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Safety and efficacy of the combination of the glucagon-like peptide-1 receptor agonist liraglutide with an oral antidiabetic drug in Japanese patients with type 2 diabetes: *Post-hoc* analysis of a randomized, 52-week, open-label, parallel-group trial

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ABSTRACT

Aims/Introduction: The aim of the present *post-hoc* analysis was to investigate the safety and efficacy of liraglutide in combination with one oral antidiabetic drug (OAD) across different OAD classes.

Materials and Methods: This was a *post-hoc* analysis using data from a 52-week, open-label, parallel-group trial, in which patients with type 2 diabetes inadequately controlled with a single OAD (α-glucosidase inhibitor, glinide, metformin or thiazolidinedione) were randomized to either pretrial OAD in combination with liraglutide 0.9 mg/day (liraglutide group) or pretrial OAD in combination with an additional OAD (additional OAD group). The primary outcome investigated in this *post-hoc* analysis was the incidence of adverse events.

Results: The proportions of patients experiencing adverse events across the different groups of pretrial OADs were comparable between liraglutide and additional OAD (α-glucosidase inhibitor 74.6 vs 70.0%; glinide 93.1 vs 87.1%; metformin 91.8 vs 87.1%; thiazolidinedione 86.2 vs 96.4%, respectively). Minor hypoglycemia was infrequent (seven episodes in two patients randomized to liraglutide, and two episodes in two patients randomized to additional OAD). The mean reduction in glycated hemoglobin appeared greater with liraglutide therapy, with the estimated mean treatment difference (95% confidence interval [CI]) for liraglutide vs additional OAD ranging from −0.14%, 95% CI: −0.48 to 0.21 (−1.5 mmol/mol, 95 CI: −5.2 to 2.3) to −0.44%, 95% CI:−0.79 to −0.09 (−4.8 mmol/mol, 95% CI: −8.6 to −1.0).

Conclusions: The present analysis suggests that Japanese patients on OAD monotherapy might benefit from a greater improvement in glycemic control, without impacting tolerability, by combining their OAD with liraglutide rather than another OAD, regardless of which OAD monotherapy they are receiving.

INTRODUCTION

Type 2 diabetes is a chronic, progressive disease, with patients typically commencing treatment with lifestyle modification followed by monotherapy with an oral antidiabetic drug (OAD)[1].

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Subsequent treatment intensification with combination and/or insulin therapy is often required as glycemic control deteriorates[2]. Currently-used OADs are associated with a number of adverse effects; these can include weight gain and the risk of hypoglycemia, each of which can influence the choice of therapy[3]. It is recommended that the glucose-lowering regimen is individualized, taking into consideration patient characteristics, such as age and comorbidities, as well as patient preference of regimen[2,4].

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of injectable drugs that mimic the effects of the incretin hormone, GLP-1, but have a longer half-life than native GLP-1[5]. GLP-1 acts by increasing insulin synthesis and secretion, as well as suppressing glucagon secretion in a glucose-dependent manner, in addition to reducing gastric emptying and appetite[5]. Global phase 3 trials have shown that the GLP-1 receptor agonist, liraglutide, is effective in a variety of antidiabetic treatment combinations and across the diabetes continuum[6–15]. The efficacy and safety of liraglutide in Japanese patients have also been established in a variety of OAD treatment combinations, including in combination with sulfonylurea (which is generally associated with an increased risk of hypoglycemia compared with other OAD–liraglutide combinations), as well as in combination with insulin[16–19].

A 52-week, open-label, randomized, parallel-group, phase 3 trial confirmed the long-term safety and efficacy of liraglutide in combination with an OAD in Japanese patients with type 2 diabetes who had inadequate glycemic control on OAD monotherapy[18]. The objective of this *post-hoc* analysis was to investigate the safety and efficacy of liraglutide (0.9 mg once daily) when added to the following pretrial OADs: α-glucosidase inhibitor, glinide, metformin or thiazolidinedione when compared with an active comparator.

METHODS

Trial design

The present *post-hoc* analysis was carried out using data from a 52-week, multicenter, open-label, randomized, parallel-group, phase 3 trial (ClinicalTrials.gov: NCT01512108). The protocol and design of this trial have previously been described in detail[18].

In brief, eligible patients (n = 363) were randomized 2:1 to liraglutide (0.9 mg/day) + pretrial OAD therapy (liraglutide group) or pretrial OAD in combination with an additional OAD (additional OAD group). Three patients randomized to liraglutide were withdrawn before being exposed to the trial product. Patients were stratified according to the type of pretrial OAD (α-glucosidase inhibitor, glinide, metformin or thiazolidinedione) at randomization (Figure S1). In patients randomized to receive additional OAD, the type, dosage and administration of the additional OAD (dipeptidyl peptidase-4 [DPP-4] inhibitor, sulfonylurea, glinide, metformin, α-glucosidase inhibitor or thiazolidinedione) were chosen by the investigator within the approved labeling in Japan.

Patients

Eligible participants (aged ≥20 years) had type 2 diabetes for ≥6 months, glycated hemoglobin (HbA1c) 7.0–10.0% (53–86 mmol/mol), body mass index <40.0 kg/m^2 and current treatment with OAD monotherapy within approved Japanese labeling, in addition to diet and exercise therapy, with unchanged dosing and type of drug for ≥8 weeks.

Key exclusion criteria were: use of GLP-1 receptor agonist, DPP-4 inhibitor or insulin within 12 weeks before screening; recurrent severe hypoglycemia or hypoglycemic unawareness (as judged by the investigator); or hospitalization for diabetic ketoacidosis within the past 6 months; or having contraindications to liraglutide and any of the OADs (according to Japanese labeling).

The trial was carried out in accordance with the Declaration of Helsinki[20] and the International Conference on Harmonization of Good Clinical Practice[21], and all patients provided written informed consent before participation.

End-points

The primary end-point was the incidence of adverse events (AEs) during 52 weeks[18]. Secondary safety end-points included the number of hypoglycemic episodes during 52 weeks, and changes from baseline in blood pressure and pulse rate. Hypoglycemia (severe, documented symptomatic, asymptomatic, probable symptomatic and relative) was classified according to the American Diabetes Association definitions[22]. In addition, a minor hypoglycemia category was included, defined as plasma glucose <56 mg/dL (3.1 mmol/L) or blood glucose <50 mg/dL (2.8 mmol/L), without a requirement for third-party assistance for any symptoms. Collectively, severe (American Diabetes Association definition) and minor (definition above) hypoglycemia were referred to as confirmed hypoglycemic episodes.

Secondary efficacy end-points, assessed after week 52, included change in HbA1c from baseline, patients achieving HbA1c target of <7.0% (53 mmol/mol), change in fasting plasma glucose (FPG) from baseline, change in bodyweight from baseline and change in β-cell function from baseline (homeostasis model assessment of β-cell function, proinsulin:insulin ratio, proinsulin:C-peptide ratio). Seven-point self-measured plasma glucose profiles were assessed (change from baseline in mean plasma glucose and mean prandial plasma glucose increment).

Statistical analysis

The sample size was determined in accordance with the requirements of the Japanese Ministry of Health, Labor and Welfare Guideline for Clinical Evaluation of Oral Hypoglycemic Agents[23].

Efficacy end-points were analyzed based on the full analysis set, which comprised all randomized patients who received at least one dose of trial product, with patients contributing 'as randomized.' The safety analyses were based on the safety analysis set, which included all patients receiving at least one dose

of trial product, with patients contributing 'as treated.' For all end-points, the last observation carried forward approach was used for patients with at least one valid post-baseline measurement.

For the primary end-point, the incidence of AEs, number and proportion of patients with at least one AE, the number of AEs and the AE rate per 100 patient-years of exposure were assessed and presented by pretrial OAD. Secondary efficacy end-points (except for patients achieving target HbA1c <7.0% [53 mmol/mol]) were analyzed using an analysis of variance model with treatment, type of pretrial OAD, and interaction between treatment and type of pretrial OAD as fixed effects, with the corresponding baseline value as a covariate. The treatment difference for each pretrial OAD was estimated with the corresponding 95% confidence interval (CI). A logistic regression model was used for the analysis of patients achieving target HbA1c <7.0% (53 mmol/mol), with treatment, type of pretrial OAD, and interaction between treatment and type of pretrial OAD as fixed effects and HbA1c at baseline as a covariate. The odds ratio for each pretrial OAD was estimated with corresponding 95% CI.

RESULTS

Demographics

The number of patients in each pretrial OAD group was comparable: α-glucosidase inhibitor (n = 93), glinide (n = 91), metformin (n = 92) and thiazolidinedione (n = 87; Figure S2). Three patients randomized to receive liraglutide were withdrawn before being exposed to the trial product, leaving a total of 360 patients in the full analysis set; this included 240 patients randomized to liraglutide and 120 to additional OAD. Baseline demographic data by pretrial OAD group are given in Table 1. Characteristics of patients, according to both pretrial OAD and treatment group (liraglutide or second OAD), were largely similar (Table 1).

Additional oral antidiabetic therapy

In the additional OAD therapy subgroups, the most commonly selected drugs were DPP-4 inhibitors and metformin, being used by 42.5 and 25.0% of patients, respectively. Thiazolidinediones (4.2%) and glinides (3.3%) were the least commonly used additional OADs (Table S1).

Of the α-glucosidase inhibitor, metformin and thiazolidinedione pretrial OAD groups, DPP-4 inhibitors were the most common additional therapy subgroup, being used by 46.7, 67.7 and 57.1% of patients, respectively. Of the glinide pretrial OAD group, α-glucosidase inhibitor and metformin additional therapy subgroups were used by 45.2 and 38.7% of patients, respectively (Table S2).

Safety and tolerability

The number of patients who withdrew during the study was highest in the α-glucosidase inhibitor and glinide pretreatment groups (Figure S1). Patient withdrawals as a result of AEs were

Table 1 | Baseline characteristics according to pretrial oral antidiabetic drug

	α-Glucosidase inhibitors		Glinide		Metformin		Thiazolidinedione	
	Liraglutide	Additional OAD	Liraglutide	Additional OAD	Liraglutide	Additional OAD	Liraglutide	Additional OAD
Full analysis set (n)	63	30	58	31	61	31	58	28
Age (years)	60.3 ± 11.6	55.8 ± 9.7	61.1 ± 11.6	61.2 ± 10.6	57.9 ± 11.6	60.3 ± 11.2	59.3 ± 11.6	59.3 ± 8.3
Duration of diabetes (years)	7.7 ± 5.8	7.7 ± 4.7	8.7 ± 6.4	9.2 ± 7.8	7.6 ± 5.8	10.0 ± 7.4	7.2 ± 5.0	6.9 ± 5.5
Female (%)	20.6	30.0	20.7	22.6	36.1	32.3	19.0	50.0
Male (%)	79.4	70.0	79.3	77.4	63.9	67.7	81.0	50.0
Bodyweight (kg)	67.9 ± 12.4	70.5 ± 14.0	68.9 ± 12.3	66.5 ± 14.4	68.6 ± 17.1	68.8 ± 12.4	72.5 ± 14.2	67.0 ± 13.9
BMI (kg/m^2)	25.1 ± 3.8	25.8 ± 3.6	25.6 ± 4.0	24.4 ± 4.0	25.7 ± 4.8	25.6 ± 3.8	26.7 ± 4.2	26.2 ± 3.2
FPG (mg/dL)	153 ± 28	169 ± 39	170 ± 30	161 ± 23	152 ± 23	160 ± 37	151 ± 31	155 ± 30
HbA1c (%)	7.9 ± 0.8	8.1 ± 0.8	8.3 ± 0.8	8.1 ± 0.7	8.0 ± 0.7	8.0 ± 0.8	8.0 ± 0.8	8.1 ± 0.7
HbA1c (mmol/mol)	63.1 ± 8.6	65.3 ± 9.2	67.1 ± 8.9	64.8 ± 8.2	63.6 ± 7.7	64.1 ± 8.3	64.4 ± 8.4	64.5 ± 8.0

Data are mean ± standard deviation. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; n, number of patients; OAD, oral antidiabetic drug.

highest in the groups pretreated with α-glucosidase inhibitors, with six patients withdrawing after the addition of liraglutide and one patient withdrawing after the addition of a second OAD. The proportion of patients experiencing AEs appeared lowest in the α-glucosidase inhibitor group (74.6% with liraglutide and 70.0% with additional OAD treatment), and appeared largely comparable in the other OAD groups (ranging from 86.2 to 93.1% in the liraglutide group and 87.1 to 96.4% in the additional OAD group; Table 2).

The AE rate per 100 exposure-years was numerically lowest in patients pretreated with α-glucosidase inhibitors (301 for liraglutide and 224 for additional OAD treatment), and numerically highest in patients pretreated with metformin (427 for liraglutide and 418 for additional OAD treatment; Table 2). The proportion of patients reporting serious AEs was low overall, and comparable between the addition of liraglutide and a second OAD across pretrial OAD groups, with the exception of patients pretreated with thiazolidinediones. Of those patients pretreated with thiazolidinediones, one (1.7%) randomized to liraglutide and six (21.4%) randomized to an additional OAD reported serious AEs. The incidence of severe AEs was low, ranging from 0 to 3.4% in the patients across all subgroups (Table 2). One death (lung neoplasm malignancy) was reported with liraglutide in the α-glucosidase inhibitor pretreated group. This event was considered unlikely to be related to liraglutide by the investigator.

The majority of AEs were mild in severity, and patients had recovered or were recovering at the end of the 52-week treatment period. Gastrointestinal AEs were commonly reported with the addition of both liraglutide and other OADs, but the proportion of patients with gastrointestinal AEs was higher in patients treated with liraglutide than with additional OAD therapy, and appeared to be highest in the metformin pretrial groups. Gastrointestinal AEs were mostly reported during the first 4 weeks of treatment with liraglutide, regardless of pretrial OAD (Figure S3).

There was no severe hypoglycemia reported during the trial. Minor hypoglycemic episodes were reported by two patients randomized to additional liraglutide (seven episodes [one in the α-glucosidase inhibitor pretrial OAD group and six in the thiazolidinedione pretrial OAD group]) and two patients randomized to an additional OAD (two episodes [one in the glinide pretrial OAD group and one in the thiazolidinedione pretrial OAD group]; Table 2). There was one minor episode of nocturnal hypoglycemia with liraglutide in the α-glucosidase inhibitor pretreated group.

Estimated mean changes in diastolic and systolic blood pressure showed a decrease from baseline in all subgroups for both liraglutide (ranging from −0.09 to −2.26 mmHg diastolic; −2.52 to −5.54 mmHg systolic) and additional OAD (ranging from −0.17 to −2.67 mmHg diastolic; −2.87 to −6.27 mmHg systolic; Table 2). Pulse rate increased in all groups; however, patients randomized to liraglutide had a greater increase in pulse rate than those given an additional OAD across all subgroups, a difference that was significant among patients pretreated with glinides (estimated treatment difference 4.12, 95% CI: 0.26–7.99, $P = 0.0364$) and with metformin (estimated treatment difference 6.69, 95% CI: 2.85–10.53, $P = 0.0007$; Table 2).

Efficacy

There was no statistically significant interaction between treatment and pretrial OAD for efficacy end-points (P-value testing for the interaction: $P > 0.05$ for all; Table 3).

The mean change in HbA1c at 52 weeks according to pretrial OAD therapy is summarized in Table 3. In all groups, the reduction in HbA1c appeared greater with liraglutide, with an estimated treatment difference for liraglutide vs additional OAD ranging from −0.14%, [95% CI: −0.48 to 0.21] (−1.49 mmol/mol, 95% CI: −5.24 to 2.26) to −0.44%, 95% CI: −0.79 to −0.09 (−4.82 mmol/mol, [95% CI: −8.61 to −1.04]). With the exception of patients pretreated with α-glucosidase inhibitors, the reduction in HbA1c observed with liraglutide compared with additional OAD did not reach statistical significance in other pretrial OAD groups (Table 3).

The proportion of patients achieving target HbA1c <7.0% (53 mmol/mol) tended to be higher with liraglutide compared with additional OAD, regardless of pretrial OAD therapy (Table 3), and the estimated odds ratio reached statistical significance for patients pretreated with α-glucosidase inhibitors and thiazolidinediones ($P < 0.05$). In those patients pretreated with glinides and metformin, although there was a numerically higher number of patients achieving target with liraglutide compared with additional OAD, the estimated odds ratio was not statistically significant (Table 3). Additionally, there was a small, statistically non-significant reduction in FPG observed with liraglutide compared with additional OAD in patients pretreated with α-glucosidase inhibitors, metformin and thiazolidinediones (Table 3). In patients pretreated with glinides, the change in FPG was comparable between addition of liraglutide and a second OAD (−21.9 vs −22.0 mg/dL, respectively; $P = 0.9824$).

With both liraglutide and additional OAD, a small, statistically non-significant reduction in bodyweight (ranging from −0.55 to −1.58 kg) was observed in patients pretreated with α-glucosidase inhibitors, glinides and metformin. Bodyweight in the thiazolidinedione group was relatively unchanged (+0.20 vs −0.11 kg with liraglutide and additional OAD, respectively; Table 3).

After 52 weeks of treatment, differences in β-cell function were observed across treatment subgroups. Patients in all pretrial treatment groups had higher homeostasis model assessment of β-cell function at 52 weeks after the addition of liraglutide compared with a second OAD, although these estimated treatment ratios did not reach statistical significance in the groups pretreated with α-glucosidase inhibitors and thiazolidinediones. In all groups, lower proinsulin:insulin ratios at 52 weeks were observed with the addition of liraglutide vs a second OAD, but this estimated treatment ratio was not

Table 2 | Treatment-emergent adverse events, hypoglycemia, blood pressure and pulse rate for liraglutide and additional oral antidiabetic drug subgroups, according to pretrial oral antidiabetic drug

	α-Glucosidase inhibitors		Glinide		Metformin		Thiazolidinedione		Test for interaction between treatment and pretrial OAD
	Liraglutide (*n* = 63)	Additional OAD (*n* = 30)	Liraglutide (*n* = 58)	Additional OAD (*n* = 31)	Liraglutide (*n* = 61)	Additional OAD (*n* = 31)	Liraglutide (*n* = 58)	Additional OAD (*n* = 28)	
AEs									
n (%)	47 (74.6)	21 (70.0)	54 (93.1)	27 (87.1)	56 (91.8)	27 (87.1)	50 (86.2)	27 (96.4)	NA
E	167	65	212	97	253	124	185	94	
R	301	224	393	329	427	418	320	353	
Serious AEs									
n (%)	2 (3.2)	2 (6.7)	6 (10.3)	2 (6.5)	2 (3.3)	0	1 (1.7)	6 (21.4)	NA
E	2	2	6	2	2		1	6	
R	4	7	11	7	3		2	23	
Severe AEs									
n (%)	1 (1.6)	1 (3.3)	2 (3.4)	1 (3.2)	1 (1.6)	0	0	0	NA
E	1	1	2	1	2				
R	2	3	4	3	3				
Probably/possibly related to investigational product[†]									
n (%)	25 (39.7)		32 (55.2)		27 (44.3)		24 (41.4)		NA
E	49		59		58		43		
R	88		109		98		74		
Gastrointestinal AEs									
n (%)	25 (39.7)	6 (20.0)	32 (55.2)	12 (38.7)	38 (62.3)	15 (48.4)	27 (46.6)	8 (28.6)	NA
E	43	9	46	16	72	48	41	13	
R	78	31	85	54	121	162	71	49	
Minor hypoglycemia									
n (%)	1 (1.6)	0	0	1 (3.2)	0	0	1 (1.7)	1 (3.6)	NA
E	1			1			6	1	
R	2			3			10	4	
Systolic blood pressure[‡] (mmHg)	−5.23	−6.27	−2.59	−2.87	−5.54	−3.23	−2.52	−3.22	*P* = 0.7676
ETD (95% CI) *P*-value	1.03 (−3.84; 5.91) *P* = 0.6771		0.28 (−4.60; 5.15) *P* = 0.9112		−2.31 (−7.15; 2.53) *P* = 0.3481		0.70 (−4.34; 5.74) *P* = 0.7842		
Diastolic blood pressure[‡] (mmHg)	−1.49	−0.17	−0.09	−2.67	−2.26	−1.72	−1.88	−1.94	*P* = 0.4366
ETD (95% CI) *P*-value	−1.32 (−4.80; 2.16) *P* = 0.4568		2.57 (−0.90; 6.04) *P* = 0.1456		−0.54 (−3.99; 2.90) *P* = 0.7560		0.06 (−3.53; 3.65) *P* = 0.9752		
Pulse[‡] (b.p.m.)	5.53	3.34	5.82	1.70	8.38	1.69	5.16	3.00	*P* = 0.3145
ETD (95% CI) *P*-value	2.18 (−1.68; 6.04) *P* = 0.2673		4.12 (0.26; 7.99) *P* = 0.0364		6.69 (2.85; 10.53) *P* = 0.0007		2.16 (−1.84; 6.16) *P* = 0.2882		

[†]Relationship to investigational product was only evaluated in the liraglutide group. [‡]Change from baseline after 52 weeks of treatment. AE, adverse event; E, number of events; ETD, estimated treatment difference; *n*, number of patients; OAD, oral antidiabetic drug; R, event rate per 100 exposure-years.

Table 3 | Efficacy parameters at week 52 for liraglutide and additional oral antidiabetic drug subgroups, according to pretrial oral antidiabetic drug

	α-Glucosidase inhibitors		Glinide		Metformin		Thiazolidinedione		Test for interaction between treatment and pretrial OAD
	Liraglutide	Additional OAD	Liraglutide	Additional OAD	Liraglutide	Additional OAD	Liraglutide	Additional OAD	
Change in HbA1c† (%)	−1.29	−0.85	−1.08	−0.93	−1.06	−0.92	−1.41	−1.06	$P = 0.5345$
ETD (95% CI) *P*-value	−0.44 (−0.79; −0.09) $P = 0.0127$		−0.15 (−0.50; 0.20) $P = 0.3964$		−0.14 (−0.48; 0.21) $P = 0.4347$		−0.35 (−0.71; 0.01) $P = 0.0548$		
Change in HbA1c† (mmol/mol)	−14.12	−9.29	−11.84	−10.20	−11.58	−10.09	−15.44	−11.61	$P = 0.5345$
ETD (95% CI) *P*-value	−4.82 (−8.61; −1.04) $P = 0.0127$		−1.64 (−5.42; 2.15) $P = 0.3964$		−1.49 (−5.24; 2.26) $P = 0.4347$		−3.83 (−7.74; 0.08) $P = 0.0548$		
Patients achieving HbA1c <7.0% (53 mmol/mol)‡, %	72.73	38.76	55.77	40.57	58.91	41.86	80.93	58.22	$P = 0.6392$
OR (95% CI) *P*-value	4.21 (1.50; 11.86) $P = 0.0065$		1.85 (0.69; 4.94) $P = 0.2220$		1.99 (0.76; 5.19) $P = 0.1586$		3.05 (1.03; 8.99) $P = 0.0439$		
Change in FPG† (mg/dL)	−29.1	−22.4	−21.9	−22.0	−26.8	−18.8	−33.8	−26.3	$P = 0.6951$
ETD (95% CI) *P*-value	−6.7 (−17.5; 4.0) $P = 0.2194$		0.1 (−10.6; 10.8) $P = 0.9824$		−7.9 (−18.5; 2.6) $P = 0.1408$		−7.5 (−18.6; 3.5) $P = 0.1796$		
Change in bodyweight† (kg)	−1.30	−0.56	−0.64	−0.55	−1.58	−0.75	0.20	−0.11	$P = 0.5652$
ETD (95% CI) *P*-value	−0.74 (−2.01; 0.54) $P = 0.2569$		−0.10 (−1.37; 1.18) $P = 0.8790$		−0.84 (−2.01; 0.43) $P = 0.1933$		0.31 (−1.01; 1.63), $P = 0.6442$		
HOMA-β‡ (%)	46.03	38.96	44.65	31.36	44.19	33.55	46.26	38.01	$P = 0.5960$
ETR (95% CI) *P*-value	1.18 (0.96; 1.45) $P = 0.1137$		1.42 (1.16; 1.75) $P = 0.0009$		1.32 (1.07; 1.62) $P = 0.0086$		1.22 (0.98; 1.51) $P = 0.0718$		
Proinsulin:Insulin ratio‡ (%)	31.63	32.36	32.44	41.70	32.03	40.07	29.29	38.25	$P = 0.3568$
ETR (95% CI) *P*-value	0.98 (0.79; 1.21) $P = 0.8335$		0.78 (0.63; 0.96) $P = 0.0219$		0.80 (0.65; 0.99) $P = 0.0381$		0.77 (0.61; 0.96) $P = 0.0185$		
Proinsulin:C-peptide ratio‡	0.025	0.028	0.026	0.029	0.024	0.031	0.022	0.031	$P = 0.4125$
ETR (95% CI) *P*-value	0.870 (0.725; 1.045) $P = 0.1355$		0.884 (0.736; 1.061) $P = 0.1845$		0.775 (0.647; 0.929) $P = 0.0060$		0.729 (0.604; 0.881) $P = 0.0011$		
Change in mean seven-point SMPG profile† (mg/dL)	−45.5	−32.5	−34.6	−25.1	−39.0	−30.6	−43.3	−34.8	0.9670
ETD (95% CI) *P*-value	−12.9 (−27.1; 1.2) $P = 0.0736$		−9.5 (−23.7; 4.8) $P = 0.1912$		−8.3 (−22.3; 5.6) $P = 0.2415$		−8.5 (−23.1; 6.0) $P = 0.2506$		
Change in mean prandial increment in SMPG for all meals† (mg/dL)	−24.7	−28.7	−18.8	−27.9	−18.6	−16.6	−16.7	−13.1	0.5422
ETD (95% CI) *P*-value	4.0 (−9.5; 17.5) $P = 0.5598$		9.1 (−4.4; 22.6) $P = 0.1846$		−2.0 (−15.3; 11.3) $P = 0.7668$		−3.7 (−17.5; 10.2) $P = 0.6049$		

†Change from baseline. ‡After 52 weeks of treatment. CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment of β-cell function; OAD, oral antidiabetic drug; OR, odds ratio; PG, plasma glucose; SMPG, self-measured plasma glucose.

statistically significant in those pretreated with α-glucosidase inhibitors. Likewise, in all groups, lower proinsulin:C-peptide ratios at 52 weeks were observed with liraglutide than with additional OAD, although these estimated treatment ratios were not statistically significant in those patients pretreated with α-glucosidase inhibitors and glinides (Table 3).

The change in the mean of the seven-point self-measured plasma glucose profile was greater, but statistically non-significant, from baseline to week 52 in all groups comparing patients randomized to liraglutide vs additional OAD (Table 3). Similarly, prandial increments in self-measured plasma glucose showed small decreases from baseline to week 52 in all subgroups, but with no statistically significant differences between liraglutide and additional OAD (Table 3).

DISCUSSION

The present *post-hoc* analysis investigated the safety and efficacy of liraglutide when added to the following pretrial OADs: α-glucosidase inhibitor, glinide, metformin or thiazolidinedione, using data from a phase 3 trial in Japanese patients with type 2 diabetes who were inadequately controlled on OAD monotherapy[18]. Across all efficacy end-points, tests for interaction showed no evidence that the treatment effects of liraglutide varied by pretrial OAD. The present analysis shows that the safety and efficacy of liraglutide were generally consistent across pretrial OAD groups, suggesting that liraglutide is well tolerated and effective, irrespective of which OAD it is used in combination with.

The numerically highest AE rates were seen in the metformin as pretrial OAD group, with both liraglutide and additional OAD. The event rates for gastrointestinal AEs were also numerically highest in the group pretreated with metformin. These findings are not unexpected, as gastrointestinal AEs are frequently reported by patients who are administered metformin[3,24]. The proportion of patients with AEs, and the event rate, appeared lower with α-glucosidase inhibitors as pretrial OAD compared with the pretrial OAD glinide, metformin or thiazolidinedione groups, despite this pretreatment group having the highest proportion of patients who withdrew as a result of AEs. Of note, this pretreatment group did not have a higher proportion of patients reporting serious or severe AEs.

While more patients randomized to liraglutide than to additional OAD reported gastrointestinal disorders during the initial weeks of treatment, this effect diminished and no notable differences between these treatments were then observed up to 52 weeks. This is consistent with previous data, which have shown that gastrointestinal disorders reported with liraglutide are generally mild in nature and transient[25].

Low rates of hypoglycemia were reported in this trial, with seven minor hypoglycemic episodes reported by two patients on liraglutide, and two episodes reported by two patients on additional OAD. No severe hypoglycemic episodes were reported in this trial. This is consistent with the glucose-dependent mechanism of action of liraglutide and previous data showing a low risk of hypoglycemia with this antihyperglycemic agent[26].

The efficacy outcomes in the overall trial population showed a reduction in HbA1c of −1.21% (−13.22 mmol/mol) with liraglutide treatment and −0.94% (−10.30 mmol/mol) with additional OAD treatment[18]. The present *post-hoc* analysis shows that all pretrial OAD groups contributed to this HbA1c reduction. Overall, there was a trend towards better glycemic efficacy with liraglutide regardless of pretrial OAD, as suggested by the results of HbA1c reduction and the proportion of patients achieving HbA1c <7.0%.

There was a small reduction in bodyweight observed with both liraglutide and additional OAD for patients in the pretrial α-glucosidase inhibitor, glinide and metformin groups. However, bodyweight was relatively unchanged with both liraglutide and additional OAD for patients pretreated with thiazolidinediones, a finding that is in line with the weight gain usually seen with this OAD[27].

There were several limitations to the present study. The analyses were carried out *post-hoc*, and the power calculations were not designed for this purpose, hence between-treatment differences were not of statistical significance for many end-points. Furthermore, the study was carried out in an unblinded study population for ethical and practical reasons. There was a relatively small number of patients in the groups stratified according to pretrial OAD, and patient selection bias might also be a confounding factor. The durability of combination treatment of liraglutide with different OADs beyond 1 year cannot be assessed.

The present *post-hoc* analysis has shown that the safety and efficacy of liraglutide was generally consistent whether added to α-glucosidase inhibitors, glinides, metformin or thiazolidinediones, and showed similar tolerability and greater efficacy compared with an active comparator. In addition, no new safety signals emerged. The safety and efficacy of liraglutide in combination with sulfonylureas have been shown in previous trials in a Japanese population[16,17]. The efficacy of liraglutide in glycemic control, when added to α-glucosidase inhibitors, glinides, metformin or thiazolidinediones, was clinically relevant and comparable overall with the effect of liraglutide seen in previous trials in Japanese patients[16–18,28,29].

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DISCLOSURE

A Kiyosue has received honoraria for lectures from Takeda, Ono, AstraZeneca, Novartis, Bayer, Sanofi, Boehringer Ingelheim, Sumitomo Dainippon Pharma, Meiji Seika Pharma,

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Combination of oral antidiabetic drugs in additional oral antidiabetic drug subgroup.
Table S2 | Number of additional oral antidiabetic drug subgroups in pretrial oral antidiabetic drug group.
Figure S1 | Participant flow.
Figure S2 | Trial design.
Figure S3 | Proportion of patients with gastrointestinal disorders over time, according to pretrial oral antidiabetic drug therapy.