# Once-Weekly Efpeglenatide Dose-Range Effects on Glycemic Control and Body Weight in Patients With Type 2 Diabetes on Metformin or Drug Naive, Referenced to Liraglutide

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## OBJECTIVE

**To explore the efficacy, safety, and tolerability of once-weekly efpeglenatide, a long-acting glucagon-like peptide 1 receptor agonist (GLP-1 RA), in early type 2 diabetes (T2D) (drug naive or on metformin monotherapy).**

## RESEARCH DESIGN AND METHODS

**EXCEED 203 was a 12-week, randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study of efpeglenatide once weekly referenced to open-label liraglutide 1.8 mg (exploratory analysis). Participants, ∼90% on metformin monotherapy, were randomized to one of five efpeglenatide doses (0.3, 1, 2, 3, or 4 mg q.w.; *n* = 181), placebo (*n* = 37), or liraglutide (≤1.8 mg daily; *n* = 36). The primary efficacy end point was change in $HbA_{1c}$ from baseline to week 13.**

## RESULTS

**From a baseline $HbA_{1c}$ of 7.7–8.0% (61.0–63.9 mmol/mol), all efpeglenatide doses ≥1 mg significantly reduced $HbA_{1c}$ versus placebo (placebo-adjusted least squares [LS] mean changes 0.6–1.2%, $P < 0.05$ for all) to a final $HbA_{1c}$ of 6.3–6.8% (45.4–50.6 mmol/mol); masked efpeglenatide 4 mg was noninferior to open-label liraglutide. Greater proportions treated with efpeglenatide ≥1 mg than placebo achieved $HbA_{1c}$ <7% (61–72% vs. 24%, $P < 0.05$ for all), and greater reductions in body weight were observed with efpeglenatide 3 and 4 mg versus placebo (placebo-adjusted LS mean differences −1.4 and −2.0 kg, respectively, $P < 0.05$ for both). Rates of nausea and vomiting were consistent with other GLP-1 RAs and rapidly subsided after the initial 2 weeks. No neutralizing antibodies were detected with efpeglenatide.**

## CONCLUSIONS

**Efpeglenatide once weekly led to significant reductions in $HbA_{1c}$ and weight, with a safety profile consistent with the GLP-1 RA class in patients with early T2D mostly on metformin monotherapy.**


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Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have emerged as effective options for the treatment of type 2 diabetes (T2D), helping patients to achieve individualized glycemic targets while minimizing weight gain and hypoglycemia (1,2). Treatment with all GLP-1 RAs lowers blood glucose and body weight by increasing insulin secretion, suppressing glucagon release, and promoting satiety, with some delaying gastric emptying (3–6). However, the long- and short-acting GLP-1 RAs differ in the degrees to which they affect each of these processes. Short-acting GLP-1 RAs reduce postprandial glucose excursions by delaying gastric emptying (7–9). Long-acting GLP-1 RAs have less of an effect on gastric emptying because of tachyphylaxis and mainly reduce fasting and postprandial blood glucose through increased insulin and reduced glucagon secretion (7–9).

Currently available once-weekly long-acting GLP-1 RAs include exenatide (10), dulaglutide (11), and semaglutide (12), which provide convenient, less frequent dosing options that may contribute to better acceptance with increased patient preference and treatment adherence (13–15). Weekly GLP-1 RAs with greater efficacy without increased adverse events (AEs), or with better tolerability and more flexible dosing options, are becoming a more acceptable addition to the T2D treatment armamentarium.

Efpeglenatide is a long-acting GLP-1 RA in development to improve glycemic control in patients with T2D by subcutaneous once-weekly administration. It is designed to provide robust glucose-lowering effects and body weight loss without compromising tolerability. In efpeglenatide, a single amino acid–modified exendin is conjugated to a fragment crystallizable (Fc) region of human Ig4 through a 3.4-kDa mini–polyethylene glycol (mini-PEG) linker using long-acting peptide/protein technology (16–18). The small size and flexibility of the mini-PEG linker minimizes the loss of intrinsic activity of the agonist, while the Fc conjugation extends duration of action. Efpeglenatide has a long half-life (between 5.6 and 7.5 days) in patients with T2D, which is comparable to the longest documented and directly measured durations of action among the GLP-1 RAs (7 days) (19,20). Additionally, efpeglenatide has demonstrated a low peak-to-trough ratio (21); such pharmacokinetic profiles may be associated with a favorable gastrointestinal (GI) tolerability profile.

Findings from in vitro and preclinical studies suggest that efpeglenatide has unique receptor properties that may explain the greater maximal GLP-1 receptor signaling and reduced desensitization seen with efpeglenatide compared with those of other GLP-1 RAs following chronic exposure (22,23). Efpeglenatide is associated with faster in vitro dissociation kinetics from the GLP-1 receptor compared with other GLP-1 RAs. These unique 'on-off' receptor engagement properties allow efpeglenatide to function as a full agonist for glucose-stimulated insulin secretion but reduce agonist-induced receptor internalization, allowing for more cell-surface receptor availability with chronic exposure (24). In mouse models of diabetes and diet-induced obesity, efpeglenatide led to greater glycemic improvements and body weight loss than liraglutide or dulaglutide (24–26). A phase 2 multiple-ascending dose study in patients with T2D demonstrated that administration of efpeglenatide once weekly was generally well tolerated and provided significant $HbA_{1c}$ reductions over placebo as well as improvement in body weight at 8 weeks of treatment (21). In a phase 2 trial in patients with obesity without T2D, treatment with efpeglenatide once weekly resulted in significant body weight loss over placebo at 20 weeks (27,28).

The objective of the EXCEED phase 2 trial was to examine the efficacy, safety, and tolerability of five doses of subcutaneous efpeglenatide once weekly in patients with T2D over 12 weeks of treatment. As an exploratory analysis, the efficacy, safety, and tolerability of efpeglenatide were also compared as a clinical reference with those of open-label liraglutide once daily.

## RESEARCH DESIGN AND METHODS

EXCEED 203 was a phase 2, randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study of efpeglenatide once weekly in patients with early T2D that included liraglutide as an open-label active control. The study included a 12-week dose-finding period and a 6-week follow-up period. The 254 patients included in the final analysis were recruited at sites in the Czech Republic, Germany, Hungary, the Netherlands, Spain, Sweden, and the U.S. (Supplementary Table 1). The trial was initiated on 30 December 2013 and ended on 12 December 2014.

Eligible patients were $\geq$18 and $<$75 years of age and had been diagnosed with T2D $\geq$3 months before screening. Patients were also required to be drug naive or taking metformin $\geq$1,500 mg, with an $HbA_{1c}$ $\geq$7.0% ($\geq$53 mmol/mol) and $\leq$10% ($\leq$86 mmol/mol) and a BMI $<$40 kg/m$^2$. Patients taking metformin at screening were to continue on the same screening dose, which was to remain stable throughout the study. Patients were excluded if they had a diagnosis of type 1 diabetes, had uncontrolled diabetes (defined as fasting plasma glucose [FPG] $>$240 mg/dL [$>$13.3 mmol/L]), were pregnant or nursing, or had experienced a significant change in body weight (at least $\pm$10%) in the 3 months before screening.

Randomization was stratified by the presence or absence of metformin use at baseline. Patients were randomized in equal ratios (1:1:1:1:1:1:1) to efpeglenatide 0.3 mg, 1 mg, 2 mg, 3 mg, or 4 mg q.w.; placebo; or open-label liraglutide 1.8 mg q.d. Treatment administration and assessment for the five efpeglenatide arms and placebo were double blind, while liraglutide was administered open label because the delivery device could not be masked.

Placebo and all doses of efpeglenatide were administered in equal volume (0.4 mL) using prefilled syringes. Patients randomized to efpeglenatide or placebo self-administered study medication by subcutaneous injection in the morning once every 7 days from day 1 to day 84. Each patient received the designated efpeglenatide dose starting on day 1 without a titration period. For patients randomized to liraglutide, the 12-week treatment period included a forced titration period (0.6 mg on days 1–7, 1.2 mg on days 8–14, and 1.8 mg on days 15–84). These patients randomized to liraglutide self-administered the study medication by subcutaneous injection every morning from day 1 to day 84. Patients on metformin during screening continued taking metformin during the study period.

Each patient received a diary to record details on injection time and injection-site reactions as well as on hypoglycemic episodes and 7-point blood glucose profiles. A blood glucose reading was obtained for

any symptoms of possible hypoglycemia. Patients were instructed to assess their 7-point self-measured plasma glucose profile every 4 weeks during the study, with seven readings per day (before and 90 min after each meal [breakfast, lunch, and dinner] and at bedtime).

Approval from the institutional review board/independent ethics committee for the study protocol was obtained before the beginning of the study (Supplementary Table 2). This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, with applicable local regulations, and with the ethical principles laid out in the Declaration of Helsinki. All patients gave written informed consent.

### Efficacy Assessments

The primary efficacy end point was defined as the change in $HbA_{1c}$ from baseline to week 13 (i.e., after 12 weeks of treatment) for efpeglenatide versus placebo. Change from baseline in $HbA_{1c}$ was also used to assess noninferiority to open-label liraglutide as an exploratory assessment; no comparisons were performed between liraglutide and placebo. Secondary efficacy end points included percentage of patients achieving $HbA_{1c}$ $<$7% ($<$53 mmol/mol) or $\leq$6.5% ($\leq$48 mmol/mol) at week 13 and change from baseline to week 13 in FPG. Values and changes from baseline in 7-point blood glucose profiles, body weight (kg and percent change), and lipid profile measures were also examined.

### Safety Assessments

Safety assessments included treatment-emergent AEs (TEAEs), clinical laboratory assessments, vital signs, electrocardiogram (ECG) variables, and injection-site reactions. Standard 12-lead ECGs were performed at screening, at baseline, during the treatment period, and at follow-up. Hypoglycemia as an AE (defined as confirmed hypoglycemia on the basis of blood glucose levels $<$70 mg/dL [$<$3.9 mmol/L]) was recorded according to Medical Dictionary for Regulatory Activities 16.1 coding; in addition, patients recorded the occurrence of hypoglycemic episodes in their diaries. Blood samples were assessed for the presence of anti-efpeglenatide antibodies.

Anti-efpeglenatide antibodies were determined by ELISA; data were acquired from a microtiter plate absorbance reader (Sunrise RC/TW TC; Tecan, Männedorf, Switzerland). Neutralizing antibodies were determined using a cell-based assay in which inhibition of intracellular cAMP level by anti-efpeglenatide was measured by the cAMP-Glo assay (Promega, Madison, WI). Data were acquired from a microtiter plate luminometer (Centro LB 960; Berthold Technologies). Both assays were validated in Synlab AG (formerly Bureco AG) in Reinach, Switzerland.

### Statistical Methods

The primary efficacy analysis was performed using mixed-model repeated-measures (MMRM) to determine the least squares (LS) mean change from baseline to week 13 in $HbA_{1c}$. MMRM was also used to analyze secondary efficacy variables, such as FPG, 7-point glucose profile values, and body weight (in both kg and percent change). Because this was a phase 2 study, no adjustments of $\alpha$-level were made for multiple comparisons.

While the study was not powered to detect statistically significant differences between efpeglenatide and liraglutide, noninferiority versus liraglutide on change in $HbA_{1c}$ was examined as an exploratory end point. For the primary efficacy parameter ($HbA_{1c}$), noninferiority to open-label liraglutide was considered if the upper limit of the two-sided 95.1% CI for the difference in $HbA_{1c}$ at week 13 was $<$0.3. Although the current sample provided only 25% power for the comparison between efpeglenatide and liraglutide, sample sizes were sufficient to demonstrate significant differences compared with placebo. In addition, for descriptive purposes, the sample sizes in this study were adequate to demonstrate that the changes observed for efpeglenatide and liraglutide were similar.

The Cochran-Mantel-Haenszel test with last observation carried forward was used to determine the proportion of patients who achieved $HbA_{1c}$ $<$7% or $\leq$6.5% at week 13. All efficacy end points were analyzed using the full analysis set, which was defined as all patients who received the study drug and had at least one efficacy or safety assessment recorded after dosing. All safety end points were analyzed using the safety set, which was defined as all patients who received any study drug.

## RESULTS

A total of 254 patients were enrolled and randomized to efpeglenatide ($n$ = 181), placebo ($n$ = 37), and liraglutide ($n$ = 36) (Supplementary Fig. 1). Two patients in the efpeglenatide 2-mg group did not receive treatment; therefore, 252 patients received at least one dose of the study drug and comprised both the full analysis set and the safety set. Similar proportions of patients in each treatment arm completed the study. Demographic and baseline characteristics were similar across the treatment arms (Table 1).

Efpeglenatide led to dose-dependent reductions in $HbA_{1c}$ values over the treatment period from baseline to week 13 (Fig. 1*A*). Treatment with efpeglenatide at doses of $\geq$1 mg resulted in a significantly greater reduction in $HbA_{1c}$ from baseline to week 13 compared with placebo (Fig. 1*B* and Table 2). From a mean baseline $HbA_{1c}$ of 7.7–8.0% (61.0–63.9 mmol/mol) to a final $HbA_{1c}$ of 6.3–6.8% (45.4–50.6 mmol/mol) by week 13, for all doses $\geq$1 mg, efpeglenatide resulted in significantly greater reductions versus placebo (LS mean change 0.6–1.2% [6.1–13.0 mmol/mol], $P < 0.05$ for all). Differences in LS mean changes from baseline between placebo and 0.3-mg, 1-mg, 2-mg, 3-mg, and 4-mg doses of efpeglenatide were −0.16% (−1.8 mmol/mol, $P$ = 0.30), −0.55% (−6.0 mmol/mol, $P < 0.05$), −0.79% (−8.7 mmol/mol, $P < 0.05$), −1.01% (−11.1 mmol/mol, $P < 0.05$), and −1.21% (−13.2 mmol/mol, $P < 0.05$), respectively. The exploratory analysis comparing double-blind treatment with efpeglenatide with open-label liraglutide as a reference found that efpeglenatide 4 mg was noninferior to liraglutide, with an LS mean (95.1% CI) difference in change in $HbA_{1c}$ of −0.23% (−0.56%, 0.10%) (−2.5 mmol/mol [−6.1, 1.1 mmol/mol]). Results of a subanalysis of metformin-treated patients alone yielded similar results to the overall population.

Significantly greater proportions of patients treated with efpeglenatide doses $\geq$1 mg achieved an $HbA_{1c}$ $<$7% at week 13 compared with placebo (70–81% with efpeglenatide and 24% with placebo) (Table 2); these proportions

**Table 1—Demographics and baseline characteristics (safety set)**

| | Placebo ($n$ = 37) | Efpeglenatide 0.3 mg ($n$ = 37) | Efpeglenatide 1 mg ($n$ = 37) | Efpeglenatide 2 mg ($n$ = 33) | Efpeglenatide 3 mg ($n$ = 36) | Efpeglenatide 4 mg ($n$ = 36) | Liraglutide 1.8 mg q.d. ($n$ = 36) |
|---|---|---|---|---|---|---|---|
| Age (years) | 55 ± 9 | 56 ± 11 | 55 ± 9 | 56 ± 10 | 54 ± 10 | 56 ± 10 | 54 ± 11 |
| Sex, % | | | | | | | |
| Female | 57 | 35 | 49 | 46 | 36 | 50 | 56 |
| Male | 43 | 65 | 51 | 55 | 64 | 50 | 44 |
| Race, % | | | | | | | |
| White | 89 | 84 | 78 | 85 | 78 | 92 | 83 |
| Black | 5 | 8 | 16 | 12 | 14 | 6 | 14 |
| Asian | 5 | 5 | 5 | 3 | 8 | 3 | 0 |
| Diabetes duration (years) | 6.3 ± 5.1 | 7.1 ± 6.2 | 5.1 ± 3.3 | 5.8 ± 5.2 | 5.9 ± 4.8 | 6.1 ± 6.4 | 6.4 ± 4.8 |
| Metformin, % | | | | | | | |
| Yes | 89 | 92 | 87 | 88 | 92 | 89 | 89 |
| No | 11 | 8 | 14 | 12 | 8 | 11 | 11 |
| Weight (kg) | 86 ± 18 | 95 ± 20 | 90 ± 18 | 90 ± 17 | 94 ± 19 | 87 ± 18 | 90 ± 16 |
| BMI (kg/m$^2$) | 31 ± 5 | 32 ± 5 | 32 ± 5 | 32 ± 4 | 32 ± 5 | 31 ± 6 | 32 ± 4 |

Data are mean ± SD unless otherwise indicated. Percentages may not total 100 because of rounding.

were relatively similar to liraglutide (61%). Significantly greater proportions of patients treated with any dose of efpeglenatide achieved $HbA_{1c}$ ≤6.5% compared with placebo (22–53% with efpeglenatide and 5% with placebo); these proportions were similar with the higher doses of efpeglenatide (2 mg, 3 mg, and 4 mg) and liraglutide (50%) (Table 2).

Efpeglenatide led to dose-dependent, rapid, and sustained reductions in FPG

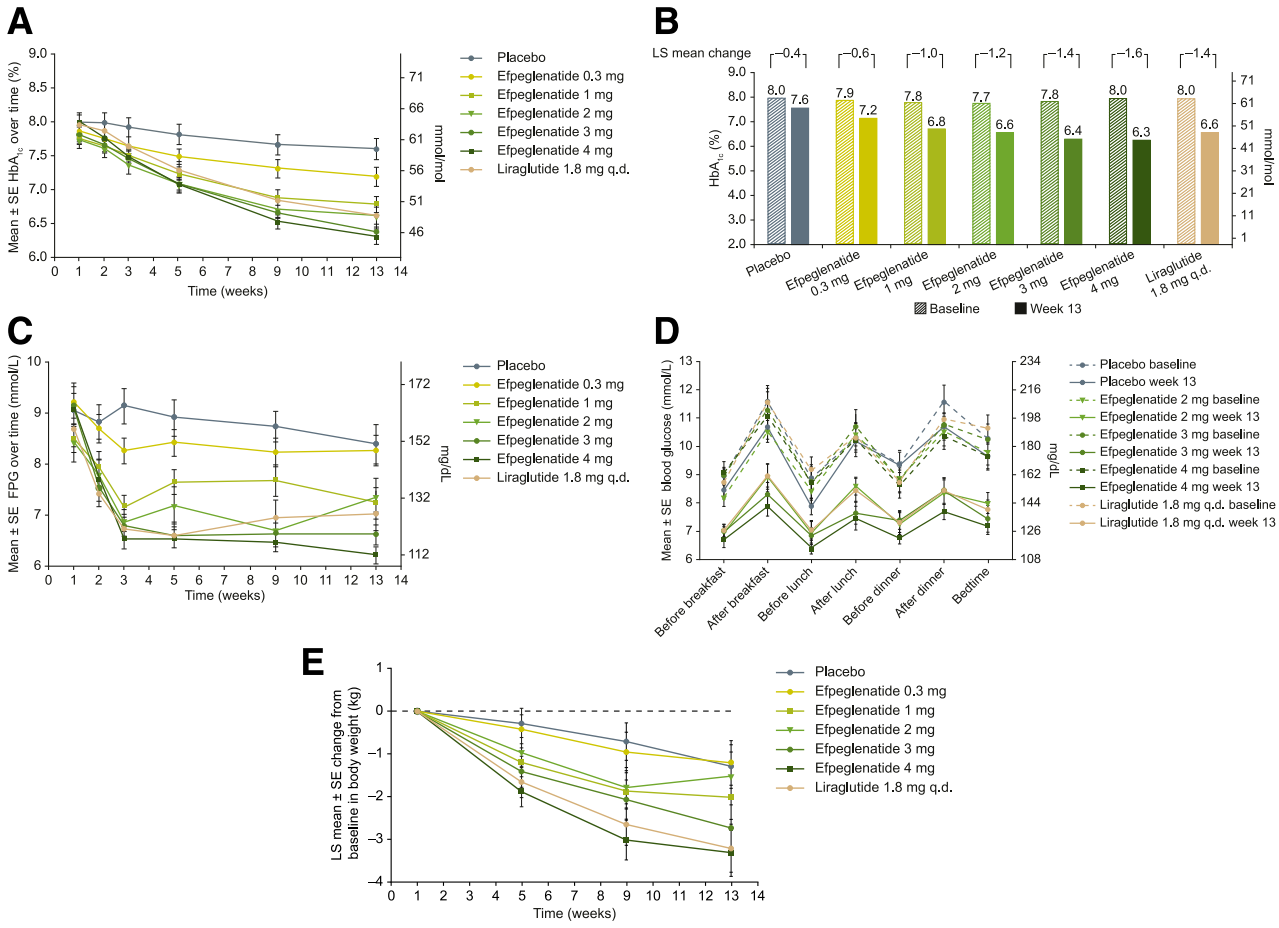


**Figure 1**—Efficacy end points, including $HbA_{1c}$ over time (*A*), $HbA_{1c}$ at baseline and end point by group (*B*), FPG over time (*C*), mean daily glucose profile at week 13 (i.e., after 12 weeks of treatment) (*D*), and body weight over time (full analysis set) (*E*).

**Table 2—Response to therapy (full analysis set)**

| Week 13 efficacy end point | Placebo ($n$ = 37) | Efpeglenatide 0.3 mg ($n$ = 37) | Efpeglenatide 1 mg ($n$ = 37) | Efpeglenatide 2 mg ($n$ = 33) | Efpeglenatide 3 mg ($n$ = 36) | Efpeglenatide 4 mg ($n$ = 36) | Liraglutide 1.8 mg q.d. ($n$ = 36) |
|---|---|---|---|---|---|---|---|
| $HbA_{1c}$ | | | | | | | |
| Mean ± SD at baseline | | | | | | | |
| % | 8.0 ± 0.8 | 7.9 ± 0.7 | 7.8 ± 0.6 | 7.7 ± 0.7 | 7.8 ± 0.9 | 8.0 ± 0.8 | 8.0 ± 0.8 |
| mmol/mol | 63.9 ± 9.1 | 62.4 ± 8.1 | 61.4 ± 6.2 | 61.0 ± 7.6 | 62.0 ± 9.5 | 63.9 ± 8.9 | 63.6 ± 8.6 |
| Mean ± SD at week 13 | | | | | | | |
| % | 7.60 ± 0.89 | 7.19 ± 0.80 | 6.78 ± 0.69 | 6.61 ± 0.68 | 6.37 ± 0.43 | 6.30 ± 0.60 | 6.61 ± 0.90 |
| mmol/mol | 59.5 ± 9.7 | 55.1 ± 8.8 | 50.6 ± 7.6 | 48.7 ± 7.5 | 46.2 ± 4.8 | 45.4 ± 6.5 | 48.7 ± 9.8 |
| LS mean ± SE change from baseline | | | | | | | |
| % | −0.40 ± 0.11 | −0.56 ± 0.11 | −0.95 ± 0.11 | −1.19 ± 0.12 | −1.41 ± 0.12 | −1.61 ± 0.12 | −1.38 ± 0.12 |
| mmol/mol | −4.4 ± 1.2 | −6.1 ± 1.2 | −10.4 ± 1.2 | −13.0 ± 1.3 | −15.4 ± 1.3 | −17.6 ± 1.3 | −15.1 ± 1.3 |
| $P$ value vs. placebo | — | 0.30 | <0.05 | <0.05 | <0.05 | <0.05 | NA |
| 95.1% CI for difference from liraglutide in $HbA_{1c}$ | | | | | | | |
| % | — | 0.50, 1.14 | 0.11, 0.75 | −0.14, 0.52 | −0.36, 0.30 | −0.56, 0.10* | — |
| mmol/mol | — | 5.4, 12.5 | 1.2, 8.2 | −1.6. 5.7 | −3.9, 3.3 | −6.1, 1.1 | — |
| Patients with $HbA_{1c}$ <7%, $n$ (%†) | 9 (24.3) | 12 (32.4) | 26 (70.3) | 23 (69.7) | 28 (77.8) | 29 (80.6) | 22 (61.1) |
| $P$ value vs. placebo | — | 0.61 | <0.05 | <0.05 | <0.05 | <0.05 | NA |
| Patients with $HbA_{1c}$ ≤6.5%, $n$ (%†) | 2 (5.4) | 8 (21.6) | 13 (35.1) | 16 (48.5) | 19 (52.8) | 19 (52.8) | 18 (50.0) |
| $P$ value vs. placebo | — | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | NA |
| FPG | | | | | | | |
| Mean ± SD at baseline | | | | | | | |
| mg/dL | 163 ± 35 | 166 ± 34 | 152 ± 30 | 152 ± 39 | 164 ± 32 | 165 ± 48 | 156 ± 36 |
| mmol/L | 9.1 ± 2.0 | 9.2 ± 1.9 | 8.5 ± 1.7 | 8.4 ± 2.1 | 9.1 ± 1.8 | 9.2 ± 2.7 | 8.7 ± 2.0 |
| Mean ± SD at week 13 | | | | | | | |
| mg/dL | 151 ± 40 | 149 ± 30 | 131 ± 30 | 132 ± 39 | 119 ± 19 | 112 ± 16 | 126 ± 32 |
| mmol/L | 8.4 ± 2.2 | 8.3 ± 1.7 | 7.3 ± 1.7 | 7.3 ± 2.1 | 6.6 ± 1.1 | 6.2 ± 0.9 | 7.0 ± 1.8 |
| LS mean ± SE change from baseline | | | | | | | |
| mg/dL | −10 ± 5 | −11 ± 5 | −25 ± 5 | −24 ± 6 | −41 ± 6 | −45 ± 5 | −27 ± 6 |
| mmol/L | −0.55 ± 0.3 | −0.6 ± 0.3 | −1.4 ± 0.3 | −1.3 ± 0.3 | −2.3 ± 0.3 | −2.5 ± 0.3‡ | −1.5 ± 0.3 |
| $P$ value vs. placebo | — | 0.88 | <0.05 | 0.05 | <0.05 | <0.05 | NA |
| Body weight | | | | | | | |
| Mean ± SD at week 13 (kg) | 85.05 ± 17.74 | 93.69 ± 19.10 | 88.02 ± 19.06 | 89.14 ± 17.81 | 91.10 ± 18.24 | 83.68 ± 17.39 | 87.94 ± 15.58 |
| LS mean ± SE change from baseline (kg) | −1.29 ± 0.51 | −1.21 ± 0.53 | −2.01 ± 0.51 | −1.52 ± 0.55 | −2.73 ± 0.55 | −3.31 ± 0.54 | −3.21 ± 0.56 |
| $P$ value vs. placebo | — | 0.91 | 0.29 | 0.75 | <0.05 | <0.05 | NA |
| LS mean ± SE percent change from baseline | −1.18 ± 0.57 | −1.10 ± 0.59 | −2.28 ± 0.57 | −1.61 ± 0.62 | −2.66 ± 0.62 | −3.47 ± 0.61 | −3.54 ± 0.62 |
| $P$ value vs. placebo | — | 0.92 | 0.16 | 0.60 | 0.07 | <0.05 | NA |

NA, not applicable. *Noninferiority to liraglutide in $HbA_{1c}$ reduction was concluded if the upper limit of the two-sided 95.1% CI for the difference in $HbA_{1c}$ at week 13 was <0.3.†Determined using Cochran-Mantel-Haenszel test with last observation carried forward, controlling for metformin use. ‡$P < 0.05$ for efpeglenatide vs. liraglutide. LS mean values were determined from MMRM.

over the treatment period (Fig. 1*C*). Significantly greater decreases in FPG were observed in the efpeglenatide 1-mg, 3-mg, and 4-mg groups compared with placebo (differences in LS mean change −15 mg/dL [−0.8 mmol/L, $P < 0.05$], −31 mg/dL [−1.7 mmol/L, $P < 0.05$], −35 mg/dL [−2.0 mmol/L, $P < 0.05$], respectively) (Table 2). Exploratory comparisons with liraglutide suggested that efpeglenatide 4 mg led to a greater reduction in FPG from baseline compared with liraglutide (difference in LS mean change −18 mg/dL [−1.0 mmol/L], nominal $P < 0.05$).

Reductions from baseline in mean 7-point self-measured plasma glucose profiles were significantly greater with efpeglenatide 1 mg, 2 mg, 3 mg, and 4 mg compared with placebo; these differences were comparable to those seen with liraglutide. Differences in LS mean changes from baseline between placebo and 1-mg, 2-mg, 3-mg, and 4-mg doses of efpeglenatide were −17 mg/dL (−0.9 mmol/L, $P < 0.05$), −26 mg/dL (−1.4 mmol/L, $P < 0.05$), −32 mg/dL (−1.8 mmol/L, $P < 0.05$), and −37 mg/dL (−2.0 mmol/L, $P < 0.05$), respectively. Reductions from baseline in mean blood glucose levels after meals (breakfast, lunch, and dinner) were significantly greater with efpeglenatide 2 mg, 3 mg, and 4 mg compared with placebo; these differences were comparable to those seen with liraglutide (Fig. 1*D*).

Treatment with efpeglenatide resulted in dose-dependent weight loss over the study period (Fig. 1*E*). Changes in body weight from baseline were significantly greater with efpeglenatide 3 mg and 4 mg (2.7 kg and 3.3 kg, respectively) compared with placebo (1.3 kg) (placebo-adjusted LS mean change −1.4 kg [$P < 0.05$] and −2.0 kg [$P < 0.05$], respectively). Reductions with efpeglenatide 3 mg and 4 mg were comparable to those seen with liraglutide. Placebo-adjusted LS mean changes from baseline in body weight for the remaining efpeglenatide doses were as follows: 0.3 mg, 0.1 kg ($P = 0.91$); 1 mg, −0.7 kg ($P = 0.29$); and 2 mg, −0.2 kg ($P = 0.75$).

LS mean percent change in body weight from baseline was significantly greater with efpeglenatide 4 mg (−3.5%) than with placebo (−1.2%) (difference in LS mean change −2.3 kg, $P < 0.05$); percent change from baseline with liraglutide was −3.5%. The proportion of patients who had a >5% reduction in body weight was significantly higher in the efpeglenatide 1-mg and 4-mg groups compared with placebo (22% and 22% vs. 5%, respectively, $P < 0.05$ for both); the proportion for the liraglutide group was 19%. The proportions of patients who had a >10% reduction in body weight were comparable between the efpeglenatide groups (0%, 5%, 0%, 3%, and 6% for 0.3 mg, 1 mg, 2 mg, 3 mg, and 4 mg, respectively) and placebo (0%) as well as liraglutide (6%).

### Safety Assessments

TEAEs (Table 3) were reported by 51–76% of patients in the efpeglenatide treatment groups, 62% of the patients in the placebo group, and 81% of patients in the liraglutide group. The most common TEAEs across all the efpeglenatide groups combined were nausea (20.1%), vomiting (9.5%), and headache (8.9%). In the placebo group, the most common TEAEs were nausea (16.2%) and headache (13.5%). In the liraglutide group, the most common TEAEs were nausea (33.3%), injection-site bruising (19.4%), and vomiting (13.9%).

Three serious AEs were reported in three patients: one was in the efpeglenatide 2-mg group (allergy to arthropod [wasp] sting), and two were in the efpeglenatide 3-mg group (device [artificial joint] failure and pneumonia). Severe TEAEs were reported in three patients, all in the efpeglenatide 3-mg group (pneumonia, anal abscess, and gout). A total of 19 TEAEs leading to discontinuation occurred in nine patients overall, five receiving efpeglenatide and four receiving liraglutide (Table 3).

### Summary of Key AEs

Rates of GI TEAEs of nausea, vomiting, and diarrhea are reported in Table 3. Rates of these TEAEs were comparable between the efpeglenatide and liraglutide groups and were generally lower in the placebo group than in the liraglutide group or in the higher efpeglenatide dose groups. Overall, the incidence of nausea and vomiting with efpeglenatide was highest at week 1 and subsided over time.

The incidence of injection-site reactions ranged from 0% to 17% across the efpeglenatide dose groups and was 28% and 11% with liraglutide and placebo, respectively. Skin and subcutaneous TEAEs were reported in ≤8% of patients in any efpeglenatide group; these rates were similar to liraglutide and placebo.

### Other Safety Assessments

At baseline, 3–8% of patients randomized to placebo or efpeglenatide were positive for anti-efpeglenatide antibodies (Table 3). Treatment-emergent antibodies, defined as treatment-induced antidrug antibodies (ADAs) with any titer or treatment-boosted ADAs with a $\log_2$-expressed titer increase by ≥2 from preexisting levels, were observed in 17.3% (31 of 179) of patients receiving efpeglenatide. Because a $\log_2$-expressed antibody titer of 0 or 1 may arise from assay variability, treatment-emergent antibodies were also assessed using a higher threshold.

For treatment-emergent antibodies defined as treatment-induced ADAs with a $\log_2$-expressed titer ≥2 or treatment-boosted ADAs with a $\log_2$-expressed titer increase by ≥2 from preexisting levels, the incidence was 8.4% (15 of 179) in patients receiving efpeglenatide. No patients receiving efpeglenatide or placebo were positive for anti-efpeglenatide neutralizing antibodies in vitro at any time.

There were no meaningful changes from baseline in vital sign parameters, including heart rate and systolic and diastolic blood pressure. Heart rate increases observed for efpeglenatide treatment (overall treatment group) appeared to be less than those observed for the reference, liraglutide (Table 3). Furthermore, no meaningful differences were observed on these parameters between the efpeglenatide treatment groups and either placebo or liraglutide. There were no meaningful mean changes from baseline in clinical laboratory assessments or ECG parameters with efpeglenatide.

Only two patients experienced hypoglycemia TEAEs during the study (one each in the efpeglenatide 0.3-mg and liraglutide groups); both cases were mild, and each patient recovered. The incidence of self-reported hypoglycemia was lower in the efpeglenatide treatment groups overall (4.5%) compared with placebo (8.1%); no self-reported events were reported in the liraglutide group. In each case of hypoglycemia, the patient recovered immediately after self-administering carbohydrates.

**Table 3—Selected safety assessments (safety set)**

| | Placebo (*n* = 37) | Efpeglenatide 0.3 mg (*n* = 37) | Efpeglenatide 1 mg (*n* = 37) | Efpeglenatide 2 mg (*n* = 33) | Efpeglenatide 3 mg (*n* = 36) | Efpeglenatide 4 mg (*n* = 36) | Liraglutide 1.8 mg q.d. (*n* = 36) |
|---|---|---|---|---|---|---|---|
| Any TEAEs | 23 (62) | 19 (51) | 26 (70) | 25 (76) | 24 (67) | 24 (67) | 29 (81) |
| Serious TEAEs | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 2 (6) | 0 (0) | 0 (0) |
| Any TEAE leading to discontinuation | | | | | | | |
| Total | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 3 (8) | 1 (3) | 4 (11) |
| Nausea | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 1 (3) | 2 (6) |
| Vomiting | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 1 (3) | 1 (3) | 2 (6) |
| GI disorders | 11 (30) | 8 (22) | 6 (16) | 12 (36) | 15 (42) | 19 (53) | 16 (44) |
| Nausea | 6 (16) | 4 (11) | 3 (8) | 9 (27) | 8 (22) | 12 (33) | 12 (33) |
| Vomiting | 0 (0) | 0 (0) | 1 (3) | 4 (12) | 4 (11) | 8 (22) | 4 (11) |
| Diarrhea | 2 (5) | 5 (14) | 1 (3) | 3 (9) | 4 (11) | 2 (5) | 5 (14) |
| Injection-site reaction | 4 (10.8) | 4 (10.8) | 6 (16.2) | 4 (12.1) | 6 (16.7) | 0 (0) | 10 (27.8) |
| Skin and subcutaneous tissue disorders | 4 (11) | 1 (3) | 1 (3) | 0 (0) | 1 (3) | 3 (8) | 3 (8) |
| Antibody formation* | | | | | | | |
| Baseline | 3 (8) | 2 (5) | 2 (5) | 1 (3) | 1 (3) | 3 (8) | NA |
| Treatment emergent (any titer)† | 0 (0) | 1 (3) | 8 (22) | 6 (18) | 8 (22) | 8 (22) | NA |
| Treatment emergent (titer ≥2)‡ | 0 (0) | 0 (0) | 5 (14) | 2 (6) | 4 (11) | 4 (11) | NA |
| Heart rate change (beats/min), mean ± SD | 0.7 ± 10.5 | 0.3 ± 7.4 | −0.5 ± 7.0 | 1.8 ± 8.4 | 3.9 ± 9.1 | 3.0 ± 10.1 | 5.6 ± 8.5 |
| Self-reported hypoglycemia | 3 (8) | 1 (3) | 2 (5) | 1 (3) | 2 (6) | 2 (6) | 0 (0) |

Data are *n* (%) unless otherwise indicated. NA, not applicable. *In the placebo group, one patient did not have any postbaseline assessments, and four patients had one missing postbaseline assessment. In the efpeglenatide group overall, three patients did not have a baseline assessment, 10 patients did not have any postbaseline assessments, and 19 patients had one missing postbaseline assessment. †Overall incidence of treatment-induced ADAs (with any titer) and treatment-boosted ADAs ($log_2$-expressed titer of preexisting ADA level boosted by at least 2). ‡Overall incidence of treatment-induced ADAs (with $log_2$-expressed titer of at least 2) and treatment-boosted ADAs ($log_2$-expressed titer of preexisting ADA level boosted by at least 2).

## CONCLUSIONS

The doses chosen for this study were based on previous pharmacokinetic/pharmacodynamic studies (29,30). Similar to those studies, this thorough dose-finding study found that efpeglenatide once weekly demonstrated significant dose-dependent glucose-lowering effects from doses of 1–4 mg compared with placebo, with consistent body weight reductions, and was generally well tolerated at doses of up to 4 mg in patients with T2D. In addition, exploratory analyses revealed that the efpeglenatide 4-mg dose was noninferior to open-label liraglutide treatment in reducing $HbA_{1c}$ levels, and we speculate that higher doses than those explored in this study may yield greater reductions. Similarly, body weight reductions with efpeglenatide 3 mg or 4 mg were significantly greater than with placebo and were comparable to those seen with liraglutide 1.8 mg.

In this study, all doses of efpeglenatide ≥1 mg examined resulted in significantly greater reductions in $HbA_{1c}$ and body weight compared with placebo, and the reductions observed were basically comparable to those reported in the literature for other long-acting GLP-1 RAs (7,31). Significantly greater proportions of patients achieved $HbA_{1c}$ <7% in all efpeglenatide treatment groups, and these proportions were also within the range of those reported for other long-acting GLP-1 RAs (7).

In general, all doses of efpeglenatide investigated were well tolerated. However, as expected, the frequency and severity of GI AEs with efpeglenatide once weekly observed in this study were consistent with other long-acting GLP-1 RAs and similarly subsided over time. However, it should be noted that no titration of efpeglenatide dose was incorporated into the study design, and evidence from simulation of titration to efpeglenatide 4 mg using data from EXCEED suggests that the incidence of GI TEAEs may be mitigated with slow, progressive dose titration in future studies (32).

Immunogenicity was also investigated because it can affect the clinical safety and efficacy of any compound (33). Immunogenicity with efpeglenatide treatment was low, with low incidences of treatment-emergent ADAs and no neutralizing antibodies. Because of differences in the molecular structure of exendin compared with native GLP-1, exendin-based GLP-1 RAs have demonstrated immunogenicity in humans. ADA response to the closely related molecule exenatide twice daily (34), as well as exenatide once weekly (34) and lixisenatide (35), have been reported in 37%, 57%, and 56–60% of patients, respectively, in clinical studies with 12–30 weeks of treatment. By contrast, efpeglenatide appears to have low immunogenic potential, as observed in the present EXCEED study and other early clinical studies (36). The aglycosylated Fc carrier conjugation by the mini-PEG linker in efpeglenatide likely interferes with presentation to MHC class II, leading to reduced T-cell activation (37).

Efpeglenatide has a long half-life and prolonged pharmacokinetic profile that permits once-weekly dosing (29,30). In this study, the glucose-lowering effects of efpeglenatide 1 mg, 2 mg, 3 mg, and 4 mg q.w. were superior to placebo, and

efpeglenatide 4 mg q.w. was noninferior to liraglutide 1.8 mg q.d. In addition, the observed safety profile of efpeglenatide was similar to once-daily or once-weekly regimens of other GLP-1 RAs, and GI AEs may be mitigated by initial slow titration (38).

Limitations of the current phase 2 study include the fact that the open-label liraglutide treatment arm was included as a reference, which could have introduced bias. Furthermore, the study was not powered to detect statistically significant differences between efpeglenatide and liraglutide. In addition, in contrast to liraglutide, there was no dose titration in the efpeglenatide treatment arms, which may have contributed to the observed rates of GI-related AEs because it is conceivable that slow titration would have mitigated the frequency of GI AEs with efpeglenatide. Finally, efpeglenatide 6 mg q.w., which is currently being tested in ongoing clinical development, was not included in this study and may have the potential for greater efficacy. These limitations, as well as the relatively short duration of the study, support the need for longer-term studies to assess the safety and efficacy of efpeglenatide once weekly. Future head-to-head, double-blind studies comparing efpeglenatide with other GLP-1 RAs are also necessary to better inform clinical practice.

In conclusion, in the EXCEED study, efpeglenatide once weekly demonstrated dose-dependent reductions in glucose and body weight in patients with early T2D with and without metformin and had a safety profile consistent with the GLP-1 RA class. Efpeglenatide once weekly at doses $\geq$1 mg led to significant reductions in $HbA_{1c}$, and efpeglenatide 4 mg q.w. was noninferior to liraglutide 1.8 mg q.d. at reducing $HbA_{1c}$. Efpeglenatide 3 mg and 4 mg q.w. also led to significant reductions in body weight, supporting further development for the treatment of patients with T2D, even exploring higher doses.

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