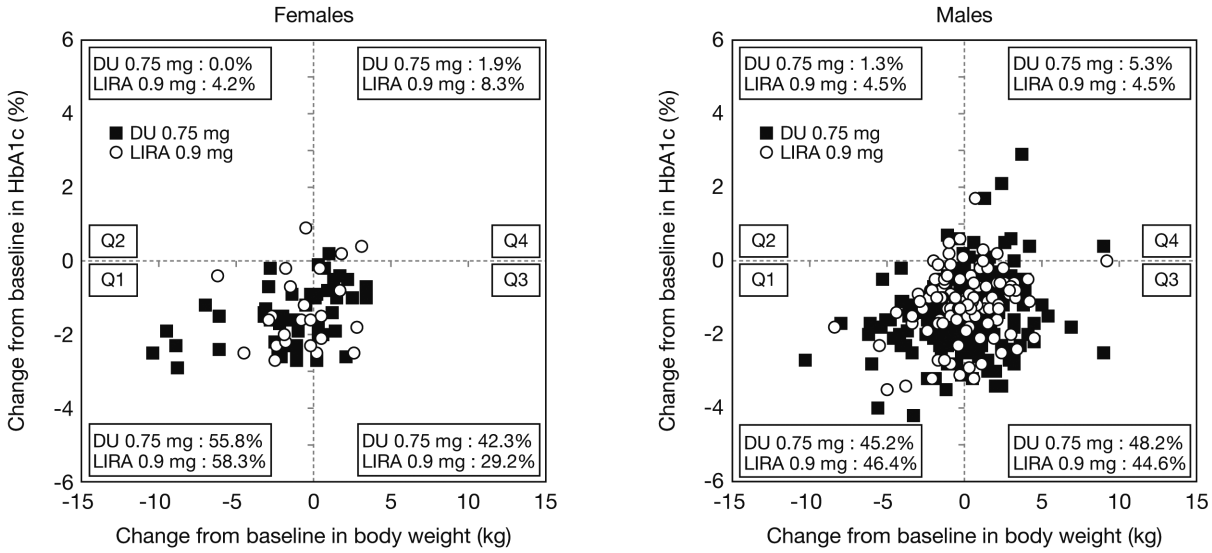

Fig. 1 Relationship between HbA1c (%) and body weight (kg) changes from baseline to week 52 by treatment and sex in the monotherapy study.

DU 0.75 mg, once weekly dulaglutide 0.75 mg; HbA1c, glycated hemoglobin; LIRA 0.9 mg, once daily liraglutide 0.9 mg; Q1: HbA1c change <0% and weight change <0 kg; Q2: HbA1c change ≥0% and weight change <0 kg; Q3: HbA1c change <0% and weight change ≥0 kg; Q4: HbA1c change ≥0% and weight change ≥0 kg.

Pearson product-moment correlations:

- Females (n=76): DU 0.75 mg: 0.436 (p=0.001), LIRA 0.9 mg: 0.175 (p=0.413)
- Males (n=341): DU 0.75 mg: 0.246 (p<0.001), LIRA 0.9 mg: 0.231 (p=0.014)

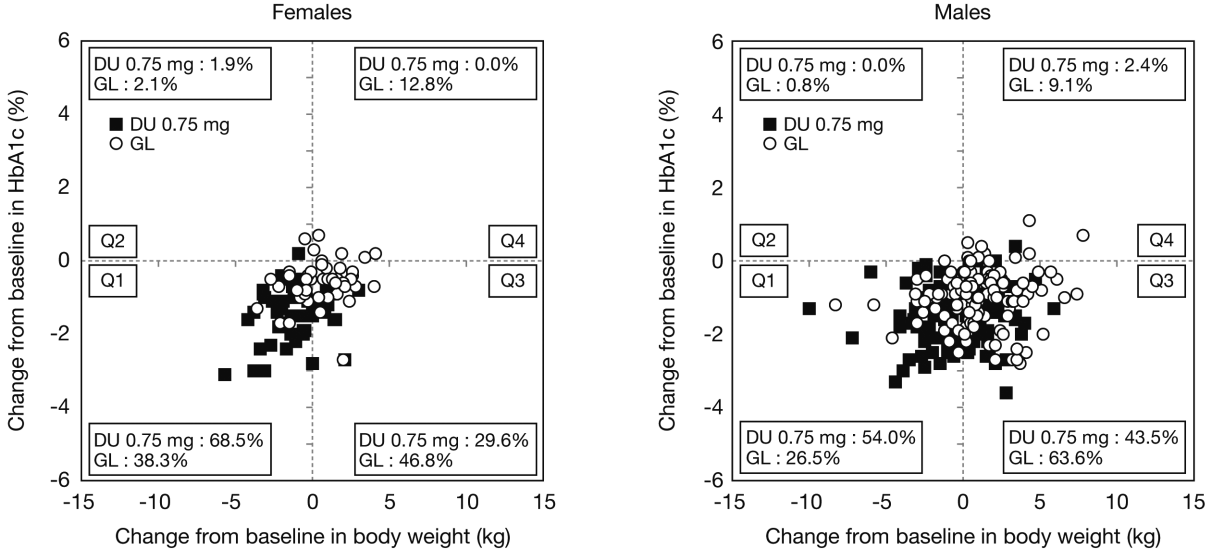

Fig. 2 Relationship between HbA1c (%) and body weight (kg) changes from baseline to week 26 by treatment and sex in the combination study.

DU 0.75 mg, once weekly dulaglutide 0.75 mg; GL, glargine; HbA1c, glycated hemoglobin; Q1: HbA1c change <0% and weight change <0 kg; Q2: HbA1c change ≥0% and weight change <0 kg; Q3: HbA1c change <0% and weight change ≥0 kg; Q4: HbA1c change ≥0% and weight change ≥0 kg.

Pearson product-moment correlations:

- Females (n=103): DU 0.75 mg: 0.262 (p=0.056), GL: 0.216 (p=0.144)
- Males (n=258): DU 0.75 mg: 0.123 (p=0.172), GL: 0.099 (p=0.257)

Table 4 Incidence of adverse events and hypoglycemia (percentages of patients) by study, treatment, and sex

	Monotherapy study (52 weeks)				Combination study (26 weeks)			
	DU 0.75 mg (N=280)		LIRA 0.9 mg (N=137)		DU 0.75 mg (N=181)		GL (N=180)	
	Female (n=52)	Male (n=228)	Female (n=24)	Male (n=113)	Female (n=56)	Male (n=125)	Female (n=47)	Male (n=133)
Patients who discontinued study treatment due to adverse event	7.7	3.5	8.3	7.1	5.4	2.4	0.0	1.5
Any adverse events	86.5	61.4	83.3	65.5	80.4	72.8	72.3	57.9
Adverse events (≥5% of patients in any treatment group in either study)								
Nasopharyngitis	28.8	16.2	33.3	14.2	23.2	28.8	29.8	24.1
Constipation	9.6	7.5	12.5	7.1	12.5	7.2	6.4	2.3
Diarrhea	13.5	5.7	8.3	3.5	14.3	11.2	2.1	2.3
Nausea	9.6	5.3	16.7	6.2	10.7	8.8	4.3	0.0
Abdominal distension	3.8	4.4	4.2	5.3	0.0	3.2	0.0	0.8
Decreased appetite	0.0	0.9	8.3	5.3	3.6	2.4	0.0	0.0
Vomiting	1.9	1.8	0.0	0.9	5.4	4.8	2.1	0.8
Lipase increased	1.9	3.9	0.0	2.7	1.8	6.4	0.0	0.8
Hypoglycemia								
Total hypoglycemia [§]	3.8	2.6	4.2	2.7	26.8	25.6	48.9	47.4
Nocturnal hypoglycemia	0.0	0.9	0.0	0.9	8.9	8.8	23.4	27.8

All data are percentages of patients. MedDRA version 17.0 (monotherapy study), 16.1 (combination study). DU 0.75 mg, dulaglutide 0.75 mg once weekly; GL, insulin glargine; LIRA 0.9 mg, liraglutide 0.9 mg once daily; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients; N, number of patients randomized and treated. [§] Symptomatic and asymptomatic hypoglycemia (blood glucose ≤70 mg/dL).

Table 5 Changes from baseline in body weight (kg) by incidence of specific gastrointestinal adverse events (diarrhea, constipation, nausea, vomiting) through 52 weeks of treatment in the monotherapy study (dulaglutide and liraglutide groups)

	DU 0.75 mg (N=280)	LIRA 0.9 mg (N=137)
Incidence of 1 or more of the 4 adverse events		
Yes		
n	50	23
Mean (SD) change from baseline in body weight	-0.90 (3.60)	-0.83 (1.65)
No		
n	230	113
Mean (SD) change from baseline in body weight	-0.03 (2.53)	-0.02 (2.42)

DU 0.75 mg, dulaglutide 0.75 mg once weekly; LIRA 0.9 mg, liraglutide 0.9 mg once daily; n, number of patients; N, number of patients randomized and treated; SD, standard deviation.

and this tendency may have affected the results in the Japanese studies.

Incidence of adverse events overall was greater for females than for males in all treatment groups in both studies; this was also true for several gastrointestinal events. In a large retrospective analysis of databases from a large postmarketing safety surveillance program, the proportions of females experiencing adverse events were greater than those of males (57% *vs*. 43% overall in more than 600 drugs across all drug classes combined, and 54% *vs*. 46% across 36 antidiabetic drugs) [15]. Therefore, it could be that females in general experience adverse events more frequently than males do and/or that they are more likely to report adverse events than males.

No sex differences were observed in incidence of total or nocturnal hypoglycemia for any of the study drugs.

Dulaglutide- and liraglutide-treated females in our analysis had both greater mean weight loss and greater incidence of gastrointestinal events compared to males (one group of dulaglutide-treated males had mean weight gain), and these results were similar to those observed in subgroup analyses of data from clinical trials of exenatide BID and QW [3, 4]. Patients in the dulaglutide and liraglutide groups in the monotherapy study experiencing certain key gastrointestinal events (17% to 18% of patients in each group) had greater mean weight loss than patients not experiencing any of the events (Table 5), but the effect of sex on the relationship between occurrence of gastrointestinal events and changes in weight was unclear.

Body weight has a significant effect on the pharmacokinetics of both dulaglutide and liraglutide [16, 17]. Since females have lower mean body weights than males, this might tend to result in higher plasma concentrations of these medications in females, but also confounds the effects of sex and body weight. Therefore, potential higher exposure of dulaglutide and liraglutide in females compared to males (though not measured) may have contributed to the sex differences in weight changes and the greater incidence of adverse events in females compared to males observed in these studies.

Overall, it appears that changes in body weight and incidence of adverse events in dulaglutide- and liraglutide-treated patients are correlated with patient sex, and these effects may be partly explained by body weight differences between the sexes. Importantly, HbA1c reductions among dulaglutide-treated patients were similar for both sexes, indicating that the glucose-lowering effect does not appear to be related to body weight loss or to the occurrence of gastrointestinal events.

Limitations of this study include the relatively small number of females among the treated patients, and the exploratory, *post hoc* nature of these analyses. In addition, the results may have been affected by confounding factors such as concomitant medications.

Sex differences among patients with T2D and in response to diabetes treatments are sometimes unrecognized by clinicians. In our analysis of 2 randomized, controlled phase 3 studies in Japan, the benefit/risk ratio for dulaglutide remains unchanged, positive for both sexes (HbA1c lowering was unaffected by patient sex and no new safety concerns were identified for either sex). Incidences of patients discontinuing dulaglutide early due to adverse event were low for both sexes, and incidences of total and nocturnal hypoglycemia were similar between the sexes for all 3 treatment groups. However, some important differences between the sexes were observed. First, across all treatment groups, females had greater weight loss or less weight gain compared to males, and greater proportions of females than males experienced reductions from baseline in both HbA1c and weight. Second, also across all treatment groups, incidences of adverse events (overall and for many gastrointestinal events, such as nausea) were greater among females than males. Our findings may help clinicians provide more personalized care for patients with T2D.

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Declaration of Interest

Y.O. has received honoraria for lectures from Novo Nordisk Pharma Ltd., MSD K.K., Eli Lilly Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Sanofi K.K. T.O., A.M., J.M., and N.I. are employees of Eli Lilly Japan K.K.

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Author Contributions

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

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