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Efficacy and safety of once-monthly efpeglenatide in patients with type 2 diabetes: Results of a phase 2 placebo-controlled, 16-week randomized dose-finding study

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Abstract

Aims: To determine the optimal dose(s) of once-monthly administration of efpeglenatide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA), in patients with type 2 diabetes (T2D) inadequately controlled on metformin.

Materials and methods: In this phase 2, randomized, placebo-controlled, double-blind trial (NCT02081118), patients were randomized 1:1:1:1 to subcutaneous efpeglenatide (8, 12 or 16 mg once monthly; n = 158) or placebo (n = 51). The 16-week treatment period included a 4-week titration phase with once-weekly efpeglenatide 4 mg, followed by one dose of efpeglenatide 8 mg once monthly and two doses of the assigned once-monthly dose. The primary endpoint was change in glycated haemoglobin (HbA1c) from baseline to week 17.

Results: All efpeglenatide doses significantly reduced HbA1c versus placebo ($P < 0.0001$ for all). Overall, the least squares mean difference in HbA1c reductions between efpeglenatide and placebo was −7.7 mmol/mol (−0.71%; baseline to week 17). At week 17, a significantly greater proportion of efpeglenatide patients had an HbA1c level <53 mmol/mol (<7%) versus placebo (48.7% vs. 30.6%; $P = 0.0320$). Significant body weight loss occurred across all efpeglenatide doses (placebo-corrected reduction −2.0 kg [efpeglenatide overall]; $P = 0.0003$). The safety profile was consistent with GLP-1RAs, with gastrointestinal (GI) disorders being the most common treatment-emergent adverse events. Fluctuations in effects on glucose levels and rates of GI events occurred between peak and trough efpeglenatide concentrations.

Conclusions: Efpeglenatide once monthly (following once-weekly titration) has significant benefits with regard to HbA1c and weight reduction versus placebo in patients with T2D. Further studies are needed to evaluate the long-term efficacy and safety of efpeglenatide once monthly.

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KEYWORDS
dose–response relationship, GLP-1 analogue, incretin, phase I-II study, type 2 diabetes (T2D)

1 | INTRODUCTION

Despite the number of treatment options available for type 2 diabetes (T2D), adherence to therapy remains suboptimal, especially with injectable agents such as insulin.[1-3] Injection burden, lack of dosing flexibility, and concerns about hypoglycaemia and weight gain are common barriers to treatment initiation and adherence to insulin therapy.[2-5] Several studies have shown that glucagon-like peptide-1 receptor agonists (GLP-1RAs) are at least as effective as basal insulin analogues, with the advantage of body weight reduction, and minimal risk of hypoglycaemia.[6] In light of this evidence, the latest version of the American Diabetes Association/European Association for the Study of Diabetes consensus recommends starting a GLP-1RA ahead of insulin whenever injectable treatment is required to ensure adequate glycaemic control.[7] The European Society of Cardiology/European Association for the Study of Diabetes 2019 guidelines on prediabetes, diabetes and cardiovascular disease also recommend the use of GLP-1RAs as initial treatment in patients with diabetes and pre-existing cardiovascular disease.[8] Different formulations of GLP-1RAs are available and, compared with once-daily injections, once-weekly injections seem to be associated with better treatment adherence.[9-13] A claims data study has found a gap between glycated haemoglobin (HbA1c) reductions in the real world versus randomized controlled trials with GLP-1RAs, with poor adherence being the key driver of the reduced efficacy observed in the real world.[14,15] Therefore, better adherence is needed to improve outcomes with GLP-1RAs.

Efpeglenatide (formerly HM11260C) is a long-acting GLP-1RA, currently being developed as a once-weekly subcutaneous administration for improvement of glycaemic control in patients with T2D. Efpeglenatide comprises a single amino acid-modified exendin conjugated to a fragment crystallizable region of human immunoglobulin 4 via a 3.4-kDa mini-polyethylene glycol linker using Long Acting Protein/Peptide (LAPS) technology.[16] Fragment crystallizable conjugation confers a pharmacokinetic (PK)/pharmacodynamic profile supporting flexible dosing frequency (from once weekly to once every 2 weeks and once monthly).[17,18] In addition, in biochemical and preclinical studies, efpeglenatide has displayed greater glucagon-like peptide-1 receptor signalling and reduced desensitization compared with other GLP-1RAs.[19,20]

In the phase 2 clinical trial EXCEED (NCT02057172), a 12-week study performed in patients with T2D who were drug-naïve or on metformin, efpeglenatide 4 mg once weekly was non-inferior to once-daily liraglutide with regard to HbA1c reduction from baseline.[21] In a separate multiple ascending-dose phase 2a study in patients with T2D on metformin (NCT01452451), once-weekly and once-monthly efpeglenatide showed significant improvements in glycaemic control and body weight reduction versus placebo over 8 weeks (three weekly doses) and 11 weeks (three monthly doses) of treatment.[18,22] In both studies, efpeglenatide was generally well tolerated.

In the present paper we report the results of a 16-week randomized, double-blind, placebo-controlled, parallel-group, phase 2 study, designed to determine the optimal monthly dose or doses of efpeglenatide (8, 12 or 16 mg) in patients with T2D inadequately controlled with stable doses of metformin.

2 | MATERIALS AND METHODS

LIBERATE 204 (NCT02081118) was a phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicentre trial initiated on February 18, 2014 (first patient screened) and concluded on April 30, 2015 (last patient completed). The study included a 16-week treatment period (4-week dose escalation with efpeglenatide 4 mg once-weekly and 12-week treatment with efpeglenatide once-monthly [initial titration dose of efpeglenatide 8 mg once monthly, followed by assigned monthly dose]) and a 6-week follow-up period (Figure S1).

Eligible patients were aged ≥18 and <75 years, diagnosed with T2D, and on a stable dose of metformin (≥1500 mg/d or maximum tolerated dose, or maximum dose according to the country-specific label) for at least 3 months before screening, with HbA1c levels of ≥53 mmol/mol (≥7.0%) and ≤86 mmol/mol (≤10%; ≥53 mmol/mol [≥7.0%] and ≤69 mmol/mol [≤8.5%] in Germany) and a body mass index of <40 kg/m^2. Key exclusion criteria included a diagnosis of type 1 diabetes, fasting plasma glucose (FPG) >13.3 mmol/L (>240 mg/dL), at least a 10% increase or decrease in body weight in the 3 months before screening, and pregnant or nursing women. Key medication exclusions are described in the Supporting information.

Patients were randomized 1:1:1:1 via an interactive voice/web response system to one of four study groups: three efpeglenatide groups (8, 12 and 16 mg) and a placebo group. The treatment period started with a titration phase in which all patients randomized to efpeglenatide received efpeglenatide 4 mg once weekly or placebo for 4 weeks (on days 1, 8, 15 and 22) and efpeglenatide 8 mg once during the following week (on day 29; Figure S1). Thereafter, patients received their assigned efpeglenatide dose (8, 12 or 16 mg) or placebo once monthly (every 28 days) in the morning (on days 57 and 85).

Patients were instructed to monitor their blood glucose levels using a provided glucometer at least twice a day (before breakfast and after dinner) after starting treatment (day 1; the glucose assessment schedule can be found in the Supporting Information). Additionally, a blood glucose reading was to be obtained for any symptoms of possible hypoglycaemia. Patients received a diary to record details of injection reactions, hypoglycaemic episodes and seven-point glucose profile measurements.

The study was designed and conducted in accordance with the guidelines for Good Clinical Practice and the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and the Declaration of Helsinki. The protocol was

approved by the institutional review board or ethics committee at each study site. All patients provided written informed consent prior to study participation.

2.1 | Interventions

Treatment administration and assessment for efpeglenatide and placebo were double blind. Randomization data were kept strictly confidential until the time of unblinding. Both efpeglenatide and placebo were administered by subcutaneous injection at 0.53 mL using prefilled syringes. Treatment identity was concealed by the use of study drug or placebo that were identical in packaging, labelling, schedule of administration, appearance, taste and odour. Additional details are described in the Supporting Information.

All patients continued taking metformin throughout the study at the same dose received during screening. Doses of other medications (ie, lipid-lowering and blood pressure medications) could only be changed if required for medical reasons. For patients meeting hyperglycaemic rescue criteria, non-study anti-hyperglycaemic therapy could be initiated per local guidelines and at the investigator's discretion (additional details are available in the Supporting Information).

2.2 | Efficacy endpoints

The primary efficacy endpoint was change in HbA1c from baseline to week 17 (16 weeks of treatment) for efpeglenatide versus placebo. Secondary efficacy endpoints included percentage of patients with HbA1c <53 mmol/mol (<7%), change from baseline to week 17 in FPG, mean daily glucose (based on seven-point glucose profile consisting of 90 minutes pre- and postprandial and bedtime glucose), and body weight. Please see the Supporting Information for details on glucose measurements. Other diabetes-related endpoints included change from baseline to week 17 in fasting insulin, C-peptide, glycated albumin and lipid profile (LDL cholesterol, HDL cholesterol and triglycerides). Because of the low sensitivity of the glucagon assay, glucagon data were not analysed.

2.3 | Pharmacokinetics

Blood samples were collected on days 29, 36, 57, 64 and 85 (weeks 5, 6, 9, 10 and 13) in preselected countries for PK assessments. On days that coincided with study-drug administration, the blood sample was taken immediately before the dose was administered.

2.4 | Safety endpoints

Safety assessments included treatment-emergent adverse events (TEAEs; defined as adverse events [AEs] with a start date or increase in severity on or after first dose), clinical laboratory assessments, amylase and lipase levels, ECG variables, vital signs and injection-site reactions (by diary). Hypoglycaemia as an AE was defined as confirmed hypoglycaemia on the basis of blood glucose levels <3.9 mmol/L (<70 mg/dL), recorded according to Medical Dictionary for Regulatory Activities 16.1 coding. In addition, patient-reported hypoglycaemic episodes were assessed based on episodes recorded by patients in their diary, based on hypoglycaemic symptoms.

Blood samples were assessed for anti-efpeglenatide antibodies using an enzyme-linked immunosorbent assay (microtitre plate absorbance reader, Sunrise RC/TW TC; Tecan, Männedorf, Switzerland). Neutralizing antibodies were determined using a cell-based assay in which inhibition of intracellular cyclic adenosine monophosphate (cAMP) level by anti-efpeglenatide antibodies was measured by the cAMP-Glo™ assay (Promega; microtitre plate luminometer [Centro LB 960; Berthold, Baden Württemberg, Germany]). Both assays were validated in SYNLAB AG (Birsfelden, Switzerland).

2.5 | Statistical analyses

A sample size of 41 completed patients per study group was needed to provide 80% power to detect a difference of 0.62% in the change in HbA1c from baseline between efpeglenatide and placebo, assuming that at a two-sided significance level of 0.05, the standard deviation is 1.00%. All endpoints beyond the primary endpoint were exploratory.

The primary efficacy endpoint was analysed using a mixed-effects model with repeated measures (MMRM) with an unstructured covariance matrix over all visits after screening. Terms for treatment, visit and their interaction were included as factors, and baseline HbA1c was included in the model as a covariate. Least squares (LS) mean estimates were obtained for each treatment and for the difference between efpeglenatide and placebo; two-sided 95.1% confidence intervals (CIs) were also calculated. A similar MMRM was used to calculate change from baseline in FPG, seven-point blood glucose profile, body weight, fasting insulin, C-peptide, glycated albumin and serum lipids. The percentage of patients with HbA1c <53 mmol/mol (<7%) was analysed using Fisher's exact test. Safety parameters were analysed only descriptively. No adjustments of α level were made for multiple comparisons.

All efficacy analyses were evaluated using the full analysis set (all patients who received the study drug and had at least one efficacy or safety assessment recorded after dosing, grouped according to randomized treatment). CIs were two-sided 95.1%, which was a required adjustment after an interim analysis was performed. Safety endpoints were analysed using the safety set (all patients who received any study drug, grouped according to the treatment actually received).

3 | RESULTS

Overall, 209 patients were randomized at 45 sites in Germany, Hungary, Spain, South Korea and the USA, with 158 patients assigned to one of three efpeglenatide groups and 51 to the placebo group. A

total of 207 patients, 157 and 50 in the efpeglenatide and placebo groups, respectively, received any study drug and were included in the safety set (Figure S2). Among the safety set, discontinuation rates during the 16-week treatment period were 21% (8 mg), 25% (12 mg), and 30% (16 mg) with efpeglenatide, and 18% with placebo, with no discontinuations during the 6-week follow-up period. The main reasons for discontinuation were AEs; rates of discontinuations due to AEs during the treatment period were 12% (8 mg), 12% (12 mg), and 15% (16 mg) with efpeglenatide, and 2% with placebo.

Baseline demographics and disease characteristics were similar across the efpeglenatide and placebo groups (Table 1).

3.1 | Primary efficacy endpoint

All doses of efpeglenatide resulted in significant reductions in HbA1c from baseline to week 17 compared with placebo (Figure 1A, Table 2 and Table S1). At week 17, differences in LS mean changes from baseline for efpeglenatide 8 mg, 12 mg, 16 mg and overall versus placebo were −7.2 mmol/mol (−0.66%; $P = 0.0001$), −7.3 mmol/mol (−0.67%; $P = 0.0001$), −8.6 mmol/mol (−0.79%; $P < 0.0001$) and −7.7 mmol/mol (−0.71%; $P < 0.0001$), respectively.

3.2 | Secondary endpoints

At week 17, a greater proportion of patients in the efpeglenatide group overall (48.7%) had HbA1c <53 mmol/mol (<7%) than in the placebo group (30.6%; $P = 0.0320$ [Table 2]). However, the differences in the proportions of patients with HbA1c <53 mmol/mol (<7%) between each of the individual efpeglenatide groups and the placebo group were not statistically significant (Figure 1B, Table 2).

Efpeglenatide treatment led to reductions in FPG levels throughout the study period (Figure 1C, Table 2 and Table S1). LS mean decreases from baseline in FPG levels in the efpeglenatide group were greatest during the titration phase (weeks 1-5), and at weeks 6, 10 and 14 (1 week after patients received their assigned monthly dose). At week 17, differences in LS mean change from baseline for efpeglenatide 8 mg, 12 mg, 16 mg and overall versus placebo were −0.70 mmol/L (−12.69 mg/dL; $P = 0.0809$), −0.38 mmol/L (−6.88 mg/dL; $P = 0.3473$), −0.72 mmol/L (−12.92 mg/dL; $P = 0.0812$) and −0.60 mmol/L (−10.83 mg/dL; $P = 0.0687$), respectively.

Change from baseline in mean daily blood glucose was significantly greater with all efpeglenatide doses compared with placebo (Figure 1D, Table 2 and Table S1). Differences in LS mean changes from baseline to week 17 in mean daily blood glucose for efpeglenatide 8 mg, 12 mg, 16 mg and overall versus placebo were −0.76 mmol/L (−13.68 mg/dL; $P = 0.0419$), −0.98 mmol/L (−17.72 mg/dL; $P = 0.0088$), −1.05 mmol/L (−18.94 mg/dL; $P = 0.0051$) and −0.93 mmol/L (−16.78 mg/dL; $P = 0.0022$), respectively. Preprandial glucose was also significantly reduced in all efpeglenatide groups (Table 2 and Table S1). Change from baseline in 90-minute postprandial glucose was significantly greater with

TABLE 1 Baseline demographics and clinical characteristics (safety set)

	Placebo (n = 50)	Efpeglenatide 8 mg (n = 52)	Efpeglenatide 12 mg (n = 52)	Efpeglenatide 16 mg (n = 53)	Efpeglenatide overall (n = 157)	Total (N = 207)
Age, years	54.7 (9.9)	56.7 (8.1)	56.0 (9.5)	56.4 (9.5)	56.4 (9.0)	56.0 (9.2)
Men/women, %	46.0/54.0	36.5/63.5	53.8/46.2	47.2/52.8	45.9/54.1	45.9/54.1
White/black/Asian/other, %	86.0/10.0/2.0/2.0	78.8/17.3/1.9/1.9	86.5/9.6/1.9/1.9	88.7/9.4/1.9/0	84.7/12.1/1.9/1.3	85.0/11.6/1.9/1.5
Known diabetes duration, years	7.2 (5.3)	9.1 (7.4)	7.4 (6.2)	7.2 (4.6)	7.9 (6.2)	7.7 (6.0)
Time on metformin, years	3.9 (4.3)	4.0 (3.9)	4.6 (5.0)	3.9 (3.5)	4.2 (4.2)	4.1 (4.2)
HbA1c, mmol/mol	62.8 (7.5)	62.8 (8.3)	59.8 (8.1)	63.0 (7.9)	61.9 (8.2)	62.1 (8.0)
HbA1c, %	7.90 (0.68)	7.90 (0.76)	7.62 (0.74)	7.91 (0.73)	7.81 (0.75)	7.83 (0.73)
FPG, mmol/L	8.70 (1.94)	8.67 (2.08)	8.62 (1.86)	8.60 (1.83)	8.63 (1.91)	8.65 (1.92)
FPG, mg/dL	156.69 (34.97)	156.28 (37.48)	155.31 (33.50)	154.86 (32.89)	155.48 (34.45)	155.77 (34.49)
Weight, kg	91.8 (19.2)	92.2 (19.2)	93.1 (15.3)	87.0 (14.8)	90.7 (16.7)	91.0 (17.3)
BMI, kg/m^2	32.4 (4.2)	32.1 (4.7)	33.0 (4.6)	30.7 (4.0)	32.0 (4.5)	32.1 (4.4)

Note: Data are mean (SD), or percent where indicated.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin.

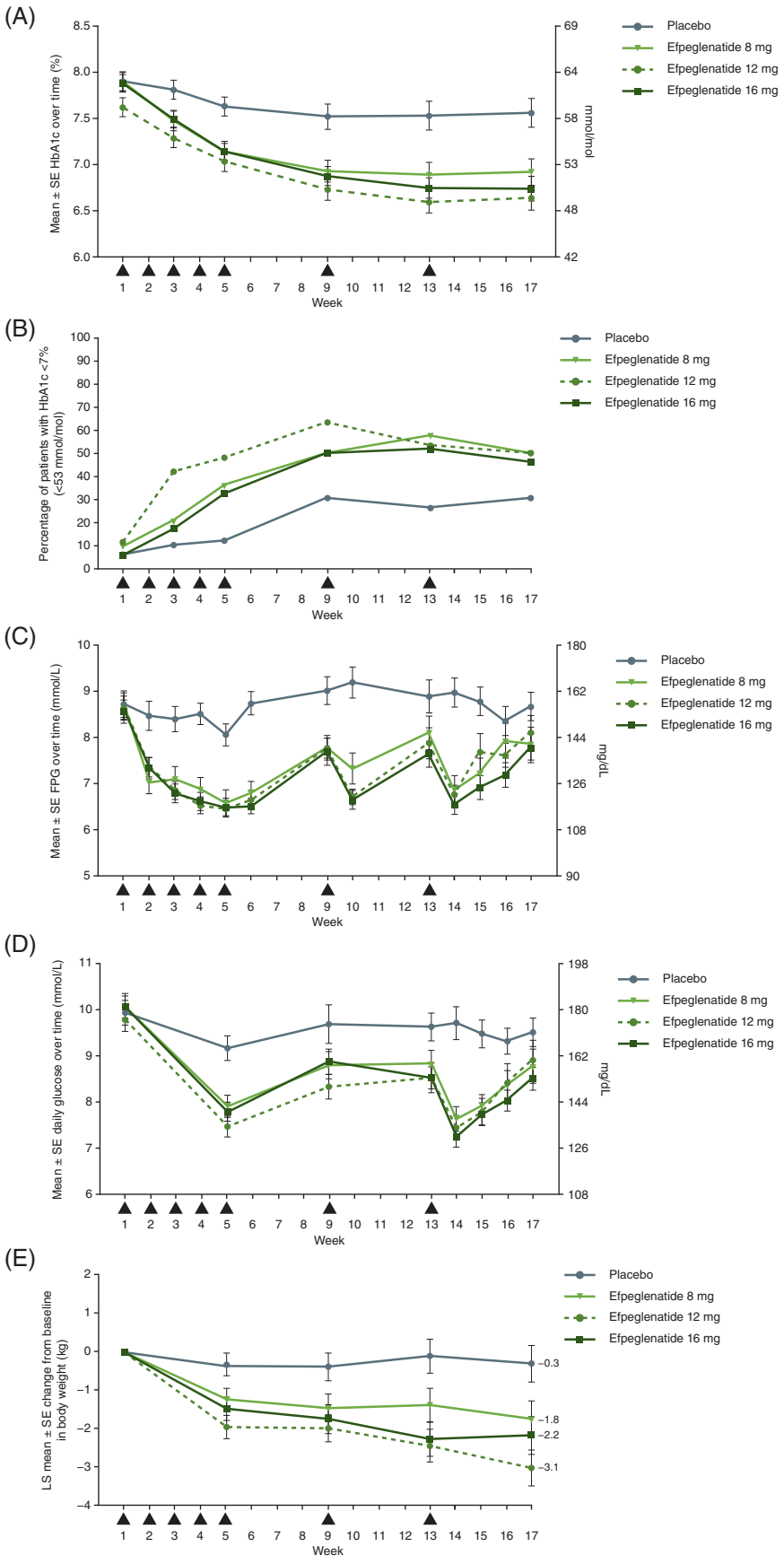

FIGURE 1 **A**, Mean glycated haemoglobin (HbA1c), **B**, percentage of patients with HbA1c <53 mmol/mol (<7%), **C**, mean fasting plasma glucose (FPG), **D**, mean daily plasma glucose, and **E**, least squares (LS) mean change in body weight from baseline over the 16-week treatment period (full analysis set). Arrows indicate days of injection, which occurred at the beginning of each week. Week 1 values are baseline values

TABLE 2 Response to treatment at week 17 (full analysis set)

	Placebo (*n* = 49)	Efpeglenatide 8 mg (*n* = 52)	Efpeglenatide 12 mg (*n* = 52)	Efpeglenatide 16 mg (*n* = 52)	Efpeglenatide overall (*n* = 156)
HbA1c (mmol/mol)					
Week 17	59.1 (11.0)	52.1 (10.1)	49.0 (8.8)	50.1 (8.9)	50.5 (9.3)
LSM (SE) change from baseline[aa]	−3.5 (1.3)	−10.7 (1.3)	−10.8 (1.3)	−12.1 (1.3)	−11.2 (0.8)
LSM difference vs placebo[aa] (95.1% CI)	-	−7.2 (−10.9, −3.6)	−7.3 (−11.0, −3.7)	−8.6 (−12.3, −4.9)	−7.7 (−10.7, −4.8)
HbA1c (%)					
Week 17	7.56 (1.01)	6.92 (0.93)	6.64 (0.80)	6.74 (0.81)	6.77 (0.85)
LSM (SE) change from baseline[aa]	-0.32 (0.12)	-0.98 (0.12)	-0.99 (0.12)	-1.11 (0.12)	-1.03 (0.07)
LSM difference vs placebo[aa] (95.1% CI)	-	-0.66 (-0.99, -0.33)	-0.67 (-1.00, -0.34)	-0.79 (-1.13, -0.45)	-0.71 (-0.98, -0.43)
P-value		0.0001	0.0001	<0.0001	<0.0001
Patients with HbA1c <53 mmol/mol (7%) at Week 17, *n* (%)	15 (30.6)	26 (50.0)	26 (50.0)	24 (46.2)	76 (48.7)
P-value	-	0.0678	0.0678	0.1522	0.0320
FPG (mmol/L)					
Week 17	8.66 (2.00)	7.86 (2.28)	8.09 (2.28)	7.76 (1.93)	7.90 (2.16)
LSM (SE) change from baseline[aa]	−0.07 (0.28)	−0.78 (0.29)	−0.45 (0.29)	−0.79 (0.30)	−0.67 (0.17)
LSM difference vs placebo[aa] (95.1% CI)	-	−0.70 (−1.50, 0.09)	−0.38 (−1.19, 0.42)	−0.72 (−1.53, 0.09)	−0.60 (−1.25, 0.05)
P-value	-	0.0809	0.3473	0.0812	0.0687
Mean daily glucose (mmol/L)					
Week 17	9.49 (1.90)	8.76 (2.13)	8.89 (2.50)	8.49 (1.43)	8.71 (2.05)
LSM (SE) change from baseline[aa]	−0.31 (0.26)	−1.07 (0.27)	−1.30 (0.27)	−1.36 (0.27)	−1.24 (0.16)
LSM difference vs placebo[aa] (95.1% CI)	-	−0.76 (−1.50, −0.03)	−0.98 (−1.72, −0.25)	−1.05 (−1.79, −0.32)	−0.93 (−1.52, −0.34)
P-value	-	0.0419	0.0088	0.0051	0.0022
90-minute preprandial glucose (mmol/L)					
Week 17	8.66 (1.81)	8.09 (2.08)	8.30 (2.86)	7.67 (1.57)	8.01 (2.22)
LSM (SE) change from baseline[aa]	−0.34 (0.26)	−1.14 (0.28)	−1.21 (0.28)	−1.34 (0.28)	−1.23 (0.16)
LSM difference vs placebo[aa] (95.1% CI)	-	−0.80 (−1.56, −0.04)	−0.87 (−1.63, −0.11)	−1.00 (−1.75, −0.24)	−0.89 (−1.50, −0.28)
P-value	-	0.0396	0.0248	0.0101	0.0046
90-minute postprandial glucose (mmol/L)					
Week 17	10.13 (2.24)	9.33 (2.32)	9.21 (2.35)	9.37 (1.86)	9.30 (2.16)
LSM (SE) change from baseline[aa]	−0.54 (0.31)	−1.10 (0.32)	−1.67 (0.32)	−1.32 (0.32)	−1.36 (0.19)
LSM difference vs placebo[aa] (95.1% CI)	-	−0.56 (−1.44, 0.32)	−1.13 (−2.01, −0.25)	−0.78 (−1.66, 0.10)	−0.82 (−1.53, −0.11)
P-value	-	0.2117	0.0122	0.0817	0.0236

(Continues)

TABLE 2 (Continued)

	Placebo (n = 49)	Efpeglenatide 8 mg (n = 52)	Efpeglenatide 12 mg (n = 52)	Efpeglenatide 16 mg (n = 52)	Efpeglenatide overall (n = 156)
Body weight (kg)					
Week 17	91.47 (20.12)	89.98 (18.12)	91.87 (15.31)	85.72 (15.58)	89.26 (16.49)
LSM (SE) change from baseline[aa]	-0.34 (0.47)	-1.78 (0.47)	-3.05 (0.47)	-2.20 (0.49)	-2.34 (0.28)
LSM difference vs placebo[aa] (95.1% CI)	-	-1.44 (-2.76, -0.13)	-2.71 (-4.02, -1.39)	-1.86 (-3.21, -0.51)	-2.00 (-3.08, -0.93)
P-value	-	0.0312	0.0001	0.0068	0.0003

Data are mean (SD) unless otherwise stated.
Week 21 values correspond to 20 weeks of treatment.
LSM difference vs placebo is calculated as the study dose group - placebo in LSM change from baseline to Week 21.
Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LSM, least squares mean; MMRM, mixed-effects model with repeated measures; SD, standard deviation; SE, standard error.
[a]From MMRM, using an unstructured covariance matrix, change from baseline as the outcome variable, baseline as a covariate, and treatment group, visit and their interaction as factors.

efpeglenatide 12 mg and efpeglenatide overall compared with placebo ($P < 0.05$).

All doses of efpeglenatide resulted in a significant reduction in body weight over the treatment period compared with placebo (Figure 1E and Table 2). At week 17, the differences in LS mean decreases from baseline versus placebo were −1.44 kg ($P = 0.0312$), −2.71 kg ($P = 0.0001$), −1.86 kg ($P = 0.0068$) and −2.00 kg ($P = 0.0003$) with efpeglenatide 8 mg, 12 mg, 16 mg and overall, respectively.

3.3 | Other diabetes-related variables

Levels of glycated albumin were significantly reduced by treatment with all doses of efpeglenatide compared with placebo (Table S2). Compared with placebo, increases from baseline in LDL cholesterol levels at week 17 in the efpeglenatide 12 mg and overall groups were significantly smaller (Table S2). There were no significant differences between efpeglenatide and placebo in change from baseline in HDL cholesterol, triglycerides, fasting insulin levels or C-peptide (Table S2).

3.4 | Pharmacokinetics

Overall, efpeglenatide plasma concentrations at each time point reflected the schedule of drug administration (Figure S3). Mean plasma concentrations were generally similar across the three treatment groups following weekly doses of 4 mg, increasing 1 week after the 8-mg dose of efpeglenatide at week 5, and decreasing in all efpeglenatide groups 3 weeks later (at week 9). Noteworthy differences among the efpeglenatide groups became evident at week 10 (1 week after patients received their assigned monthly dose), increasing with increasing dose. At week 13 (4 weeks after receiving the assigned monthly dose), plasma concentrations had decreased in all three efpeglenatide groups but remained higher with increasing efpeglenatide dose.

3.5 | Safety assessments

Overall, 703 TEAEs occurred in 161/207 patients (77.8%). In total, 129/157 patients (82.2%) in the efpeglenatide groups and 32/50 patients (64.0%) in the placebo group had ≥1 TEAE. The proportions of patients with any TEAEs were similar among the efpeglenatide groups and ranged from 81.1% to 82.7% (Table 3). Treatment-related AEs were reported in 90 patients (57.3%) in the efpeglenatide group overall and in eight patients (16.0%) in the placebo group. Serious TEAEs occurred in eight patients (5.1%) in the efpeglenatide group overall and in two patients (4.0%) in the placebo group. No deaths were reported during the study.

No hypoglycaemia TEAEs (blood glucose ≤3.9 mmol/L [≤70 mg/dL]) were reported in any group. A total of 67 patient-reported

TABLE 3 Selected safety assessments (safety set)

	Placebo[a] (n = 50)	Efpeglenatide 8 mg (n = 52)	Efpeglenatide 12 mg (n = 52)	Efpeglenatide 16 mg (n = 53)	Efpeglenatide overall[b] (n = 157)
Any TEAE	32 (64.0)	43 (82.7)	43 (82.7)	43 (81.1)	129 (82.2)
GI disorders	10 (20.0)	26 (50.0)	29 (55.8)	31 (58.5)	86 (54.8)
Nausea	1 (2.0)	14 (26.9)	24 (46.2)	23 (43.4)	61 (38.9)
Vomiting	2 (4.0)	8 (15.4)	13 (25.0)	17 (32.1)	38 (24.2)
Diarrhoea	4 (8.0)	9 (17.3)	8 (15.4)	11 (20.8)	28 (17.8)
Injection-site reaction	2 (4.0)	4 (7.7)	4 (7.7)	2 (3.8)	10 (6.4)
Antibody formation					
Baseline	2 (4.0)	5 (9.6)	4 (7.7)	7 (13.2)	16 (10.2)
Treatment-emergent (any titre)[c]	1 (2.0)	6 (11.5)	8 (15.4)	6 (11.3)	20 (12.7)
Treatment-emergent (titre ≥2)[d]	1 (2.0)	5 (9.6)	6 (11.5)	4 (7.5)	15 (9.6)
Any TEAE leading to discontinuation	1 (2.0)	6 (11.5)	7 (13.5)	8 (15.1)	21 (13.4)
SAEs					
Any	2 (4.0)	0 (0.0)	5 (9.6)	3 (5.7)	8 (5.1)
GI disorders	1 (2.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)
Injury, poisoning and procedural complications	1 (2.0)	0 (0.0)	1 (1.9)	1 (1.9)	2 (1.3)
Neoplasms: benign, malignant and unspecified	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)	2 (1.3)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)	2 (1.3)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)
Self-reported hypoglycaemic episodes[e]	2 (4.0)	5 (9.6)	7 (13.5)	10 (18.9)	22 (14.0)

Note: Data are n (%).

Abbreviations: ADA, antidrug antibody; GI, gastrointestinal; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Ten patients were missing one or more post-baseline measurement.

[b]One patient did not have a baseline measurement; 35 patients were missing one or more post-baseline measurement.

[c]Overall incidence of treatment-induced ADAs (with any titre) and treatment-boosted ADAs (log 2-expressed titre of pre-existing ADA level boosted by at least 2).

[d]Overall incidence of treatment-induced ADAs (with log 2-expressed titre of at least 2) and treatment-boosted ADAs (log 2-expressed titre of pre-existing ADA level boosted by at least 2).

[e]Patients who experienced any self-reported hypoglycaemic episodes based on hypoglycaemic feelings between study day 1 and 155 (follow-up visit).

hypoglycaemic episodes based on hypoglycaemic feelings occurred in 22 patients (14.0%) in the efpeglenatide group overall (8 mg: five patients [9.6%]; 12 mg: seven patients [13.5%]; and 16 mg: 10 patients [18.9%]) and in two patients (4.0%) in the placebo group (Table 3). In general, patients recovered immediately following a sugar-containing snack or drink.

Gastrointestinal (GI) events were the most commonly reported TEAEs in the efpeglenatide groups (Table 3). In general, GI events subsided over the titration period (with 4 mg once-weekly doses), although recurrent GI events occurred with the second monthly dose onward for the two highest doses of efpeglenatide (Figure S4).

Injection-site reactions were reported in 3.8% to 7.7% of patients in the efpeglenatide groups, and in 4.0% of patients in the placebo group (Table 3). The incidence of treatment-emergent antibodies was low in all treatment groups, and no neutralizing antibodies were detected in any patient receiving efpeglenatide or placebo at any time (Table 3).

There were no meaningful mean changes from baseline in heart rate, temperature, systolic blood pressure or diastolic blood pressure, or differences between individual efpeglenatide treatment groups and placebo, at any post-baseline time point from week 2 to week 17 or at follow-up (week 23; Figure S5). There was a trend toward increased heart rate and decreased blood pressure, which appeared to correlate with efpeglenatide PK profile (Figures S3 and S5). In general, ≤10% of the safety population within any one treatment group had a shift from normal levels of serum chemistry variables at baseline to any post-baseline assessment.

Mean amylase levels were within normal levels at baseline and remained within the normal range throughout the study period (Table S3). A post-baseline amylase level of >300 units/L was reported in one patient in the efpeglenatide 16 mg group during the treatment period. Mean lipase levels were generally high at baseline. Lipase levels of >153 units/L were reported in eight patients (5.1%) in the efpeglenatide group overall compared with two patients (4.0%) in the placebo group. No AEs of acute or chronic pancreatitis were reported during the study. Liver function tests were within the normal range for all patients, with the exception of one patient in the efpeglenatide 8 mg group (abnormal liver function test, a moderate TEAE that resolved and was considered unlikely to be related to study drug).

4 | DISCUSSION

In this study, once-monthly efpeglenatide at doses of 8, 12 and 16 mg (after initial titration with efpeglenatide 4 mg once weekly and further titration with efpeglenatide 8 mg once monthly for the 12 and 16 mg once-monthly doses) provided greater glycaemic control and weight reduction versus placebo in patients with T2D inadequately controlled on metformin. Treatment with efpeglenatide resulted in significant reductions in HbA1c as well as reductions in seven-point blood glucose profile and body weight compared with placebo. The safety profile was generally as expected for the GLP-1RA drug class, with GI disorders reported as the most common TEAEs.[6,23,24]

There was a dose–response relationship between efpeglenatide dose and plasma levels of efpeglenatide, but not for all efficacy and safety endpoints. Although statistical comparisons of effects across efpeglenatide treatment arms were not part of the prespecified analyses, placebo-corrected changes from baseline in glycaemic variables and body weight appeared similar for the three efpeglenatide doses, with overlapping CIs. There was no clear relationship between dose and the incidence of TEAEs. Although there appeared to be a slight increase in the proportion of patients discontinuing treatment at higher doses of efpeglenatide, the overall incidences of TEAEs leading to discontinuation were similar across efpeglenatide treatment groups (six to eight cases). The rates of overall TEAEs were comparable across efpeglenatide doses.

While it is important to recognize the limitations of indirect comparisons across studies with different experimental designs and dosing regimens, indirect comparisons of the weekly and monthly dosing regimens suggest that efpeglenatide once weekly is slightly more effective with regard to HbA1c reduction, and both regimens have comparable effects on body weight reduction. In the present study, treatment with efpeglenatide 16 mg once monthly (including the titration period of four weekly doses and one 8-mg monthly dose) resulted in placebo-adjusted LS mean changes from baseline in HbA1c and body weight of −8.6 mmol/mol (−0.79%) and −1.86 kg, respectively. In a previous phase 2 trial, EXCEED, 12-week treatment with efpeglenatide 4 mg once-weekly resulted in placebo-adjusted LS mean changes from baseline in HbA1c and body weight of −13.2 mmol/mol (−1.21%) and −2.02 kg, respectively.[21] However, once-monthly administration of efpeglenatide does not seem to provide an FPG reduction as sustained as the one observed with once-weekly administration.[25] In this study, the time course of FPG changes appeared to correlate with the efpeglenatide PK profile, with greater reductions at peak concentrations and diminishing effects toward the end of each 4-week period following the monthly dose. There was clearly a more sustained effect on FPG with once-weekly dosing in the titration phase due to the much lower PK fluctuations after once-weekly dosing compared with once-monthly dosing. In an ascending-dose study, the half-life ($t_{1/2}$) of efpeglenatide was ~135 to 180 hours after a single dose[17]; the $t_{1/2}$ is long enough to lead to drug accumulation and PK profile flattening after once-weekly but not after once-monthly dosing. In general, plasma concentrations of efpeglenatide reflected the schedule of drug administration, indicating that efpeglenatide levels are dose-dependent at the dosages used in this study. The rate of GI TEAEs also correlated with the PK profile, with peaks in GI events, such as nausea, coinciding with increased drug concentrations. While dose escalation has been shown to mitigate GI AEs with GLP-1RAs,[26-28] greater fluctuations in PK variables with the once-monthly dosing may limit tolerability compared with weekly administration, in line with the drug half-life.

Similar effects have been reported with the long-acting GLP-1RA albiglutide, which showed steady and consistent improvements in glycaemic control with weekly dosing but did not produce stable FPG reductions between doses with monthly administration.[29] The time course of GI AEs with albiglutide also correlated with the PK profile, which showed greater peak/trough fluctuations with less frequent administration.[29]

It is important to note that there are very few studies of other GLP-1RAs with monthly dosing regimens to put the GI AE and discontinuation rates seen with efpeglenatide once monthly into context. In a 20-week, phase 2 trial of exenatide once monthly (5, 8 and 11 mg doses), rates of GI AEs (32%–60%) were comparable to those seen with efpeglenatide once-monthly dosing in the present study; however, discontinuation rates were lower in the exenatide study (6.5%–10%).[30] Indirect comparisons with weekly, long-acting GLP-1RAs suggest that rates with efpeglenatide once monthly were comparable to those seen with semaglutide once weekly, but higher versus dulaglutide once weekly.[31,32] Discontinuation rates (21%–30%) and rates of GI AEs (50%–59%) with efpeglenatide once monthly were similar to those observed with 0.1 to 1.6 mg semaglutide once weekly in a 12-week dose-ranging phase 2 trial in patients with T2D with or without metformin, which reported GI AE rates of 21% to 79% and discontinuation rates of 11% to 33%.[33] In contrast, rates of AEs were higher than those observed with 0.1 to 3.0 mg dulaglutide once weekly in a 12-week phase 2 study in patients with T2D with or without metformin, in which discontinuation rates were 0% to 14% and rates of nausea and vomiting were 0% to 12% and 0% to 7%, respectively.[32] It is important to note that the titration scheme used in this study may not have been optimal, as there was no titration to the 4-mg once-weekly dose and limited titration up to the once-monthly doses. There is evidence to suggest that slower initial titration of GLP-1RAs may help mitigate GI AEs[26-29]; however, it is not yet known if slower titration to once-monthly dosing would have similar mitigating effects.

Although tolerability and safety are critical for the final dose selection of efpeglenatide, the treatment effects demonstrated by once-monthly administration are consistent with its long duration of action and suggest the potential for flexibility in weekly dosing. The significant improvements in glycaemic control as well as the trend for reductions in body weight observed with once-monthly dosing (vs placebo) suggest that the once-weekly dosing regimen may still be effective even if a weekly dose is missed. This greater flexibility, compared with many of the existing treatment options for diabetes, may lead to better adherence and, ultimately, better glycaemic control, although such a possibility will have to be directly tested in longer studies.[34]

One limitation of this trial was the inclusion of only patients who were on a background therapy of metformin. It is unknown if efficacy and safety outcomes observed in this patient population would translate to patients on more complicated background therapy, particularly agents prone to producing hypoglycaemia. In addition, due to the limited study follow-up, no patient-reported outcomes, such as satisfaction, were obtained. Patient experience and perspective on once-monthly dosing remain to be explored in future studies. Furthermore, the short duration of this study, which included only two administrations of the assigned monthly dose, did not allow the evaluation of long-term efficacy and safety outcomes. Although sample sizes were appropriate for this phase 2 study and provided adequate power for the primary analyses, all *P* values beyond the primary endpoint were descriptive, and control for multiplicity of *P* values was not taken into account.

In conclusion, the GLP-1RA class has an established clinical profile with benefits with regard to glycaemic and body weight control and low risk of hypoglycaemia. Efpeglenatide improved glycaemic control and body weight when administered once monthly (after an initial weekly titration phase) by subcutaneous injection in patients with T2D receiving metformin. Although FPG reductions were not stable between dosing with a once-monthly efpeglenatide dosing schedule, the reductions in HbA1c and safety profile observed with this monthly administration were in line with class effects associated with a weekly dose. This suggests that treatment with a weekly dose may be effective, even if the patient does not adhere strictly to the dosing regimen. Further trials are needed to assess if the potential flexibility benefit of efpeglenatide once weekly compared with many of the existing treatment options will lead to better glycaemic outcomes. The lower PK fluctuations associated with efpeglenatide once-weekly dosing are associated with superior and more sustained treatment effects and improved tolerability compared with once-monthly dosing. Consequently, the weekly dosing regimen has been selected for further clinical development for the treatment of T2D. A robust phase 3 clinical development programme (AMPLITUDE) is being conducted to establish the benefit–risk profile with efpeglenatide once weekly and to explore fully the dose–response relationship with multiple doses of efpeglenatide once weekly.

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CONFLICT OF INTEREST

S.D.P. has received honoraria from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceutical, Merck Sharp & Dohme, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier and Takeda, and research support from AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme and Novartis. J.K. was an employee of Hanmi Pharmaceutical at the time of research. M.E.T. is a consultant of ProSciento and a shareholder of Eli Lilly, and has received consulting fees from AstraZeneca, Intarcia and Servier. J.S. and C.H.S. are employees and shareholders of Sanofi. M.D. has received honoraria and research support from AstraZeneca, Bayer, Eli Lilly and Sanofi. A.S. has received consulting fees from AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novartis, Novo Nordisk and Sanofi. K-H.Y. has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceutical, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda, and research support from AstraZeneca and Takeda.

AUTHOR CONTRIBUTIONS

S.D.P., M.D. and A.S. contributed to data acquisition, data analysis/interpretation and critical revision of the manuscript for important intellectual content. M.E.T. and J.K. contributed to study conception and design, data analysis/interpretation and critical revision of the manuscript for important intellectual content. J.S., C.H. S. and K-H.Y. contributed data analysis/interpretation and critical revision of the manuscript for important intellectual content. All authors confirm that they meet the International Committee of Medical Journal Editors uniform requirements for authorship and that all authors have read, reviewed and agreed to the final version.

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SUPPORTING INFORMATION

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

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