CLINICAL TRIAL

A randomized trial to investigate the efficacy and safety of once-daily liraglutide 1.8 mg in Japanese adults with type 2 diabetes exhibiting an inadequate response to liraglutide 0.9 mg

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ABSTRACT

Aims/Introduction: The present trial compared the efficacy and safety of once-daily liraglutide 1.8 mg with liraglutide 0.9 mg in Japanese patients with type 2 diabetes to assess the incremental effects of liraglutide 1.8 mg in those who exhibited an inadequate response to 0.9 mg.

Materials and Methods: This 26-week randomized trial (NCT02505334) enrolled Japanese adults with type 2 diabetes across 47 sites in Japan. Participants with glycated hemoglobin (HbA_{1c}) 7.5–10.0% were included and those on insulin treatment were excluded. Participants discontinued pre-trial oral antidiabetic drug and initiated liraglutide 0.9 mg for a 12-week run-in period, after which those with HbA_{1c} ≥7.0% (466) were randomized (1:1) to two treatment arms: continuing liraglutide 0.9 mg or dose escalation to 1.8 mg. The change from baseline in HbA_{1c} (primary endpoint) and treatment-emergent adverse events (secondary endpoint) were measured at the end of 26 weeks.

Results: After 26 weeks of treatment, liraglutide 1.8 mg was more effective compared with 0.9 mg in lowering HbA_{1c} levels, with an estimated treatment difference of −0.40% (95% confidence interval [CI] −0.55, −0.24; $P < 0.0001$). Liraglutide 1.8 mg was associated with significantly greater odds of participants reaching HbA_{1c} <7.0% (estimated odds ratio [EOR] 3.87; 95% CI 2.12, 7.08; $P < 0.0001$) and ≤6.5% (EOR 3.78; 95% CI 1.36, 10.54; $P = 0.0109$) compared with 0.9 mg. Both doses were well tolerated.

Conclusions: Liraglutide 1.8 mg had better efficacy in improving HbA_{1c} levels after 26 weeks treatment vs 0.9 mg in Japanese patients, with both doses well tolerated.

INTRODUCTION

Type 2 diabetes is primarily characterized by a decline in β-cell function and worsening insulin resistance[1], and in 2016, Japan recorded 10 million people with type 2 diabetes[2]. Persistent hyperglycemia can lead to serious micro- and macrovascular complications, which increase morbidity and mortality[3–5], whereas good glycemic control decreases the risk of such complications[6,7]. Normalizing glycemic control and minimizing weight gain to prevent complications are important when treating individuals with type 2 diabetes[8]. In Japanese individuals with type 2 diabetes, it is particularly important to maintain pancreatic β-cell function and insulin secretion[9,10]. Usually, the basal and maximum insulin concentrations are lower in Japanese individuals compared with Caucasians, attributable to pathophysiological differences in type 2 diabetes between these cohorts[10,11].

Japanese individuals have lower insulin secretion and resistance[12], and so may benefit particularly from incretin-based therapies, such as glucagon-like peptide-1 receptor agonists

(GLP-1 RAs)[13,14], because GLP-1 RAs have a greater effect in lowering glycated hemoglobin (HbA$_{1c}$) in Asians with type 2 diabetes when compared with non-Asians[15]. Liraglutide (a GLP-1 RA) at 0.9 mg was first approved in 2010 for Japanese individuals with type 2 diabetes unable to achieve sufficient glycemic control with diet and exercise alone or in combination with sulfonylurea[16–18]. In 2014, this approval was broadened for individuals with type 2 diabetes without any prior treatment limitations[19]. Several trials in Japanese participants have demonstrated the efficacy and safety of liraglutide 0.9 mg alone or combined with an oral antidiabetic drug (OAD) or insulin[17,18,20,21]. Although about 60% of participants completing the trials met the HbA$_{1c}$ target of <7.0%, the remaining participants did not, suggesting they might benefit from higher doses of liraglutide (>0.9 mg). Compliance to treatment generally decreases with increased dosing regimen complexity[22]. Hence, increasing the liraglutide dose to >0.9 mg/day could improve glycemic control without any dosing complexities.

In countries other than Japan, the maximum approved liraglutide dose has always been once-daily 1.8 mg with weekly increments of 0.6 mg for patients with type 2 diabetes[9,23]. In Japan, the liraglutide 1.8 mg dose was approved in May 2019[24], based on two clinical studies; one of these was a phase-3 trial in the Japanese population investigating the effects of the fixed-ratio combination of IDegLira compared with the individual components – insulin degludec and liraglutide 1.8 mg – in addition to pre-trial OAD[25].

Data from the present trial also contributed to the approval of once-daily liraglutide 1.8 mg in Japan. The present trial evaluated whether Japanese participants with type 2 diabetes with inadequately controlled HbA$_{1c}$ on once-daily liraglutide 0.9 mg may benefit from a 1.8 mg dose.

MATERIALS AND METHODS

Trial design

This 26-week, randomized, parallel, two-arm, open-label, multi-center trial (NCT02505334) compared the efficacy and safety of once-daily liraglutide 1.8 mg with 0.9 mg in Japanese participants with type 2 diabetes and inadequately controlled HbA$_{1c}$. It was conducted at 47 sites (of which 45 sites randomized participants) in Japan during July 21, 2015–November 9, 2017. Japanese participants aged ≥20 years, diagnosed with type 2 diabetes ≥6 months prior to screening, on one stable-dose OAD and with HbA$_{1c}$ of 7.5–10.0% were included. Participants who received insulin in the 12 weeks prior to screening or with a history of pancreatitis, malignant neoplasms, myocardial infarction, or stroke were excluded.

The trial comprised a run-in period (weeks −12 to −1), a main treatment period (weeks 0–26) and an extension period (weeks 27–52; Figure S1). Participants meeting the inclusion criteria discontinued their concurrent pre-trial OAD (Table S1) and initiated once-daily liraglutide 0.9 mg (started with 0.3 mg with weekly dose escalation from 0.3 mg up to 0.9 mg/day) for the 12-week run-in period to identify those with inadequately controlled HbA$_{1c}$ (≥7.0%). Participants with HbA$_{1c}$ ≥7.0% at the end of the run-in period were randomized to two treatment arms: continuing once-daily liraglutide 0.9 mg for 26 weeks (main treatment period) or dose escalation to liraglutide 1.8 mg for 52 weeks (main + 26-week extension period). Dose escalation followed weekly escalation of 0.3 mg/day to achieve the maximum 1.8 mg dose.

Outcomes

Baseline data were collected at randomization. The primary efficacy endpoint was a change from baseline in HbA$_{1c}$ at the end of the main treatment period. Key secondary efficacy endpoints at the end of the main treatment period included the number of participants achieving HbA$_{1c}$ targets of <7.0 and ≤6.5% and a change from baseline in self-measured blood glucose (SMBG; mean of the 7-point profile, mean postprandial increment across all meals), fasting plasma glucose (FPG), body weight, body mass index (BMI), systolic and diastolic blood pressure (SBP, DBP), and fasting C-peptide and glucagon levels.

The key secondary safety endpoints assessed during the main period were treatment-emergent adverse events (TEAEs), including pre-defined special interest safety areas (i.e. fatal events, cerebrovascular events, acute coronary syndrome, heart failure requiring hospitalization, neoplasms, thyroid disorders requiring thyroidectomy, pancreatitis or suspicion of pancreatitis), treatment-emergent symptomatic hypoglycemic episodes (classified as 'severe or blood glucose [BG]-confirmed' [BG <3.1 mmol/L or 56 mg/dL] or as per the American Diabetes Association [ADA] recommendations[26]) and physical examinations.

After the extension period, the primary endpoint, secondary efficacy endpoints and secondary safety endpoints were evaluated again in the liraglutide 1.8 mg arm.

Statistical analysis

Sample size determination was based on the primary objective and endpoint. The superiority of once-daily liraglutide 1.8 mg over 0.9 mg was confirmed if the 95% confidence interval (CI) for the treatment difference (liraglutide 1.8 mg minus 0.9 mg) for HbA$_{1c}$ change from baseline was entirely below 0%. A sample size of 235 participants in each treatment arm (total: 470 participants) enabled the detection of a −0.3% treatment difference for the primary endpoint with a power of at least 90%, under the assumption of a 1.0% standard deviation (SD) using a two-sided test of a 5% significance level.

The full analysis set (FAS) included all randomized participants. Statistical evaluation of the FAS followed the intent-to-treat principle and participants contributed to the evaluation 'as randomized'. The safety analysis set (SAS) included all participants receiving at least one liraglutide dose and contributed to the evaluation 'as treated'. The efficacy and safety endpoints were summarized using the FAS and the SAS, respectively. Missing values were imputed using the last observation carried forward (LOCF) method. Where no parameter data after

randomization were available, the baseline value for the relevant parameter was carried forward.

The primary endpoint and all continuous secondary efficacy endpoints were analyzed separately using an analysis of covariance model, with treatment as a fixed effect and the baseline value of the parameter as a covariate. The HbA_{1c} levels were analyzed using a logistic regression model, with treatment as factor and baseline response as covariate. TEAEs were presented descriptively. The robustness of the primary analysis result was assessed through sensitivity analyses using a mixed model for repeated measurements and a pattern mixture model approach mimicking an intention-to-treat scenario where multiple imputation was performed based on the liraglutide 0.9 mg values for withdrawn participants in both arms.

SAS version 9.4 was used for data analysis.

Ethical approval
The trial was conducted according to the Declaration of Helsinki and International Council for Harmonization – Good Clinical Practice[27,28]. All participants signed an informed consent form for trial participation. The protocol, consent form, and participant information sheet were reviewed and approved according to local regulations by the appropriate health authority and site-level Institutional Review Boards.

RESULTS
Participant disposition
Following screening of 786 participants and a 12-week run-in period, 466 participants were randomized 1:1 to liraglutide 1.8 mg (n = 233) and liraglutide 0.9 mg (n = 233) treatment (Figure 1) using an interactive voice/web response system. In total, 412 and 194 participants completed the main treatment period and main+extension period, respectively.

Baseline characteristics
Baseline characteristics were similar in both treatment arms (Table 1). The mean (±SD) age overall was 55.01 (±10.43) years and approximately two-thirds were male. Overall, the mean (±SD) values for diabetes duration, HbA_{1c} and FPG were 9.27 (±5.54) years, 8.12% (±0.95) and 172.3 (±38.5) mg/dL, respectively.

Change from baseline in HbA_{1c} levels
At screening, the mean (±SD) HbA_{1c} was 8.60% (±0.70). At the end of the run-in period, i.e. baseline, the mean (±SD) HbA_{1c} levels were similar in the liraglutide 1.8 mg (8.14% [±1.02]) and 0.9 mg (8.10% [±0.87]) arms. At the end of the main treatment period (26 weeks post-randomization), the mean HbA_{1c} change from baseline with liraglutide 1.8 mg was −0.23% vs +0.17% in the liraglutide 0.9 mg arm, with an estimated treatment difference (ETD) of −0.40%, (95% CI −0.55, −0.24; P < 0.0001) (Figure 2). Results from the sensitivity analyses were consistent with the primary statistical analysis (data not shown). After the extension period (52 weeks post-

randomization), the mean (±SD) change in HbA_{1c} was −0.09% (±1.05) in the liraglutide 1.8 mg arm.

Participants achieving HbA_{1c} target
After the main treatment period, 22.7 and 7.7% of participants in the liraglutide 1.8 mg arm achieved the HbA_{1c} targets <7.0 and ≤6.5%, respectively, compared with 7.7 and 2.1% participants in the liraglutide 0.9 mg arm, respectively. Correspondingly, liraglutide 1.8 mg was associated with significantly greater odds of participants reaching HbA_{1c} targets <7.0% vs liraglutide 0.9 mg (estimated odds ratio [EOR] 3.87; 95% CI 2.12, 7.08; P < 0.0001) and ≤6.5% vs liraglutide 0.9 mg (EOR 3.78; 95% CI 1.36, 10.54; P = 0.0109).

Changes in glucose metabolism-related parameters
At the end of the main treatment period, the participants treated with liraglutide 1.8 mg, compared with participants continuing liraglutide 0.9 mg, had a further decrease from baseline in mean values for 7-point SMBG profile, FPG, and postprandial increment across all meals. The ETD between the liraglutide 1.8 mg and 0.9 mg arms after the main period was statistically significantly in favor of liraglutide 1.8 mg for the mean 7-point SMBG profile (−13.8 mg/dL [95% CI −20.6,−7.0]; P < 0.0001), mean FPG (−9.2 mg/dL [95% CI −14.8,−3.5]; P = 0.0015), and mean postprandial increment across all meals (−6.8 mg/dL [95% CI −13.1,−0.6]; P = 0.0326).

Changes in other measures
At the time of screening, the overall mean body weight of participants was approximately 75 kg (mean±SD, for those later assigned to liraglutide 1.8 mg: 75.05 ± 15.05 kg; 0.9 mg: 75.71 ± 16.26 kg). A back-traced assessment of the screening and run-in data sets of the randomized participants in the two arms revealed that, at the end of the run-in period, the mean (±SD) weight was reduced from screening to 74.67 kg (±15.24) and 75.13 kg (±16.46) in the liraglutide 1.8 mg and 0.9 mg arms, respectively (Figure S2A). Participants in the liraglutide 1.8 mg arm reported statistically insignificant small and continuous decreases, from baseline, in mean (±SD) body weight (mean change: −0.77 kg [±2.01] vs −0.95 kg [±2.19]) (Figure S2B) and BMI (mean change: −0.28 kg/m^2 [±0.72] vs −0.33 kg/m^2 [±0.78]) vs the 0.9 mg arm during the main treatment period.

After the main treatment period, liraglutide 1.8 mg, vs liraglutide 0.9 mg, was associated with reduced SBP (ETD −2.5 mmHg; 95% CI −4.5, −0.6; P = 0.0094), but there was no significant difference in DBP (ETD −1.2 mmHg; 95% CI −2.6, 0.1; P = 0.0769). Data on fasting C-peptide and glucagon levels are in the Appendix S1.

Number of TEAEs during 26 weeks and 52 weeks of treatment
A total of 528 adverse events (AEs) were reported by 291 participants (45.9%) during the run-in period, of which 98.9% were non-serious. The most common AEs during the run-in
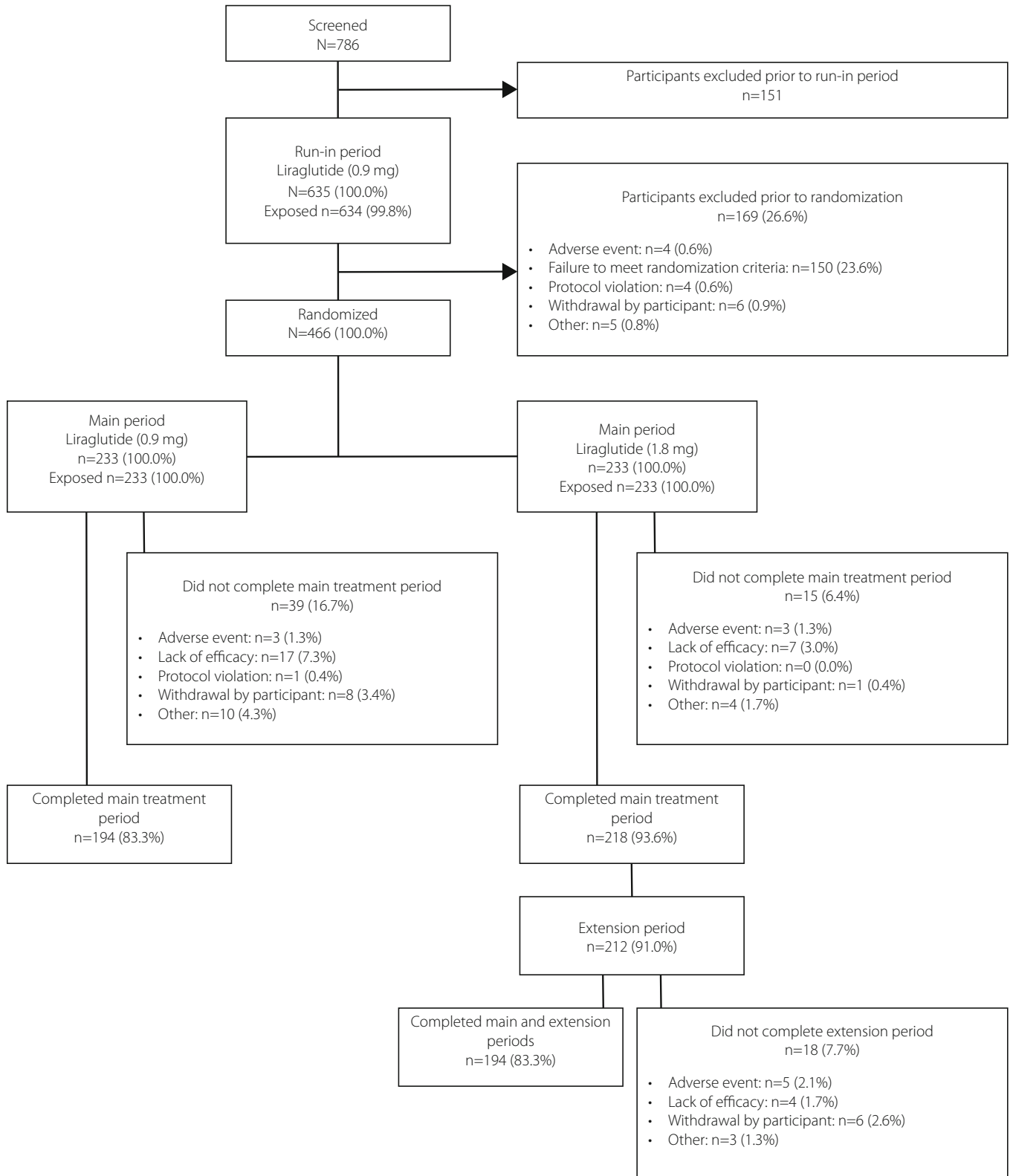
Figure 1 | Participant flow diagram. Main period = 26 weeks; extension period = 26 weeks.

Table 1 | Participant disposition and baseline characteristics

	Liraglutide 1.8 mg (n = 233) Mean (SD)	Liraglutide 0.9 mg (n = 233) Mean (SD)	Total (n = 466) Mean (SD)
Age, years	55.07 (10.27)	54.96 (10.61)	55.01 (10.43)
Duration of diabetes, years	9.40 (5.70)	9.15 (5.40)	9.27 (5.54)
Female; Male, %[†]	33.0; 67.0	29.2; 70.8	31.1; 68.9
Body weight, kg	74.67 (15.24)	75.13 (16.46)	74.90 (15.85)
Body mass index, kg/m²	27.34 (4.80)	27.20 (4.72)	27.27 (4.76)
Fasting plasma glucose, mg/dL	172.5 (38.7)	172.0 (38.3)	172.3 (38.5)
HbA$_{1c}$, %	8.14 (1.02)	8.10 (0.87)	8.12 (0.95)

HbA$_{1c}$, glycated hemoglobin; SD, standard deviation. [†]Data are presented in %.
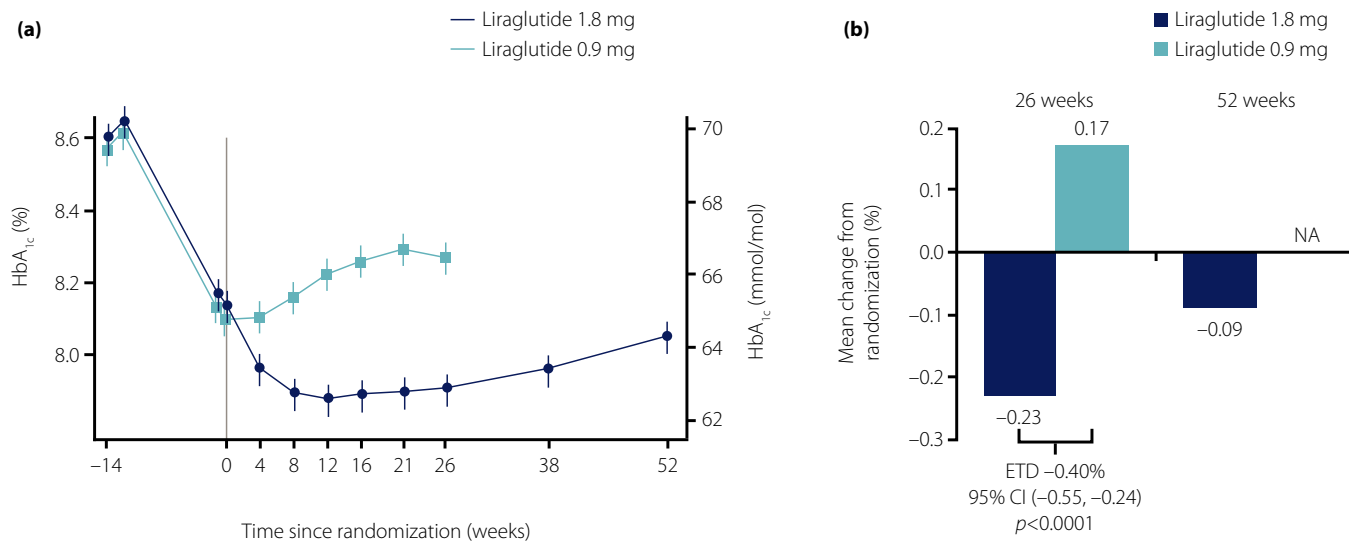

Figure 2 | (a) Mean (±SE) HbA$_{1c}$ levels after 26 and 52 weeks of treatment with liraglutide 1.8 mg and 0.9 mg; (b) mean change in HbA$_{1c}$ levels from randomization after 26 and 52 weeks of treatment with liraglutide 1.8 mg and 0.9 mg. Missing data were imputed using the last observation carried forward method. n = 233 at each time point for both treatment arms. Gray line denotes randomization timepoint and error bars represent SE. CI, confidence interval; ETD, estimated treatment difference; HbA$_{1c}$, glycated hemoglobin; NA, not applicable; SE, standard error.

period were gastrointestinal (GI) disorders, reported in 19.9% of participants, followed by infections and infestations (19.2%). No unexpected safety issues were identified in the main treatment period (Table 2); no fatalities occurred during the trial and there were very few events of special interest (Table S2). The proportion of participants with AEs and their respective rates in the liraglutide 1.8 mg arm (67.8% and 311 events per 100 patient-years of exposure [PYE], respectively) were higher compared with the liraglutide 0.9 mg arm (60.5% and 243 events per 100 PYE, respectively).

The GI AE incidence was higher with liraglutide 1.8 mg (24.0%) than liraglutide 0.9 mg (11.6%) in the main treatment period. This higher GI AE incidence was observed during the initial 3 weeks of the main period (liraglutide 1.8 mg: 3.0–4.3% of participants; liraglutide 0.9 mg: 0.9–2.1% of participants) and it remained comparable between the two arms thereafter. The most common disorders were constipation (5.6 vs 2.1%),

diarrhea (3.9 vs 2.6%), and nausea (3.4 vs 2.1%) in the liraglutide 1.8 mg and 0.9 mg arms. Overall, both doses were well tolerated during the main treatment period. After the extension period, 270 events per 100 PYE (588 events) were reported in 76.0% of participants receiving 1.8 mg liraglutide. However, approximately 98.9% of the AEs in the liraglutide 1.8 mg arm were non-serious.

Number of hypoglycemic episodes within 26 weeks and 52 weeks of treatment

Hypoglycemic episodes were observed in both treatment arms within the main period (Table 2). According to the ADA classification[26], seven hypoglycemic episodes in four (1.7%) participants and three episodes in three (1.3%) participants in the liraglutide 1.8 mg and 0.9 mg treatment arms were reported during the main period, respectively. However, no severe or BG-confirmed (BG <3.1 mmol/L [56 mg/dL]) symptomatic

Table 2 | Treatment-emergent adverse events and hypoglycemic episodes during 26 weeks (main period) and 52 weeks (main plus extension period) of treatment with liraglutide

	Main period (26 weeks post-randomization)								Main plus extension period (52 weeks post-randomization)			
	Liraglutide 1.8 mg				Liraglutide 0.9 mg				Liraglutide 1.8 mg			
	N	%	*E*	Rate	*N*	%	*E*	Rate	*N*	%	*E*	Rate
Treatment-emergent adverse events												
Number of participants (PYE)	233 (117.5)	–	–	–	233 (109.6)	–	–	–	233 (217.7)	–	–	–
Adverse events	158	67.8	365	311	141	60.5	266	243	177	76.0	588	270
Serious	1	0.4	1	1	3	1.3	3	3	8	3.4	9	4
Severe	1	0.4	1	1	2	0.9	2	2	1	0.4	1	<1
Events leading to withdrawal	3	1.3	3	3	2	0.9	2	2	7	3.0	8	4
Related to trial product												
Probable	16	6.9	22	19	4	1.7	4	4	18	7.7	25	11
Possible	47	20.2	71	60	26	11.2	35	32	55	23.6	87	40
Outcome not recovered/not resolved	53	22.7	78	66	48	20.6	65	59	79	33.9	156	72
Hypoglycemic episodes												
Severe or BG-confirmed symptomatic	0	–	–	–	0	–	–	–	0	–	–	–
ADA classification[†]	4	1.7	7	6	3	1.3	3	3	6	2.6	9	4
Severe	0	–	–	–	0	–	–	–	0	–	–	–
Documented symptomatic	0	–	–	–	0	–	–	–	0	–	–	–
Asymptomatic	2	0.9	2	2	1	0.4	1	1	3	1.3	3	1
Probable-hypoglycemia	1	0.4	3	3	1	0.4	1	1	2	0.9	4	2
Pseudo-hypoglycemia	2	0.9	2	2	1	0.4	1	1	2	0.9	2	1
ADA unclassifiable	0	–	–	–	0	–	–	–	0	–	–	–

ADA, American Diabetes Association; BG, blood glucose; BG-confirmed, BG <3.1 mmol/L (56 mg/dL); *E*, number of adverse events or hypoglycemic episodes; *N*, number of participants; PYE, patient-year of exposure; rate, events rate per 100 PYE. [†]See Ref. [26]

hypoglycemia was reported in either arm during this period. According to the ADA classification[26], nine hypoglycemic episodes in six (2.6%) participants in the liraglutide 1.8 mg arm were reported during the extension period. Furthermore, no severe or BG-confirmed symptomatic hypoglycemia was reported during the extension period in the liraglutide 1.8 mg arm.

DISCUSSION

This 26-week, randomized, parallel, two-arm, open-label, multi-center trial demonstrated that once-daily liraglutide 1.8 mg was more efficacious than liraglutide 0.9 mg in reducing HbA$_{1c}$ levels in Japanese participants with type 2 diabetes who had inadequately controlled HbA$_{1c}$ after an initial 12-week run-in period of treatment with 0.9 mg.

The present trial reported that liraglutide 1.8 mg was associated with an additional HbA$_{1c}$ benefit compared with a lower liraglutide dose, consistent with the findings from the LEAD-3 trial[29]. In the present trial, an initial reduction in HbA$_{1c}$ was observed during the run-in phase. Post-randomization, the HbA$_{1c}$ decline continued in the liraglutide 1.8 mg arm, while there was an increase in HbA$_{1c}$ levels in the 0.9 mg arm. This finding somewhat contradicts results from other

trials evaluating the same dose in Japanese participants[17,18,20,21]. A probable reason for this could be the complex design of the present trial, which was different from LEAD-3 and the other liraglutide trials conducted previously in the Japanese population. While LEAD-3 followed a parallel-group, random assignment to test different doses[29], the present trial had a complex design involving a run-in phase to standardize monotherapy with liraglutide 0.9 mg in all participants, followed by randomization of only those with a poor glycemic response to receive further treatment with liraglutide over 26 weeks (main treatment period). Additionally, the pre-trial OAD was discontinued by participants at the initiation of the run-in stage of the present trial.

Findings from the present trial with liraglutide 0.9 mg, however, also differ from a 24-week phase-3 trial which had a 4–6 week run-in/screening period and a 2-week dose escalation period (from 0.3 mg/day to 0.9 mg/day by weekly increments of 0.3 mg)[18]. The run-in phase of that 24-week trial involved only a wash-out of previous OADs, whereas in this present trial, liraglutide 0.9 mg was administered to all the participants in the run-in period, after which randomization occurred. Notably, in the present trial, only those participants inadequately controlled on liraglutide 0.9 mg received an increased

dose of 1.8 mg or continued with 0.9 mg. The discordance in HbA$_{1c}$ levels between these two trials could be partially explained by differences in the responsiveness to treatment. While in the present trial all participants were using an OAD before randomization, around 19% of participants in the previously published phase-3 trial were drug-naïve for type 2 diabetes and the remaining 81% were using an OAD before switching to liraglutide[18]. The mean age of Japanese patients with type 2 diabetes was lower in the present trial compared with other Japanese studies[18,25,30]. A direct comparison of the present trial results with any of the previously concluded trials may, therefore, not be appropriate.

This was a regulatory trial, whose design was agreed with the Pharmaceuticals and Medical Devices Agency (PMDA) to assess the incremental effect of liraglutide 1.8 mg in participants who did not respond sufficiently to a 0.9 mg dose. Another 52-week phase-3 trial with a more clinically relevant add-on design in Japanese participants reported a 1.8% reduction in HbA$_{1c}$ levels with liraglutide 1.8 mg[25]. This is greater than the change in HbA$_{1c}$ reported in this trial and, again, likely due to trial design and selection of people who did not respond well to liraglutide in the first 12 weeks of treatment.

Examining the secondary efficacy endpoints of this trial in the context of other trials showed some similarities. The HbA$_{1c}$ improvements with liraglutide 1.8 mg in this present trial was reflected by a greater proportion of participants achieving HbA$_{1c}$ targets <7.0 and ≤6.5% compared with 0.9 mg after the main period. These findings were similar to those from LEAD-3, where a higher proportion of participants in the liraglutide 1.8 mg group achieved HbA$_{1c}$ targets <7.0 and ≤6.5% vs liraglutide 1.2 mg[29]. Consistent with the HbA$_{1c}$ findings in the present trial, liraglutide 1.8 mg had greater effects in reducing SMBG, FPG, postprandial plasma glucose (PPG), and fasting glucagon levels vs 0.9 mg after 26 weeks treatment. LEAD-3 also reported significantly greater reductions in FPG levels with liraglutide 1.8 mg compared with a lower dose (1.2 mg), and reductions in PPG and fasting glucagon levels from baseline with liraglutide[29]. Minimizing the risk of weight gain is another key goal in treating individuals with type 2 diabetes[8,9]. Japanese patients with type 2 diabetes and obesity had an effective weight reduction over 6 months of treatment with liraglutide 0.9 mg[31]. The LEAD-3 trial reported that liraglutide 1.8 mg was associated with weight reduction from baseline in participants with type 2 diabetes[29]. While the weight loss in the liraglutide 1.8 mg arm continued up until 52 weeks in the present trial, the dose escalation from 0.9 mg to 1.8 mg did not confer additional weight-loss benefits at the end of the main period. Consistently, in the published literature and within this trial, liraglutide was associated with weight loss, indicating its potential usefulness in patients with type 2 diabetes.

The present trial showed that once-daily liraglutide 1.8 and 0.9 mg doses were well tolerated by Japanese participants. The percentage of participants with AEs was similar to findings from the 24-week phase-3 trial with liraglutide 0.9 mg[18] and

from the LEAD-3 trial[29]. LEAD-3 demonstrated a higher incidence of hypoglycemic events with liraglutide 1.8 mg vs 1.2 mg[29]. However, fewer hypoglycemic episodes were observed in the present trial compared with LEAD-3[29]. The hypoglycemia rates were quite low generally in this trial, with a similar incidence in the two treatment arms, demonstrating that liraglutide may be suitable for patients concerned about such events.

The present trial had few limitations. The trial design was complex, limiting direct comparisons with other trials. The LOCF method is considered to be limited[32], but there was consistency between the primary and sensitivity analyses. Additionally, this trial did not investigate liraglutide added to OADs regarding HbA$_{1c}$ levels. It was also designed for regulatory purposes and therefore enrolled Japanese participants only, possibly limiting the clinical generalizability of the results to other countries.

The present trial confirmed that liraglutide 1.8 mg had better efficacy in reducing HbA$_{1c}$ levels after 26 weeks of the main treatment period, compared with liraglutide 0.9 mg, in Japanese patients with type 2 diabetes. During 26 weeks of the main period, both doses were well tolerated. Liraglutide 1.8 mg was well tolerated during 52 weeks, with no severe or BG-confirmed symptomatic hypoglycemia events reported.

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DISCLOSURE

shareholders. YT: honoraria (advisory boards) from MSD, Boehringer Ingelheim, Tanabe-Mitsubishi, Daiichi Sankyo, Novo Nordisk, Eli Lilly, Sanofi, Astellas Pharma, AstraZeneca and Teijin; honoraria (lectures) from MSD, Ono, Boehringer Ingelheim, Takeda, Tanabe-Mitsubishi, Daiichi Sankyo, Sanwa Kagaku Kenkyusho, Novo Nordisk, Eli Lilly, Sanofi, Dainippon-Sumitomo, Shionogi, Bayer Yakuhin, Astellas and AstraZeneca; research funding from MSD, Ono, Boehringer Ingelheim, Novartis, Takeda, Daiichi Sankyo, Novo Nordisk, Eli Lilly, Sanofi, Dainippon-Sumitomo and AstraZeneca.

The trial was conducted in accordance with Declaration of Helsinki and ICH Good Clinical Practice.

Approval of the research protocol: Prior to trial initiation, the protocol, consent form, and subject information sheet were reviewed and approved according to local regulations by the appropriate health authority, and by multiple site-level institutional review boards. All protocol amendments were reviewed and approved as required according to local regulations, prior to implementation.

Informed consent: All participants provided signed, dated informed consent before trial participation.

Approval date of registry and registration no. of the study/trial: 05/15/2015; NCT02505334.

Animal studies: N/A.

REFERENCES

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2021. *Diabetes Care* 2021; 44: S15–S33.

2. Ministry of Health, Labour and Welfare. Summary of National Health and Nutrition Survey Results 2016. Available from: https://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakukenkouzoushinka/kekkagaiyou_7.pdf Accessed July 7, 2021.

3. International Diabetes Federation (IDF). IDF Diabetes Atlas, 9th edn. Brussels, Belgium, International Diabetes Federation; 2019. Available from: https://www.diabetesatlas.org Accessed November 14, 2021.

4. Laakso M. Heart in diabetes: a microvascular disease. *Diabetes Care* 2011; 34: S145–149.

5. Beckman JA, Creager MA. Vascular complications of diabetes. *Circ Res* 2016; 118: 1771–1785.

6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–853.

7. Nathan DM, Genuth S, Lachin J, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986.

8. DeFronzo RA, Abdul-Ghani MA. Preservation of β-cell function: the key to diabetes prevention. *J Clin Endocrinol Metab* 2011; 96: 2354–2366.

9. Kaku K. Liraglutide for the treatment of diabetes mellitus in Japan. *Diabetes Manage* 2011; 1: 451–463.

10. Møller JB, Dalla Man C, Overgaard RV, *et al*. Ethnic differences in insulin sensitivity, β-cell function, and hepatic extraction between Japanese and Caucasians: a minimal model analysis. *J Clin Endocrinol Metab* 2014; 99: 4273–4280.

11. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci* 2013; 1281: 64–91.

12. Fukushima M, Usami M, Ikeda M, *et al*. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. *Metabolism* 2004; 53: 831–835.

13. Yabe DKH, Iwasaki M, Seino Y. Why are incretin-based therapies more efficient in East Asians? Perspectives from the pathophysiology of type 2 diabetes and East Asian dietary habits. *Eur Med J Diabetes* 2015; 3: 57–65.

14. Yabe D, Kuroe A, Watanabe K, *et al*. Early phase glucagon and insulin secretory abnormalities, but not incretin secretion, are similarly responsible for hyperglycemia after ingestion of nutrients. *J Diabetes Complications* 2015; 29: 413–421.

15. Kim YG, Hahn S, Oh TJ, *et al*. 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: 900–909.

16. Report on the Deliberation Results. 2019. Available from: https://www.pmda.go.jp/files/000153180.pdf Accessed June 10, 2021.

17. Kaku K, Rasmussen MF, Clauson P, *et al*. Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes. *Diabetes Obes Metab* 2010; 12: 341–347.

18. Seino Y, Rasmussen MF, Nishida T, *et al*. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. *Curr Med Res Opin* 2010; 26: 1013–1022.

19. New Drugs Approved in FY. 2014. Available from: https://www.pmda.go.jp/files/000229076.pdf Accessed August 09, 2021.

20. Seino Y, Kaneko S, Fukuda S, *et al*. Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: a 36-week, randomized, double-blind, parallel-group trial. *J Diabetes Investig* 2016; 7: 565–573.

21. Kaku K, Kiyosue A, Ono Y, *et al*. Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: a randomized, 52-week, open-label, parallel-group trial. *J Diabetes Investig* 2016; 7: 76–84.

22. Jin J, Sklar GE, Min Sen OHV, *et al*. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag* 2008; 4: 269–286.

23. Ito D, Iuchi T, Kurihara S, et al. Efficacy and clinical characteristics of liraglutide in Japanese patients with type 2 diabetes. *J Clin Med Res* 2015; 7: 694–699.

24. New Drugs Approved in FY. 2019. Available from https://www.pmda.go.jp/files/000235289.pdf Accessed June 10, 2021.

25. Kaku K, Araki E, Tanizawa Y, et al. Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naïve Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial. *Diabetes Obes Metab* 2019; 21: 2674–2683.

26. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; 36: 1384–1395.

27. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191–2194.

28. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf Accessed May 01, 1996.

29. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; 373: 473–481.

30. Usui R, Yabe D, Kuwata H, et al. Retrospective analysis of safety and efficacy of liraglutide monotherapy and sulfonylurea-combination therapy in Japanese type 2 diabetes: association of remaining β-cell function and achievement of HbA1c target one year after initiation. *J Diabetes Complications* 2015; 29: 1203–1210.

31. Fujishima Y, Maeda N, Inoue K, et al. Efficacy of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, on body weight, eating behavior, and glycemic control, in Japanese obese type 2 diabetes. *Cardiovasc Diabetol* 2012; 11: 107.

32. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; 367: 1355–1360.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Trial design.

Figure S2 | (a) Body weight by treatment week and (b) mean change in body weight from baseline at week 26 and 52.

Table S1 | Pre-trial OAD at screening

Table S2 | Number of participants with adverse events of special interest

Parameters related to glucose homeostasis.