ORIGINAL ARTICLE

Efficacy and safety of adding liraglutide to existing insulin regimens in Japanese patients with type 2 diabetes mellitus: A *post-hoc* analysis of a phase 3 randomized clinical trial

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ABSTRACT

Aims/Introduction: To determine the efficacy and safety of adding liraglutide to three different insulin regimens in Japanese patients with type 2 diabetes mellitus.

Materials and Methods: In this *post-hoc* analysis, results from a 36-week, randomized, double-blind, *placebo*-controlled, parallel-group trial are reported. Individuals with type 2 diabetes mellitus were stratified according to their pre-trial insulin regimen (basal, basal–bolus and premix). The primary objective was to determine whether adding liraglutide (0.9 mg/day) to fixed-dose insulin therapy was superior vs fixed-dose insulin monotherapy, assessed by the effect on glycemic control after 16 weeks of treatment.

Results: The treatment effect on glycated hemoglobin reduction was independent of the pre-trial insulin regimen. Comparing liraglutide with a *placebo*, liraglutide was associated with glycated hemoglobin reduction in all insulin regimens, with *placebo*-corrected reductions at 16 weeks ranging from −1.45 to −1.17%, and maintained at 36 weeks. Liraglutide resulted in a greater reduction in mean plasma glucose obtained from seven-point self-monitoring, and greater proportions of patients achieved target glycated hemoglobin. With liraglutide, slightly higher proportions of patients receiving basal and basal–bolus insulin reported confirmed hypoglycemia from 0 to 16 weeks.

Conclusions: The efficacy and safety of adding liraglutide to insulin therapy was confirmed, regardless of pre-trial insulin regimen.

INTRODUCTION

The global prevalence of diabetes is increasing, with cases recently estimated at 415 million by the International Diabetes Federation[1]. As with most countries around the world[1], the burden of diabetes in Japan is a growing concern[2].

Accounting for 90% of cases of diabetes, type 2 diabetes mellitus is a progressive disease, so patients might require treatment intensification over time to achieve and maintain appropriate glycemic control[3,4]. For those treated with basal insulin therapy, intensification (beyond dose titration) can include converting to a basal–bolus regimen by the addition of mealtime rapid-acting insulin, or switching to a premix insulin formulation[3–5]. Alternatively, when compared with continued and titrated insulin therapy, the addition of a glucagon-like peptide 1 receptor agonist (GLP-1RA) can improve glycated hemoglobin (HbA1c) levels without an elevated risk of hypoglycemia, while at the same time avoiding weight gain[6–9].

A meta-analysis of 15 studies by Kim *et al.*[10] showed that GLP-1RAs lowered HbA1c to a greater extent in studies where the cohorts were predominantly Asian than in studies with predominantly non-Asian cohorts. However, bodyweight changes were comparable between both cohort types. In addition, hypoglycemia tended to be more common in Asian-dominant studies than in non-Asian dominant studies[10]. The aim of the present *post-hoc* analysis, which was based on data from the phase 3b Efficacy and Safety of Liraglutide in Combination With Insulin Therapy Compared to Insulin Alone in Japanese Subjects With Type 2 Diabetes (LIRA-ADD2INSULIN JAPAN)

trial (ClinicalTrials.gov NCT01572740)[6], was to assess the efficacy and safety of the GLP-1 analog, liraglutide, in combination with insulin (basal, basal–bolus or premix) compared with insulin monotherapy in Japanese patients with type 2 diabetes mellitus.

METHODS
Trial design
LIRA-ADD2INSULIN JAPAN was a 36-week, randomized, multicenter, double-blind, *placebo*-controlled, parallel-group trial involving 257 Japanese patients with type 2 diabetes mellitus[6].

The trial design and protocol have been described previously[6]. In brief, participants were randomized (1:1) to once-daily subcutaneous liraglutide (0.9 mg) or *placebo* added to their existing insulin regimen. Participants were stratified according to the type of pre-trial insulin regimen at randomization. The insulin dose was fixed at the pre-study dose for the first 16 weeks then subsequently down- or uptitrated based on participants' self-measured plasma glucose (SMPG; measured using hand-held OneTouch® UltraVue™ meters; Johnson & Johnson, New Brunswick, NJ, USA) values and an insulin titration algorithm for the remaining study period[6].

Eligibility criteria
Eligible participants were men or women, aged ≥20 years, with type 2 diabetes mellitus for ≥6 months, HbA1c 7.5–11.0% (59–97 mmol/mol; inclusive) and body mass index <45.0 kg/m². In addition to diet and exercise, all participants received a basal, basal–bolus or premix insulin regimen that had to have been stable (maximum daily fluctuation in dose, ±20%) at a total daily dose ≥10 U/day for ≥12 weeks before screening. Participants could not have been taking an oral antidiabetic drug or a GLP-1RA within the previous 12 weeks before screening.

All participants provided written informed consent before participation, and the trial was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice.

End-points
The primary end-point was the change in HbA1c from baseline after 16 weeks. Secondary efficacy end-points (assessed at 16 and 36 weeks, unless otherwise stated) included change from baseline in: HbA1c (36 weeks); insulin dose (36 weeks); fasting plasma glucose (FPG); seven-point SMPG profiles (change from baseline in mean plasma glucose [PG] and mean prandial PG increment); bodyweight; participants achieving target HbA1c values <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol); participants achieving target HbA1c <7.0 and ≤6.5% without weight gain; and participants achieving target HbA1c <7.0 and ≤6.5% with no confirmed hypoglycemia (recorded PG <3.1 mmol/L [56 mg/dL] or participant unable to treat himself/herself) during the previous 4 weeks. Safety end-points of the trial included changes in blood pressure and pulse, number of hypoglycemic events during 36 weeks of treatment (confirmed and nocturnal confirmed hypoglycemic events [the period between 00.01 and 05.59 h, with both times included]) and adverse events (AEs; including gastrointestinal disorders) during 36 weeks of treatment. These end-points were also analyzed by insulin regimen for the *post-hoc* analysis.

Statistical analysis
The analysis of efficacy end-points was based on the full analysis set, defined as all randomized participants who received at least one dose of the trial product, with each participant contributing as randomized. Continuous efficacy end-points were analyzed using an analysis of variance model, with treatment, insulin regimen, and the interaction between treatment and insulin regimen as fixed effects, and the corresponding baseline value as a covariate. The treatment difference for each type of insulin regimen was estimated with the corresponding 95% confidence interval (CI). The proportions of participants achieving target HbA1c <7.0% (<53 mmol/mol), target HbA1c ≤6.5% (≤48 mmol/mol) and composite end-points were summarized descriptively by the insulin regimen subgroup. For all analyses, missing data were imputed using the last observation carried forward method.

The analysis of safety end-points was based on the safety analysis set, defined as all participants who received at least one dose of the trial product, with each participant contributing as treated. For safety end-points, the number and proportion of participants with at least one event, the number of events, and the event rate per 100 patient years of exposure (PYE) were assessed and presented by insulin regimen subgroup.

RESULTS
Demographics
Of 296 Japanese patients screened, 257 were randomized (liraglutide: 127 patients, *placebo*: 130 patients). Patients were distributed in an approximate 2:1:2 ratio between basal insulin (n = 100), basal–bolus insulin (n = 55) and premix insulin (n = 102) regimens. Participant disposition stratified by insulin regimen subgroup is summarized in Figure S1.

Baseline characteristics are summarized in Table 1. Minor differences in duration of diabetes, baseline HbA1c, sex distribution and total daily insulin dose were observed among the three insulin regimen subgroups (Table 1).

Efficacy end-points
Primary end-point: change in HbA1c from baseline at 16 weeks
Across all insulin subgroup regimens, reductions in HbA1c from baseline to week 16 were greater with liraglutide compared with the *placebo* (−1.81% vs −0.35%, −1.63% vs −0.37% and −1.71% vs −0.54% in the basal, basal–bolus and premix subgroups, respectively; Figure 1). When comparing estimated treatment differences (ETDs) between liraglutide and the *placebo* in change in HbA1c at 16 weeks by insulin subgroup regimen, the effect of liraglutide appeared to be larger in the basal insulin subgroup compared with the basal–bolus and premix

Table 1 | Baseline characteristics

Insulin therapy	Basal		Basal–bolus		Premix	
Add-on therapy	Liraglutide	*Placebo*	Liraglutide	*Placebo*	Liraglutide	*Placebo*
FAS (*n*)	50	50	27	28	50	52
Age (years)	58.6 ± 11.5	60.1 ± 10.7	59.2 ± 11.8	57.2 ± 13.1	65.1 ± 9.0	60.9 ± 10.8
Duration of diabetes (years)	12.24 ± 7.07	11.83 ± 7.13	14.34 ± 7.08	17.19 ± 7.40	16.39 ± 10.86	16.08 ± 9.80
Female (%)	36.0	36.0	51.9	53.6	52.0	42.3
Male (%)	64.0	64.0	48.1	46.4	48.0	57.7
Bodyweight (kg)	67.6 ± 12.6	65.2 ± 12.5	70.0 ± 21.2	66.1 ± 13.5	66.5 ± 13.8	66.4 ± 13.5
BMI (kg/m^2)	25.9 ± 3.8	24.7 ± 3.6	26.6 ± 6.5	26.1 ± 4.7	26.2 ± 4.8	25.1 ± 4.1
FPG (mg/dL)	144 ± 45	147 ± 39	174 ± 49	163 ± 49	152 ± 36	167 ± 47
HbA1c (%)	9.0 ± 0.9	9.0 ± 0.9	8.9 ± 0.9	8.6 ± 0.8	8.5 ± 1.0	8.8 ± 0.9
C-peptide (ng/mL)	0.98 ± 0.68	0.98 ± 0.67	1.06 ± 0.86	0.94 ± 0.73	1.06 ± 0.60	1.14 ± 0.91
Total daily insulin dose (units)	23 ± 12	20 ± 11	41 ± 15	43 ± 21	29 ± 12	29 ± 14

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin. Full analysis set (FAS) values are mean ± standard deviation unless otherwise indicated.

Figure 1 | Change in glycated hemoglobin (HbA1c; % [mmol/mol]) from baseline in participants receiving liraglutide or a *placebo* in addition to basal insulin (*n* = 100), basal–bolus insulin (*n* = 55) or premix insulin therapy (*n* = 102), after 16 and 36 weeks of treatment. The analysis of efficacy end-points was based on the full analysis set, defined as all randomized participants who received at least one dose of trial product, with each participant contributing as randomized. [†]Test for interaction *P* = 0.3353 between treatment and pre-trial insulin at 16 weeks. [‡]Test for interaction *P* = 0.4511 between treatment and pre-trial insulin at 36 weeks. CI, confidence interval; ETD, estimated treatment difference; LS, least squares.

insulin subgroups, with respective ETDs of −1.45% (95% CI −1.73 to −1.18, *P* < 0.0001), −1.26% (95% CI −1.62 to −0.89, *P* < 0.0001) and −1.17% (95% CI −1.44 to −0.90, *P* < 0.0001; Figure 1). However, the test for interaction did not find any evidence of difference in the treatment effect (the difference between liraglutide and *placebo*) across insulin regimens (*P* = 0.3353).
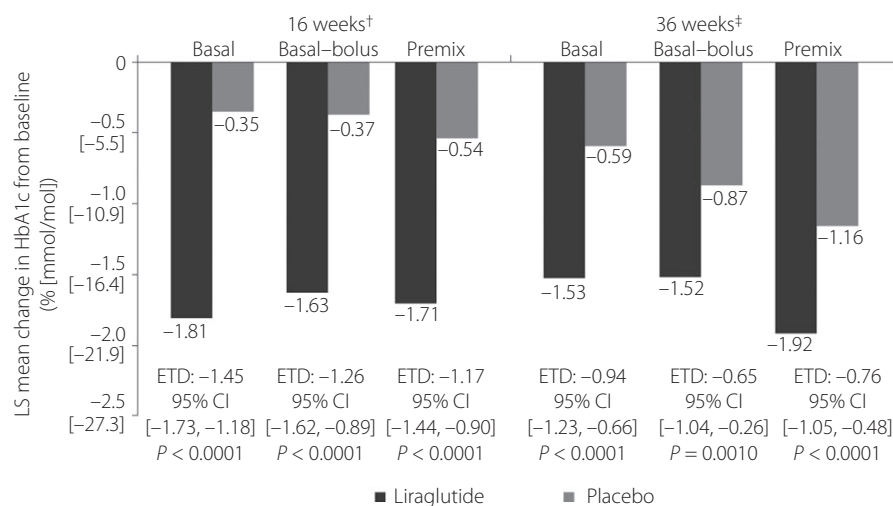
Change in HbA1c from baseline at 36 weeks

Across all insulin regimens, reductions in HbA1c from baseline to week 36 were also greater with liraglutide than with the *placebo* (Figure 1). As at week 16, the ETD between

liraglutide and the *placebo* for the change in HbA1c after 36 weeks appeared to be largest in the basal insulin subgroup (Figure 1), but the test for interaction did not find any evidence of difference in treatment effect across insulin regimens (*P* = 0.4511).

Change in actual daily insulin dose from baseline at 36 weeks

There was an attenuated increase from baseline in actual daily insulin dose comparing liraglutide with the *placebo* in the basal (3.6 vs 7.4 units, respectively), basal–bolus (4.1 vs 9.0 units, respectively) and premix insulin subgroups (9.5 vs 15.8 units, respectively) at 36 weeks. The test for interaction in actual daily

insulin dose at 36 weeks did not find any evidence of difference in the treatment effect across insulin regimens ($P = 0.6317$; Table 2).

Change in FPG from baseline at 16 and 36 weeks

At 16 weeks, there were greater reductions in FPG in participants treated with liraglutide compared with the *placebo* in the basal (ETD −18.1 mg/dL, 95% CI −31.7 to −4.6, $P = 0.0089$) and basal–bolus insulin subgroups (ETD −25.7 mg/dL, 95% CI −44.0 to −7.4, $P = 0.0061$), but this was not observed in the premix insulin subgroup (ETD −5.8 mg/dL, 95% CI −19.3 to 7.8, $P = 0.4039$]). At 36 weeks, the ETDs were comparable (ETDs from −5.3 to −3.9 mg/dL) across insulin subgroups (Table 2). The test for interaction did not find any evidence of difference in the treatment effect across insulin regimens ($P = 0.1907$ and $P = 0.9896$ at 16 and 36 weeks, respectively).

Change in mean seven-point SMPG and mean prandial glucose increment from baseline at 16 and 36 weeks

Decreases in mean PG derived from the seven-point SMPG profiles from baseline to weeks 16 and 36 were greater with liraglutide than *placebo* in all insulin subgroups (Table 2; Figure S2). Although the reduction in mean PG from the seven-point SMPG appeared largest with liraglutide compared with the *placebo* in the basal insulin subgroup, the test for interaction did not find any evidence of difference in the treatment effect across insulin regimens ($P = 0.1787$ and $P = 0.3150$, respectively).

The decrease in mean prandial glucose increments from baseline to week 16 was greater with liraglutide than the *placebo* in the basal insulin subgroup (ETD −21.8 mg/dL, 95% CI −35.2 to −8.3, $P = 0.0016$]), whereas non-statistically significant reductions were observed in the basal–bolus (ETD −10.7 mg/dL, 95% CI −28.9 to 7.5, $P = 0.2472$) and premix insulin subgroups (ETD −5.9 mg/dL, 95% CI −19.5 to 7.7, $P = 0.3954$; Table 2). At 36 weeks, the decrease in mean prandial glucose increments from baseline was not significantly different with liraglutide as compared with the *placebo* in any of the three insulin subgroups (basal insulin ETD −9.1 mg/dL, 95% CI −25.6 to 7.3, $P = 0.2760$]; basal–bolus ETD −0.6 mg/dL, 95% CI −22.7 to 21.6, $P = 0.9599$; premix insulin ETD −8.8 mg/dL, 95% CI −25.6 to 8.1, $P = 0.3058$). In addition, the test for interaction did not find any evidence of difference in the treatment effect across insulin regimens ($P = 0.2505$ and $P = 0.8061$ at 16 and 36 weeks, respectively).

Change in bodyweight from baseline at 16 and 36 weeks

A modest reduction in bodyweight from baseline at week 36 was observed with liraglutide compared with the *placebo* in the premixed insulin subgroup (ETD −0.96 kg, −1.83 to −0.08, $P = 0.0318$; Table 2). The test for interaction did not find any evidence of difference in the treatment effect across insulin regimens for either week 16 or 36 ($P = 0.1621$, $P = 0.2148$, respectively; Table 2).

Achievement of target HbA1c values and composite end-points at 16 and 36 weeks

A greater proportion of participants reached target HbA1c levels with liraglutide compared with the *placebo* at 16 and 36 weeks, irrespective of insulin subgroup (Figure 2; Table S1).

The proportion of participants achieving target HbA1c <7.0% (<53 mmol/mol) after 16 weeks appeared to be greatest in the premix insulin subgroup (62.0% vs 5.9% with liraglutide and the *placebo*, respectively) than in the basal (50.0% vs 0.0%) and basal–bolus insulin subgroups (40.7% vs 3.6%; Figure 2). Similar trends were observed for target HbA1c ≤6.5% (≤48 mmol/mol; Table S1).

With regard to the composite end-points, greater proportions of participants randomized to liraglutide achieved target HbA1c (<7.0 and ≤6.5%) without weight gain or confirmed hypoglycemia compared with the *placebo*, irrespective of insulin subgroup at 16 and 36 weeks (Figure 2; Table S1).

Safety end-points

Vital signs

At week 36, there was an observed decrease in systolic blood pressure with liraglutide across all insulin subgroups, and a small increase with *placebo*. There was an increase in diastolic blood pressure with liraglutide in the basal and basal–bolus insulin subgroups, a small decrease with liraglutide in the premix subgroup, and a small increase with the *placebo* across all subgroups. Increases in pulse rate were noted with liraglutide compared with the *placebo* across all insulin subgroups (Table S2).

Hypoglycemia

Hypoglycemia data are summarized in Table 3. In the basal and basal–bolus subgroups, the event rate (expressed as events per 100 PYE) of confirmed hypoglycemia appeared higher at 0–36 weeks in participants randomized to liraglutide compared with those receiving the *placebo*. In the premix subgroup, however, the event rate was notably lower with liraglutide compared with the *placebo*. In the premix subgroup, the proportion of participants with confirmed hypoglycemic events was similar with liraglutide and the *placebo* at 0–36 weeks, but in the basal and basal–bolus subgroups, a larger proportion of participants had confirmed hypoglycemic events with liraglutide compared with the *placebo* (Table 3). No severe hypoglycemic events occurred during the trial. In all insulin subgroups, the occurrence of nocturnal confirmed hypoglycemic events was low with both liraglutide and the *placebo*.

Within the first 16 weeks, when insulin doses were stable, a greater proportion of participants reported confirmed hypoglycemic events with liraglutide than the *placebo* in the basal and basal–bolus subgroups. In the premix subgroup, the proportions of participants who reported hypoglycemic events were largely similar (Table 3). During the same time-period, the event rate for confirmed hypoglycemic events was also higher with liraglutide than with the *placebo* in the basal and basal–bolus subgroups, but was lower in the premix subgroup.

Table 2 | Efficacy results

Insulin therapy	Basal		Basal–bolus		Premix	
Add-on therapy	Liraglutide	*Placebo*	Liraglutide	*Placebo*	Liraglutide	*Placebo*
FAS (*n*)	50	50	27	28	50	52
Change in HbA1c (%) from baseline						
16 weeks	−1.81	−0.35	−1.63	−0.37	−1.71	−0.54
36 weeks	−1.53	−0.59	−1.52	−0.87	−1.92	−1.16
ETD [95% CI], *P*-value						
16 weeks	−1.45 [−1.73; −1.18], <0.0001		−1.26 [−1.62; −0.89], <0.0001		−1.17 [−1.44; −0.90], <0.0001	
36 weeks	−0.94 [−1.23; −0.66], <0.0001		−0.65 [−1.04; −0.26], 0.0010		−0.76 [−1.05; −0.48], <0.0001	
Interaction between treatment and pre-trial insulin at 16 weeks (*P*-value)	0.3353					
Interaction between treatment and pre-trial insulin at 36 weeks (*P*-value)	0.4511					
Actual daily insulin dose, log-transformed[†] (units)	26.34	33.46	27.10	30.84	31.65	37.97
Observed mean change from baseline in actual daily insulin dose at 36 weeks (units)	3.6	7.4	4.1	9.0	9.5	15.8
ETR [95% CI], *P*-value	0.79 [0.69; 0.90], 0.0008		0.88 [0.73; 1.06], 0.1713		0.83 [0.73; 0.96], 0.0094	
Interaction between treatment and pre-trial insulin at 36 weeks (*P*-value)			0.6317			
Change in FPG (mg/dL)						
16 weeks	−27.0	−8.9	−22.6	3.1	−20.7	−15.0
36 weeks	−26.8	−22.9	−27.7	−22.4	−29.1	−24.2
ETD [95% CI], *P*-value						
16 weeks	−18.1 [−31.7; −4.6], 0.0089		−25.7 [−44.0; −7.4], 0.0061		−5.8 [−19.3; 7.8], 0.4039	
36 weeks	−3.9 [−16.6; 8.8], 0.5451		−5.3 [−22.4; 11.9], 0.5458		−5.0 [−17.7; 7.7], 0.4407	
Interaction between treatment and pre-trial insulin at 16 weeks (*P*-value)	0.1907					
Interaction between treatment and pre-trial insulin at 36 weeks (*P*-value)	0.9896					
Change in mean PG, from 7-point SMPG (mg/dL)						
16 weeks	−46.0	−1.8	−47.1	−18.7	−38.4	−12.1
36 weeks	−42.5	−11.6	−50.5	−32.1	−51.2	−33.4
ETD [95% CI], *P*-value						
16 weeks	−44.1 [−58.3; −30.0], <0.0001		−28.4 [−47.4; −9.3], 0.0037		−26.3 [−40.6; −12.0], 0.0004	
36 weeks	−30.9 [−43.9; −17.9], <0.0001		−18.4 [−35.9; −0.8], 0.0403		−17.8 [−30.9; −4.7], 0.0079	
Interaction between treatment and pre-trial insulin at 16 weeks (*P*-value)	0.1787					
Interaction between treatment and pre-trial insulin at 36 weeks (*P*-value)	0.3150					
Change in mean prandial glucose increment, all meals (mg/dL)						
16 weeks	−21.8	−0.0	−36.3	−25.6	−19.6	−13.7
36 weeks	−15.4	−6.2	−31.1	−30.6	−29.0	−20.3

Table 2 (*Continued*)

Insulin therapy Add-on therapy	Basal Liraglutide	*Placebo*	Basal–bolus Liraglutide	*Placebo*	Premix Liraglutide	*Placebo*
ETD [95% CI], *P*-value						
16 weeks	−21.8 [−35.2; −8.3], 0.0016		−10.7 [−28.9; 7.5], 0.2472		−5.9 [−19.5; 7.7], 0.3954	
36 weeks	−9.1 [−25.6; 7.3], 0.2760		−0.6 [−22.7; 21.6], 0.9599		−8.8 [−25.6; 8.1], 0.3058	
Interaction between treatment and pre-trial insulin at 16 weeks (*P*-value)	0.2505					
Interaction between treatment and pre-trial insulin at 36 weeks (*P*-value)	0.8061					
Change in bodyweight (kg)						
16 weeks	0.02	−0.29	−0.31	−0.09	−0.93	−0.38
36 weeks	0.32	0.32	0.47	0.35	−0.15	0.81
ETD [95% CI], *P*-value						
16 weeks	0.31 [−0.32; 0.94], 0.3328		−0.21 [−1.06; 0.63], 0.6199		−0.55 [−1.17; 0.08], 0.0858	
36 weeks	−0.00 [−0.88; 0.88], 0.9982		0.12 [−1.07; 1.31], 0.8412		−0.96 [−1.83; −0.08], 0.0318	
Interaction between treatment and pre-trial insulin at 16 weeks (*P*-value)	0.1621					
Interaction between treatment and pre-trial insulin at 36 weeks (*P*-value)	0.2148					

CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; FAS, full analysis set; FPG, fasting plasma glucose; PG, plasma glucose; SMPG, self-measured plasma glucose. Values are least squares mean changes from baseline unless otherwise indicated. [†]The log-transformed actual daily insulin dose after 36 weeks of treatment was analyzed using an ANCOVA method with treatment, pre-trial insulin at screening and interaction between treatment and pre-trial insulin at screening as fixed effects, and log-transformed actual daily insulin dose at baseline as a covariate.

At >16–36 weeks, similar proportions of participants reported confirmed hypoglycemic events with liraglutide and the *placebo* in the basal and basal–bolus subgroups. In the premix subgroup, a lower proportion of participants randomized to liraglutide reported confirmed hypoglycemic events compared with the *placebo*. During the same time-period, the confirmed hypoglycemic event rates were lower with liraglutide than the *placebo* in the basal and premix subgroups, but not in the basal–bolus subgroup.

AEs

The proportion of participants with AEs was generally comparable among insulin subgroups (Table S3), with AE rates per 100 PYE appearing to be slightly higher with liraglutide compared with the *placebo* in the basal and premix subgroups. The majority of AEs were mild, and the most frequently reported AE overall was nasopharyngitis. The proportion of participants with serious AEs and the event rates per 100 PYE appeared to be similar with liraglutide and the *placebo* in the basal and basal–bolus insulin subgroups, and higher with liraglutide compared with the *placebo* in the premix subgroup. However, the incidence of serious AEs was low overall.

The proportion of participants with gastrointestinal AEs was numerically higher in the liraglutide groups, independent of the insulin regimen. In the premix subgroup, there were two withdrawals as a result of AEs (one each in the liraglutide and *placebo* groups, respectively). No deaths were reported during the trial.

DISCUSSION

The present *post-hoc* analysis shows that the superior efficacy of liraglutide compared with the *placebo* observed in the overall cohort[6] was not dependent on the type of pre-trial insulin regimen, and that insulin-treated Japanese patients with type 2 diabetes mellitus not achieving glycemic targets can be considered for liraglutide treatment, irrespective of their current insulin regimen.

Patients receiving liraglutide experienced greater reductions in HbA1c and mean seven-point SMPG than those receiving the *placebo* across all three insulin subgroups, whereas FPG was reduced more with liraglutide in the basal and basal–bolus insulin subgroups at week 16. Furthermore, the proportions of participants achieving target HbA1c of <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/
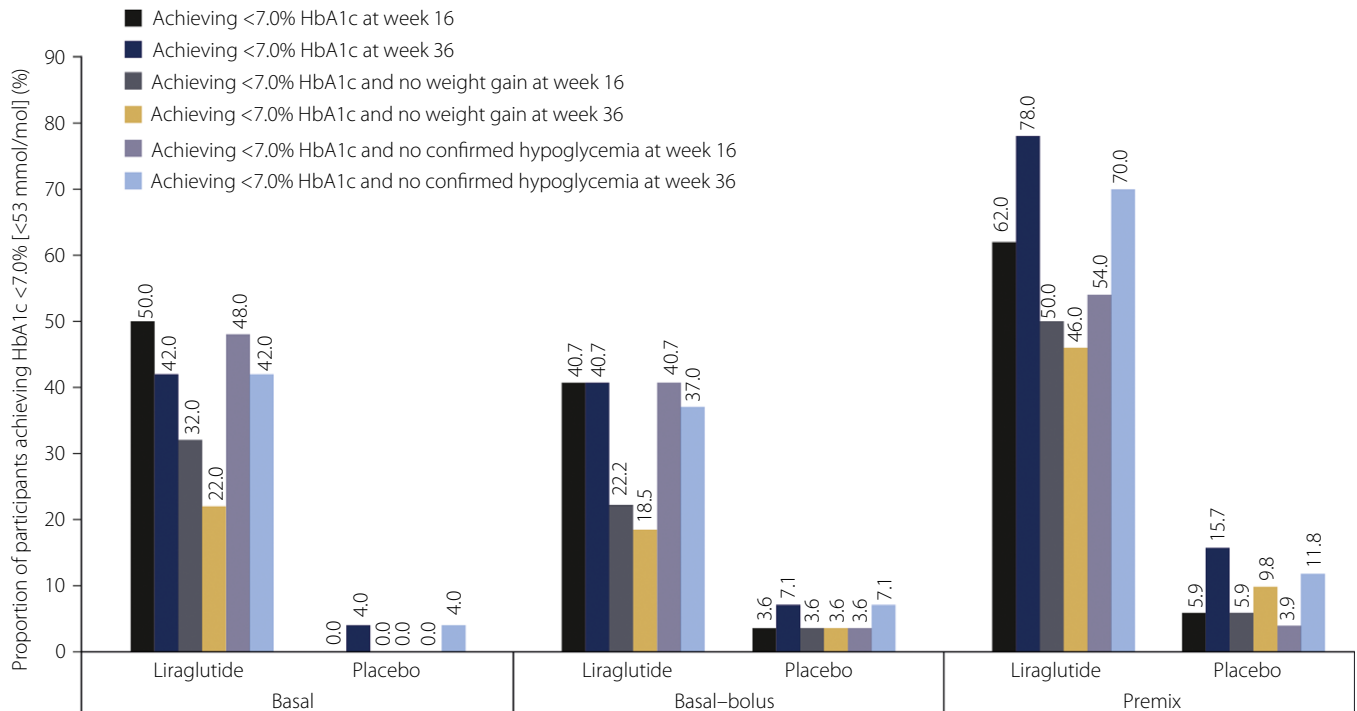
Figure 2 | Proportion of participants who achieved glycated hemoglobin (HbA1c) <7.0% (<53 mmol/mol), HbA1c <7.0% with no weight gain and HbA1c <7.0% with no confirmed hypoglycemia (after 16 and 36 weeks of treatment) with addition of liraglutide or *placebo* to basal insulin (*n* = 100), basal–bolus insulin (*n* = 55) or premix insulin therapy (*n* = 102). The analysis of efficacy end-points was based on the full analysis set defined as all randomized participants who received at least one dose of the trial product, with each participant contributing as randomized.

mol) were higher with liraglutide compared with the *placebo*. These findings are in line with results from other trials investigating liraglutide added to basal and basal–bolus insulin, and with previous meta-analyses of trials investigating the addition of GLP-1RAs to insulin[8,9,11–14]. Liraglutide showed greater *placebo*-adjusted HbA1c reductions when added to basal insulin than when added to basal–bolus or premix; however, no statistical significance at either week 16 or 36 was shown in the interaction tests between the treatment and insulin regimens. Consequently, there was no evidence of any apparent differences in the treatment effect of liraglutide by insulin regimen.

There was an attenuated increase from baseline in actual daily insulin dose with the addition of liraglutide regimens after 36 weeks of treatment. This is supported by previous studies that explored liraglutide as an add-on therapy to insulin[8,9,14–16]. Furthermore, the reduction in prandial glucose increment was observed to be larger with liraglutide than the *placebo* in the basal insulin subgroup at 16 weeks (when the insulin dose was capped), and the same trend was observed for the basal–bolus and premix subgroups. The difference between the liraglutide and *placebo* arms was, however, diminished by week 36 (after insulin titration was allowed). As prandial insulin therapy aims to reduce upward prandial glucose fluctuation, it could be anticipated that liraglutide used as an add-on therapy would have less of an effect on this parameter when prandial insulins

are used. Liraglutide can, however, perform a similar role in enhancing postprandial glucose reduction when added to a basal-only insulin regimen.

When insulin dose was stable, in weeks 0 to ≤16, the mean prandial glucose increment was still reduced with liraglutide relative to the *placebo*, by 36.3 and 19.6 mg/dL for the basal–bolus and premix subgroups, respectively, although this benefit was greater in the basal-only insulin subgroup than in the basal–bolus or premix subgroups. These data are supported by Ogawa *et al.*[13], who observed reduced postprandial glucose and prandial insulin dose when liraglutide was added to basal–bolus therapy, and by Lind *et al.*[14], who observed reduced postprandial glucose and total insulin dose. In this regard, daily prandial and premix insulin doses could potentially also be reduced in a real-world setting.

Individuals with type 2 diabetes mellitus often do not reach glycemic targets, because they might be reluctant to intensify insulin therapy as a result of concerns over bodyweight gain[17]. In previous trials investigating liraglutide in combination with insulin therapy, weight loss was observed[8,9,11,12,14]. However, in the LIRA-ADD2INSULIN JAPAN trial, very limited changes in bodyweight were observed with either liraglutide or *placebo* across all insulin subgroups, despite higher insulin doses with *placebo* in all subgroups. The difference in glycemic control could imply under-dosing of insulin by the study participants, perhaps as a result of fear of hypoglycemia or weight gain.

Table 3 | Hypoglycemia analysis†

Insulin therapy	Basal								Basal–bolus								Premix							
Add-on therapy	Liraglutide				Placebo				Liraglutide				Placebo				Liraglutide				Placebo			
Safety analysis set (n)	50				50				27				28				50				52			
	n	%	E	R	n	%	E	R	n	%	E	R	n	%	E	R	n	%	E	R	n	%	E	R
Hypoglycemic events by classification and time (0 to 36 weeks)																								
Confirmed	8	16.0	19	57	4	8.0	11	32	13	48.1	52	290	9	32.1	45	242	21	42.0	52	157	23	44.2	105	311
Nocturnal confirmed	2	4.0	2	6	2	4.0	3	9	1	3.7	3	17	2	7.1	8	43	3	6.0	5	15	7	13.5	17	50
Hypoglycemic events by classification and time (0 to ≤16 weeks)																								
Confirmed	8	16.0	18	119	3	6.0	5	33	9	33.3	24	300	5	17.9	22	264	12	24.0	18	120	11	21.2	35	232
Nocturnal confirmed	1	2.0	1	7	2	4.0	2	13	1	3.7	1	12	2	7.1	4	48	3	6.0	4	27	1	1.9	4	27
Hypoglycemic events by classification and time (>16 to 36 weeks)																								
Confirmed	1	2.0	1	5	3	6.1	6	32	7	26.9	28	281	8	29.6	23	224	17	35.4	34	188	22	44.9	70	376
Nocturnal confirmed	1	2.0	1	5	1	2.0	1	5	1	3.8	2	20	1	3.7	4	39	1	2.1	1	6	7	14.3	13	70

†No severe hypoglycemia occurred during the trial. Confirmed hypoglycemia: participant unable to treat himself/herself and/or have a recorded plasma glucose <3.1 mmol/L (56 mg/dL). Nocturnal period: the period between 00.01 and 05.59 h (both included). %, Percentage of participants; E, number of events; R, event rate per 100 patient exposure years.

The reductions in systolic blood pressure and increases in pulse rate that were observed with liraglutide in the present *post-hoc* analysis have also been observed previously[18]. In the current analysis, this effect did not appear to differ across insulin regimens. Increases in resting heart rate have been reported with GLP-1RAs, and although the underlying physiological mechanisms have not yet been defined, the activation of the GLP-1 receptors in the sinoatrial node could play a role[19]. Although an increase in heart rate was also seen in the recently reported Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial[20], lower rates of cardiovascular events and death from any cause were confirmed with liraglutide compared with the *placebo* when added to the standard of care.

Gastrointestinal AEs were more common with liraglutide, and overall rates of AEs were also slightly higher, regardless of the insulin regimen used. From baseline to week 16, where the insulin dose was kept stable, a larger proportion of participants reported confirmed hypoglycemic events with liraglutide than the *placebo* in the basal and basal–bolus subgroups. From >16 to 36 weeks, when insulin titration was allowed, similar proportions of participants reported confirmed hypoglycemic events with liraglutide and the *placebo* in the basal and basal–bolus subgroups. In the same time-period, a slightly lower proportion of participants reported confirmed hypoglycemia with liraglutide compared with the *placebo* in the premix subgroup. This observation might suggest that liraglutide could be added to any insulin regimen without an increased risk of hypoglycemia provided attention is also given to insulin dose adjustment.

In the period of 0–16 weeks, hypoglycemic event rates were similar with liraglutide treatment between the basal and premix subgroups. Overall, however, hypoglycemic event rates were much lower in the basal insulin subgroup (both liraglutide and *placebo*) than in the basal–bolus and premix subgroups, despite the greater efficacy shown in the basal subgroup with liraglutide. This supports the notion that prandial insulin is responsible for the majority of hypoglycemic events, and that liraglutide can be used as an alternative to prandial insulins.

The limitations of the present study include the fact that the data might not be reflective of routine clinical practice, and the original trial was not powered to perform this *post-hoc* analysis in which the comparator groups are small. There were also differences in baseline characteristics; such variation would be expected as a result of inherent distinctions between participants being empirically selected for dissimilar insulin regimens rather than being randomized. There is also likely to have been variation in the efficacy and safety profiles of the different insulin regimens, which might have confounded the results. Nevertheless, these limitations do not invalidate the conclusion that liraglutide can be added to all three insulin regimens with the expectation of achieving clinical benefits.

In summary, the present *post-hoc* analysis confirmed the efficacy and safety of adding liraglutide to ongoing insulin therapy in Japanese patients with type 2 diabetes mellitus, regardless of the insulin regimen used. The analysis also suggested there was no difference in the treatment effect of liraglutide across insulin regimens.

DISCLOSURE

K Nishijima is a Novo Nordisk Pharma Ltd employee. H Bosch-Traberg is a Novo Nordisk A/S employee. Y Seino is a medical advisor to Astellas, BD, Boehringer Ingelheim, Eli Lilly, GSK, Johnson & Johnson, Novo Nordisk, Otsuka, Sanofi, Taisho Pharmaceutical Co., Ltd and Takeda. S Kaneko has conflicts of interest in respect to Takeda, Lilly, Novartis, Novo Nordisk, Astellas, Boehringer Ingelheim, AstraZeneca, Kowa, Mitsubishi Tanabe Pharma, Sanofi, Daiichi Sankyo, Sumitomo Dainippon Pharma and Ono. K Kaku is an advisor to Novo Nordisk, Sanwa Kagaku Kogyo, Takeda and Taisho Pharmaceutical Co., Ltd; received honoraria for lectures from MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Novo Nordisk, Takeda and Mitsubishi Tanabe Pharma; and received scholarship grants from AstraZeneca, Nippon Boehringer Ingelheim Co., Ltd, Chugai, Daiichi Sankyo, MSD, Novartis, Novo Nordisk, Sanofi and Takeda.

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SUPPORTING INFORMATION

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

Table S1 | Observed proportions of participants achieving glycated hemoglobin ≤6.5% (≤48 mmol/mol) at weeks 16 and 36, and associated composite end-points.

Table S2 | Mean changes in vital signs from baseline to week 36.

Table S3 | Adverse events.

Figure S1 | Participant disposition.

Figure S2 | Mean seven-point self-measured plasma glucose profiles at baseline and at 16 and 36 weeks for participants randomized to (a,c,e) liraglutide or (b,d,f) *placebo* in addition to (a,b) basal insulin, (c,d) basal–bolus insulin or (e,f) premix insulin therapy.