Received: 16 October 2019 | Revised: 4 March 2020 | Accepted: 11 March 2020

DOI: 10.1111/dom.14032

ORIGINAL ARTICLE

WILEY

Pharmacokinetic and dose-finding studies on efpeglenatide in patients with type 2 diabetes

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Funding information
In November 2015, Sanofi obtained an exclusive license from Hanmi Pharmaceutical for the worldwide development and commercialization of efpeglenatide, an experimental, long-acting diabetes treatment. The single- and repeated-dose studies were conducted by Hanmi Pharmaceutical between May 2010 and May 2013.

Abstract

Aim: To assess the efficacy, safety and pharmacokinetic/pharmacodynamic properties of efpeglenatide, a long-acting glucagon-like peptide-1 receptor agonist, in patients with type 2 diabetes (T2D).

Research design and methods: Two randomized, double-blind, placebo-controlled phase 2 trials were conducted. The single-dose study (n = 48) was a first-in-patient, sequential dose-escalation study. Patients received a single subcutaneous injection of efpeglenatide (2–100 μg/kg) or placebo. The repeated-dose study (n = 71) was a multiple-ascending-dose trial. Patients received weekly (1, 2 or 4 mg once weekly; 8-week period) or monthly (8, 12 or 16 mg once monthly; 9-week period) subcutaneous injections of efpeglenatide or placebo (without titration).

Results: Both studies demonstrated dose-proportional increases in efpeglenatide serum concentrations. The median time to attain maximum serum concentration (t_{max}) for efpeglenatide ranged from 72 to 144 hours in the single-dose study and from 48 to 120 hours in the repeated-dose study (following final dose). Geometric mean $t_{1/2}$ ranged from 135 to 180 hours across studies. Peak-to-trough ratios in the repeated-dose study ranged from 1.3 to 1.4 with once-weekly dosing and from 5.9 to 12.9 with once-monthly dosing. Following a single dose of efpeglenatide 14–100 μg/kg, fasting plasma glucose and postprandial plasma glucose levels were decreased at week 1 and remained below baseline levels for ≥3 weeks post-dosing. Repeated doses of efpeglenatide led to significant reductions in glycated haemoglobin vs placebo. In both studies, efpeglenatide was generally well tolerated. Gastrointestinal disorders were the

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most frequently reported treatment-emergent adverse events in efpeglenatide-treated patients.

Conclusions: The delayed $t_{max,}$ long half-life, and low peak-to-trough ratios observed demonstrate potential for improved efficacy and dosing flexibility, with good tolerability of efpeglenatide in patients with T2D.

KEYWORDS

antidiabetic drug, clinical trial, GLP-1 analogue, pharmacodynamics, pharmacokinetics, type 2 diabetes

1 | INTRODUCTION

Although many new therapeutic options are available for treating patients with type 2 diabetes (T2D), achieving individualized targets remains challenging. For many patients, guidelines now recommend avoidance of hypoglycaemia and weight gain as important therapeutic targets in addition to achieving glycaemic control.[1]

Glucagon-like peptide-1 (GLP-1) is an incretin that also inhibits glucagon secretion, slows gastric emptying by reducing upper gastrointestinal (GI) motility, and suppresses appetite and food intake.[2] Consequently, GLP-1 receptor agonists (GLP-1RAs) are thought to address T2D through several mechanisms. GLP-1RAs improve glycaemic control with a low risk of hypoglycaemia and are associated with weight loss[3–5] as a result of reduced energy intake.[6]

Despite the known risks of undertreatment, adherence to injectable antidiabetic drugs is often poor.[7,8] Reduced dosing frequency could mitigate injection burden and improve patient adherence.[8] Flexible dosing is likely to increase the utility of an injectable treatment for T2D.[9] With this in mind, long-acting GLP-1RAs have been designed to allow for less frequent dosing compared with earlier, short-acting agents,[3,4] and may provide for relatively flexible dosing. However, it is important to note that further reduction of the frequency of administration (eg, biweekly, monthly) of long-acting GLP-1RAs may result in fluctuations in peak-to-trough ratios, which may be associated with an increase in GI adverse events (AEs).[10]

Most GLP-1RAs are administered once or twice daily or once weekly.[3] However, there exists an unmet need for a GLP-1RA with a longer duration of efficacy that could permit less frequent dosing (eg, >1 week) and help facilitate treatment adherence and subsequently improve glycaemic control.[8,11] Long-acting GLP-1RAs administered once weekly could also allow greater dosing flexibility as efficacy may be maintained despite missing a dose.

Efpeglenatide is a long-acting GLP-1RA based on a single amino acid-modified exendin analogue and long-acting peptide/protein technology[12–14]; a subcutaneous (s.c.) once-weekly formulation is under development to improve glycaemic control in patients with T2D. *In vitro*, efpeglenatide exhibits unique GLP-1 receptor engagement properties compared with other GLP-1RAs: efpeglenatide is associated with faster dissociation from the GLP-1 receptor and reduced receptor internalization (allowing more cell-surface receptors to remain available for signalling) and greater accumulation of cyclic adenosine monophosphate and insulinotropic activity compared with liraglutide and dulaglutide following chronic exposure.[13,15] These unique receptor properties could help explain the greater maximal signalling and reduced desensitization seen with efpeglenatide versus other GLP-1RAs following chronic exposure in biochemical and preclinical studies.[13,16]

In the present study, we report the findings of two phase 2 trials that assessed the efficacy, tolerability and pharmacokinetic (PK) and pharmacodynamic (PD) properties of efpeglenatide with escalating single and repeated doses in patients with T2D.

2 | RESEARCH DESIGN AND METHODS

Both phase 2 trials were conducted in compliance with the International Conference on Harmonization for Good Clinical Practice, along with all applicable local regulations. The study protocols and related documents received institutional review board or independent ethics committee approval. All participants provided written, informed consent prior to entering the study.

2.1 | Single-dose study

The single-dose study (EudraCT 2010-019665-28) was a first-in-patient, randomized, double-blind, placebo-controlled, sequential dose-escalation study, conducted at a single site in the Netherlands from May 20, 2010 to April 22, 2011. Eight cohorts of six patients with T2D each received a single s.c. injection of efpeglenatide (2, 4, 8, 14, 20, 40, 60 or 100 μg/kg) or placebo (5:1 ratio), as further described in the Supporting Information (Appendix S1).

The patients were men and women aged 18 to 75 years, with T2D, a fasting plasma glucose (FPG) level <13.3 mmol/L (<240 mg/dL), a glycated haemoglobin (HbA1c) concentration of 42 to 86 mmol/mol (6%–10%) for ≥3 months, and a body mass index ≥25 and ≤40 kg/m^2, who were treated with diet and exercise alone or a stable dose of oral anti-hyperglycaemic drugs (such as metformin with or without a sulphonylurea) for 2 months before screening. Finally, patients had to be willing and able to wash out glucose-lowering

medications for 14 days prior to dosing. Any patient who reported an FPG >13.3 mmol/L during the treatment washout period was advised to restart their prior diabetes medication immediately and was not included in the randomized treatment phase of the study.

The primary objective of the study was to evaluate the safety and tolerability of single, escalating s.c. doses of efpeglenatide in patients with T2D. Secondary objectives were to evaluate PK profiles, dose–response relationships between PK and PD characteristics, and immunogenicity.

Safety and tolerability assessments comprised AE recording, vital signs assessment, 12-lead ECG recording, clinical laboratory measures, and physical examination.

Derived PK parameters included time to attain maximum serum concentration (t_{max}), terminal elimination half-life ($t_{1/2}$), observed maximum serum concentration (C_{max}), area under the serum concentration–time curve up to the last quantifiable concentration ($AUC_{[0-last]}$), and total area under the serum concentration–time curve from time 0 to infinity ($AUC_{[0-inf]}$). PD assessments included 24-hour glucose profiles such as FPG and postprandial plasma glucose (PPG).

2.2 | Repeated-dose study

The repeated-dose study (NCT01452451) was a randomized, double-blind, placebo-controlled, multiple ascending-dose trial, conducted across nine sites in the United States from February 14, 2012 to May 28, 2013. Six cohorts of 12 patients with T2D received s.c. injections of efpeglenatide or placebo, randomized in a 3:1 ratio. Patients received either 1-, 2- or 4-mg once-weekly efpeglenatide over 8 weeks (eight injections) or 8-, 12- or 16-mg once-monthly efpeglenatide over 9 weeks (three injections), with additional follow-up at week 13. No dose titration was applied in any cohort.

Dose cohorts were staggered such that dose escalation could be stopped based on safety and tolerability criteria, including the incidence of vomiting.

Patients were men and women aged 18 to 65 years with T2D, who were required to be receiving a stable dose of metformin for ≥3 months and have an HbA1c concentration of 53 to 86 mmol/mol (7–10%). Key exclusion criteria were: FPG levels >13.3 mmol/L (240 mg/dL) at screening, significant change in body weight (at least 10%) in the 3 months prior to screening and previous treatment with a GLP-1 analogue, prior to insulin use for >1 week within the 3 months before screening, or any insulin within the 2 weeks before screening. Patients were required to have discontinued any anti-hyperglycaemic agents (with the exception of metformin) or incretin therapy 3 months prior to screening, respectively.

The primary objective of the study was to evaluate the safety and tolerability of repeated doses of s.c. efpeglenatide once weekly or once monthly in patients on stable metformin. Secondary objectives were to evaluate the PK and PD profiles after repeat dosing. Schedules of blood sampling are described in Appendix S1.

Change from baseline to week 12 in HbA1c was the primary efficacy endpoint. Other PD assessments included change in FPG and body weight. PPG control was measured through a mixed-meal tolerance test (MMTT), using change in MMTT glucose AUC_{0-2h} (glucose area under the concentration–time curve above baseline from 0 to 2 hours during the MMTT; additional details regarding procedure can be found in Appendix S1). Safety and tolerability assessments included AE recording, vital signs, 12-lead ECG, clinical laboratory measures, immunogenicity, and physical examination.

Please see Appendix S1 for additional methodological details for blood sampling procedures and PD, PK and immunogenicity assays for both studies.

2.3 | Statistical methods for the single- and repeated-dose studies

In both studies, the full analysis set or PD set was used to assess PD variables, and comprised all patients who had received treatment. In the repeated-dose study, this population also included only patients who did not receive an incorrect study treatment at any time during the study, did not take a prohibited concomitant medication during the study, and had at least one PD assessment after dosing. Safety endpoints were assessed using the safety set, which comprised all patients who received any study drug. PK data were evaluated in the PK set, which comprised all patients who received efpeglenatide and had sufficient concentration data for calculation of PK characteristics. In the repeated-dose study, all analyses using the full analysis set grouped patients according to randomized treatment, whereas analyses using the safety or PK set grouped patients according to the most recent treatment actually received.

In the single-dose study, an exploratory analysis of dose proportionality was performed based on log-transformed values of C_{max} and AUC (see Appendix S1 for more details); however, there were no statistical comparisons made between groups. For the repeated-dose study, PD analyses used least squares (LS) mean values based on ANCOVA, with treatment cohort as a main effect and baseline response as a covariate. *P* values were calculated from the ANCOVA model for all efpeglenatide doses versus placebo within weekly and monthly cohorts, with no adjustment for multiple comparisons. Hypothesis tests were two-sided at the 5% significance level.

3 | RESULTS

A total of 48 and 71 patients were randomized and received treatment in the single- and repeated-dose studies, respectively. Patient disposition for both studies is shown in Figure S1. Baseline demographics and characteristics were largely comparable between treatment groups within each study (Table S1). Given the small sample size of the placebo population, there were some differences in sex and race composition of these groups versus the larger pooled efpeglenatide groups in both studies.

3.1 | PK profile

3.1.1 | Single-dose efpeglenatide

There was a dose-proportional increase in efpeglenatide serum concentrations within the 2 to 100 µg/kg dose range (Figure 1A; Table S2). For all dose levels, serum concentrations of efpeglenatide increased slowly after administration. Across doses, the median t_{max} for efpeglenatide ranged from 72 to 144 hours post-dose (Table 1). Geometric mean $t_{1/2}$ ranged from 135 to 180 hours and appeared to be consistent over the dose range studied. Geometric mean C_{max}, $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ clearly indicated a dose-related increase in efpeglenatide concentrations.

3.1.2 | Repeated-dose efpeglenatide

For both the first and final doses of efpeglenatide, higher doses were associated with greater geometric mean serum concentrations of

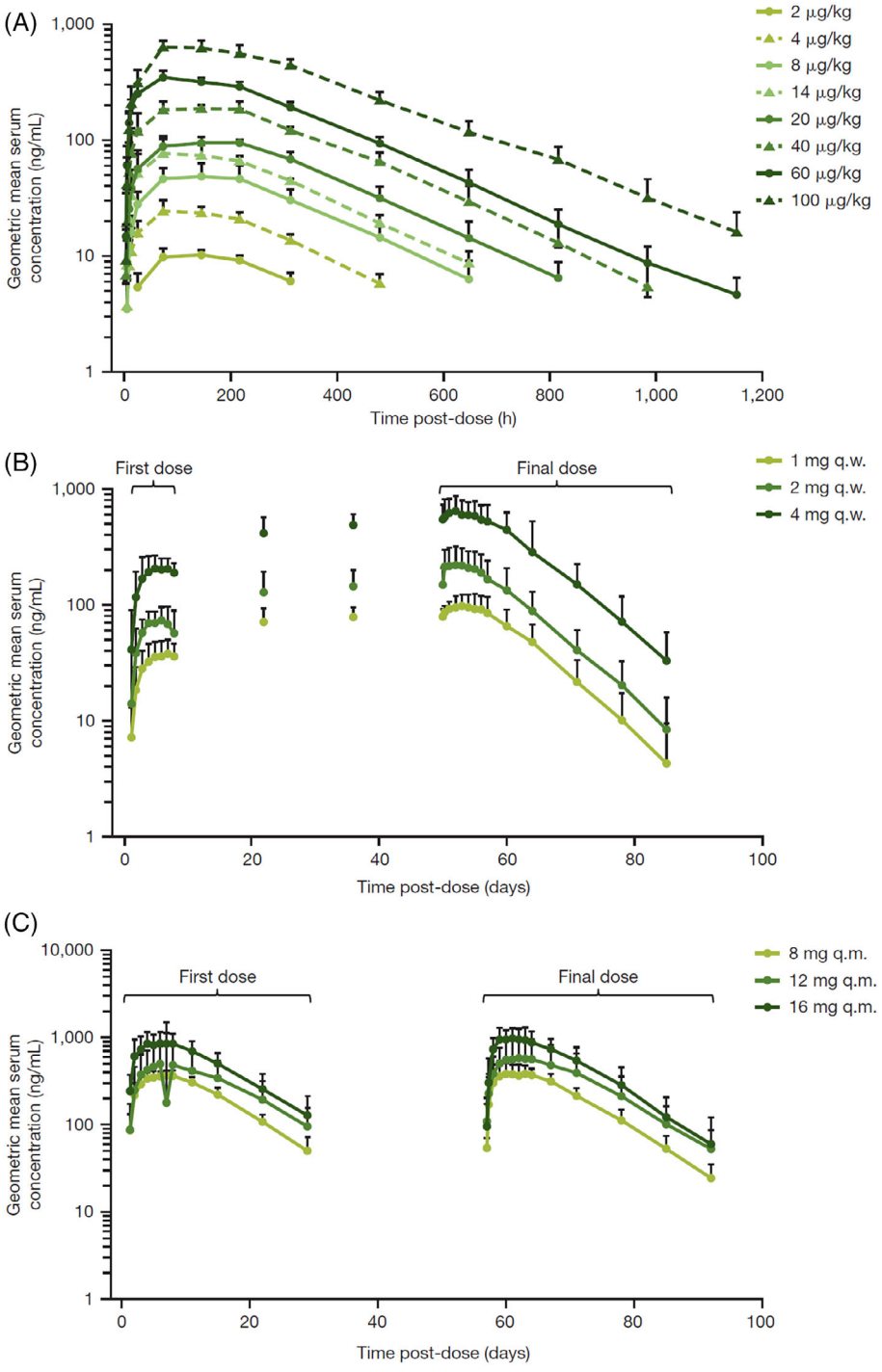

FIGURE 1 Pharmacokinetic (PK) profiles of efpeglenatide after **A**, one dose in the single-dose study and after the first and final doses in the repeated-dose study with **B**, weekly and **C**, monthly dosing (PK set). Abbreviations: PK, pharmacokinetic; q.m., once monthly; q.w., once weekly

TABLE 1 Key pharmacokinetic characteristics of efpeglenatide after a single dose or repeated doses (following final dose)

Single-dose study					
Efpeglenatide dose, μg/kg	**C_{max}, ng/mL**	**t_{max}, h[a]**	**$t_{1/2}$, h**	**$AUC_{(0-last)}$, ng h/mL**	**$AUC_{(0-inf)}$, ng h/mL**
2	10.4 (11)	144.00 (72.06–216.76)	NA	2913 (19)	NA
4	25.7 (16)	72.06 (72.00–216.80)	144 (10)	7911 (12)	9060 (12)
8	45.1 (5)	72.06 (72.00–144.00)	147 (19)	16 842 (11)	17 784 (11)
14	80.3 (28)	144.00 (72.00–216.76)	135 (8)	27 574 (12)	28 781 (12)
20	102 (6)	144.00 (72.00–216.78)	147 (6)	40 149 (10)	41 391 (10)
40	202 (14)	144.00 (72.00–216.78)	141 (10)	78 430 (13)	79 233 (13)
60	349 (13)	72.00 (72.00–144.00)	154 (9)	129 672 (6)	130 793 (6)
100	643 (12)	72.00 (72.00–216.90)	180 (12)	270 829 (13)	275 322 (14)

Repeated-dose study							
Efpeglenatide dose	**C_{max} (ng/mL)**	**t_{max} (h)[a]**	**$t_{1/2}$ (h)**	**$AUC_{(0-last)}$ (ng h/mL)**	**$AUC_{(0-inf)}$ (ng h/mL)**	**Accumulation ratio[bc]**	**PTR[b]**
1 mg once weekly	100.82 (29.6)	71.95 (24.00–119.97)	155.03 (12.0)	35 678.88 (40.4)	37 396.62 (41.2)	3.49 (2.16)	1.40 (0.49)
2 mg once weekly	225.43 (36.5)	72.00 (24.05–96.00)	151.53 (14.9)	74 023.27 (37.8)	76 110.79 (37.8)	3.51 (0.68)	1.42 (0.21)
4 mg once weekly	660.02 (31.1)	48.00 (8.12–96.00)	155.85 (16.2)	234 303.42 (33.5)	242 468.55 (34.8)	3.71 (1.87)	1.32 (0.12)
8 mg once monthly	442.13 (36.6)	120.00 (21.55–168.00)	159.95 (19.4)	154 811.39 (16.3)	161 181.10 (15.4)	1.07 (0.10)	10.35 (7.28)
12 mg once monthly	616.28 (73.9)	95.95 (47.67–168.00)	170.62 (13.3)	256 033.40 (73.2)	269 717.68 (73.0)	1.19 (0.08)	5.86 (1.10)
16 mg once monthly	1016.54 (31.7)	72.05 (44.35–143.88)	161.76 (15.5)	385 341.57 (35.1)	401 556.42 (36.5)	1.13 (0.05)	12.94 (7.55)

Abbreviations: $AUC_{(0-inf)}$, area under the concentration–time curve from time 0 to infinity; $AUC_{(0-last)}$, area under the serum concentration–time curve up to the last quantifiable concentration; C_{max}, observed maximum serum concentration; CV, coefficient of variation; NA, not applicable; PK, pharmacokinetic; PTR, peak-to-trough ratio; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time to attain maximum serum concentration. Data are presented as geometric mean (%CV of the arithmetic mean) except as noted. For the 2 μg/kg dose, it was not possible to calculate $t_{1/2}$ and, therefore, derived values dependent on half-life estimates could also not be calculated.

[a]Median (min, max).

[b]Mean (SD).

[c]Accumulation ratio was defined as ratio of $AUC_{0-\tau}$ from the last dose to $AUC_{0-\tau}$ from the first dose. The value of τ (ie, dosing interval) was 168 and 672 hours for the weekly and monthly cohorts, respectively.

efpeglenatide for both once-weekly (Figure 1B) and once-monthly (Figure 1C) dosing regimens.

After the last dose, the median t_{max} for efpeglenatide ranged from 48 to 72 hours in the once-weekly treatment groups and from 72 to 120 hours in the once-monthly treatment groups (Table 1). Also after the last dose, the geometric mean $t_{1/2}$ was comparable among once-weekly and once-monthly treatment groups, ranging from 152 to 156 hours and from 160 to 171 hours, respectively. With both once-weekly and once-monthly dosing regimens, geometric mean total exposures (AUC) and peak exposures (C_{max}) of efpeglenatide increased with dose. Mean peak-to-trough ratios (calculated as C_{max}/C_{min}) ranged from 1.3 to 1.4 with once-weekly dosing and from 5.9 to 12.9 with once-monthly dosing. Clearance rates are summarized in Table S4.

With weekly dosing, serum concentrations of efpeglenatide generally appeared higher following the final dose compared with the first dose (Figure 1B). Plasma concentrations of efpeglenatide after once-monthly dosing, however, appeared comparable following administration of the first and final doses (Figure 1C). For weekly dosing, mean accumulation ratios (Table 1) ranged from 3.49 to 3.71 across dose groups, indicating mild drug accumulation after weekly administration for 8 weeks. For monthly dosing, mean accumulation ratios ranged from 1.07 to 1.19 across dose groups, indicating no accumulation after monthly dosing for 3 months.

3.2 | PD/efficacy profile

3.2.1 | Single-dose efpeglenatide

Following treatment with a single dose of efpeglenatide 14–100 μg/kg, FPG levels were decreased at week 1 and remained below

baseline levels for at least 3 weeks post-dosing (Figure 2A). Efpeglenatide 2–8 μg/kg was also associated with reductions from baseline over 2 weeks, although these reductions were smaller than those observed for the higher doses (data not shown). PPG levels decreased by the first week and remained below baseline levels for at least 2 weeks following treatment with all single doses of efpeglenatide 14 μg/kg and above (Figure 2B). No notable changes in PPG were seen with efpeglenatide 2–8 μg/kg. There were some small reductions in FPG and PPG levels from baseline over the first 2 to 3 weeks with placebo.

3.2.2 | Repeated-dose efpeglenatide

The HbA1c levels at baseline were comparable across treatment groups (Table S1). Repeated doses of efpeglenatide led to significant LS mean reductions in HbA1c from baseline versus placebo (Figure 3). Significant decreases in HbA1c were observed for each of the once-weekly dose groups compared with placebo at day 29 ($P \leq 0.003$ for all) and at day 57 ($P \leq 0.021$ for all; Figure 3A). Similarly, significant decreases in LS mean HbA1c were observed for all once-monthly dose groups at day 29 ($P \leq 0.047$ for all; Figure 3B). On day 57, there were statistically significant LS mean decreases in HbA1c in patients treated with efpeglenatide 8 and 12 mg once monthly ($P = 0.006$ and $P = 0.015$, respectively); however, the reductions seen with efpeglenatide 16 mg once monthly on day 57 were not statistically significant. In addition, numerically greater proportions of patients treated with efpeglenatide once weekly and once monthly achieved a treatment target of HbA1c <53 mmol/mol (<7.0%) compared with those treated with placebo (Figure 3C,D).

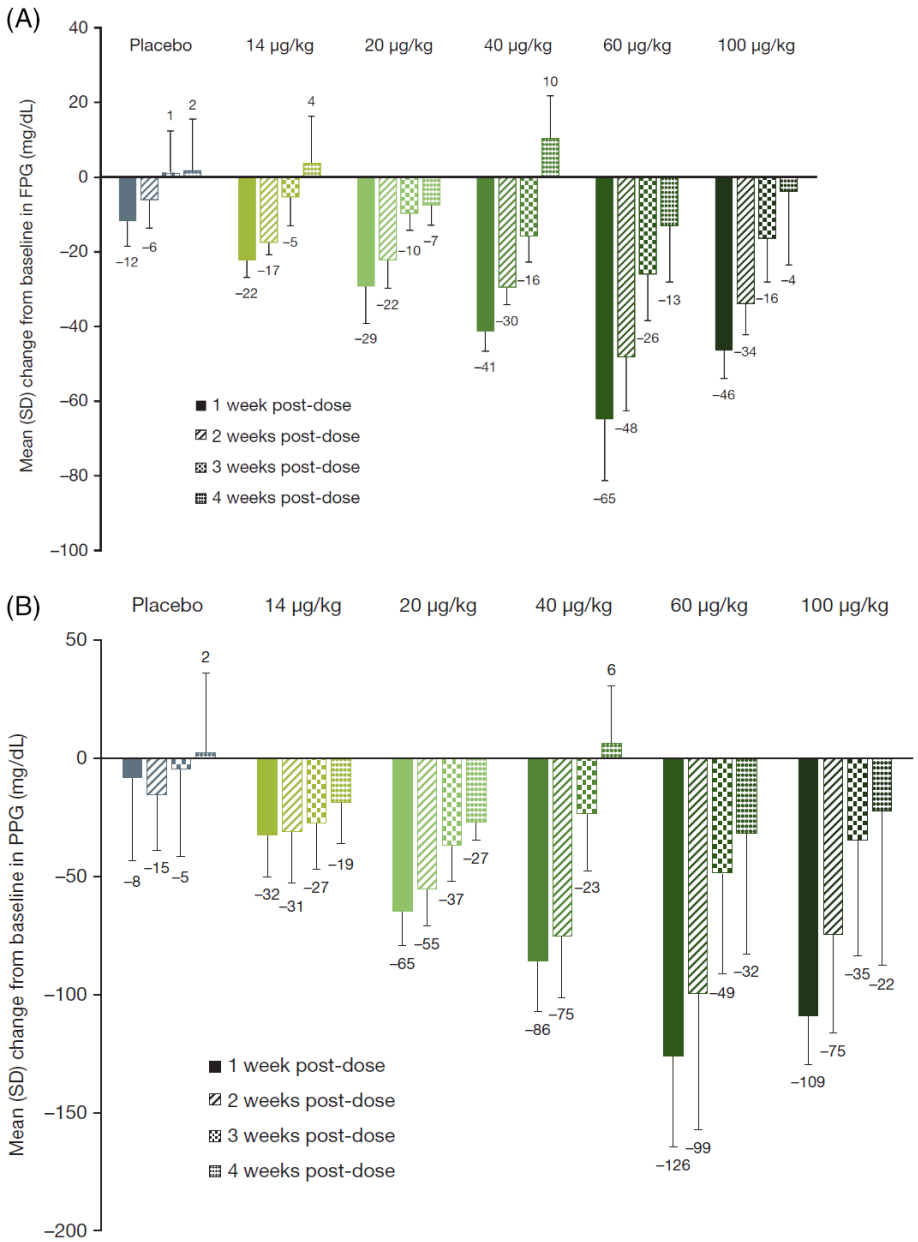

FIGURE 2 Pharmacodynamic (PD) effects of single doses of efpeglenatide on absolute changes from baseline in **A**, fasting plasma glucose (FPG) and **B**, postprandial plasma glucose (PPG) in the single-dose study (PD set)

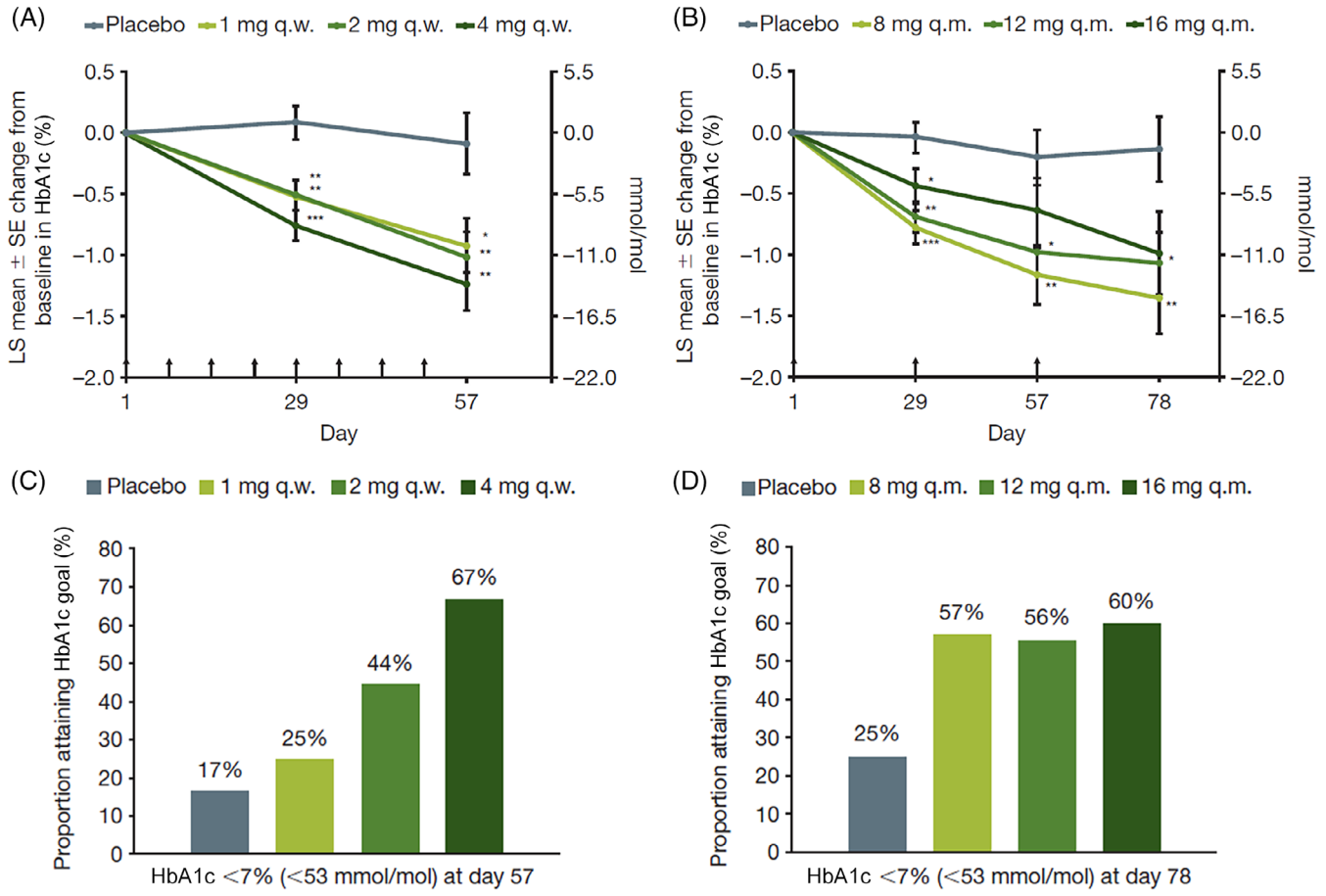

FIGURE 3 Effects of repeated dosing with efpeglenatide on glycated haemoglobin (HbA1c). Change from baseline over dosing period with **A**, weekly and **B**, monthly dosing, and proportion of patients achieving HbA1c treatment target of <53 mmol/mol (<7.0%) on **C**, day 57 after weekly dosing and on **D**, day 78 after monthly dosing in the repeated-dose study (full analysis set). Arrows indicate days of injection. Least squares (LS) mean values based on an ANCOVA with treatment cohort as a main effect and baseline response as a covariate. *P* values were calculated from the ANCOVA model for all efpeglenatide doses vs. placebo within weekly and monthly cohorts, with no multiple comparisons adjustment. **P* <0.05, ***P* <0.01 and ****P* <0.001 vs placebo. q.m., once monthly; q.w., once weekly

Repeated dosing with efpeglenatide was associated with greater LS mean reductions in FPG from baseline versus placebo after final doses, which were statistically significant for the 1- and 4-mg once-weekly and 8-mg once-monthly doses (Table S3).

Effects on PPG were not directly measured in this study. However, no significant differences were found in change in LS mean MMTT glucose AUC_{0-2h} from baseline between efpeglenatide and placebo groups (Table S3).

Statistically significant LS mean reductions in body weight from baseline to after the final dose were seen with repeated dosing at the highest once-weekly and once-monthly doses (Figure S2). In the efpeglenatide 4-mg once-weekly group, a significant LS mean decrease in body weight from baseline was observed on day 57, with a treatment-effect estimate of −2.63 kg (*P* = 0.029), and a corresponding placebo-adjusted percentage change in body weight of −3.29% (*P* = 0.010). In the 16-mg once-monthly group, a significant LS mean decrease in body weight was also observed on day 78, with a treatment-effect estimate of −2.82 kg (*P* = 0.031; placebo-adjusted percentage change of −3.30% [*P* = 0.008]).

3.3 | Safety

3.3.1 | Single-dose efpeglenatide

Overall, 83% of patients (*n* = 40) reported a total of 181 treatment-emergent AEs (TEAEs); 75% of the placebo group (*n* = 6) reported a total of 25 TEAEs, and 85% of patients (*n* = 34) across all efpeglenatide dose groups combined reported 156 TEAEs. There were no deaths or serious AEs reported during the study, and no TEAEs resulted in study discontinuation.

Overall, the most frequently reported TEAEs were GI disorders, which occurred in 56% of patients (73 events in 27 patients), including diarrhoea (17 events in 14 patients [29%]) and flatulence (11 events in 10 patients [21%]). TEAEs of nausea and vomiting occurred, respectively, in 17% and 6% of patients treated with efpeglenatide. No patient in the placebo group had TEAEs of nausea or vomiting. General disorders and administration-site conditions occurred in 40% of patients (29 events in 19 patients), with 10% of patients reporting injection-site pain (five events in five

patients) and 8% reporting catheter-site pain (five events in four patients).

Seventy-eight TEAEs reported by 24 patients (50%) were considered to be related to the study medication. Drug-related TEAEs reported most frequently were diarrhoea (12 events) and headache (10 events).

Most TEAEs were mild in severity. A total of 22 moderate TEAEs, and no severe TEAEs, were reported. Moderate TEAEs that were considered related to study medication (eight events in five patients [10%]) occurred in the higher dose groups (20–100 μg/kg efpeglenatide). The incidence of drug-related TEAEs was higher with the two highest doses of efpeglenatide (60 and 100 μg/kg; 42 events in nine patients) versus the lower-dose levels (2–40 μg/kg; 26 events in 12 patients) and placebo (10 events in three patients).

There were no clinically relevant abnormalities in vital signs, clinical laboratory assessments (including amylase, lipase, liver enzymes and haematological variables) and physical examinations, and no signs of arrhythmia or ECG changes due to QTc prolongation or conduction disorders were observed with efpeglenatide.

No incidences of hypoglycaemia or pancreatitis were reported as AEs in any treatment group. No patient treated with efpeglenatide developed anti-efpeglenatide antibodies.

3.3.2 | Repeated-dose efpeglenatide

The percentage of patients reporting AEs was lower in the efpeglenatide groups (68.6%, both once-weekly and once-monthly groups combined; *n* = 35/51 patients) compared with placebo (83.3%; *n* = 15/18 patients). GI disorders such as nausea were the most frequently reported TEAEs in efpeglenatide-treated patients. AEs considered to be drug-related, as assessed by the investigator according to definitions provided in the study protocol, occurred in 49.0% (97 events in 25 patients) of the overall efpeglenatide-treated group and in 55.6% (28 events in 10 patients) of the placebo group. The most common drug-related AEs were nausea and vomiting, experienced by 33.3% (31 events in 17 patients) and 17.6% (18 events in nine patients) of patients, respectively, in the combined efpeglenatide group and by 27.8% (seven events in five patients) and 11.1% (four events in two patients) of patients, respectively, in the combined placebo group.

Incidences of nausea and vomiting events were low in the efpeglenatide once-weekly groups (Figure S3). The overall incidences of nausea and vomiting were similar in the efpeglenatide once-weekly and placebo groups; however, the incidence appeared to increase with higher doses of efpeglenatide, with the highest incidence reported with 16 mg once monthly. The efpeglenatide 16-mg once-monthly cohort reached the predefined stopping criteria for dose escalation in the study as there were more than three patients with moderate vomiting.

Overall, most AEs in the placebo and efpeglenatide groups were mild or moderate in intensity. Severe AEs were reported for one patient each in the placebo (5.6%) and efpeglenatide groups (2.0%; 16 mg once monthly), none of which were considered to be related to the study treatment.

There was no significant change from baseline in haematological, serum chemistry or urine analysis variables for any treatment group. In general, vital signs remained stable over time. A total of four patients treated with efpeglenatide had anti-efpeglenatide antibodies at baseline (once-weekly cohort: 1/27 [3.7%]; once-monthly cohort: 3/24 [12.5%]). However, none of these patients developed treatment-emergent or treatment-induced antibodies. In terms of other TEAEs of special interest, hypoglycaemia as an AE was only reported in one patient treated with efpeglenatide (4 mg once weekly group; 1/51 [2.0%]), and no cases of pancreatic injury were reported in any patient receiving efpeglenatide.

4 | DISCUSSION

Efpeglenatide demonstrated a dose-proportional PK profile, with an extended half-life and slow absorption in patients with T2D. The PK and PD results of repeated weekly doses of efpeglenatide also revealed a low peak-to-trough ratio that permits weekly dosing. There is evidence to suggest that GLP-1RA dosing regimens with lower peak-to-trough ratios may be associated with fewer fluctuations in FPG and fewer GI AEs.[10]

Single doses of efpeglenatide 14–100 μg/kg had beneficial effects on FPG and PPG that lasted for up to 3 weeks post-dose. In the repeated-dose study, both efpeglenatide once monthly and once weekly demonstrated statistically significant reductions in HbA1c in patients with T2D compared with placebo. Reductions in FPG were not consistently statistically significant, although reductions in FPG from baseline were significantly greater than placebo for the 1- and 4-mg once-weekly and 8-mg once-monthly doses. In addition, the highest doses of efpeglenatide once weekly and once monthly were associated with significant reductions in body weight.

The efficacy and safety of efpeglenatide in patients with T2D have been examined further in the EXCEED 203 (NCT02057172) and LIBERATE 204 (NCT02081118) phase 2 studies.[17,18] Top-line results from these studies were consistent with the findings of the dose-ranging studies presented here.

The impact of greater doses of efpeglenatide on HbA1c seemed to vary between the weekly and monthly dosing regimens. In the weekly dosing groups, higher efpeglenatide doses seemed to be associated with greater reductions in HbA1c, yet in the monthly dosing groups the opposite trend was observed. However, variability was relatively high, as evidenced by the overlapping SE bars in Figures 3A and B, so it is not clear whether these are truly distinct results, and no inferential statistics were used to compare the efpeglenatide doses to each other, so it is difficult to draw any specific conclusions. The significance of this finding is unclear as the proportion of patients achieving glycaemic targets appeared comparable across monthly dosing groups (Figure 3D), and similar results were not observed in the LIBERATE 204 study, which examined the same monthly doses of

efpeglenatide as in the present studies, but over a longer period of time.

In the two studies reported here, efpeglenatide was generally well tolerated in patients with T2D, whether administered as single doses or repeated weekly or monthly doses. In both studies, GI disorders such as nausea were the most frequently reported TEAEs in efpeglenatide-treated patients. Particularly with once-weekly dosing, however, the incidence of GI side effects decreased over time. It is important to note that no slow dose introduction or dose titration was used in this study; starting GLP-1RAs at lower doses and increasing over time substantially reduces GI AEs.[19–22] The safety profile for efpeglenatide observed in these studies was consistent with the known effects of GLP-1 RAs.[23–25] In addition, hypoglycaemia was not reported in the single-dose study, and was only reported in one patient in the repeated-dose study. Finally, the absence of treatment-induced antibodies suggests that efpeglenatide has a low immunogenic potential compared with other exendin-based GLP-1 RAs.[26–28]

As expected, the ranges of t_{max} and $t_{1/2}$ for efpeglenatide (once weekly and once monthly) indicated by the repeated-dose study are substantially longer than those reported in the literature for the GLP-1RAs that are dosed once daily (Table S4).[25] Compared with the longer-acting GLP-1RAs (ie, those dosed once weekly), the range of t_{max} observed for efpeglenatide was either comparable to or longer than those reported. The t_{max} for efpeglenatide once weekly and once monthly occurred approximately 2 to 3 days and 3 to 5 days after dosing, respectively. The reported t_{max} values for albiglutide and dulaglutide (other once-weekly GLP-1RAs) ranged from 1 to 4 days. The estimated $t_{1/2}$ values for efpeglenatide once weekly and once monthly were approximately 6 days and 6 to 7 days, respectively, which were within the ranges reported for albiglutide, dulaglutide and semaglutide (5–8 days).[6,25,29]

As with similar PK and dose-finding studies, the limitations of this study included duration and sample size. As these were short-term studies, they do not provide information regarding long-term efficacy. In addition to the low sample sizes, which limit the statistical power to make multiple comparisons, the patients included do not necessarily reflect the real-world population of patients with diabetes. Overall, however, efpeglenatide has been shown to have a dose-proportional PK profile with a low peak-to-trough ratio with efpeglenatide once weekly that supports its potential clinical efficacy, safety and tolerability in patients with T2D.

In conclusion, both single and repeated doses of efpeglenatide were effective and well tolerated across the doses and dosing regimens investigated. Efpeglenatide once weekly was associated with a long, flat PK curve; this suggests a reduced potential for AEs, as a low peak-to-trough ratio and maintenance of drug serum levels may be associated with improved tolerability. The observed PK/PD profile of efpeglenatide could also support a flexible dosing frequency because of its slow elimination and prolonged duration of action. Therefore, the findings from these randomized PK and dose-ranging studies demonstrate the potential for improved efficacy and dosing flexibility with efpeglenatide in patients with T2D. Tolerance may be further improved by a titration regimen with lower introductory doses. This evidence supports further development of efpeglenatide once weekly to improve glycaemic control in patients with T2D.

ACKNOWLEDGMENTS

Editorial assistance was provided by Jennifer Steeber, PhD, of Caudex (New York, NY, USA) and was funded by Sanofi. The authors thank the investigators and patients who participated in this study.

CONFLICTS OF INTEREST

K-H.Y. has served as a consultant for Novo Nordisk and MSD, and has received honoraria as a speaker from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceutical, MSD, Novo Nordisk, Sanofi and Takeda, and research support from AstraZeneca and Takeda. J.K. was an employee of Hanmi Pharmaceutical at the time the research was conducted and the manuscript developed. S.C.K. is an employee of Hanmi Pharmaceutical. M.E.T. has served as a consultant for AstraZeneca, Intarcia, ProSciento and Servier, and is a shareholder of Eli Lilly. M.H. is an employee and shareholder of ProSciento. J.S. and C.H.S. are employees and shareholders of Sanofi.

AUTHOR CONTRIBUTIONS

K-H.Y., M.E.T., M.H., J.S. and C.S.H. contributed data analysis/interpretation and critical revision of the manuscript for important intellectual content. J.K. and S.C.K. contributed study conception and design, 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.

How to cite this article: Yoon K-H, Kang J, Kwon SC, et al. Pharmacokinetic and dose-finding studies on efpeglenatide in patients with type 2 diabetes. *Diabetes Obes Metab*. 2020;22:1292–1301. https://doi.org/10.1111/dom.14032