Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE-M Randomized Controlled Trial

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OBJECTIVE

To assess the efficacy and safety of the glucagon-like peptide 1 receptor agonist (GLP-1 RA) efpeglenatide versus placebo in patients with type 2 diabetes inadequately controlled with diet and exercise alone.

RESEARCH DESIGN AND METHODS

AMPLITUDE-M was a phase 3, double-blind, placebo-controlled, multicenter trial that randomized adults with type 2 diabetes suboptimally controlled with diet and exercise alone to once-weekly efpeglenatide (2, 4, or 6 mg) or placebo for up to 56 weeks. The primary objective was to demonstrate the superiority of efpeglenatide versus placebo for HbA_{1c} reduction at week 30. Secondary objectives included changes in other measures of glycemic control and body weight at weeks 30 and 56.

RESULTS

At week 30, HbA_{1c} was reduced from a baseline of 8.1% (65 mmol/mol) to 6.9% (52 mmol/mol), 6.6% (49 mmol/mol), and 6.4% (47 mmol/mol) with efpeglenatide 2, 4, and 6 mg, respectively. Least squares mean HbA_{1c} reductions from baseline were statistically superior for each efpeglenatide dose versus placebo (2 mg, −0.5% [95% CI −0.9, −0.2; $P = 0.0054$]; 4 mg, −0.8% [−1.2, −0.5; $P < 0.0001$]; 6 mg, −1.0% [−1.4, −0.7; $P < 0.0001$]). A greater proportion of efpeglenatide-treated patients (all doses) achieved HbA_{1c} <7% (53 mmol/mol) versus placebo by week 30 ($P < 0.0001$ for all), and significant reductions in body weight and fasting plasma glucose were also observed for efpeglenatide (4 and 6 mg doses) versus placebo at week 30 ($P < 0.05$ for all). Consistent with the GLP-1 RA class, gastrointestinal adverse events were most commonly reported; these were generally transient and mild/moderate in severity. Few patients reported hypoglycemia.

CONCLUSIONS

As monotherapy in patients with type 2 diabetes, once-weekly efpeglenatide significantly improved glycemic control and body weight with a safety and tolerability profile similar to that of other GLP-1 RAs.

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Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are currently recommended as the first injectable agent for patients with type 2 diabetes inadequately controlled on oral glucose-lowering medications (1,2) because of their glycemic efficacy, low risk of hypoglycemia, and favorable effects on body weight (3). Furthermore, GLP-1 RAs with proven cardiovascular disease benefit should also be considered as monotherapy or combination therapy, independently of baseline HbA_{1c} or individualized HbA_{1c} target, for patients with diabetes who are at high risk of or who have preexisting atherosclerotic cardiovascular disease (2), given that once-daily liraglutide and once-weekly GLP-1 RAs, such as semaglutide, dulaglutide, and efpeglenatide, have demonstrated cardiovascular and renal benefits in this patient population (4–9).

Efpeglenatide is a long-acting GLP-1 RA composed of a single amino acid–modified exendin (CA-exendin-4) conjugated to a fragment crystallizable (Fc) region of human immunoglobulin 4 via a mini-polyethylene glycol linker (10,11). The amino acid modification found in CA-exendin-4 reduces the extent of its degradation by dipeptidyl peptidase 4, and it is thought that the large size of the overall molecule may reduce its rate of renal clearance (11); therefore, efpeglenatide has a pharmacokinetic/pharmacodynamic profile allowing flexible dosing, with a phase 2 study suggesting this could range from once weekly to potentially once monthly (12).

The EXCEED 203 and LIBERATE 204 phase 2 studies explored use of efpeglenatide by people with type 2 diabetes who were either drug naïve or treated with metformin monotherapy (in EXCEED 203) (13) or on a maximum tolerated dose of metformin (in the LIBERATE 204 study) (14). Results of these studies demonstrated that efpeglenatide provided superior HbA_{1c} reduction and body weight benefit compared with placebo (13,14). Findings from exploratory analyses of the EXCEED 203 study also showed that HbA_{1c} reductions with efpeglenatide (4 mg) were noninferior to those with liraglutide (1.8 mg) (13). Encouraging results were also reported in the recent phase 3 AMPLITUDE-O trial, which included patients with type 2 diabetes and either a history of atherosclerotic cardiovascular disease or current kidney disease plus at least one additional cardiovascular risk factor. Results of this long-term cardiovascular outcomes trial demonstrated that risks of major adverse cardiovascular events and composite renal outcome events were significantly lower for patients receiving efpeglenatide (4 or 6 mg once weekly) versus placebo (4). Of note, in addition to the cardiorenal benefit, efpeglenatide treatment resulted in significantly greater reduction in HbA_{1c} versus placebo (least squares [LS] mean difference −1.2%) during the follow-up period, despite greater use of additional glucose-lowering therapies in the placebo group based on a trial designed with the aim of achieving glycemic control equipoise (4).

In the current phase 3 study, efficacy and safety of once-weekly administration of three doses of efpeglenatide (2, 4, or 6 mg) were assessed in comparisons with placebo in patients with type 2 diabetes inadequately controlled with diet and exercise alone.

RESEARCH DESIGN AND METHODS

Study Design and Patients

AMPLITUDE-M was a multicenter, 56-week, randomized, double-blind, placebo-controlled phase 3 trial conducted at 54 sites in five countries. The study comprised four periods (Supplementary Fig. 1): a screening period of up to 3 weeks; a 30-week core treatment period, for primary efficacy end point and safety assessment; a 26-week treatment extension period in which patients remained on the same masked treatment/dose of study drug; and a 6-week (±1 week) safety follow-up period. The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, as well as the International Council for Harmonization Guidelines for Good Clinical Practice with all applicable laws, rules, and regulations. The protocol was approved by local institutional review boards, and informed consent was obtained from all patients prior to the conduct of any study-related procedures.

Inclusion criteria included inadequately controlled type 2 diabetes (HbA_{1c} ≥7 and ≤10% [53–86 mmol/mol]) at screening. Key exclusion criteria were any glucose-lowering therapy within the 3 months prior to screening, clinical history of gastrointestinal (GI) disease associated with prolonged nausea and vomiting, history of pancreatitis, and end-stage renal disease (estimated glomerular filtration rate <15 mL/min/1.73 m^2). A full list of inclusion and exclusion criteria can be found in Supplementary Table 1. Eligible patients were randomly assigned in a 1:1:1:1 manner to one of three doses of efpeglenatide (2, 4, or 6 mg) or placebo to be administered subcutaneously once weekly. Efpeglenatide dose was started at 2 mg once weekly for all patients. For patients assigned to 4 or 6 mg once weekly, efpeglenatide dose was escalated by 2-mg increments every 2 weeks until the randomized dose was reached. Patients assigned to placebo received placebo during the entire treatment period.

Receipt of open-label rescue medication (including oral antihyperglycemic drugs or insulin and excluding dipeptidyl peptidase 4 inhibitors and other GLP-1 RA) for treatment of hyperglycemia was recommended according to predefined criteria at the discretion of the investigator and in accordance with local standards of care and prescribing practices (Supplementary Table 2).

Efficacy Measures and Safety Assessments

The primary objective was to demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, or 6 mg versus placebo in HbA_{1c} change from baseline to week 30 in patients with type 2 diabetes inadequately controlled with diet and exercise. Key secondary efficacy objectives included demonstrating superiority of efpeglenatide 2, 4, or 6 mg versus placebo in HbA_{1c} change from baseline to week 56, HbA_{1c} <7% (53 mmol/mol) target achievement at week 30, change in fasting plasma glucose (FPG) from baseline to week 30, and change in body weight from baseline to weeks 30 and 56. These end points were assessed in a hierarchical testing procedure detailed in *STATISTICAL ANALYSIS*.

Safety assessments included hypoglycemia events, which were defined as per American Diabetes Association classification and included level 1, <70 to ≥54 mg/dL (<3.9 to ≥3.0 mmol/L); level 2, <54 mg/dL (<3.0 mmol/L); and level 3, (severe; characterized by altered mental or physical status and requiring assistance for resolution) events (15). Other safety assessments included adverse events (AEs), predefined AEs of special interest (pregnancy,

symptomatic overdose, and elevated liver enzyme levels) and AEs requiring specific monitoring (prespecified events including severe GI and pancreatic and selected cardiovascular events [Supplementary Table 3]). The impact of study drug on immunogenicity (i.e., presence of anti-drug antibodies [ADAs]) was also assessed at various time points.

Statistical Analysis

A sample size of ~100 patients in each study arm was calculated to have 89% and 96% power to detect a treatment difference in HbA_{1c} change from baseline to week 30 of –0.5% and –0.6%, respectively, between each dose of efpeglenatide and placebo, assuming a common SD of 1.1% (two sided $\alpha = 0.05$) for each comparison. An intent-to-treat (ITT) population was delineated for efficacy analyses and was defined as all randomized patients, irrespective of compliance with the study protocol and procedures, analyzed according to the treatment group allocated by randomization. The safety population was defined as randomized population who received at least one dose or part of a dose of the study drug, analyzed according to the treatment received. Patients who did not complete the 30-week core treatment period were included in the ITT and safety populations and in all analyses.

Missing data for the primary end points were handled using regression imputation, with missing data imputed 10,000 times. Completed data sets were analyzed with ANCOVA with treatment group, randomization strata (screening $HbA_{1c} <$ or $\geq$8% [64 mmol/mol], baseline BMI $<$ or $\geq$30 kg/m^2), and geographical region as fixed effects and baseline HbA_{1c} as a continuous covariate. The majority of secondary efficacy end points were assessed with the same ANCOVA model as performed for the primary analysis; HbA_{1c} target achievement was assessed with a Cochran-Mantel-Haenszel test with stratification by screening HbA_{1c} ($<$ of $\geq$8% [64 mmol/mol]), baseline BMI ($<$ of $\geq$30 kg/m^2), and geographical region as fixed effects. Continuous data on demographics and baseline characteristics were summarized with use of descriptive statistics for each treatment group. We summarized categorical and ordinal data using the number and percentage of patients in each treatment group.

A hierarchical testing procedure was applied to adjust for multiplicity of comparison. For the primary end points, the three doses were tested for superiority versus placebo in the order of 6, 4, and 2 mg. If superiority for all primary end points was determined, hierarchical testing was continued on key secondary end points in the order shown in Supplementary Table 4. Two-sided statistical tests for superiority were performed at the α-level of 0.05. If superiority was not obtained in a step, the sequential testing procedure was stopped.

Collection of baseline data and primary end point data (at week 30) was not affected by the coronavirus disease 2019 (COVID-19) pandemic; however, some later data subsequent to week 30 were collected during a period of national restrictions caused by COVID-19. Sensitivity analyses on the HbA_{1c} and body weight end points were performed for assessment of the impact of the COVID-19 pandemic.

RESULTS

Patient Disposition and Baseline Characteristics

Patients were recruited from Germany, Poland, U.K., U.S., and Ukraine. Of the 54 active recruitment sites, 48 assigned at least one patient to randomized treatment. The first patient visit occurred in December 2017, and the final patient visit occurred in September 2020. Baseline demographics and disease characteristics were generally similar between treatment groups (Table 1). Of the 900 patients screened, 406 were randomized to efpeglenatide (2 mg dose, $N = 100$; 4 mg dose, $N = 101$; 6 mg dose, $N = 103$) or placebo ($N = 102$). All randomized patients subsequently received study treatment. Overall, 78.6% and 72.2% of patients completed the 30-week and 56-week treatment periods, respectively, on treatment (Supplementary Fig. 2). The proportion of patients completing the 56-week study period (with or without study treatment) was 80.8%. It should be noted that the proportion of patients who completed the 56-week treatment period (regardless of whether treatment was continued) decreased with increasing efpeglenatide dose (Supplementary Fig. 2). The COVID-19 pandemic began during the latter stages of the study. No patients discontinued or withdrew from treatment due to COVID-19, and very few patients had missing efficacy data related to COVID (no patients at week 30 and $n = 8$, $n = 8$ and $n = 9$ patients for HbA_{1c}, FPG, and body weight, respectively, at week 56).

Efficacy Outcomes

Mean change in HbA_{1c} from baseline to week 30 was greater for all efpeglenatide doses compared with placebo (Fig. 1 and Supplementary Table 5). From a mean HbA_{1c} of 8.1% (65 mmol/mol), LS mean ± SE decreases were seen for 2 mg (−1.1 ± 0.1% [−12 ± 1 mmol/mol]), 4 mg (−1.4 ± 0.1% [−15 ± 1 mmol/mol]), and 6 mg (−1.6 ± 0.1% [−17 ± 1 mmol/mol]), leading to mean HbA_{1c} values of 6.9 ± 1.0% (52 ± 11 mmol/mol), 6.6 ± 0.8% (49 ± 9 mmol/mol), and 6.4 ± 0.7% (47 ± 7 mmol/mol), respectively, at week 30. In the placebo group, from a mean HbA_{1c} of 8.0 ± 0.9% (64 ± 10 mmol/mol) at baseline, an LS mean reduction of −0.6 ± 1.2% (−6 ± 1 mmol/mol) was seen, with a mean HbA_{1c} of 7.5 ± 1.0% (59 ± 11 mmol/mol) at week 30.

LS mean differences in HbA_{1c} versus placebo were statistically significant for all three efpeglenatide dose groups (2 mg −0.5% [95% CI −0.9 to −0.2], −6 mmol/mol [−9 to −2], $P = 0.0054$; 4 mg −0.8% [−1.2 to −0.5], −9 mmol/mol [−13 to −5], $P < 0.0001$]; 6 mg −1.0% [−1.4 to −0.7], −11 mmol/mol [−15 to −8], $P < 0.0001$]), demonstrating superiority of all doses of efpeglenatide over placebo in HbA_{1c} reductions from baseline to week 30.

Secondary Outcomes

Results of hierarchical testing for efficacy end points are presented in Supplementary Table 4. The HbA_{1c} reductions seen at week 30 were maintained at week 56 (Fig. 1 and Supplementary Table 5). LS mean ± SE change from baseline to week 56 was as follows: efpeglenatide 2 mg −1.2 ± 0.2% (−13 ± 2 mmol/mol), efpeglenatide 4 mg −1.3 ± 0.2% (−14 ± 2 mmol/mol), efpeglenatide 6 mg −1.3 ± 0.2% (−15 ± 2 mmol/mol), and placebo −0.4 ± 0.3% (−5 ± 4 mmol/mol). At week 56, mean ± SD HbA_{1c} values were as follows: efpeglenatide 2 mg 6.9 ± 0.9% (52 ± 10 mmol/mol), efpeglenatide 4 mg 6.6 ± 0.7% (49 ± 8 mmol/mol), efpeglenatide 6 mg 6.6 ± 1.0% (49

Table 1—Baseline demographics and disease characteristics (ITT population)

	Efpeglenatide 2 mg (*N* = 100)	Efpeglenatide 4 mg (*N* = 101)	Efpeglenatide 6 mg (*N* = 103)	Placebo (*N* = 102)
Age (years)	58.6 ± 10.5	56.3 ± 11.5	59.6 ± 10.7	59.5 ± 11.7
Duration of type 2 diabetes (years)	5.3 ± 5.3	4.9 ± 5.0	5.2 ± 5.2	5.0 ± 4.9
Sex				
Male	55 (55.0)	52 (51.5)	61 (59.2)	51 (50.0)
Female	45 (45.0)	49 (48.5)	42 (40.8)	51 (50.0)
Race				
White	93 (93.0)	86 (85.1)	92 (89.3)	90 (88.2)
Black or African American	6 (6.0)	13 (12.9)	8 (7.8)	10 (9.8)
Other*	1 (1.0)	2 (2.0)	3 (2.9)	2 (2.0)
Ethnicity				
Hispanic or Latino	20 (20.0)	25 (24.8)	21 (20.4)	20 (19.6)
Not Hispanic or Latino	80 (80.0)	76 (75.2)	82 (79.6)	82 (80.4)
Screening HbA_{1c} (%)	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 1.0	8.0 ± 0.9
Screening HbA_{1c} (mmol/mol)	64.9 ± 9.4	64.9 ± 10.1	64.5 ± 10.4	63.6 ± 9.8
Baseline FPG (mmol/L)	9.9 ± 2.6	9.7 ± 2.8	9.8 ± 2.7	9.6 ± 3.2
Baseline body weight (kg)	98.0 ± 21.6	95.2 ± 22.7	96.4 ± 20.9	97.9 ± 22.7
Baseline BMI (kg/m^2)	34.4 ± 6.4	33.8 ± 6.6	33.8 ± 6.9	34.8 ± 7.1
Baseline eGFR ($mL/min/1.73\ m^2$)	101.3 ± 26.1	106.1 ± 29.0	102.3 ± 38.8	95.3 ± 31.1

Data are means ± SD or *n* (%). BMI, body mass index; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; SD, standard deviation. *Includes data for Asian, multiple, and other.

± 11 mmol/mol), and placebo 7.4 ± 0.9% (57 ± 10 mmol/mol). LS mean differences were statistically significant for efpeglenatide 4 mg (−0.9% [95% CI −1.6 to −0.1], −10 mmol/mol [−18 to −1]) and 6 mg (–0.9% [−1.6 to −0.2], −10 mmol/mol [−18 to −2]) versus placebo at week 56. Numerically greater reductions in LS mean difference were also shown for efpeglenatide 2 mg versus placebo (−0.8% [−1.5 to 0.0], −9 mmol/mol [−16 to 0]) at week 56.

A significantly higher proportion of patients achieved HbA_{1c} values of <7% (53 mmol/mol) at week 30 in the efpeglenatide groups versus placebo (2 mg 60.0%, 4 mg 65.3%, 6 mg 73.8%, placebo group 25.5%; $P < 0.0001$ for all comparisons) (Fig. 2*A*). The proportion of patients at HbA_{1c} <7% (53 mmol/mol) remained significantly higher versus placebo at week 56 ($P < 0.0001$ for all comparisons). Similar results were shown in a post hoc analysis of HbA_{1c} ≤6.5% (48 mmol/mol) attainment at week 30 for efpeglenatide versus placebo ($P < 0.0001$ for all comparisons) (Fig. 2*A*); the proportion of patients achieving this HbA_{1c} target in each efpeglenatide group remained significantly higher versus placebo at week 56 ($P < 0.0001$ for all comparisons). In patients with HbA_{1c} ≥8% (64 mmol/mol) at baseline, the proportion achieving a value ≤6.5% (48 mmol/mol) at week 30 was higher in all efpeglenatide groups versus placebo and increased with increased efpeglenatide dose. A significantly greater proportion of patients in the efpeglenatide 4 and 6 mg groups (but not the 2 mg group) attained this goal at week 56 compared with placebo (Supplementary Fig. 3).

Significantly greater improvements in FPG from baseline to week 30 were observed with efpeglenatide versus placebo in the 4 mg and 6 mg groups (Fig. 2*B* and Supplementary Table 5). LS mean differences versus placebo were as follows: 4 mg −27 mg/dL (95% CI −41 to −13), −1 mmol/L (2–1; $P = 0.0003$), and 6 mg −35 mg/dL (−49 to −22), −2 mmol/L (−3 to −1; $P < 0.0001$).

Significantly greater reductions in body weight with efpeglenatide versus placebo were observed in both the 4 mg and 6 mg efpeglenatide groups at week 30; LS mean differences versus placebo at week 30 were as follows: 4 mg −2.3 kg (95% CI −3.9 to −0.7; $P < 0.005$), 6 mg −2.2 kg (−3.5 to –0.9; $P = 0.001$). A statistically superior reduction in body weight was observed only in the 4 mg group at week 56; LS mean difference for efpeglenatide 4 mg versus placebo at week 56 was −3.6 kg (−6.8 to −0.4; $P = 0.03$) (Fig. 2*C* and Supplementary Table 5). Two outliers were noted in the efpeglenatide 4 and 6 mg groups (one in each group); further details of these outliers are provided in Supplementary Table 6. In an analysis of mean body weight change excluding these outliers, robust weight reductions were still observed at weeks 30 and 56 (Supplementary Fig. 4).

Safety Outcomes

Mean duration of exposure was similar in all treatment groups (efpeglenatide 2 mg 323.4 days, efpeglenatide 4 mg 312.4 days, efpeglenatide 6 mg 322.7 days, and placebo 321.4 days). The proportion of patients with any treatment-emergent AE (TEAE) during the 56-week treatment period in the efpeglenatide groups ranged from 78.4% (2 mg) to 83.8% (6 mg), while 77.5% of placebo-treated patients experienced a TEAE (Table 2). Serious TEAEs were reported by 9–11% of patients across all treatment arms, and no deaths were reported. The proportion of patients with TEAEs leading to treatment discontinuation was higher for the efpeglenatide

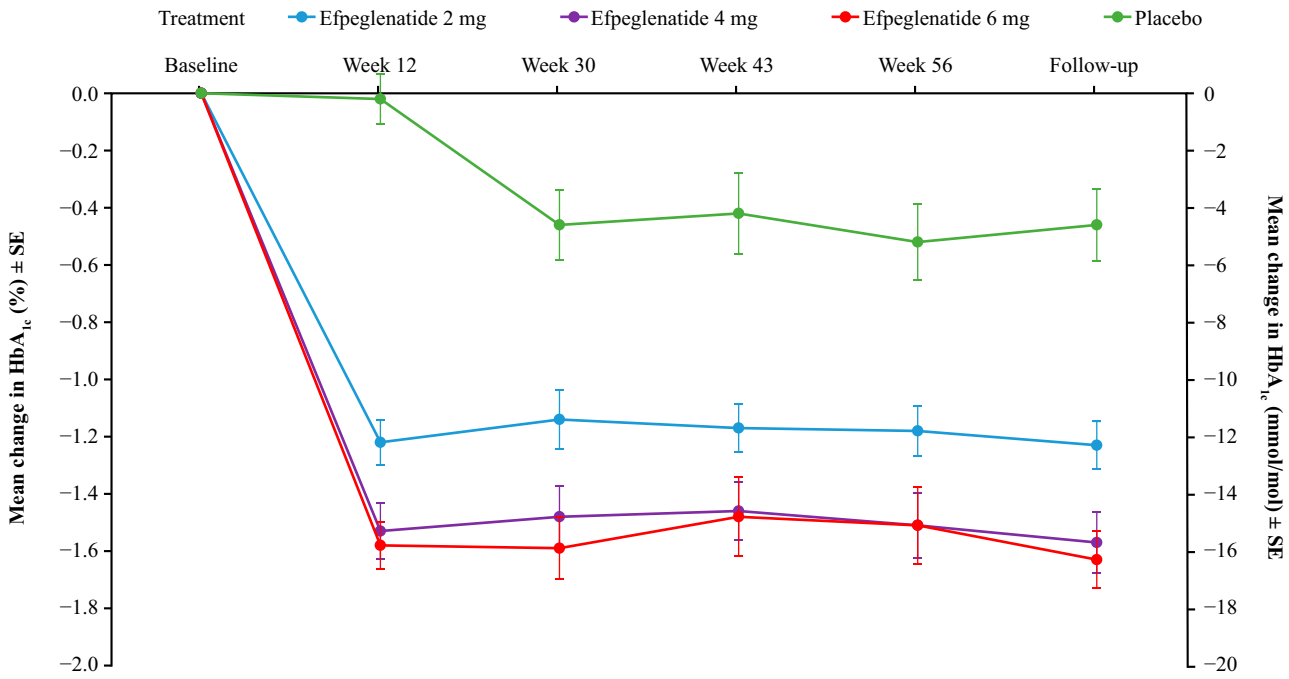

Figure 1—Mean change in HbA_{1c} over time.

treatment groups compared with placebo (8.8–17.2% vs. 4.9%, respectively) and increased with increasing efpeglenatide dose. GI events were the main cause of TEAEs leading to treatment discontinuation in the efpeglenatide treatment groups (range 3.9–13.1%), while few patients in the placebo group discontinued for this reason (2.0%). Up to 2.9% of patients reported AEs of special interest, and AEs requiring specific monitoring occurred in <9% of patients (Supplementary Table 3). A total of two patients (in the efpeglenatide 6 mg group) reported mild diabetic retinopathy as a TEAE; in both cases, diabetic retinopathy developed after patients had completed the study period (i.e., several weeks after discontinuation of study treatment).

GI events were the most commonly reported class of AE, with diarrhea, nausea, and constipation most frequently reported (Table 2); however, these events were generally mild to moderate in severity and subsided over time. Incidence of nausea, vomiting, and diarrhea increased with increasing efpeglenatide dose. Severe GI events were reported by 1.0 – 3.9% of patients in any treatment group and included diarrhea, gastroesophageal reflux disease, abdominal distension and constipation, upper abdominal pain, colitis, and gastroenteritis (Supplementary Table 3). Pancreatitis and cholecystitis were categorized as AEs requiring specific monitoring. During the 56-week treatment period, one patient in the efpeglenatide 2 mg group experienced pancreatitis; there were no reports of cholecystitis in any treatment groups.

Incidence and event rates of hypoglycemia were low across all treatment groups, including clinically relevant level 2 and 3 hypoglycemia events (Table 2). Level 1 hypoglycemia was reported by 0–7.1% of patients and level 2 by 0–1.0% of patients, respectively. Level 3 (severe) hypoglycemia was reported by only one patient (4 mg group); this patient's glucose level was not measured at the time of the event. The patient was reported to have required third-party assistance due to exhibited symptoms (drowsiness/dizziness and sweating) but recovered promptly following consumption of carbohydrates. There was no change in study drug administration due to this event.

Overall, >95% of patients in the efpeglenatide treatment groups were ADA negative at baseline. The proportion of patients experiencing treatment-emergent ADAs was low in the efpeglenatide 2 mg group (4.1%) and increased with increasing dose level (efpeglenatide 4 mg 12.7% and efpeglenatide 6 mg 16.3%). Among these, ADA response was classified as persistent in ≥50% of cases (Supplementary Table 3). No association was found between presence of ADAs and efficacy (e.g., HbA_{1c}, FPG, body weight) or safety parameters (e.g., allergic reaction/injection site reaction). There were no trends or notable differences from baseline in electrocardiogram, heart rate, or blood pressure results during the study in any treatment groups (Supplementary Table 3).

CONCLUSIONS

The results of AMPLITUDE-M confirm previous efficacy and safety findings for efpeglenatide in patients with type 2 diabetes inadequately controlled with diet and exercise (13,14). The three efpeglenatide doses provided superior HbA_{1c} reductions versus placebo from baseline at week 30, thus meeting the primary objective. Reductions in HbA_{1c} were seen soon after initiation of efpeglenatide (by week 12) and were sustained over the full 56-week treatment period. Efpeglenatide also facilitated a greater proportion of patients reaching glycemic target (HbA_{1c} <7% [53 mmol/mol]) along with improvements in body weight and FPG, and incidence of hypoglycemia was low. In line with the known tolerability profile for GLP-1 RAs, incidence of GI AEs was higher in efpeglenatide-treated patients than in the placebo group, with the

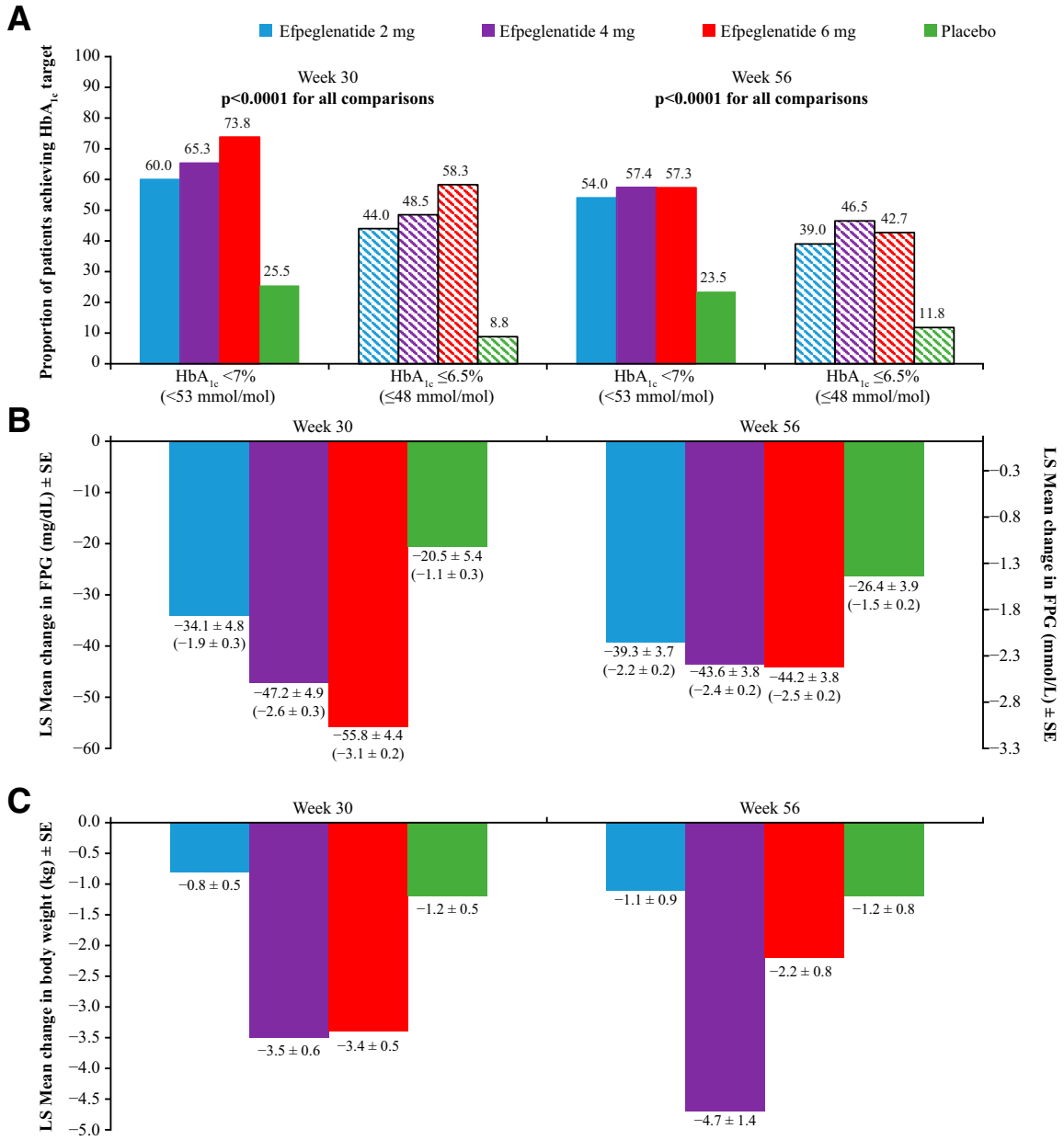

Figure 2—Secondary efficacy end points: proportion of patients achieving HbA_{1c} targets (*A*), LS mean ± SE change in FPG (*B*), and LS mean change in body weight (*C*) for each dose group vs. placebo from baseline to weeks 30 and 56. FPG, fasting plasma glucose; LS, least squares; SD, standard deviation; SE, standard error.

incidence increasing with dose level. Treatment-emergent ADAs occurred in <20% of patients in any treatment group and did not appear to have any impact on the efficacy or safety/tolerability of study treatment.

While it is important to recognize the limitations of indirect comparisons across studies with different experimental designs and different baseline patient characteristics, the results of the current study are generally aligned with previous reports of the efficacy of other once-weekly GLP-1 RAs as monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise. HbA_{1c} reductions reported in the current study compare favorably with those reported elsewhere. The LS mean HbA_{1c} reductions observed with efpeglenatide at the 6 mg dose (−1.6% [−17 mmol/mol] at week 30 and −1.3% [−15 mmol/mol] at week 56) were generally similar to mean HbA_{1c} reductions seen with once-weekly subcutaneous semaglutide in the SUSTAIN-1 study after 30 weeks (semaglutide 0.5 mg −1.5% [−16 mmol/mol], semaglutide 1.0 mg −1.6% [−17 mmol/mol]), with studies having comparable mean baseline HbA_{1c} (8.1% [65 mmol/mol]) (16). LS mean HbA_{1c} reduction was greater with efpeglenatide in the current study than with dulaglutide in the AWARD-3 study after 52 weeks (dulaglutide 0.75 mg −0.6% [−6 mmol/mol], dulaglutide 1.5 mg −0.7% [−8 mmol/mol]); however, baseline HbA_{1c} was lower in the AWARD-3 study compared with the current study (7.6% [60 mmol/mol] vs. 8.1% [65 mmol/mol], respectively) and consequently smaller reductions could be expected (17). Both the 4 and 6 mg efpeglenatide doses met the primary end point. A dose-dependent effect on

Table 2—TEAEs and hypoglycemia incidence/events during whole on-treatment period (safety population)

	Efpeglenatide 2 mg (*N* = 102)	Efpeglenatide 4 mg (*N* = 103)	Efpeglenatide 6 mg (*N* = 99)	Placebo (*N* = 102)
Patients with any TEAEs	80 (78.4)	79 (76.7)	83 (83.8)	79 (77.5)
Patients with GI TEAEs	37 (36.3)	48 (46.6)	60 (60.6)	27 (26.5)
Nausea	6 (5.9)	15 (14.6)	22 (22.2)	2 (2.0)
Diarrhea	9 (8.8)	17 (16.5)	25 (25.3)	9 (8.8)
Constipation	9 (8.8)	14 (13.6)	16 (16.2)	6 (5.9)
Vomiting	3 (2.9)	8 (7.8)	9 (9.1)	0
Patients with any serious TEAEs	11 (10.8)	6 (5.8)	6 (6.1)	9 (8.8)
Patients with any TEAEs leading to permanent treatment discontinuation	9 (8.8)	10 (9.7)	17 (17.2)	5 (4.9)
Patients with any GI TEAEs leading to permanent treatment discontinuation	4 (3.9)	7 (6.8)	13 (13.1)	2 (2.0)
Patients with any TEAEs leading to death	0	0	0	0
Patients with any treatment-related TEAEs	35 (34.3)	39 (37.9)	55 (55.6)	16 (15.7)
Patients with any hypoglycemia events during whole on-treatment period	10 (9.8)	14 (13.6)	14 (14.1)	2 (2.0)
Level 1 events	0	3 (2.9)	7 (7.1)	0
Level 2 events	0	1 (1.0)	1 (1.0)	0
Level 3 events	0	1 (1.0)	0	0
Hypoglycemia events per patient-year of exposure, *n* (event rate)	12 (0.13)	34 (0.39)	37 (0.42)	3 (0.03)
Level 1	0	4 (0.05)	12 (0.14)	0
Level 2	0	2 (0.02)	6 (0.07)	0
Level 3	0	1 (0.01)	0	0

Data are *n* (%) unless otherwise indicated. Hypoglycemia events were categorized as per American Diabetes Association classification: level 1, <70 to ≥54 mg/dL (<3.9 to ≥3.0 mmol/L); level 2, <54 mg/dL (<3.0 mmol/L); and level 3, severe and characterized by altered mental or physical status and requiring assistance for resolution (15). GI, gastrointestinal; TEAE, treatment-emergent adverse event.

HbA_{1c} was not observed between these two doses, possibly due to the relatively low baseline HbA_{1c} (~8.1% [65 mmol/mol]). It is possible that dose dependency could be demonstrated with a higher baseline HbA_{1c}. Importantly, findings from exploratory analyses from AMPLITUDE-O (4) indicate a dose-dependent cardiovascular benefit, supporting use of the 6 mg efpeglenatide dose.

The majority of patients in each efpeglenatide treatment group (60–74% at week 30 and 54–57% at week 56) achieved HbA_{1c} <7% (53 mmol/mol), in line with once-weekly semaglutide and dulaglutide in SUSTAIN-1 and AWARD-3, respectively (16,17). Approximately one-half (44–58%) of patients across all efpeglenatide dose groups reached the more stringent target of HbA_{1c} ≤6.5% (48 mmol/mol); these results are also in alignment with those of SUSTAIN-1 and AWARD-3.

Significant reductions in body weight versus placebo were reported for the efpeglenatide 4 and 6 mg doses at week 30 and for the efpeglenatide 4 mg dose at week 56. This finding for the 4 mg dose is in line with results observed in the recent AMPLITUDE-O trial, in which patients receiving efpeglenatide experienced a greater degree of long-term weight reduction versus placebo (adjusted LS mean difference −2.6 kg) (4). Efpeglenatide was associated with greater reductions in body weight compared with dulaglutide in AWARD-3 but slightly lower reductions compared with semaglutide in SUSTAIN-1 (16,17). Of note, while weight loss from baseline was observed in all groups, the degree of weight loss from baseline decreased slightly from weeks 30 to 56 in the efpeglenatide 4 and 6 mg groups; however, this was ameliorated in a separate analysis with exclusion of two outlier patients. While difficult to explain, this change in extent of body weight reduction did not appear to be due to ADAs and was likely to have been a chance finding, which may have been due in part to differing rates of discontinuation in efpeglenatide treatment groups versus placebo.

The safety profile of efpeglenatide was consistent with that of the GLP-1 RA class. Notably, GI events were the most commonly reported TEAEs, with 8.8–25.3% of patients reporting diarrhea, 5.9–22.2% reporting nausea, 8.8–16.2% reporting

constipation, and 2.9–9.1% reporting vomiting. Incidence increased with efpeglenatide dose level, in line with expectations for this drug class, but events were generally mild/moderate and tended to subside over time. As previously noted, rates of discontinuation due to TEAEs increased with increasing efpeglenatide dose (up to 17.2% in the 6 mg dose group), with the majority of discontinuations related to GI AEs. Rates of discontinuation due to TEAEs in this study were higher than those reported in previous phase 2 dose-finding studies for efpeglenatide (EXCEED 203, 0.3–4.0 mg weekly, discontinuation rate 3–8% [13] and LIBERATE 204, 8–16 mg monthly, discontinuation rate 11.5–15.1% [14]). Notably, these studies had a shorter duration than the current study (12–16 weeks, including titration period) (13,14); however, the long-duration AMPLITUDE-O trial (median follow-up time 1.8 years) had lower discontinuation rates than the present analysis (5.4% for efpeglenatide 4 and 6 mg weekly) (4), suggesting that study length was not a factor. Rates of discontinuation due to TEAEs in the current study were also higher than those reported for the SUSTAIN-1 and AWARD-3 studies (SUSTAIN-1, 6% for 0.5 mg semaglutide and 5% for 1.0 mg semaglutide, and AWARD-3, 3.0 for dulaglutide 0.75 mg and 5.2% for dulaglutide 1.5 mg) (16,17). The reason for this difference is unclear, although it should be noted that the doses used in the SUSTAIN-1 and AWARD-3 studies were much lower than those used in the current study. Interestingly, the proportion of participants reporting GI AEs overall in these studies was either generally similar to (17) or higher (16) than seen in the present analysis. Despite the relatively high discontinuation rate(s), adherence to study treatment was generally high for those who continued treatment throughout the study. Very few level 2 or level 3 (severe) hypoglycemia events occurred, as expected given efpeglenatide's mechanism of action. Drug-related immunogenicity was generally low in comparison with other exenatide-based drugs in the GLP-1 RA class (18,19).

The main strength of this study lies in its double-blind randomized controlled trial design and the relatively long duration (56 weeks). Key limitations are also linked to the nature of the study design, which may not be fully generalizable to real-life clinical practice, since patients were required to not have used any glucose-lowering agents during the preceding 3 months. However, it should be noted that this may serve as a strength, since it allows more direct attribution of outcomes to the impact of efpeglenatide treatment. Finally, the occurrence of the COVID-19 pandemic should be noted; this global event began during the course of the study but did not appear to influence either data collection or incidence of protocol deviation, and primary end point data were unaffected. Therefore, the COVID-19 pandemic did not have a significant impact on this study.

In summary, in patients with type 2 diabetes managed with diet and exercise alone, monotherapy with once-weekly efpeglenatide significantly improved glycemic control, lowering mean HbA_{1c} levels to $<7\%$ (53 mmol/mol) with meaningful body weight loss. The incidence of hypoglycemia among efpeglenatide-treated patients was low, and its safety and tolerability profile was consistent with that of the GLP-1 RA class.

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