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BRIEF REPORT

Subgroup Analysis Stratified by Baseline Pancreatic β-cell Function in a Japanese Study of Dulaglutide in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: This analysis investigated the relationship between baseline fasting pancreatic β-cell function and efficacy in Japanese patients with type 2 diabetes (T2D) treated with once-weekly dulaglutide 0.75 mg (dulaglutide) or once-daily liraglutide 0.9 mg (liraglutide) for up to 52 weeks.

Methods: In a 52-week study of monotherapy in Japanese patients with T2D, patients were categorized into three subgroups defined by tertiles (low, medium, and high) of baseline values of three pancreatic β-cell function parameters [fasting C-peptide, C-peptide index, and secretory units of islets in transplantation (SUIT) index]. Associations between these parameters and efficacy [defined by changes from baseline in glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PBG), mean of all meals blood glucose excursion, and body weight] in the dulaglutide group (280 patients) or the liraglutide group (137 patients) were evaluated.

Results: Patients in the subgroups with high insulin-secreting ability (based on pancreatic β-cell function) were younger and had shorter disease duration and higher body mass index compared to those with low insulin-secreting ability. No specific trend was observed between baseline pancreatic β-cell function and changes in HbA1c or FBG. Reductions from baseline in mean PBG and excursion were greatest for patients in the low β-cell function tertiles. Inconsistent trends in body weight were observed across the treatment groups and β-cell function parameters.

Conclusion: In Japanese patients with T2D, changes in HbA1c and body weight after 52 weeks of treatment with dulaglutide or liraglutide could not be predicted by patients' fasting pancreatic β-cell function before treatment.

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Keywords: β-cell function; Dulaglutide; GLP-1 receptor agonist; Liraglutide; Subgroup analysis; Type 2 diabetes

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INTRODUCTION

Type 2 diabetes (T2D) is an increasingly common endocrine disorder characterized by progressive loss of β-cell function. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) enhance glycemic control mainly by

modulation of glucose-dependent insulin secretion from β-cells [1] and are considered to be effective in the treatment of patients with T2D who have remaining endogenous insulin secretory capacity. The proportion of patients failing the switch from insulin to liraglutide due to hyperglycemia was increased in patients with reduced β-cell function [2]. It has also been reported that GLP-1 RAs improve glycemic control by mechanisms other than β-cell function, such as slowing of gastric emptying and reduction of glucagon levels [3].

Dulaglutide is a once-weekly GLP-1 RA which is approved in Japan at a dose of 0.75 mg. Three phase 3 studies were conducted in Japan in patients with T2D: two randomized studies [4–6] and one nonrandomized safety study [7].

To assess the relationship between the efficacy of dulaglutide 0.75 mg (dulaglutide) and remaining insulin secretory capacity in Japanese patients with T2D, we conducted post hoc subgroup analyses of data from the dulaglutide monotherapy clinical trial [5, 6] for dulaglutide compared with once-daily liraglutide 0.9 mg (liraglutide). The pancreatic β-cell function parameters we evaluated (using baseline values only) were fasting C-peptide (CPR), fasting C-peptide index (CPI), and fasting secretory units of islets in transplantation (SUIT) index [8], because these are often used by Japanese physicians in clinical settings to evaluate whether patients need insulin therapy [9, 10]. We also evaluated changes from baseline in updated homeostatic model assessment of β-cell function (HOMA2-%β) [11] as supportive data.

We hypothesized that efficacy outcomes after treatment with dulaglutide or liraglutide may have been affected by baseline pancreatic β-cell function, because GLP-1 RAs might not be effective for patients with inadequate insulin secretion capability.

MATERIALS AND METHODS

Study Design and Patient Population

This analysis used data from a randomized, double-blind (for dulaglutide and placebo), and open-label (for liraglutide) 52-week study of dulaglutide 0.75 mg in Japan (the primary endpoint was at 26 weeks) [5, 6]. Patients were randomized to once-weekly dulaglutide 0.75 mg, once-daily liraglutide 0.9 mg, or placebo; after 26 weeks of treatment, patients receiving placebo were switched to dulaglutide. To be enrolled in the study, patients were required to have had a diagnosis of T2D according to the World Health Organization (WHO) diagnostic criteria based on blood glucose concentration. In addition, patients were required to be naïve to oral antihyperglycemic medications (OAMs) (only treated with diet and exercise) or to be receiving OAM monotherapy (excluding thiazolidinediones). Finally, patients were required to have a confirmed glycated hemoglobin (HbA1c) value at the randomization visit between 7.0% and 10.0%. The analyses were conducted only for the patients randomized to dulaglutide or liraglutide. Patients in the full analysis set (patients randomized and treated with at least one dose of study drug) were included in the analyses. Baseline characteristics were available for 417 patients (dulaglutide, 280; liraglutide, 137); postbaseline efficacy data were available for 416 patients (dulaglutide, 280; liraglutide, 136).

All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki 428 Declaration of 1964, as revised in 2013, and Good Clinical Practice.

Analysis Methods

For this exploratory analysis, patients were classified into three subgroups based on tertiles of pancreatic β-cell function parameters (CPR, CPI, and SUIT index) at baseline (Table 1). CPI was calculated as 100 × CPR (ng/mL)/fasting serum glucose (FSG) (mg/dL) [9], and SUIT index was calculated as (CPR × 1500)/(FSG − 63) [8, 12]. Baseline FSG was measured at the central laboratory. HOMA2-%β was calculated using the updated homeostatic model assessment of β-cell function [11].

Analyses of changes in efficacy parameters after 52 weeks of treatment used analysis of

Table 1 Baseline β-cell function (all patients)

	N	Mean (SD)	33th percentile	67th percentile	Subgroups		
					Low	Medium	High
Fasting C-peptide (ng/mL)	486	1.41 (0.68)	1.00	1.51	< 1.00	≥ 1.00–< 1.51	≥ 1.51
C-peptide index	486	0.87 (0.42)	0.62	0.96	< 0.62	≥ 0.62–< 0.96	≥ 0.96
SUIT index	486	22.15 (11.99)	15.27	23.98	< 15.27	≥ 15.27–< 23.98	≥ 23.98

N number of patients, *SD* standard deviation, *SUIT* secretory units of islets in transplantation

covariance (ANCOVA) models which included treatment, body mass index (BMI) group (< 25 or ≥ 25 kg/m^2), prestudy therapy (OAM: yes/no), β-cell function tertile groups (low, medium, and high), and interaction between β-cell function groups and treatment as fixed effects and the baseline value as the covariate. Fasting blood glucose (FBG) was the self-monitored blood glucose (SMBG) value collected before the first morning meal; mean postprandial blood glucose (PBG) was the mean of the three SMBG values collected 2 h after meals. Mean excursion was the mean of the blood glucose excursion (PBG − pre-meal blood glucose) from all three meals based on SMBG data. For FBG, mean PBG, and mean excursion, means and standard deviations (SDs) were calculated by subgroup. Missing data at week 52 were imputed with an available last observation carried forward (LOCF) value if necessary. Analyses were conducted using SAS version 9.2 or greater.

RESULTS

Patient Characteristics

Baseline values for the three β-cell function parameters ranged as follows for patients in the dulaglutide and liraglutide treatment groups: CPR, 0.42–5.74 ng/mL; CPI, 0.28–2.81; SUIT index, 5.63–72.91. Patient demographics by baseline tertiles of the β-cell function parameters are presented in Table 2. For each of the three pancreatic β-cell function parameters (CPR, CPI, and SUIT index), mean age and duration of T2D were highest in the low tertile and lowest in the high tertile. Mean body weight and BMI were lowest in the low tertile and highest in the high tertile for all three β-cell function parameters. Mean FBG was lowest in the low tertile and highest in the high tertile of CPR but highest in the low tertile and lowest in the high tertile of CPI and the SUIT index. Mean PBG and mean excursion values were generally similar in each tertile of CPR and were highest in the low tertile and lowest in the high tertile of CPI and the SUIT index.

Efficacy

Each figure presents least-squares (LS) mean (SE) changes from baseline in efficacy parameters after 52 weeks of treatment (LOCF) by treatment and baseline tertiles of β-cell function parameters. Similar trends in changes from baseline in the efficacy parameters across the β-cell function subgroups were generally observed in both treatment groups (dulaglutide and liraglutide).

In both treatment groups, reductions from baseline in HbA1c (Fig. 1) and FBG (Fig. 2) were clinically relevant and similar across the tertiles of all three β-cell function parameters. Changes from baseline in HbA1c ranged from − 1.32% to − 1.50% in the dulaglutide group and from − 1.11% to − 1.34% in the liraglutide group. Changes from baseline in FBG ranged from − 34.92 to − 39.66 mg/dL in the dulaglutide group and from − 28.18 to − 36.08 mg/dL in the liraglutide group. There were no significant effects of treatment or β-cell function on changes in HbA1c or FBG.

Table 2 Baseline demographics by tertiles of β-cell function parameters at baseline (patients randomized to dulaglutide or liraglutide)

	Fasting C-peptide			C-peptide index			SUIT index		
	Low $N = 132$	Medium $N = 134$	High $N = 151$	Low $N = 136$	Medium $N = 138$	High $N = 143$	Low $N = 134$	Medium $N = 144$	High $N = 139$
Female, *n* (%)	27 (20.5)	24 (17.9)	25 (16.6)	21 (15.4)	30 (21.7)	25 (17.5)	20 (14.9)	30 (20.8)	26 (18.7)
Age (years)	60.9	57.8	54.0	61.0	56.2	55.1	60.6	56.8	55.0
Body weight (kg)	62.2	71.4	78.1	63.8	71.1	77.6	65.1	70.7	76.9
BMI (kg/m^2)	23.0	25.6	27.8	23.2	25.7	27.8	23.6	25.5	27.6
HbA1c (%)	8.0	8.1	8.2	8.3	8.0	8.1	8.4	8.1	7.9
Duration of T2D (years)	8.7	6.6	4.8	8.8	6.5	4.7	8.7	6.8	4.5
Fasting blood glucose (mg/dL)	160.7	166.5	171.9	177.3	163.3	159.7	185.9	163.6	151.2
Mean of all postprandial blood glucose (mg/dL)	239.5	244.6	242.7	255.4	240.6	231.6	264.1	238.8	225.0
Mean of all meals excursion (mg/dL)[a]	75.5	77.1	69.6	79.0	75.9	67.2	82.2	73.2	66.7
Fasting insulin (mU/L)	4.1	7.6	15.1	4.6	7.9	14.9	5.2	7.8	14.6
Fasting C-peptide (ng/mL)	0.79	1.20	2.18	0.85	1.25	2.15	0.91	1.30	2.05
C-peptide index	0.51	0.75	1.31	0.49	0.76	1.35	0.49	0.78	1.35
SUIT index	13.6	19.1	32.8	11.7	19.5	35.1	11.4	19.4	35.8

Data are means unless otherwise indicated. Low, medium, and high defined by tertiles of the indices
BMI body mass index, *HbA1c* glycated hemoglobin, *n* number of patients in category, *N* number of patients treated, *SUIT* secretory units of islets in transplantation, *T2D* type 2 diabetes
[a] Excursion = mean (postprandial blood glucose − fasting blood glucose) from breakfast, lunch, dinner

In both treatment groups, reductions from baseline in mean PBG (Fig. 3) and mean excursion (Fig. 4) from SMBG were clinically relevant. For both parameters, patients in the low β-cell function tertile subgroups had the greatest reductions regardless of treatment. The effect of treatment on changes in PBG was significant in the analyses based on CPR and CPI, and the effect of β-cell function subgroup on changes in PBG was significant for all three parameters. There were no significant effects of treatment or β-cell function on changes in mean excursion.

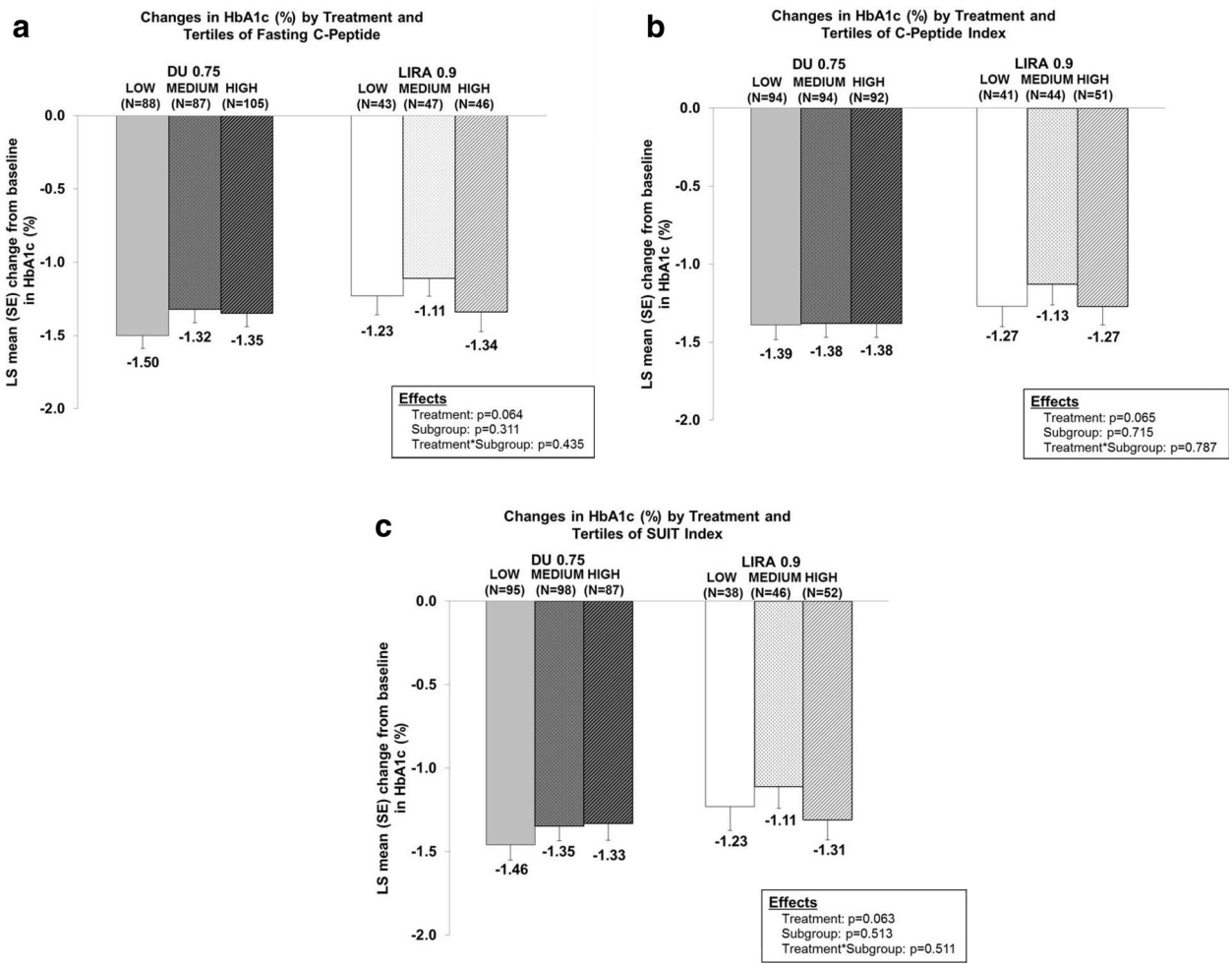

Fig. 1 LS mean ± SE changes from baseline to week 52 (LOCF) in HbA1c (%) by tertiles of β-cell function parameters at baseline by treatment. **a** By fasting C-peptide. **b** By C-peptide index. **c** By SUIT index. *DU 0.75* once-weekly dulaglutide 0.75 mg, *HbA1c* glycated hemoglobin, *LIRA* 0.9 once-daily liraglutide 0.9 mg, *LOCF* last observation carried forward, *LS mean* least-squares mean, *N* number of patients, *SE* standard error, *SUIT* secretory units of islets in transplantation

No consistent patterns in changes in body weight were observed across the treatment groups and β-cell function parameters: LS mean changes in the dulaglutide group ranged from − 0.51 to 0.35 kg and in the liraglutide group ranged from − 0.38 to 0.26 kg (Fig. 5). There were no significant effects of treatment or β-cell function on changes in body weight.

Results of analyses of changes from baseline in HbA1c and body weight by HOMA2-%β (using fasting C-peptide or insulin) tertiles were generally consistent with the changes in HbA1c and body weight by tertiles of CPR, CPI, and SUIT index (data not shown).

DISCUSSION

In this study, subgroup analyses of dulaglutide efficacy {measured by changes in glycemic control [HbA1c and SMBG parameters (FBG, PBG, and mean excursion)] and weight} by baseline β-cell function (measured by CPR, CPI, and SUIT index) were conducted in Japanese patients with T2D. Contrary to our hypothesis,

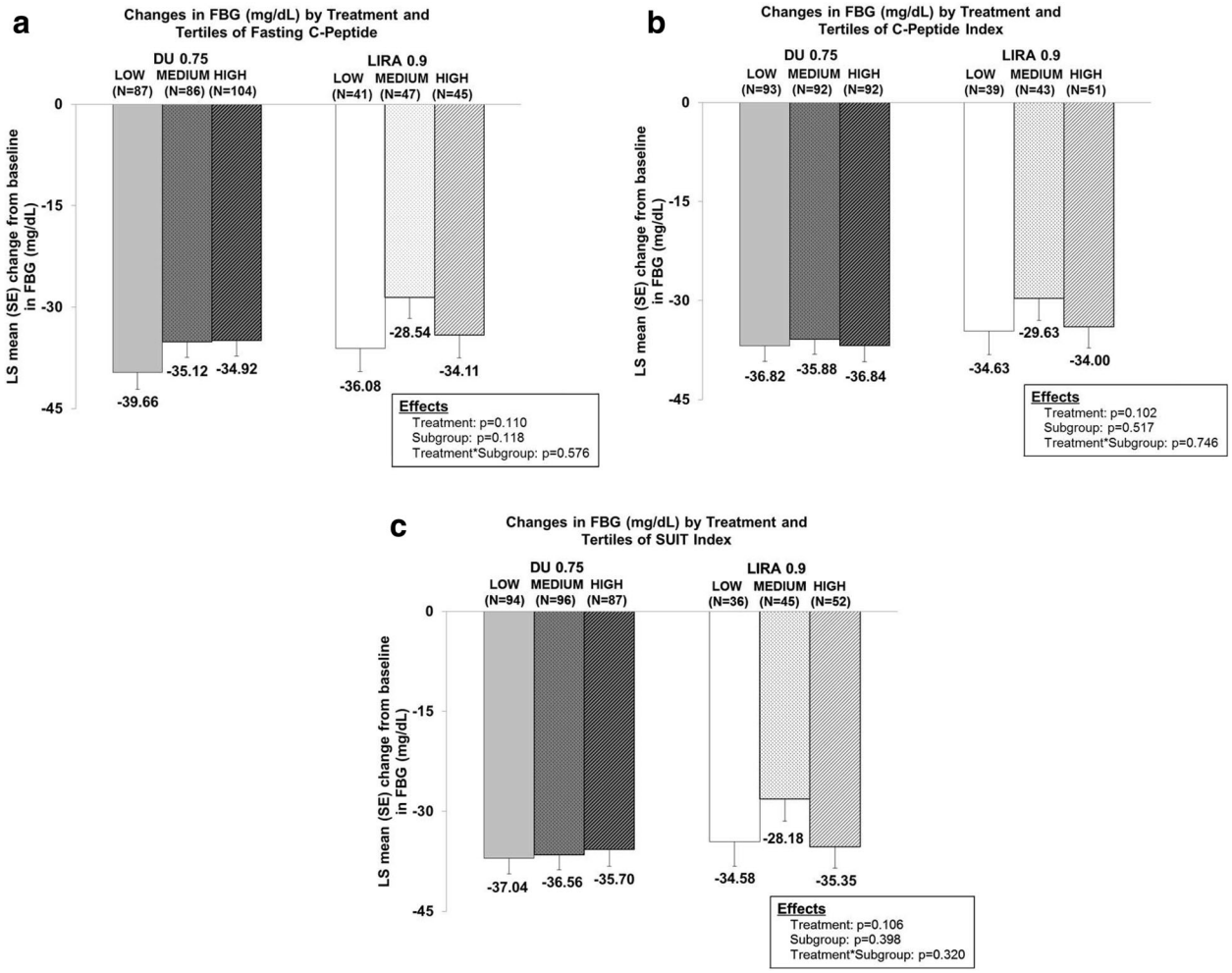

Fig. 2 LS mean ± SE changes from baseline to week 52 (LOCF) in FBG (mg/dL) by tertiles of β-cell function parameters at baseline by treatment. **a** By fasting C-peptide. **b** By C-peptide index. **c** By SUIT index. *DU 0.75* once-weekly dulaglutide 0.75 mg, *FBG* fasting blood glucose, *LIRA 0.9* once-daily liraglutide 0.9 mg, *LOCF* last observation carried forward, *LS mean* least-squares mean, *N* number of patients, *SE* standard error, *SUIT* secretory units of islets in transplantation

treatment with dulaglutide or liraglutide for up to 52 weeks resulted in similar, clinically relevant reductions in HbA1c and FBG across the tertiles of the three β-cell function parameters. In both treatment groups, reductions from baseline in mean PBG and mean excursion from SMBG were greatest for patients in the low tertiles of all three β-cell function parameters; it appears that this may have been partially because these patients generally had the highest PBG and excursion values at baseline. Inconsistent trends in body weight were observed across the treatment groups and β-cell function parameters.

There are some differences between short- and long-acting GLP-1 RAs in the mechanisms of action. It is reported that the primary mechanism of action of short-acting GLP-1 RAs is on PBG, through inhibition of gastric emptying, while long-acting GLP-1 RAs have effects on both FBG and postprandial excursions, suggesting that the primary mechanism of action is through insulinotropic and glucagonostatic modification [3, 13]. Lixisenatide, a short-acting

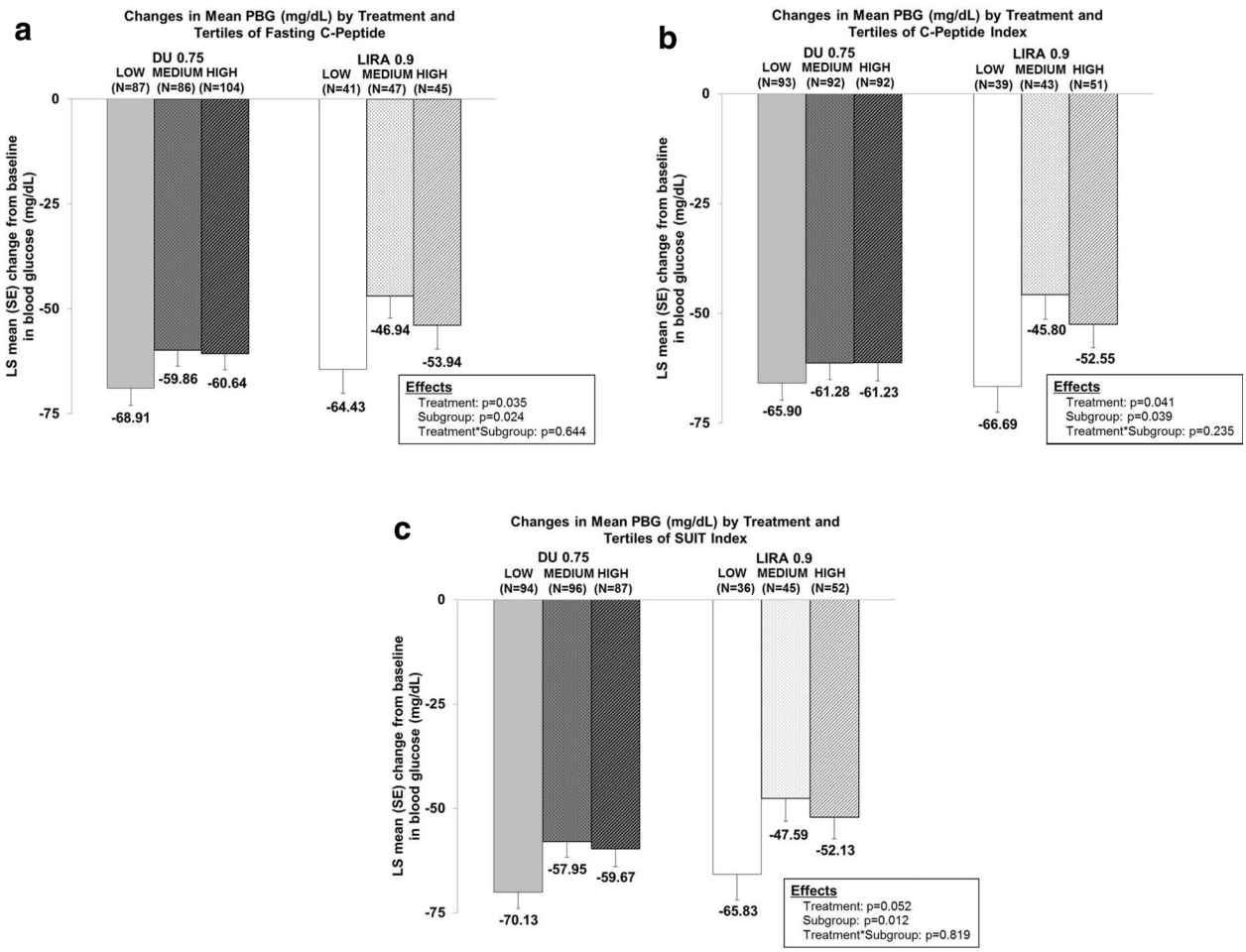

Fig. 3 LS mean ± SE changes from baseline to week 52 (LOCF) in mean PBG from SMBG (mg/dL) by tertiles of β-cell function parameters at baseline by treatment. **a** By fasting C-peptide. **b** By C-peptide index. **c** By SUIT index. *DU 0.75* once-weekly dulaglutide 0.75 mg, *LIRA 0.9* once-daily liraglutide 0.9 mg, *LOCF* last observation carried forward, *LS* mean least-squares mean, *N* number of patients, *PBG* postprandial blood glucose, *SE* standard error, *SMBG* self-monitored blood glucose, *SUIT* secretory units of islets in transplantation

GLP-1 RA, demonstrated similar reductions in HbA1c and FBG across all SUIT quartiles [14]. However, the greatest improvement in PBG was observed in patients with the lowest SUIT quartiles, which suggested that lixisenatide may affect glycemic control via delayed gastric emptying and release of glucagon (independent of β-cell function) [14]. Because dulaglutide and liraglutide are both long-acting GLP-1 RAs, results of this study were expected to be different from results of a similar study of lixisenatide, a short-acting GLP-1 RA [14]. However, contrary to expectations, results for dulaglutide- and liraglutide-treated patients were consistent with those observed in lixisenatide-treated patients: treatment with either dulaglutide or liraglutide resulted in similar reductions in HbA1c and FBG across all levels of β-cell function. In both treatment groups, the greatest improvements in mean PBG and mean excursion from SMBG were observed in patients with the lowest insulin-secretion capacity. It is known that dulaglutide suppresses glucagon and enhances insulin secretion [3]; therefore, it seems that dulaglutide and liraglutide were appropriate treatments for the patients in this study, who had relatively short duration of diabetes. On the other hand, dulaglutide also

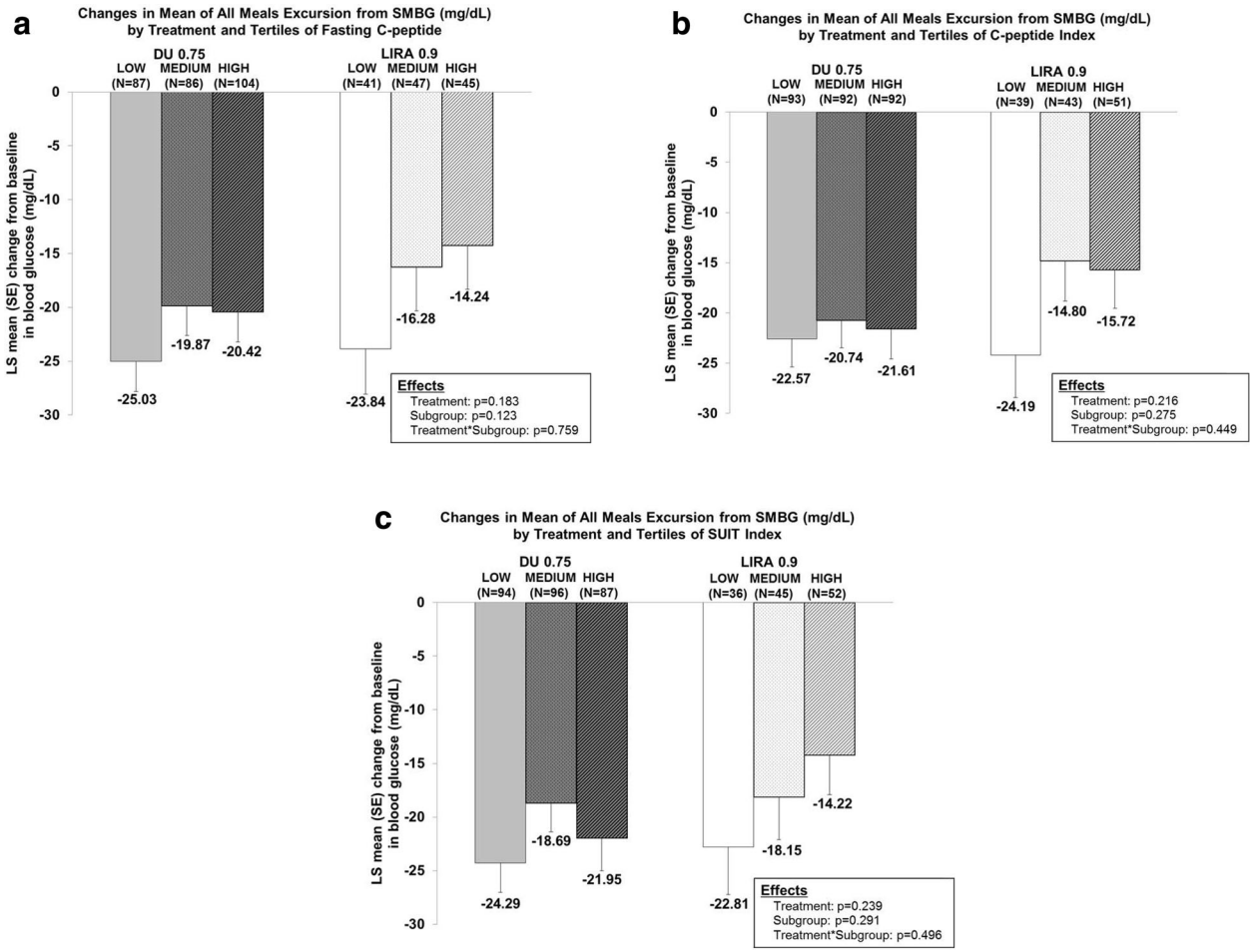

Fig. 4 LS mean ± SE changes from baseline to week 52 (LOCF) in mean of all meals blood glucose excursion from SMBG (mg/dL) by tertiles of β-cell function parameters at baseline by treatment. **a** By fasting C-peptide. **b** By C-peptide index. **c** By SUIT index. Excursion = Postprandial blood glucose − fasting blood glucose. *DU 0.75* once-weekly dulaglutide 0.75 mg, *LIRA 0.9* once-daily liraglutide 0.9 mg, *LOCF* last observation carried forward, *LS mean* least-squares mean, *N* number of patients, *SE* standard error, *SMBG* self-monitored blood glucose, *SUIT* secretory units of islets in transplantation

seems to be appropriate treatment for patients with longer duration of diabetes, because analysis of clinical trial data has shown that dulaglutide improves HbA1c regardless of duration of diabetes (using subgroups of < 7, ≥ 7 years in Japanese studies, and < 5, ≥ 5 and < 10, ≥ 10 years in global studies) [15, 16].

Compared with their Caucasian counterparts, Asian patients with T2D are less obese and tend to have a pathophysiology of decreased insulin secretion rather than insulin resistance [17]. If the glucose-lowering effect of incretin-based therapies depends predominantly on insulin-secretion capacity, it is expected that glucose-lowering efficacy would be lower in Asian patients than Caucasian patients. However, results of meta-analyses of incretin therapies have shown the opposite (i.e., glucose-lowering efficacy was greater in Asian patients than Caucasian patients) [18, 19]. This suggests that the glucose-lowering effect of incretin-based therapies might not depend on only insulin-secretion capacity.

Because the incidence of hypoglycemia was low overall in this monotherapy study [6], we

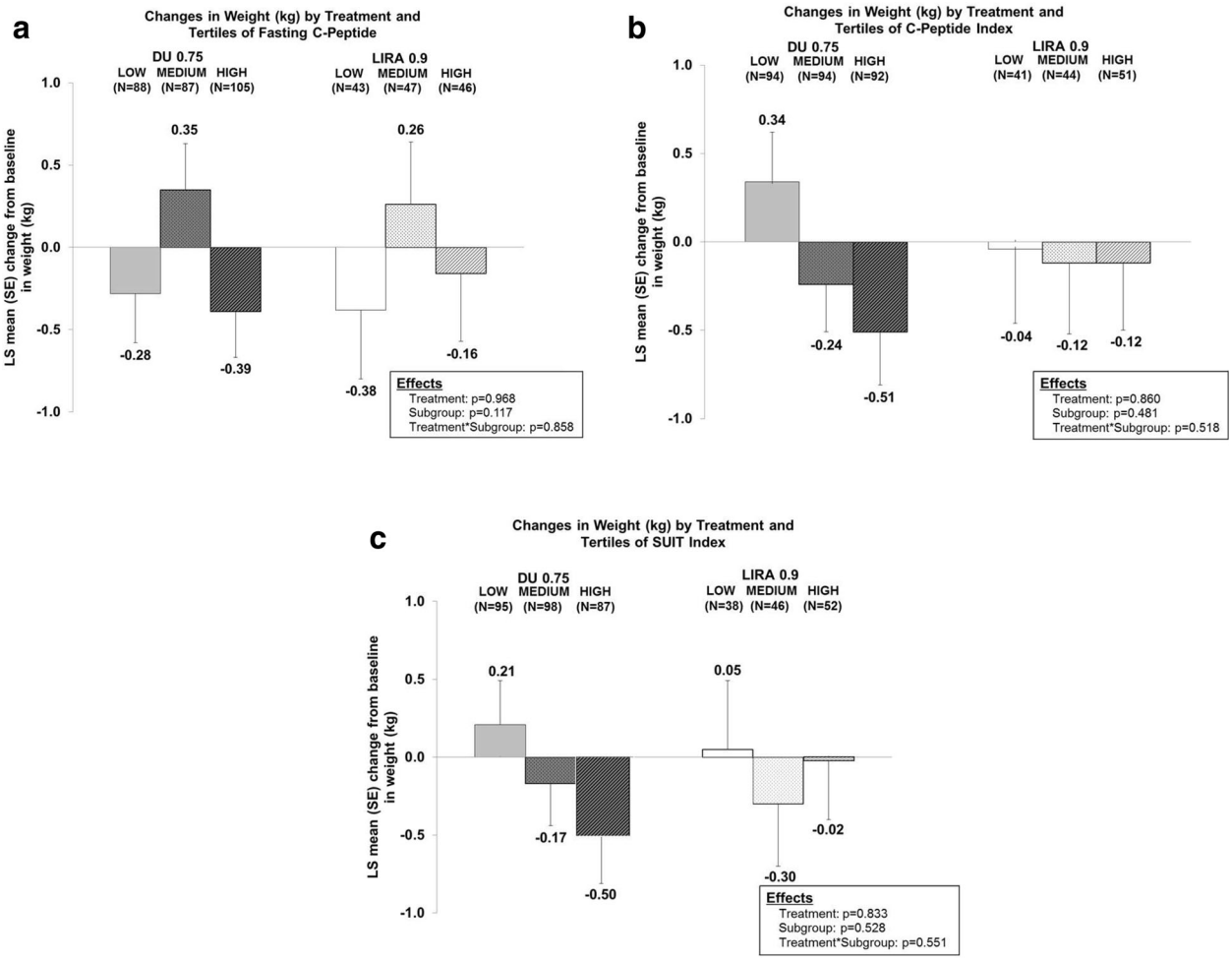

Fig. 5 LS mean ± SE changes from baseline to week 52 (LOCF) in body weight (kg) by tertiles of β-cell function parameters at baseline by treatment. **a** By fasting C-peptide. **b** By C-peptide index. **c** By SUIT index. *DU 0.75* once-weekly dulaglutide 0.75 mg, *LIRA 0.9* once-daily liraglutide 0.9 mg, *LOCF* last observation carried forward, *LS mean* least-squares mean, *N* number of patients, *SE* standard error, *SUIT* secretory units of islets in transplantation

did not evaluate incidence of hypoglycemia by β-cell function. In the combination group with dulaglutide and sulfonylurea in another study in Japan [7], there were no significant differences in incidence of hypoglycemia based on β-cell function, but the highest incidence of hypoglycemia was observed in patients with the lowest insulin-secretion capacity: incidence of hypoglycemia through 52 weeks of treatment was 41.9%, 34.1%, and 25.0% for patients in the low, medium, and high tertiles of CPI, respectively. The patients in this treatment group ($n = 131$) had longer mean duration of diabetes (9.4 vs. 6.8 years) than the dulaglutide-treated patients in this study [5, 7]. In the safety study, sulfonylurea doses were similar among patients in all three tertiles of CPR, CPI, and SUIT index (data not shown).

There were several limitations to this analysis. The patient population studied was limited: only patients with HbA1c $\geq$ 7.0 and $\leq$ 10.0% at randomization, with relatively short duration of T2D (mean 6.6 years), participated in this clinical study, a monotherapy study in which

concomitant OAMs were prohibited. The analyses were conducted post hoc. The β-cell parameters were estimated using only one point of fasting C-peptide at baseline, and more accurate results may be achieved by using the C-peptide response after a glucose tolerance test or glucagon stimulation test. Since standardized meals were not used in this study, differences in meals might have affected PBG and excursion values from SMBG within and between patients. The results were not adjusted for other potential confounding factors.

CONCLUSION

In a 1-year monotherapy study in Japanese patients with T2D treated with once-weekly dulaglutide 0.75 mg or once-daily liraglutide 0.9 mg, changes in HbA1c and weight could not be predicted by fasting pancreatic β-cell function before treatment.

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Authorship. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analyses. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. Noriyuki Iwamoto, Akiko Matsui, Hirotaka Kazama, and Tomonori Oura prepared the first draft of the manuscript. Tomonori Oura was responsible for statistical considerations. Noriyuki Iwamoto 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.

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Disclosures. Noriyuki Iwamoto, Akiko Matsui, and Tomonori Oura are employees of Eli Lilly Japan K.K, and Noriyuki Iwamoto and Tomonori Oura have the company stock option. Hirotaka Kazama contributed to this work as a former full-time employee of Eli Lilly Japan K.K. The opinions expressed in this work are solely his and do not represent his current affiliation, Sanofi K.K.

Compliance with Ethics Guidelines. This study is a subgroup analysis of a primary publication [5, 6]. The study protocol was approved at each site by an institutional review board. All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013, and Good Clinical Practice. Written informed consent was obtained from all patients before participation.

Data Availability. The datasets analyzed during the current study are not publicly available. Lilly provides access to the individual patient data from studies on approved medicines and indications as defined by the sponsor-specific information on http://clinicalstudydatarequest.com. Researchers need to have an approved research proposal submitted through http://clinicalstudydatarequest.com. Access to the data will be provided in a secure data sharing environment after signing a data sharing agreement.

REFERENCES

1. Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. Diabetes Metab Res Rev. 2016;32:776–90.

2. Usui R, Yabe D, Kuwata H, et al. Retrospective analysis of safety and efficacy of insulin-to-liraglutide switch in Japanese type 2 diabetes: a caution against inappropriate use in patients with reduced β-cell function. J Diabetes Investig. 2013;4:585–94.

3. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8:728–42.

4. Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M, Imaoka T. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab. 2015;17:994–1002.

5. Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. Diabetes Obes Metab. 2015;17:974–83.

6. Odawara M, Miyagawa J, Iwamoto N, Takita Y, Imaoka T, Takamura T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study. Diabetes Obes Metab. 2016;18:249–57.

7. Emoto M, Terauchi Y, Ozeki A, Oura T, Takeuchi M, Imaoka T. A 1-year safety study of dulaglutide in Japanese patients with type 2 diabetes on a single oral hypoglycemic agent: an open-label, nonrandomized, phase 3 trial. Endocr J. 2015;62:1101–14.

8. Yamada Y, Fukuda K, Fujimoto S, et al. SUIT, secretory units of islets in transplantation: an index for therapeutic management of islet transplanted patients and its application to type 2 diabetes. Diabetes Res Clin Pract. 2006;74:222–6.

9. Funakoshi S, Fujimoto S, Hamasaki A, et al. Utility of indices using C-peptide levels for indication of insulin therapy to achieve good glycemic control in Japanese patients with type 2 diabetes. J Diabetes Investig. 2011;2:297–303.

10. Iwata M, Matsushita Y, Fukuda K, et al. Secretory units of islets in transplantation index is a useful predictor of insulin requirement in Japanese type 2 diabetic patients. J Diabetes Investig. 2014;5:570–80.

11. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27:1487–95.

12. Matsumoto S, Noguchi H, Hatanaka N, et al. SUITO index for evaluation of efficacy of single donor islet transplantation. Cell Transplant. 2009;18:557–62.

13. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2015;37:2159–67 (Errata in Diabetes Care. 2014;37:2895 and 2015;38:1393–1394).

14. Yabe D, Ambos A, Cariou B, et al. Efficacy of lixisenatide in patients with type 2 diabetes: a post hoc analysis of patients with diverse β-cell function in the GetGoal-M and GetGoal-S trials. J Diabetes Complicat. 2016;30:1385–92.

15. Onishi Y, Oura T, Nishiyama H, Ohyama S, Takeuchi M, Iwamoto N. Subgroup analysis of phase 3 studies of dulaglutide in Japanese patients with type 2 diabetes. Endocr J. 2016;63:263–73.

16. Gallwitz B, Dagogo-Jack S, Thieu V, et al. Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c. Diabetes Obes Metab. 2017. https://doi.org/10.1111/dom.13086.

17. Yabe D, Seino Y, Fukushima M, Seino S. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. Curr Diab Rep. 2015;15:602.

18. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia. 2013;56:696–708.

19. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16:900–9.