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RESEARCH LETTER

WILEY

CGM-derived efficacy and overall safety of once-weekly insulin efsitora alfa (efsitora) relative to day of administration in adults with type 2 diabetes

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1 | BACKGROUND

As type 2 diabetes (T2D) progresses, the addition of basal insulin to a treatment regimen is often needed to maintain glycaemic control. However, daily basal insulins, which require at least 365 injections per year, can negatively impact treatment adherence and increase the perceived burden associated with diabetes management. Once-weekly basal insulins have the potential to reduce treatment burden and positively impact adherence and glycaemic control.[1,2]

Insulin efsitora alfa (efsitora), a once-weekly basal insulin, has a flat pharmacokinetic (PK) profile with a peak-to-trough ratio of 1.16, similar to physiological insulin profiles.[3] Efsitora also showed a consistent glucose-lowering effect across the week during a euglycaemic clamp study. Phase 3 efsitora studies demonstrated similar efficacy and safety profiles compared to the once-daily basal insulin comparators in adults with T2D.[4–7] The consistency of glucose control and safety between weekly injections of basal insulin has not been characterised for the efsitora T2D phase 3 study populations.

This post-hoc analysis aimed to assess the impact of the flat efsitora PK and pharmacodynamic (PD) profiles on time in glucose range and rates of hypoglycaemia across the week, in adults with T2D.

2 | METHODS

This post-hoc analysis assessed the glycaemic efficacy and hypoglycaemic rates across the week using data from participants treated with efsitora in three phase 3 trials in adults with T2D: QWINT-2

(insulin naïve), QWINT-3 (basal insulin-treated), and QWINT-4 (basal and prandial insulin-treated). The primary methods and results from these trials were published previously.[4–6,8]

Participants were randomised to receive weekly efsitora or the daily basal insulin comparator (QWINT-2 and QWINT-3: degludec; QWINT-4: glargine) to reach a target fasting glucose (FG) concentration of 4.4–6.6 mmol/L (80–120 mg/dL). Efsitora was administered subcutaneously once weekly, and titrated weekly for the first 12 weeks and a minimum of monthly thereafter. The daily basal insulin comparator was administered daily and titrated weekly based on a titration algorithm. Titration of efsitora and the daily basal insulin comparators was based on the median of the three most recent self-monitored FG values and the occurrence and severity of hypoglycaemia.[8]

QWINT-2, QWINT-3, and QWINT-4 had 52-, 78-, and 26-week treatment periods, with primary endpoints at week 52, 26, and 26, respectively. Periodic 4-week masked continuous glucose monitoring (CGM) sessions were included in the three studies to characterise the 24-h glycaemic control over time.

For each trial, metrics from intermittent masked CGM data collections (time in range [TIR; 3.9–10.0 mmol/L (70–180 mg/dL)], time below range [TBR: <3.0 mmol/L (54 mg/dL) or 3.0–3.9 mmol/L (54–70 mg/dL)], and time above range [TAR: 10.0–13.9 mmol/L (180–250 mg/dL) or >13.9 mmol/L (250 mg/dL)]), were calculated relative to the day of efsitora administration (Day 0). The daily insulin comparator CGM metric data were derived such that the first day of the CGM session was considered 'Day 0' and the successive days of the CGM session represented Days 1–6 and repeated until the end of the session. Because CGM was not conducted during the entire treatment duration, participant-reported events of hypoglycaemia based on self-monitored blood glucose were analysed to characterise the overall rate of hypoglycaemia during the entire treatment period. The rate of combined level 2 (<54 mg/dL; 3.0 mmol/L) or level 3 (severe) participant-reported hypoglycaemia was analysed relative to the day of efsitora administration for the entire treatment period.

Summary statistics are provided.

3 | RESULTS

3.1 | Participant demographics

Participant demographics for QWINT-2 ($N = 928$), QWINT-3 ($N = 986$), and QWINT-4 ($N = 730$) were reported previously.[4–6] All three trials included adults with T2D, with a mean duration of diabetes of 11.6, 15.3, and 16.7 years for QWINT-2, QWINT-3, and QWINT-4, respectively. Baseline HbA1c values were similar between treatment arms in each study at 8.2%, 7.8%, and 8.2%, respectively. There were no notable differences in baseline characteristics between treatment arms within each trial.

3.2 | CGM metrics

In all three studies, there was consistent TIR for efsitora, across the week relative to the day of administration during the CGM session conducted in the 4 weeks prior to the primary endpoint (Figure 1). Between weeks 48 and 52 in QWINT-2, the percent TIR for efsitora ranged from 69.0% to 71.8% for each day across the week. For QWINT-3, the percent TIR between weeks 22 and 26 ranged from 62.2% to 63.5%. For QWINT-4, the percent TIR between weeks 22 and 26 ranged from 61.1% to 62.3%. The TBR (level 1 and level 2) was consistently low and similar to the daily basal insulin comparator for the three studies. Similar to the overall study populations, in the subgroup of participants who achieved the recommended target of >70% TIR over 24 h, TBR was similar across the week and well below recommended consensus guidelines (Figures S1–S3).

3.3 | Rates of hypoglycaemia

The participant-reported combined level 2 or 3 hypoglycaemia rates were consistent across the week for the treatment period of each trial (Figure 2). Rates of level 2 or 3 hypoglycaemia were less than one event/participant/year throughout the week for both efsitora and degludec in QWINT-2 (efsitora range: 0.47–0.65 vs. degludec: 0.30–0.54 event/participant/year) and QWINT-3 (efsitora: 0.60–0.99 vs. degludec: 0.58–0.85 event/participant/year). For QWINT-4, the rates of hypoglycaemia were comparable between participants treated with efsitora and glargine (efsitora: 5.1–6.5 vs. glargine: 5.0–5.7 events/participant/year).

4 | DISCUSSION

Efsitora treatment resulted in consistent TIR and TBR throughout the week, relative to the day of administration, for adults with T2D. The rates of combined level 2 or 3 hypoglycaemia were also consistent across the week for efsitora, and hypoglycaemia was well below the guideline-recommended target of <4% TBR (<70 mg/dL; 3.9 mmol/L) throughout the week.[9] Overall, these findings indicate that once-weekly efsitora provides safe and steady glycaemic control between doses.

These data complement the flat PK and PD profiles of efsitora,[3] as well as the reductions in HbA1c and the observed low rates of hypoglycaemia in the phase 3 trials.[4–7] The consistent efficacy and safety data throughout the week may provide reassurance for healthcare providers and individuals with diabetes who are considering use of once-weekly efsitora. Future real-world data may provide insight into how the consistency of once-weekly efsitora on glycaemic parameters and the reduced frequency of injections impact the perceived treatment burden for patients with T2D.

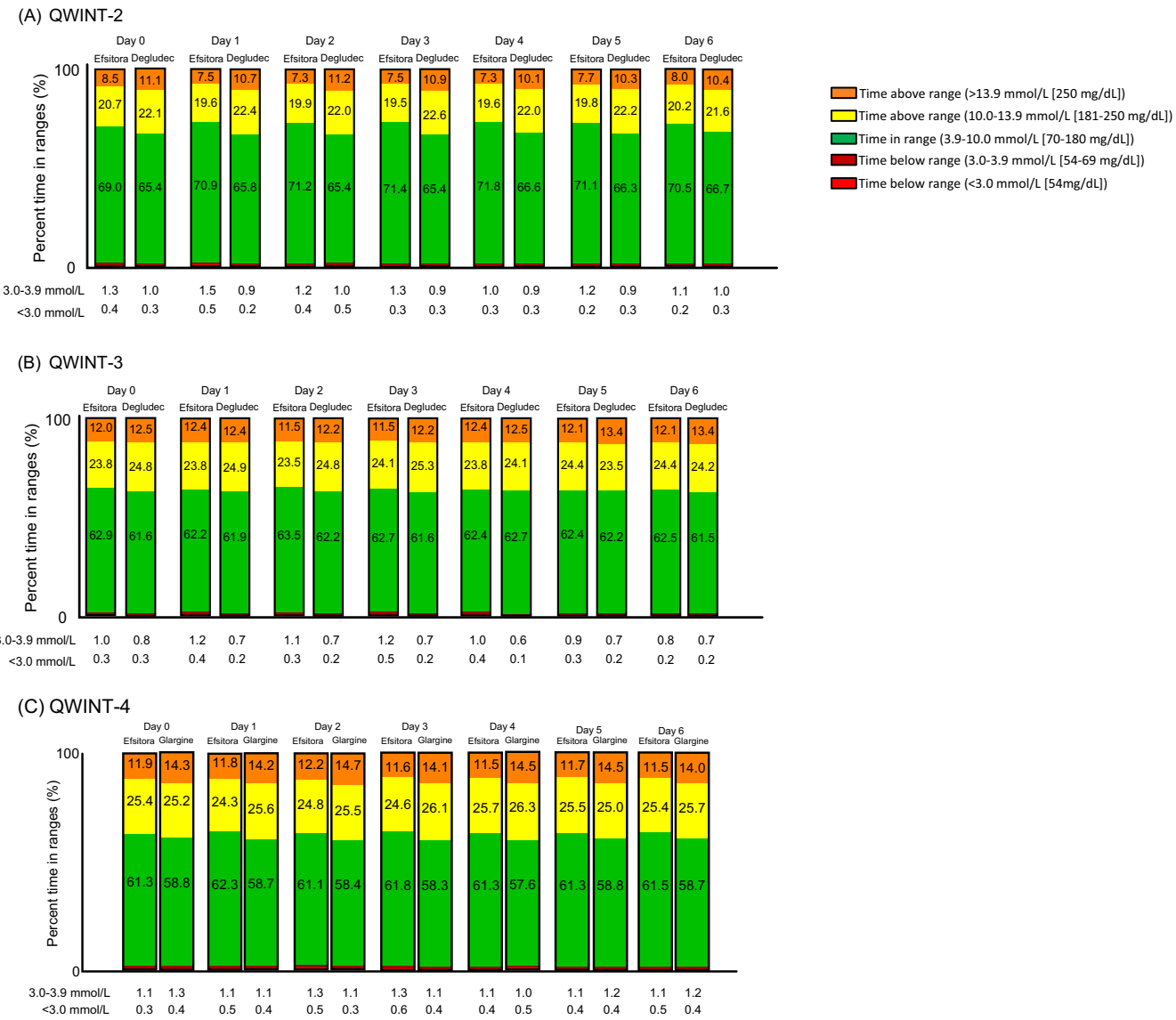

FIGURE 1 Masked CGM parameters by day. The mean percentage of time spent in glucose ranges over the course of the week (Days 0 to Day 6) during the CGM session prior to the primary endpoint for (A) QWINT-2– weeks 48–52, (B) QWINT-3 – weeks 22–26, and (C) QWINT-4 – weeks 22–26. For efsitora, Day 0 corresponds to the day of administration, while Days 1 to 6 indicate 1- to 6-days post-administration, respectively, during the CGM session. For the daily basal comparator, Day 0 represents the first day of the CGM session, with Day 0 to Day 6 repeating until the conclusion of the CGM session. The mean percentage of time spent in hypoglycaemic ranges (3.0–3.9 mmol/L and <3.0 mmol/L) for each day is presented below the figure. CGM, continuous glucose monitoring.

5 | LIMITATIONS

While these data provide valuable insights into the consistency of efsitora glycaemic control throughout the week, the CGM data were not continuous throughout the treatment period. Furthermore, the achievement of >70% TIR for the trial participants was constrained by the fact that the studies were designed as basal-insulin non-inferiority studies rather than TIR optimisation studies. However, the subgroup analyses indicate that the TBR for participants who achieved the recommended target of >70% TIR over 24 h was still below the consensus guideline-based recommendations. Furthermore, trial exclusion criteria limited the use of noninsulin glucose-lowering agents to those less likely to contribute to hypoglycaemia, such as excluding sulfonylureas in QWINT-3 and -4. Both these factors potentially impacted the reported rates of level 2 or 3 hypoglycaemia.

6 | STRENGTHS

These limitations were balanced by the strengths of this post hoc analysis. Namely, the trials included both insulin degludec and glargine as active comparators, and the masked CGM sessions were conducted at multiple time points for each study. The masked CGM prevented potential bias of participants proactively treating a hypoglycaemia alert. Additionally, the large global populations of participants at various stages of diabetes treatment included in the trials lend to the

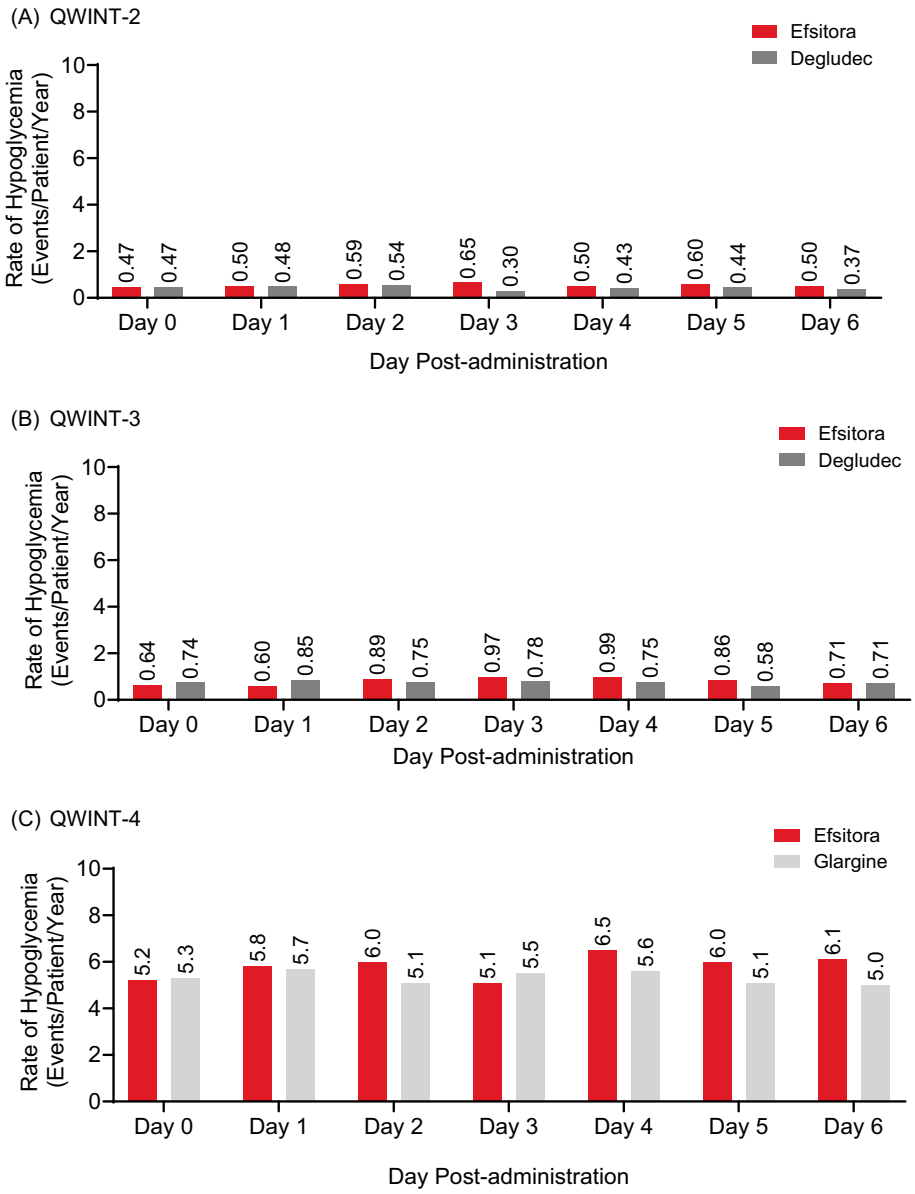

FIGURE 2 Rates of combined level 2 or level 3 hypoglycaemia. The mean aggregate rate per year of combined level 2 or level 3 hypoglycaemia over the course of the week for the treatment period for (A) QWINT-2 – 52 weeks, (B) QWINT-3 – 78 weeks, and (C) QWINT-4 – 26 weeks. For efsitora, Day 0 corresponds to the day of administration, while Days 1 to 6 indicate 1- to 6-days post-administration, respectively, for the treatment period. If the interval between 2 injections was longer than 7 days, the days after Day 6 were not counted. For the daily basal comparator, Day 0 represents the visit day, with Day 0 to Day 6 repeating until the subsequent visit for the treatment period.

generalisability of the results. Finally, the FG targets were within the recommended guidelines for these populations.

7 | CONCLUSION

Adults with T2D treated with efsitora, regardless of prior insulin experience, demonstrated consistent glycaemic control and rates of hypoglycaemia throughout the week. This post-hoc analysis indicates that efsitora is a safe and steady alternative to current daily basal insulin therapies with the potential to reduce treatment burden.

AUTHOR CONTRIBUTIONS

Thomas Martens, Rebecca J. Threlkeld, Xiaoqi Li, Ada Leticia Murro, Kristen Syring, and Vidhi Patel were involved in the study design and data analyses. Xiaoqi Li conducted the statistical analysis. All authors participated in the interpretation of study results and in the critical revision and approval of the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Thomas Martens reported grants from Abbott, Dexcom, Insulet, Lilly, Medtronic, Novo Nordisk, Sanofi, and Tandem during the conduct of the study as well as grants from Medscape, a patent for an ambulatory glucose profile CGM visualisation format pending, and a salary from

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable request to the corresponding author.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees overseeing the phase-3 studies upon which this post-hoc analysis was based (QWINT-2, QWINT-3 and QWINT-4) and have been previously reported.[4–6] All procedures performed were conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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REFERENCES

1. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381(9861):117-124.
2. Qiao Q, Ouwens MJ, Grandy S, Johnsson K, Kostev K. Adherence to GLP-1 receptor agonist therapy administered by once-daily or once-weekly injection in patients with type 2 diabetes in Germany. *Diabetes Metab Syndr Obes*. 2016;9:201-205.
3. Leohr J, Klein O, Heise T, et al. 802-P: steady-state pharmacokinetics and glucodynamics of once-weekly insulin efsitora alfa (efsitora) in individuals with type 2 diabetes (T2D). *Diabetes*. 2025;74(Supplement_1):802.
4. Blevins T, Dahl D, Pérez Manghi FC, et al. Once-weekly insulin efsitora alfa versus once-daily insulin glargine U100 in adults with type 2 diabetes treated with basal and prandial insulin (QWINT-4): a phase 3, randomised, non-inferiority trial. *Lancet*. 2025;405(10497):2290-2301.
5. Philis-Tsimikas A, Bergenstal RM, Bailey TS, et al. Once-weekly insulin efsitora alfa versus once-daily insulin degludec in adults with type 2 diabetes currently treated with basal insulin (QWINT-3): a phase 3, randomised, non-inferiority trial. *Lancet*. 2025;405(10497):2279-2289.
6. Wysham C, Bajaj Harpreet S, Del Prato S, et al. Insulin efsitora versus degludec in type 2 diabetes without previous insulin treatment. *N Engl J Med*. 2024;391(23):2201-2211.
7. Rosenstock J, Bailey T, Connery L, et al. Weekly fixed-dose insulin efsitora in type 2 diabetes without previous insulin therapy. *N Engl J Med*. 2025;393(4):325-335.
8. Bergenstal RM, Philis-Tsimikas A, Wysham C, et al. Once-weekly insulin efsitora alfa: design and rationale for the QWINT phase 3 clinical development programme. *Diabetes Obes Metab*. 2024;26(8):3020-3030.
9. Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol*. 2023;11(1):42-57.

SUPPORTING INFORMATION

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

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