



Efficacy and Safety of Liraglutide Added to Capped Insulin Treatment in Subjects With Type 1 Diabetes: The ADJUNCT TWO Randomized Trial

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OBJECTIVE

To investigate the efficacy and safety of liraglutide added to capped insulin doses in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

A 26-week, placebo-controlled, double-blind, parallel-group trial enrolling 835 subjects randomized 3:1 receiving once-daily subcutaneous liraglutide (1.8, 1.2, and 0.6 mg) or placebo added to an individually capped total daily dose of insulin.

RESULTS

Mean baseline glycated hemoglobin (HbA_{1c}) (8.1% [65.0 mmol/mol]) was significantly decreased with liraglutide versus placebo at week 26 (1.8 mg: −0.33% [3.6 mmol/mol]; 1.2 mg: −0.22% [2.4 mmol/mol]; 0.6 mg: −0.23% [2.5 mmol/mol]; placebo: 0.01% [0.1 mmol/mol]). Liraglutide significantly reduced mean body weight (−5.1, −4.0, and −2.5 kg for 1.8, 1.2, and 0.6 mg, respectively) versus placebo (−0.2 kg). Significant reductions in daily insulin dose and increases in quality of life were seen with liraglutide versus placebo. There were higher rates of symptomatic hypoglycemia (21.3 vs. 16.6 events/patient/year; *P* = 0.03) with liraglutide 1.2 mg vs. placebo and of hyperglycemia with ketosis >1.5 mmol/L with liraglutide 1.8 mg vs. placebo (0.5 vs. 0.1 events/patient/year; *P* = 0.01).

CONCLUSIONS

In a broad population of subjects with long-standing type 1 diabetes, liraglutide added to capped insulin reduced HbA_{1c}, body weight, and insulin requirements but with higher rates of hypoglycemia for liraglutide 1.2 mg and hyperglycemia with ketosis for liraglutide 1.8 mg.

Most people with type 1 diabetes do not currently reach glycemic targets (1), as both patients and providers are often reluctant to intensify glycemic therapy because of reasons such as concern about hypoglycemia and/or weight gain (2). Moreover, a recent study using electronic health records from the U.S. reported that 47.8% of people with type 1 diabetes are obese (3). Therefore, noninsulin adjunctive treatments with a low intrinsic risk of hypoglycemia and weight gain offer a potential means of complementing intensive insulin therapy in people

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*A complete list of the members of the ADJUNCT TWO Investigators can be found in the Supplementary Data online.

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with type 1 diabetes (4). However, the evidence base for such treatments is limited (5), and only pramlintide, an analog of human amylin (6), is currently approved by the U.S. Food and Drug Administration for use with mealtime insulin in people with type 1 diabetes (7).

In people with type 2 diabetes, liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is known to stimulate insulin secretion, improve β -cell function, and inhibit glucagon release from α -cells in a glucose-dependent manner (8). Furthermore, liraglutide decreases food intake (9) and has weight loss benefits in type 2 diabetes (10–14). Whether similar responses exist in people with type 1 diabetes is uncertain. Small, nonrandomized studies in subjects with type 1 diabetes suggest that GLP-1RA treatment results in reduction in fasting and postprandial hyperglycemia, postprandial glucagon plasma levels, glucose excursions, hypoglycemic events, insulin requirements, and body weight, but these results have not yet been confirmed in larger studies with longer duration (15–23). Recently, two such randomized controlled trials (RCTs) investigating the efficacy and safety of liraglutide added to insulin in subjects with type 1 diabetes have been completed (ADJUNCT ONE [NCT01836523] [24] and ADJUNCT TWO [NCT02098395]). Here we report findings from the ADJUNCT TWO trial.

The primary aim of ADJUNCT TWO was to confirm, in a large, multicenter, randomized study, superiority of liraglutide compared with placebo, both adjunct to capped insulin treatment, on glycemic control, after 26 weeks of treatment in subjects with established type 1 diabetes and inadequate glycemic control.

RESEARCH DESIGN AND METHODS

Trial Design

This was a 26-week, randomized, insulin-capped, placebo-controlled, double-blind, parallel-group, phase 3 trial performed at 59 centers in North America, Europe, and Africa.

After a screening visit (week –2), eligible subjects attended the randomization visit (week 0) and were randomized using a telephone or web-based system (IV/WRS) by Novo Nordisk (Clinical Supplies Coordination) (stratified by glycated hemoglobin [HbA_{1c}] [$<8.5\%$; <69.4 mmol/mol and $\geq 8.5\%$; ≥ 69.4 mmol/mol] and BMI

[≤ 27 and >27 kg/m²]). Subjects were randomized 3:1 to liraglutide 1.8, 1.2, and 0.6 mg, or liraglutide placebo 0.3, 0.2, or 0.1 mL, respectively, as adjunct to insulin treatment for a period of 26 weeks. Treatment with liraglutide (or the corresponding placebo volume) was started at 0.6 mg/day at week 0 and increased by 0.6 mg every 2nd week until the randomized dose level was reached. In order to obtain a dose response, dose reduction of liraglutide was not permitted on randomized dose.

To ensure treatment uniformity between the trial sites, as well as to ensure that subjects received treatment according to the trial protocol, titration algorithms were developed specifying recommended insulin dose adjustments at different plasma glucose levels. Subjects were instructed to perform self-monitoring of plasma glucose (SMPG) (4-, 7-, and 9-point profiles) on days before site and phone contacts and after new liraglutide dose escalation. The insulin cap was determined for each subject individually prior to randomization and, as it is acknowledged that people with type 1 diabetes can have large fluctuations in insulin dose on a daily basis, was defined as the average of the previous 7 consecutive days' total daily insulin dose. No range limit or lower limit for insulin requirement was set. No postprandial glucose targets were set. However, adjustments based on postprandial glucose within the limits of the insulin cap were at the discretion of the investigator in accordance with local practice/standard of medical care. The total daily preresearch randomization insulin dose was reduced by 25% for at least 1 day when liraglutide or placebo was initiated, and by a further 10% for at least 1 day when liraglutide/placebo doses were escalated. Thereafter, the insulin dose could be adjusted weekly by subjects and at least biweekly by investigators, based on 4-point glucose (premeal) values, toward the insulin cap as defined previously. In case of severe deterioration of glycemic control, rescue treatment was to be initiated (Supplementary Fig. 1).

Trial Population

Key inclusion criteria comprised the following: type 1 diabetes duration ≥ 1 year, age ≥ 18 years, BMI ≥ 20 kg/m², treatment with multiple daily injections

(MDI) of insulin or continuous subcutaneous insulin infusion (CSII) for at least 6 months, and HbA_{1c} 7.0–10.0% (53.0–85.8 mmol/mol) with a stable insulin dose (as judged and documented by the investigator) for at least 3 months. In order to increase applicability of results to clinical practice, “fragile” subjects (i.e., subjects with hypoglycemic unawareness, history of severe hypoglycemia, mildly to severely decreased renal function [based on chronic kidney disease definitions] [25], or a recent history of diabetic ketoacidosis) were not excluded. Key exclusion criteria comprised the following: any prior use of GLP-1RAs or dipeptidyl peptidase-4 inhibitors, any medication (except insulin) that could interfere with glycemic control or affect a subject's safety, or an estimated glomerular filtration rate <30 mL/min/1.73 m².

Outcome Measures

The primary end point was change from baseline in HbA_{1c} after 26 weeks of treatment. Secondary end points included change from baseline in body weight, total daily insulin dose, 1,5-anhydroglucitol, fasting plasma glucose, 9-point SMPG (using a self-measured blood glucose device calibrated to report plasma glucose), fasting plasma glucagon, plasma C-peptide, and quality of life (treatment-related impact measures-diabetes [TRIM-D], TRIM-hypoglycemia [TRIM-HYPO], and short-form 36 questionnaires) and proportions of subjects achieving HbA_{1c} targets ($HbA_{1c} <7.0\%$ [<53.0 mmol/mol]; composite targets [$HbA_{1c} <7.0\%$ (<53.0 mmol/mol) and no severe hypoglycemia; HbA_{1c} reduction $>1\%$ (>10.9 mmol/mol) and no severe hypoglycemia) after 26 weeks of treatment.

Safety end points included incidence of symptomatic hypoglycemic episodes, defined as severe according to the American Diabetes Association (ADA) (26) or by a plasma glucose value of <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycemia (Novo Nordisk definition). Furthermore, documented symptomatic, asymptomatic, severe, and nocturnal (12:01–05:59 A.M., both inclusive) hypoglycemic episodes were reported (26). Asymptomatic hypoglycemic episodes according to the Novo Nordisk definition (plasma glucose <3.1 mmol/L [<56 mg/dL] and no symptoms) were investigated as a

post hoc end point. Hyperglycemic episodes (plasma glucose >16.7 mmol/L [>300 mg/dL]), hyperglycemic episodes with ketosis (plasma ketone >1.5 mmol/L [based on vendor's user recommendations for the ketostick]), and adverse events (AEs) were also reported. Subjects were advised to measure ketones at each plasma glucose excursion >16.7 mmol/L (>300 mg/dL).

Subgroup Analyses

Analyses were performed to identify potential subgroups of subjects with an improved treatment effect. Prespecified analyses included baseline variables such as age, sex, type 1 diabetes duration, method of insulin administration (MDI versus CSII), body weight, BMI, HbA_{1c}, hypoglycemia unawareness status, and severe hypoglycemia within the last 12 months. No subgroup analysis was performed related to the prandial insulin-adjusting algorithm, as it was based on clinical judgement. Post hoc analyses included baseline variables such as C-peptide level.

Statistical Analyses

Sample size was determined to detect a difference of 0.4% (4.4 mmol/mol) in HbA_{1c} change and 2.5 kg in body weight change after 26 weeks of treatment between the liraglutide 1.8 mg dose and placebo with 90.0 and 99.9% power, respectively. Sample size calculation was based on a two-sided Student *t* test of 5% and an SD of 1.1% (12.0 mmol/mol) in HbA_{1c} change after 26 weeks of treatment. The required sample size was 160 subjects per group, assuming no patients withdrew. Adopting an overall 20% dropout rate evenly distributed among treatment groups, the required sample size was 200 subjects per group. With a 50% efficacy retention in the dropouts, a treatment difference of 0.36% was then expected.

Continuous data were analyzed using a mixed model for repeated measurements, with treatment, stratification, and country as fixed factors and baseline as a covariate, all nested within visit. Binary data were analyzed by a logistic regression model, with treatment and stratification as factors and HbA_{1c} value at baseline as a covariate. Missing HbA_{1c} data were imputed from the mixed model for repeated measurements used for the analysis of HbA_{1c}. Numbers of on-treatment hypoglycemic/

hyperglycemic episodes were analyzed using a negative binomial regression model, with a log-link function and the logarithm of the time period in which the episodes were considered treatment emergent as offset, with treatment, stratification, and country as factors and the HbA_{1c} value at baseline as a covariate.

RESULTS

Subject Disposition

Of the 835 randomized subjects, 832 were exposed to liraglutide or placebo in addition to insulin during the trial (liraglutide 0.6 mg, *n* = 211; 1.2 mg, *n* = 209; 1.8 mg, *n* = 206; placebo, *n* = 206) and 661 subjects completed week 26 without discontinuation of trial product or use of rescue treatment (intensification of usual insulin dose) (liraglutide 0.6 mg, *n* = 177; 1.2 mg, *n* = 157; 1.8 mg, *n* = 157; placebo, *n* = 170) (Supplementary Fig. 1). Overall, rescue treatment was needed in 42 (5.0%) subjects. More subjects in the liraglutide 1.2 mg group required rescue treatment (*n* = 16, 7.7%) than in the other treatment groups (liraglutide 1.8 mg: *n* = 8, 3.9%; 0.6 mg: *n* = 9, 4.2%; placebo: *n* = 9, 4.3%). In total, 127 (15.2%) subjects withdrew from the trial: *n* = 42 (20.3%), *n* = 32 (15.3%), *n* = 26 (12.3%), and *n* = 27 (13.0%) in the liraglutide 1.8, 1.2, and 0.6 mg and placebo groups, respectively.

Baseline Characteristics

On average, the trial population had longstanding (mean duration 21.1 years) type 1 diabetes with inadequate glycemic control (mean HbA_{1c} 8.1% [65.0 mmol/mol]) and was moderately overweight (mean body weight 83.9 kg; mean BMI 28.9 kg/m²) (Table 1). In total, 125 (15.2%) subjects had C-peptide levels greater than the lower limit of quantification (>LLOQ: 0.030 nmol/L) (Supplementary Table 1) and 213 (25.6%) subjects were receiving CSII. Overall, mean (geometric) total daily insulin dose was 10.0 units higher in subjects receiving MDI of insulin than in subjects receiving CSII. Almost half of the subjects had some symptoms or diagnosis of long-term diabetes complications, 47 (5.7%) subjects had hypoglycemia unawareness, and 61 (7.3%) had a history of severe hypoglycemia.

Efficacy

HbA_{1c} reductions occurred in the first 3 months of the trial, after which HbA_{1c}

levels increased gradually. From baseline to week 26, HbA_{1c} was largely unchanged with placebo (0.01% [0.1 mmol/mol]), whereas a statistically significant reduction in HbA_{1c} was seen for all liraglutide doses versus placebo (estimated treatment difference [ETD]: 1.8 mg, −0.35%/−3.8 mmol/mol [95% CI −0.50; −0.20], *P* < 0.0001; 1.2 mg, −0.23%/−2.5 mmol/mol [95% CI −0.38; −0.08], *P* = 0.0021; 0.6 mg, −0.24%/−2.6 mmol/mol [95% CI −0.39; −0.10], *P* = 0.0011) (Fig. 1A). The reduction in HbA_{1c} reported with liraglutide 1.8 mg was accompanied by a significantly greater increase in mean 1,5-anhydroglucitol compared with placebo (end-of-trial values: 3.11 µg/mL and 2.68 µg/mL, respectively; estimated treatment ratio: 1.16 [95% CI 1.05; 1.28], *P* = 0.0026) and, with the 9-point SMPG profiles, apparent reductions in postbreakfast, postlunch, and bedtime glucose (Supplementary Fig. 2). With liraglutide 1.2 and 0.6 mg, there was no significant effect (compared with placebo) on 1,5-anhydroglucitol and no apparent reductions in 9-point SMPG profiles. There were no significant differences between any of the liraglutide doses and placebo for mean fasting plasma glucose, mean fasting plasma glucagon, or mean plasma C-peptide at 26 weeks.

A significant dose-dependent decrease in mean (geometric) total daily insulin dose was reported with all liraglutide doses at 26 weeks compared with placebo (estimated treatment ratio: 1.8 mg, 0.90 [95% CI 0.86; 0.93], *P* < 0.0001; 1.2 mg, 0.93 [95% CI 0.90; 0.96], *P* < 0.0001; 0.6 mg, 0.95 [95% CI 0.92; 0.99], *P* = 0.0075) (Fig. 1B). This insulin dose reduction in the liraglutide groups was achieved mainly through a prandial insulin reduction. The mean decrease of prandial insulin was −4 to −5 units and −3 to −5.5 units in subjects receiving MDI of insulin and CSII, respectively, whereas the dose decrease in basal insulin was −0.9 to 0.2 units and −0.1 to −0.9 units, respectively.

A dose-dependent statistically significant decrease in mean body weight from baseline to week 26 was reported with liraglutide (1.8 mg, −5.1 kg; 1.2 mg, −4.0 kg; 0.6 mg, −2.5 kg; placebo, −0.2 kg, all *P* < 0.0001) (Fig. 1C).

At 26 weeks, significantly more subjects receiving liraglutide 1.8 mg compared with placebo achieved the ADA

Table 1—Demographics and baseline characteristics

	Liraglutide 1.8 mg (n = 205)	Liraglutide 1.2 mg (n = 209)	Liraglutide 0.6 mg (n = 211)	Placebo (n = 206)
Age (years) [†]	43.2 (18; 75)	42.8 (18; 73)	43.9 (19; 87)	42.7 (18; 70)
Female:male (%)	55:45	51:49	56:44	54:46
Duration of type 1 diabetes (years) [†]	21.4 (1; 53)	21.1 (1; 52)	21.0 (1; 58)	20.7 (1; 54)
MDI*	75 (67/33)	73 (70/30)	75 (66/34)	75 (62/38)
Total insulin dose MDI (units/day)**	58.4	58.8	58.8	61.7
CSII (%)	25	27	25	25
Total insulin dose CSII (units/day)**	50.1	46.8	47.9	50.3
Hypoglycemic unawareness (yes/no) (%)	5/95	7/93	8/92	3/97
Severe hypoglycemia within last year (0/>1) (%)	93/7	91/9	92/8	95/5
Body weight (kg)	83.6	84.7	83.1	84.2
BMI (kg/m ²)	28.9	28.8	28.9	28.9
HbA _{1c} (%)	8.04	8.07	8.09	8.12
HbA _{1c} (mmol/mol)	64.4	64.7	64.9	65.2
Fasting plasma C-peptide (nmol/L)	0.037	0.031	0.052	0.033
<LLOQ (%)	84	84	83	89
≥LLOQ (%)	16	16	17	11
eGFR (mL/min/1.73 m ²)	94	94	94	97
Diabetic retinopathy (%)	38	29	37	35
Diabetic neuropathy (%)	21	20	27	22
Diabetic nephropathy (%)	9	3	11	12
Diabetic macroangiopathy (%)	3	1	3	4
Hypertension (%)	31	38	37	38

eGFR, estimated glomerular filtration rate. [†]Mean (minimum; maximum); *% (% basal once daily/% ≥ b.i.d.); **geometric mean.

target of HbA_{1c} <7.0% (<53.0 mmol/mol) (18.8 vs. 10.0%, respectively, odds ratio [OR] 2.12 [95% CI 1.11; 4.06], *P* = 0.0231) (Fig. 2A). There was no significant effect of liraglutide 1.2 and 0.6 mg compared with placebo on this end point. Significantly more subjects receiving liraglutide 1.8 mg (but not those receiving liraglutide 1.2 or 0.6 mg) versus placebo achieved the composite target of HbA_{1c} <7.0% (<53.0 mmol/mol) with no severe hypoglycemia (18.2 vs. 10.0%, respectively, OR 2.02 [95% CI 1.05; 3.87], *P* = 0.0343) (Fig. 2B). Similarly, significantly more subjects receiving liraglutide 1.8 mg (15.3%), 1.2 mg (11.3%), and 0.6 mg (11.1%) versus placebo (3.7%) achieved the composite target of HbA_{1c} reduction >1.0% (>10.9 mmol/mol) and no severe hypoglycemia (1.8 mg: OR 5.36 [95% CI 2.21; 12.96], *P* = 0.0002; 1.2 mg: OR 3.48 [95% CI 1.41; 8.59], *P* = 0.0069; 0.6 mg: OR 3.39 [95% CI 1.38; 8.34], *P* = 0.0078) (Fig. 2C).

Safety

Overall, rates of AEs increased with liraglutide in a dose-dependent manner (11.5, 9.6, and 7.0 events per patient

year of exposure [PYE] for liraglutide 1.8, 1.2, and 0.6 mg, respectively, compared with 6.3 events per PYE for placebo) (Table 2). However, there was a similar proportion of subjects with serious AEs across the treatment groups (6.8, 10.0, and 9.5% for liraglutide 1.8, 1.2, and 0.6 mg, respectively, compared with 6.8% for placebo). There was a higher rate of study discontinuation due to AEs in the liraglutide group than in the placebo group. Nausea, which increased dose dependently (2.0, 1.3, and 0.8 events per PYE for liraglutide 1.8, 1.2, and 0.6 mg, respectively, and 0.4 events per PYE for placebo), was the most frequently reported AE with liraglutide. In all liraglutide groups, new-onset nausea tended to occur within the first weeks of treatment (i.e., during dose initiation and escalation); after this time, the incidence of nausea decreased.

Throughout the trial, there were four adjudicated cardiovascular events (three acute coronary syndromes [one with liraglutide 0.6 mg, one with liraglutide 1.2 mg, and one with placebo] and one cerebrovascular event [liraglutide

1.8 mg]), four neoplasms (three benign [liraglutide 1.8 mg, liraglutide 1.2 mg, and placebo] and one malignant [liraglutide 1.8 mg]), and one thyroid event requiring thyroidectomy (C-cell hyperplasia [liraglutide 1.8 mg]) (Supplementary Material). There was no apparent pattern with regards to treatment dose of liraglutide. There was a single confirmed case of diabetic ketoacidosis requiring hospitalization with liraglutide 1.2 mg (in a subject who was not compliant with treatment algorithms) and no fatal events in any treatment group. Mean lipase and amylase levels increased significantly in all liraglutide treatment groups (Supplementary Table 2). However, the majority of subjects in each treatment group had postbaseline lipase and amylase values within the normal range. There were transient elevations of lipase greater than three times the upper limit of normal in all liraglutide groups (1.8 mg, *n* = 4 [1.9%]; 1.2 mg, *n* = 4 [1.9%]; 0.6 mg, *n* = 2 [1.0%]). One subject in the placebo group had a transient elevation of amylase greater than three times the upper limit of normal. No cases of pancreatitis were reported in any treatment

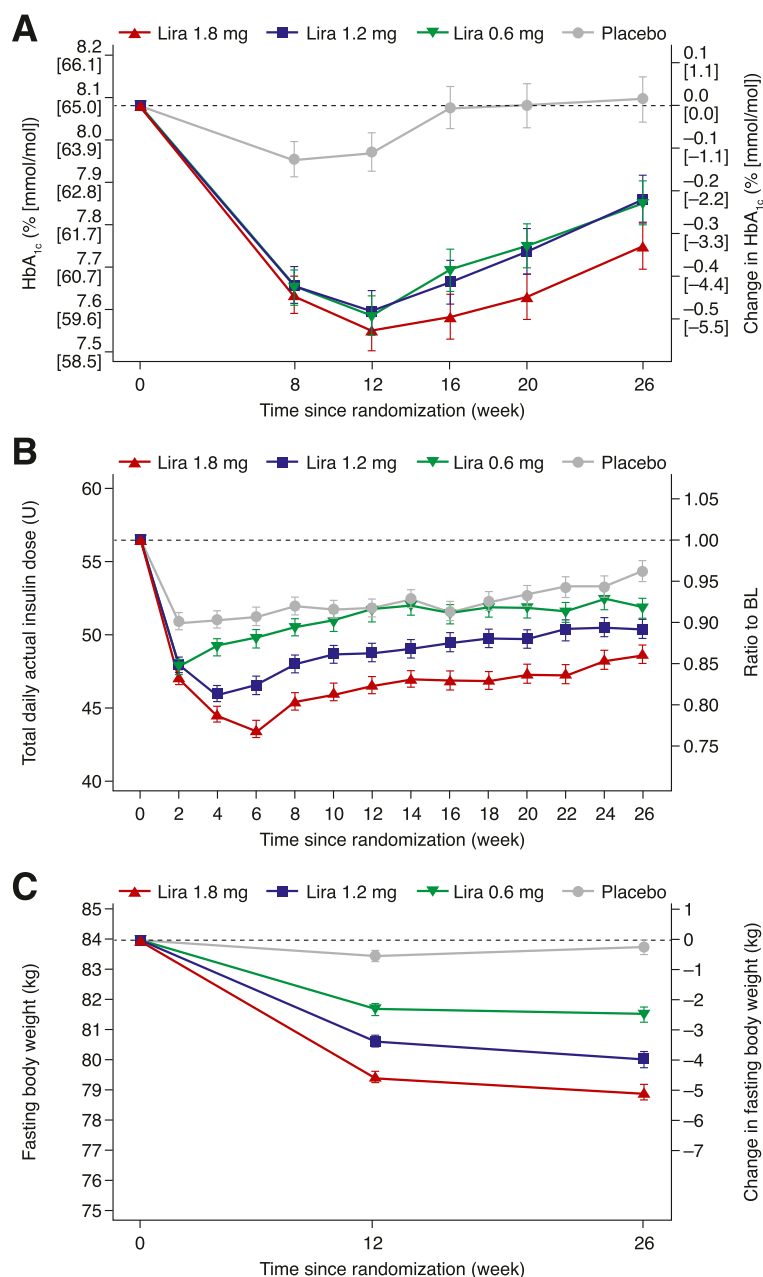


Figure 1—A: Mean change in HbA_{1c} by treatment week. B: Mean change in total insulin dose by treatment week. C: Mean change in body weight by treatment week. Error bars are SEM. BL, baseline; Lira, liraglutide.

group. There was no apparent difference between the treatment groups in the proportion of subjects who had calcitonin categorized as either <LLOQ or ≥LLOQ at weeks −2 and 26 as well as for median, minimum, and maximum values (Supplementary Table 2). Mean pulse and systolic blood pressure significantly increased and decreased, respectively, in all liraglutide treatment groups (Supplementary Table 2). There was no significant effect on mean diastolic blood pressure.

Hypoglycemic Episodes

In total, 92–98% of subjects reported at least one hypoglycemic episode during the trial, and hypoglycemic episodes were uniformly distributed throughout the trial period. For most hypoglycemia end points, the number of episodes was similar across treatment groups (Table 2). There was a higher rate of symptomatic (estimated rate ratio [ERR] 1.31 [95% CI 1.03; 1.68], $P = 0.0289$) and documented symptomatic (ERR 1.33 [95% CI 1.07; 1.67], $P = 0.0114$)

hypoglycemic episodes only with liraglutide 1.2 mg compared with placebo (21.3 vs. 16.6 events per PYE and 42.4 vs. 33.6 events per PYE, respectively). For all liraglutide doses, there was no significant difference in rate of severe or nocturnal hypoglycemic episodes compared with placebo. Rates of asymptomatic hypoglycemic episodes, with plasma glucose <3.1 mmol/L (<56 mg/dL) (Novo Nordisk definition), were 4.9, 4.4, 4.8, or 5.5 events per PYE on liraglutide 1.8, 1.2, or 0.6 mg or placebo, respectively. Rates of asymptomatic hypoglycemic episodes, with plasma glucose <3.9 mmol/L (<70 mg/dL), were also similar between treatment groups (Table 2).

Hyperglycemic Episodes

Overall, there were no differences in the rates of hyperglycemic episodes with liraglutide compared with placebo (40.5, 44.8, and 40.0 events per PYE for liraglutide 1.8, 1.2, and 0.6 mg, respectively, compared with 45.7 events per PYE for placebo). Hyperglycemic episodes were uniformly distributed throughout the trial period. There was a higher rate of hyperglycemic episodes with ketosis >1.5 mmol/L with liraglutide 1.8 mg compared with placebo (42 events in 17 subjects and 10 events in 9 subjects [0.5 vs. 0.1 events per PYE], respectively, ERR 3.96 [95% CI 1.49; 10.55], $P = 0.0059$). There were higher rates of hyperglycemic episodes with ketosis reported with liraglutide 1.2 and 0.6 mg compared with placebo (20 events in 13 subjects and 23 events in 17 subjects [0.2 and 0.2 vs. 0.1 events per PYE], respectively); however, these differences were not statistically significant. Hyperglycemic episodes with ketosis occurred more frequently in the first 8 weeks of the trial.

Subgroup Analyses

With the exception of C-peptide–positive/negative subjects, the analyses of the previously mentioned subgroups showed comparable findings to the overall results. In the current trial, ~15% of subjects ($n = 125$) had C-peptide levels above the LLOQ, ranging between 0.08 and 0.12 nmol/L. These subjects also differed from the overall population by a slightly higher baseline HbA_{1c} and shorter type 1 diabetes duration (Supplementary Table 1). These subjects showed an improved treatment effect

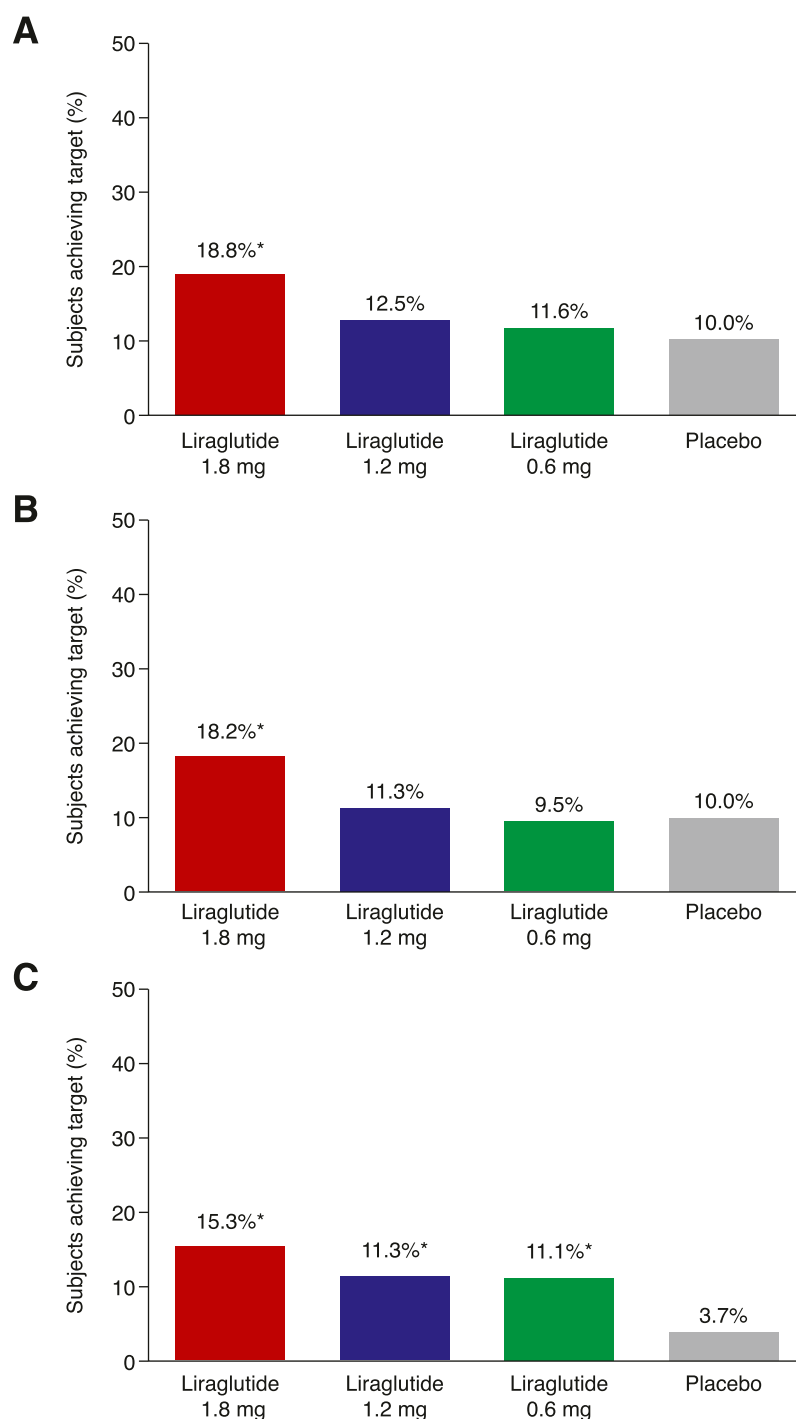


Figure 2—Subjects achieving targets at week 26. A: HbA_{1c} < 7.0% (< 53.0 mmol/mol). B: HbA_{1c} < 7.0% (< 53.0 mmol/mol) and no severe hypoglycemia. C: HbA_{1c} reduction > 1% (> 10.9 mmol/mol) and no severe hypoglycemia. **P* < 0.05.

on HbA_{1c} with all liraglutide doses (1.8 mg: estimated mean placebo-corrected HbA_{1c} reduction of -0.77% [-8.4 mmol/mol] compared with -0.27% [-3.0 mmol/mol] for subjects without measurable C-peptide, treatment interaction *P* = 0.0302; 1.2 mg: -0.69% [-7.5 mmol/mol] and -0.14% [-1.6 mmol/mol], respectively, *P* =

0.0140; 0.6 mg: -0.65% [-7.1 mmol/mol] and -0.17% [-1.9 mmol/mol], respectively, *P* = 0.0293). Of note, of all episodes of hyperglycemia with ketosis > 1.5 mmol/L (42, 20, 23, and 10 episodes in the liraglutide 1.8, 1.2, and 0.6 mg and placebo groups, respectively), only one episode occurred in a subject with measurable residual C-peptide (in the

liraglutide 0.6 mg group). Regarding symptomatic hypoglycemia, there were more episodes with liraglutide 1.2 mg only compared with placebo in both the baseline C-peptide groups (\geq LLOQ 8.5, 14.0, 10.6, and 7.4 events per PYE and $<$ LLOQ 19.2, 22.6, 16.1, and 17.8 events per PYE for liraglutide 1.8, 1.2, and 0.6 mg and placebo, respectively).

Quality of Life

Mean TRIM-D management score was reduced from baseline with placebo (-1.48), which reflects a reduced quality of life. However, with all liraglutide doses, mean TRIM-D management score was increased from baseline (1.8 mg: 7.46, 1.2 mg: 4.15, and 0.6 mg: 3.55), reflecting improved quality of life. Increases in TRIM-D management score were significantly greater with all liraglutide doses than with placebo (1.8 mg: ETD 8.94 [95% CI 4.33; 13.55], *P* = 0.0002; 1.2 mg: ETD 5.64 [1.01; 10.26], *P* = 0.0170; 0.6 mg: ETD 5.04 [0.54; 9.54], *P* = 0.0282), reflecting improved quality of life. At 26 weeks and compared with placebo, an increase in mean TRIM-D total score (driven by the corresponding increase in mean TRIM-D management score) was reported with liraglutide 1.8 mg (3.42 vs. 5.93, respectively, ETD 2.51 [95% CI 0.29; 4.73], *P* = 0.0269). There was no significant effect of liraglutide 1.2 and 0.6 mg on TRIM-D total score compared with placebo. There was no overall effect of any dose of liraglutide on TRIM-HYPO total three domains score or short-form 36 overall physical or mental scores compared with placebo.

CONCLUSIONS

ADJUNCT TWO is the first large-scale RCT designed to investigate the efficacy and safety of adding liraglutide to an individually capped insulin dose in subjects with type 1 diabetes and inadequate glycemic control. The current trial demonstrates that liraglutide (1.8, 1.2, and 0.6 mg) added to capped insulin treatment results in greater mean reductions in HbA_{1c}, body weight, and insulin dose but higher rates of hypoglycemia (1.2 mg) and hyperglycemia with ketosis (1.8 mg) compared with placebo. These findings are largely in agreement with those from ADJUNCT ONE, a 52-week randomized, placebo-controlled, double-blind, parallel-group, treat-to-target,

Table 2—Safety end points: on-treatment summary

	Liraglutide 1.8 mg (n = 206)			Liraglutide 1.2 mg (n = 209)			Liraglutide 0.6 mg (n = 211)			Placebo (n = 206)		
	n	%	R	n	%	R	n	%	R	n	%	R
AEs												
All AEs	180	87.4	11.5	184	88.0	9.6	173	82.0	7.0	160	77.7	6.3
Serious	14	6.8	0.2	21	10.0	0.3	20	9.5	0.3	14	6.8	0.2
Leading to discontinuation	33	16.0	0.7	20	9.6	0.4	12	5.7	0.3	2	1.0	0.0
Nausea	102	49.5	2.0	98	46.9	1.3	68	32.2	0.8	34	16.5	0.4
Vomiting	35	17.0	0.8	30	14.4	0.5	19	9.0	0.3	8	3.9	0.1
Diarrhea	30	14.6	0.5	27	12.9	0.4	14	6.6	0.2	17	8.3	0.2
Decreased appetite	50	24.3	0.6	40	19.1	0.5	21	10.0	0.2	9	4.4	0.1
Hypoglycemia												
All episodes	201	97.6	54.1	204	97.6	58.7	200	94.8	47.9	189	91.7	50.6
Symptomatic*	160	77.7	17.4	175	83.7	21.3	166	78.7	15.0	162	78.6	16.6
Severe or BG confirmed*	179	86.9	22.3	185	88.5	25.7	177	83.9	19.8	169	82.0	22.1
Documented symptomatic	187	90.8	36.8	189	90.4	42.4	184	87.2	31.5	178	86.4	33.6
Asymptomatic	163	79.1	16.6	172	82.3	15.6	153	72.5	15.7	151	73.3	16.5
Severe	5	2.4	0.1	13	6.2	0.2	15	7.1	0.2	10	4.9	0.1
Nocturnal	124	60.2	6.0	127	60.8	6.4	126	59.7	5.5	124	60.2	6.0
Hyperglycemia												
All episodes	175	85.0	40.5	188	90.0	44.8	185	87.7	40.0	191	92.7	45.7
Symptomatic	130	63.1	14.7	137	65.6	19.9	130	61.6	18.0	134	65.0	18.6
With ketosis	17	8.3	0.5	13	6.2	0.2	17	8.1	0.2	9	4.4	0.1
Symptomatic with ketosis	15	7.3	0.2	12	5.7	0.2	10	4.7	0.1	4	1.9	0.0

Symptomatic, severe according to the ADA classification (25) or a plasma glucose value of <3.1 mmol/L (<56 mg/dL), with symptoms consistent with hypoglycemia; severe or BG confirmed, hypoglycemic episodes that are either severe according to ADA or a plasma BG value of <3.1 mmol/L (<56 mg/dL); documented symptomatic, typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (≤ 70 mg/dL); asymptomatic, no typical symptoms of hypoglycemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (≤ 70 mg/dL); severe, see symptomatic; nocturnal, onset was between 12:01 and 05:59 A.M., both included; hyperglycemia, plasma glucose values >16.7 mmol/L (>300 mg/dL); ketosis, plasma ketone values >1.5 mmol/L. BG, blood glucose; n, number of subjects experiencing at least one event; R, event rate per PYE; %, percentage of subjects experiencing at least one event. *Novo Nordisk definition.

phase 3 trial carried out at 177 centers in 17 countries (24).

Considering efficacy, the mean reduction in HbA_{1c} reported with liraglutide 1.8 mg in the current trial was modest (despite the greatest decrease in pretrial insulin) but comparable to that achieved with pramlintide (-0.5% [-5.5 mmol/mol]) (27). Subgroup analysis in the current study indicates that in C-peptide-positive subjects, the mean placebo-corrected reduction in HbA_{1c} with liraglutide 1.8 mg is significantly greater than in C-peptide-negative subjects (i.e., -0.8 vs. -0.3%). In the overall analysis, with liraglutide 1.8 mg, there was an increase in mean 1,5-anhydroglucitol as well as nonsignificant (compared with placebo) reductions in postbreakfast, postlunch, and bedtime SMPG measurements that, together, suggest improvements in both overall and postprandial glycemic control. HbA_{1c} reductions that occurred were more pronounced within the first 3 months of the trial, after which HbA_{1c} levels steadily increased toward placebo levels. This suggests that insulin dose increases could have been more aggressive. Whether

expected insulin-associated weight gain could have impacted the decision to intensify insulin treatment further throughout the trial remains speculative.

In the current trial, the insulin cap was imposed to reflect the added effect on glycemic control in people who, in clinical practice, may be reluctant to intensify insulin treatment. Despite the HbA_{1c} reduction obtained, the mean total daily insulin dose did not return to the mean cap, and mean total daily insulin doses were ~ 10 – 15% below baseline values at week 26. It is noteworthy that most, if not all, of the reduction in total daily insulin dose was due to prandial insulin. A recent study reports a reduction in carbohydrate intake, associated with appetite suppression, and a reduction in postprandial glucagon in subjects with type 1 diabetes being treated with liraglutide (28). It could, therefore, be speculated that in the current study, liraglutide may have inhibited energy intake and postprandial glucagon secretion, thereby limiting the exogenous insulin requirement. However, in ADJUNCT

TWO, neither possibility was specifically investigated.

Weight loss and improvements in quality of life were additional benefits of liraglutide treatment in the current trial. Liraglutide 1.8 mg resulted in a mean reduction in body weight of -5.1 kg, and this is comparable with findings from a recent RCT involving a population with type 1 diabetes and obesity (-6.8 kg) (22). Intensive insulin treatment in people with type 1 diabetes is often associated with an increased prevalence of overweight and obesity over time (29). In the DCCT study after 6 years of treatment, for example, 4.75 kg more weight gain than conventionally treated counterparts was observed (30). Furthermore, both overweight and obesity are associated with insulin resistance, dyslipidemia, increased blood pressure, and atherosclerosis in a population with type 1 diabetes (31). The improvement in quality of life as evidenced by the increased mean TRIM-D total score and the mean TRIM-D management score suggests that adjunctive liraglutide treatment may improve adherence with potential longer-term benefits (32–34).

Considering safety, higher numbers of symptomatic hypoglycemia were seen with liraglutide (1.2 mg) than with placebo (21.3 vs. 16.6 events per PYE, respectively). An explanation as to why only one of the liraglutide doses showed higher rates remains unclear. It has been considered that this may relate to the insulin dose titration, nausea, satiety, or misjudged food intake. However, currently no specific reason is directly supported by collected data. Whether this is an intrinsic problem with the use of GLP-1RAs in type 1 diabetes or if it could be mitigated by patient selection, dosing, continuous glucose monitoring, or education remains speculative. It is of note that liraglutide added to insulin treatment does not affect the counter-regulatory hormone responses during hypoglycemia or glycemic recovery from hypoglycemia in subjects with type 1 diabetes (21,35); consequently, the higher incidence of hypoglycemia with liraglutide is probably not dependent on defective counter-regulation. Increased hyperglycemia with ketosis was also observed with liraglutide compared with placebo. In the liraglutide group, the reduction in daily total insulin dose may have contributed to this observation. Interestingly, whereas there were >80 events of hyperglycemia with ketosis in the C-peptide-negative population on liraglutide, there was only one event in the C-peptide-positive population. The increases in mean amylase, lipase, and pulse and reductions in mean systolic blood pressure reported in the liraglutide groups are of unknown clinical significance. Furthermore, these observations are similar to those seen in type 2 diabetes-focused trials involving this drug class (36–38).

Considering trial limitations, the results may have benefited from the assessment of food intake; moreover, the use of continuous glucose monitoring, absent from this trial, would have gathered more comprehensive data on glycemic variability, postprandial excursions, and time in glycemic objectives. The lack of standardization between test centers in insulin titration methodology could also be considered a limitation. Furthermore, the capped insulin dose is rarely used in clinical trials in subjects with type 1 diabetes, making comparisons with other trials a challenge.

In summary, the ADJUNCT TWO trial demonstrated benefits of liraglutide as an adjunct to insulin treatment in subjects with type 1 diabetes with a capped insulin dose with respect to glycemic control, insulin dose, weight, and quality of life. The higher number of hypoglycemia and of hyperglycemia with ketosis in some of the liraglutide groups emphasizes the need for proper insulin titration and may ultimately limit the clinical utility of GLP-1RAs in a less well-supervised population with type 1 diabetes.

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