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BRIEF REPORT

The combination of dulaglutide and biguanide reduced bodyweight in Japanese patients with type 2 diabetes

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The efficacy and safety of once-weekly dulaglutide 0.75 mg (dulaglutide) in Japanese patients with type 2 diabetes (T2D) were evaluated according to subgroups defined by concomitant oral hypoglycaemic agents. This exploratory analysis included data from a randomized, open-label, phase III study that compared dulaglutide with insulin glargine (glargine) (n = 361). The three subgroups were dulaglutide or glargine in combination with sulphonylurea (SU) alone, biguanide (BG) alone or SU and BG combined. There were no clinically relevant differences in glycated haemoglobin (HbA1c) changes among the three subgroups in the dulaglutide group; in the glargine group, a numerically greater reduction was observed in combination with BG alone compared to the other two groups (SU alone and SU + BG). Weight loss was observed with dulaglutide in combination with BG alone or with SU + BG. The incidence of adverse events among subgroups was significantly different in the glargine group but not in the dulaglutide group. Incidence of hypoglycaemia was highest in combination with SU for both treatments. For patients with T2D, dulaglutide added to concomitant BG may be more likely to result in weight loss than dulaglutide added to concomitant SU.

KEYWORDS

dulaglutide, GLP-1 receptor agonist, insulin glargine, subgroup analysis, type 2 diabetes

1 | INTRODUCTION

Dulaglutide is a long-acting injectable glucagon-like peptide-1 (GLP-1) receptor agonist that mimics some of the effects of endogenous GLP-1.[1] In randomized phase III studies in Japan, once-weekly dulaglutide 0.75 mg (dulaglutide) has shown superiority to placebo and insulin glargine (glargine) and non-inferiority to once-daily liraglutide 0.9 mg in glycated haemoglobin (HbA1c) changes.[2,3] In a 52-week, open-label, non-randomized, phase III study in Japan, patients treated with dulaglutide in combination with a single oral hypoglycaemic agent (OHA) had comparable HbA1c changes from baseline, but body weight changes varied [significant increases in combination with thiazolidinediones; no significant changes in combination with sulphonylureas (SU) or glinides; and significant reductions in combination with biguanides (BG) or alpha-glucosidase inhibitors].[4] A higher incidence of hypoglycaemia was observed in combination with SU compared with any of the other combinations. However, because this was a non-randomized study, it was difficult to compare effects across groups, and there was no comparator treatment.

To better understand the clinical effects of concomitant use of dulaglutide and OHAs, we performed an exploratory analysis of the randomized, glargine-controlled study, in which SU and BG were the concomitant OHAs, to enable comparisons among the subgroups and to compare the effects of combination therapy in patients receiving dulaglutide or glargine.[3] These results may be of particular interest to clinicians in Japan, where SUs are widely used as concomitant OHAs with GLP-1 receptor agonists in the treatment of patients with T2D.

2 | METHODS

2.1 | Study design and patients

The study was a 26-week, phase III, randomized, open-label, non-inferiority study comparing the efficacy and safety of once-weekly

dulaglutide 0.75 mg with once-daily glargine in Japanese patients with T2D inadequately controlled with monotherapy (SU or BG) or dual therapy (SU and BG).[3]

Analysis methods are described in File S1, Supporting Information. Some of the OHA subgroup analyses reported here were pre-specified in the study analysis plan, while others were *post hoc*. There was no adjustment for multiplicity.

3 | RESULTS

3.1 | Patient characteristics

Demographics for all 361 patients, according to treatment and OHA subgroup, are presented in Table S1, Supporting Information. The majority of patients (71%) were male. Mean age was 57 years, mean weight was 71 kg, and mean body mass index (BMI) was 26.0 kg/m². Mean duration of diabetes was nine years; the mean duration differed significantly among OHA subgroups in the dulaglutide group [range: 6.7 years (BG) to 10.8 years (BG + SU); p < .001]. Mean HbA1c was 8.0% (64 mmol/mol); there were significant differences among OHA subgroups in the dulaglutide group [range: 7.8% (62 mmol/mol) (BG) to 8.3% (67 mmol/mol) (SU); p = .010] and in the glargine group [range: 7.8% (62 mmol/mol) (BG) to 8.3% (67 mmol/mol) (SU); p = .025]. Mean doses of concomitant SU and BG were similar in both treatment groups at baseline and mostly unchanged at week 26.

Table S2, Supporting Information displays mean daily glargine doses at baseline and week 26 for patients randomized to glargine.

3.2 | Efficacy

In the dulaglutide group, mean changes from baseline in HbA1c after 26 weeks ranged from −1.37% (−15.0 mmol/mol) (SU + BG) to −1.48% (−16.2 mmol/mol) (BG alone and SU alone); in the glargine group, mean changes ranged from −0.78% (−8.5 mmol/mol) (SU) to −1.02% (−11.2 mmol/mol) (BG) (Figure 1A). In all three subgroups,

dulaglutide reduced HbA1c significantly compared to glargine (p < .001, all). There were no statistically significant differences in HbA1c changes among the subgroups (BG vs. SU, BG vs. SU + BG, SU vs. SU + BG) in either treatment group (p ≥ .069, all).

In the dulaglutide group, patients receiving BG or SU + BG lost weight at week 26 on average, while patients receiving SU gained weight; in the glargine group, patients in all three OHA subgroups gained weight on average (Figure 1B). In the BG and SU + BG subgroups, dulaglutide significantly reduced weight compared to glargine (p < .001, both); in the SU subgroup, weight increase in the dulaglutide group was significantly less than that in the glargine group (p = .041). In the dulaglutide group, weight change was significantly different between the SU subgroup and the BG subgroup (p = .013); there were no other statistically significant differences in pairwise comparisons of changes in weight between the OHA subgroups within either treatment group (all other p ≥ .089).

3.3 | Safety

Table 1 summarizes the most frequent adverse events and incidence of hypoglycaemia through week 26 according to treatment and OHA subgroup. A significantly greater percentage of dulaglutide-treated patients experienced adverse events compared to glargine-treated patients (p = .007)[3]; the difference may have been primarily because of gastrointestinal adverse events. In the dulaglutide group, there were no significant differences among OHA subgroups in adverse events overall or in any of the most frequent adverse events. In the glargine group, the incidence of adverse events overall varied significantly among subgroups [range: 39 (SU) to 70% (BG); p = .011]; the significance may have been primarily because of differences in the incidence of nasopharyngitis [range: 9% (SU) to 30% (BG)]. No patients experienced severe hypoglycaemia. The incidences of total and nocturnal hypoglycaemia throughout 26 weeks were significantly greater in glargine-treated patients compared to dulaglutide-treated patients (p < .001, both).[3] There were significant differences in the
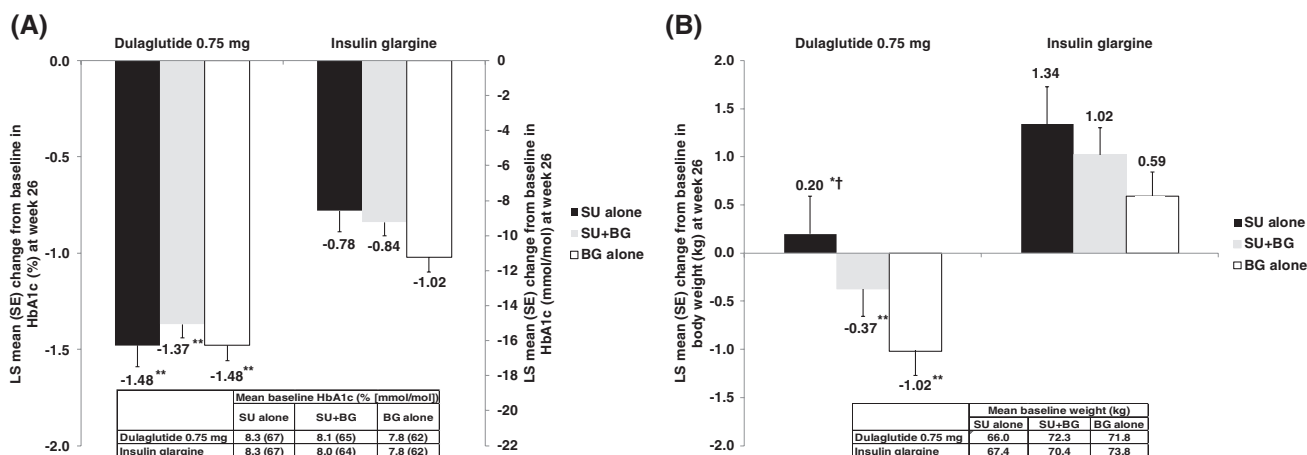
FIGURE 1 A, LS mean (SE) changes from baseline in HbA1c by treatment and OHA subgroup. B, LS mean (SE) changes from baseline in body weight (kg) by treatment and OHA subgroup. *p < .05 for dulaglutide vs. insulin glargine within subgroup. **p < .001 for dulaglutide vs. insulin glargine within subgroup. †p < .05 for BG vs. SU subgroups in the dulaglutide group. BG, biguanides; HbA1c, glycated haemoglobin; LS, least-squares; OHA, oral hyperglycaemic agent; SE, standard error; SU, sulphonylureas; SU + BG, sulphonylureas and biguanides.

TABLE 1 Commonly observed treatment-emergent adverse events and incidence of hypoglycaemia through week 26 by treatment and OHA subgroup

	All patients (N = 361)	Dulaglutide 0.75 mg (N = 181)					Insulin glargine (N = 180)				
		All dulaglutide 0.75 mg (N = 181)	SU alone (n = 34)	SU + BG (n = 83)	BG alone (n = 64)	Overall p[1]	All insulin glargine (N = 180)	SU alone (n = 33)	SU + BG (n = 81)	BG alone (n = 66)	Overall p[1]
Patients with at least one TEAE[2]	247 (68)	136 (75)	24 (71)	60 (72)	52 (81)	.365	111 (62)	13 (39)	52 (64)	46 (70)	.011
Nasopharyngitis	95 (26)	49 (27)	10 (29)	27 (33)	12 (19)	.166	46 (26)	3 (9)	23 (28)	20 (30)	.054
GI disorders	87 (24)	62 (34)	11 (32)	25 (30)	26 (41)	.399	25 (14)	4 (12)	13 (16)	8 (12)	.750
Diarrhoea	26 (7)	22 (12)	4 (12)	6 (7)	12 (19)	.105	4 (2)	0 (0)	2 (3)	2 (3)	.833
Nausea	19 (5)	17 (9)	2 (6)	8 (10)	7 (11)	.713	2 (1)	0 (0)	1 (1)	1 (2)	1.000
Constipation	22 (6)	16 (9)	4 (12)	8 (10)	4 (6)	.619	6 (3)	1 (3)	5 (6)	0 (0)	.089
Vomiting	11 (3)	9 (5)	0 (0)	4 (5)	5 (8)	.291	2 (1)	1 (3)	0 (0)	1 (2)	.301
Lipase increased	10 (3)	9 (5)	1 (3)	3 (4)	5 (8)	.542	1 (<1)	0 (0)	1 (1)	0 (0)	1.000
Patients with total hypoglycaemia[3]	133 (37)	47 (26)	12 (35)	27 (33)	8 (13)	.009	86 (48)	21 (64)	50 (62)	15 (23)	<.001
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	
Nocturnal	64 (18)	16 (9)	7 (21)	8 (10)	1 (2)	.006	48 (27)	12 (36)	28 (35)	8 (12)	.003

Data are number (percent) of patients. Adverse events occurring in ≥5% of patients in either treatment group overall are presented.

BG, biguanides; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients with data; N, number of patients randomized and treated; OHA, oral anithyperglycemic agent; SU, sulphonylureas; SU + BG, sulphonylureas and biguanides; TEAE, treatment-emergent adverse event.

[1]P-values for comparisons among three baseline OHA regimen groups within treatment group are from Chi-square test if at least 80% of cells had an expected value ≥5; otherwise Fisher's exact test was used.

[2]Adverse events coded with MedDRA version 16.1.

[3]Hypoglycaemia was defined as a blood glucose concentration of ≤3.9 mmol/L and/or symptoms and/or signs attributable to hypoglycaemia. Severe hypoglycaemia was defined as an episode requiring the assistance of another person to actively administer therapy.

incidences of total and nocturnal hypoglycaemia between subgroups in both treatment groups (p ≤ .009, all); incidences of total and nocturnal hypoglycaemia were highest in both treatment groups in combination with SU.

4 | DISCUSSION

A subgroup analysis using pooled data from the three Japanese phase III studies of dulaglutide 0.75 mg has been reported previously.[5] In that analysis, use of concomitant SU and use of concomitant BG were two of the baseline characteristics evaluated. Higher incidence of hypoglycaemia was observed with dulaglutide in combination with SU, and greater weight reduction was observed in combination with BG. However, it was difficult to evaluate the pure influence of SU or BG because 33% of patients receiving SU and 40% of patients receiving BG were treated with both drugs, and the comparator arms in the studies were not included in the analyses. Therefore, in this analysis, we evaluated the efficacy and safety of dulaglutide compared with glargine, stratified by use of concomitant SU alone, BG alone, or SU and BG combined.

Because most patients in the USA and European Union are concomitantly treated with metformin rather than SU when initiating treatment with GLP-1 receptor agonists, there have been no studies evaluating the influence of concomitant SU compared to concomitant BG on the efficacy and safety of GLP-1 receptor agonists in Western patients with T2D.[6] However, in Japan, SU is widely used as a

concomitant treatment with GLP-1 receptor agonists, so the results of this analysis may be of particular interest there.

In this analysis, there were no statistically significant differences in changes from baseline in HbA1c over 26 weeks among the OHA subgroups for dulaglutide. GLP-1 receptor agonists, including dulaglutide, have various mechanisms of action, such as suppression of appetite, inhibition of gastric emptying and glucagonostatic actions, in addition to insulinotropic effects[7]; these non-insulinotropic actions may contribute to the glucose-lowering effects.

Mean weight reduction was observed with dulaglutide in combination with BG alone or with SU and BG together; all other combination groups in this analysis resulted in mean weight increase. The detailed mechanism for these results is unknown; however, the non-insulinotropic glucose-lowering effects of BG may contribute to weight loss.

Incidence of hypoglycaemia in this study was highest with SU. Concomitant use of SU is a known risk for hypoglycaemia, and the Committee for Proper Use of Incretin Drugs [GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors] in Japan recommends reducing concomitant SU doses when treatment with incretin drugs is initiated.[8]

Significant differences in the incidence of adverse events among the OHA subgroups were observed in the glargine group but not in the dulaglutide group.

The subgroup analyses reported here had potential limitations. First, the results of this analysis should be interpreted with caution with respect to the OHA subgroups, as the OHAs were background

therapies and were not assigned to patients randomly. Also, because the once-weekly dulaglutide dose of 0.75 mg used in Japan[9] is lower than the once-weekly 1.5 mg dose typically used in Western countries,[10,11] these results may not be generalizable in other populations. Further, these were exploratory, primarily *post hoc* analyses, so the sample size may not be enough to detect differences between the OHA subgroups. In addition, there were no multiplicity adjustments for the statistical tests. Finally, analyses of efficacy parameters (HbA1c and weight) adjusted for potential confounding factors (baseline values and BMI group), but analyses of safety parameters (hypoglycaemia and adverse events) did not.

In conclusion, once-weekly dulaglutide 0.75 mg improved blood glucose control (compared to baseline and compared to glargine) as measured by HbA1c after 26 weeks regardless of concomitant OHA (SU, BG or SU + BG). Dulaglutide in combination with BG alone resulted in weight loss and lower incidence of hypoglycaemia compared to dulaglutide in combination with SU. For patients with T2D, dulaglutide in addition to concomitant BG may be more likely to result in weight loss than dulaglutide in addition to concomitant SU.

Conflict of interest

N. I. has received grants from MSD, Eli Lilly, Shiratori, Mitsubishi Tanabe Pharma and Roche Diagnostics and has received research endowments from Kissei, Taisho Toyama, Sanofi, Pfizer, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Takeda, Japan Tobacco, Kyowa Hakko Kirin, Sumitomo Dainippon Pharmaceutical Astellas, MSD, Sanwa Kagaku, Boehringer Ingelheim, Japan Diabetes Foundation and Ono. E. A. has received research endowments from Astellas, Shionogi, Takeda, Taisho, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Boehringer Ingelheim and Novo Nordisk and has received lecture fees from MSD, Astellas, AstraZeneca, Ono, Sanofi, Takeda, Taisho and Mitsubishi Tanabe Pharma. T.O., A.M. and M.T. are employees of Eli Lilly Japan K.K, and M.T. has the company stock option. Y.T. has received a grant and research endowments from Eli Lilly, research endowments from Boehringer Ingelheim, Kowa, Kyowa Hakko Kirin, Sanofi and Taisho Toyama, lecture fees from AstraZeneca, NovoNordisk and Ono and research endowments and lecture fees from Astellas, Daiichi Sankyo, Mitsubishi Tanabe Pharma, MSD, Novartis, Sumitomo Dainippon Pharmaceutical and Takeda.

Author contributions

N. I., E. A. and Y. T. were trial investigators and participated in data collection. T. O., A. M. and M. T. prepared the first draft of the manuscript. T. O. was responsible for the 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 approved the final version of the manuscript and take full responsibility for the content.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.