ORIGINAL ARTICLE

Weekly Fixed-Dose Insulin Efsitora in Type 2 Diabetes without Previous Insulin Therapy

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ABSTRACT

BACKGROUND

In previous treat-to-target trials, adjustments to the dose of basal insulin have been made at least weekly, according to fasting blood glucose levels. A fixed-dose regimen of insulin efsitora alfa (efsitora), a once-weekly basal insulin, may provide a benefit in adults with type 2 diabetes who have not received previous insulin therapy.

METHODS

We conducted a 52-week, phase 3, open-label, treat-to-target trial involving adults with type 2 diabetes who had not previously received insulin therapy. Participants were randomly assigned in a 1:1 ratio to receive once-weekly efsitora or once-daily insulin glargine U100 (glargine). Treatment with efsitora was initiated as a single dose of 100 U administered once weekly, with dose adjustments made every 4 weeks, as needed, at fixed doses of 150, 250, and 400 U to achieve fasting blood glucose levels of 80 to 130 mg per deciliter. Doses of glargine were adjusted weekly or more often according to a standard algorithm to reach the same glycemic goals. The primary end point, tested for noninferiority (noninferiority margin, 0.4 percentage points), was the change from baseline in the glycated hemoglobin level at 52 weeks.

RESULTS

A total of 795 participants underwent randomization. The mean glycated hemoglobin level decreased from 8.20% at baseline to 7.05% at week 52 with efsitora (least-squares mean change, −1.19 percentage points) and from 8.28% to 7.08% with glargine (least-squares mean change, −1.16 percentage points); the estimated between-group difference of −0.03 percentage points (95% confidence interval [CI], −0.18 to 0.12) confirmed the noninferiority of efsitora to glargine. Superiority was not shown (P=0.68). The rate of combined clinically significant hypoglycemia (glucose level, <54 mg per deciliter) or severe hypoglycemia (level 3; requiring assistance for treatment) was lower with efsitora than with glargine (0.50 events per participant-year of exposure with efsitora vs. 0.88 with glargine; estimated rate ratio, 0.57 [95% CI, 0.39 to 0.84]). At week 52, the mean total weekly insulin dose was 289.1 U per week with efsitora and 332.8 U per week with glargine (estimated between-group difference, −43.7 U per week; 95% CI, −62.4 to −25.0); the median number of dose adjustments needed was 2 with efsitora and 8 with glargine.

CONCLUSIONS

In adults with type 2 diabetes who had not previously received insulin, once-weekly efsitora, administered in a fixed-dose regimen, was noninferior to once-daily glargine in reducing glycated hemoglobin levels. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT05662332.)

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*A complete list of investigators in the QWINT-1 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 22, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2502796

Treatment guidelines recommend that patients with type 2 diabetes should receive basal insulin when noninsulin glucose-lowering agents maintain glycemic control inadequately.[1,2] Thus far, basal insulin regimens in treat-to-target, randomized, controlled trials have used traditional dosing algorithms, with dose adjustments made at least once per week according to fasting blood glucose levels. Such regimens are often ineffective in clinical practice owing to their complexity and result in therapeutic inertia (i.e., delayed intensification of insulin therapy) and chronic hyperglycemia.[3] In addition, daily injections of basal insulin can be burdensome for many patients.[4] Once-weekly basal insulin in a fixed-dose regimen with a straightforward method of administration might facilitate and simplify insulin treatment, lessen the injection burden, and possibly reduce the therapeutic inertia seen with initiation of basal insulin therapy and subsequent dose adjustments. In addition, fixed dosing is advantageous owing to the existing familiarity with the widely used once-weekly single dosing of incretin-based therapies, which are recommended as first-line injectable treatment for patients with type 2 diabetes.[1,2]

Insulin efsitora alfa (efsitora) is a basal insulin with a flat pharmacokinetic profile and long half-life that allows for once-weekly administration. The QWINT (once-weekly [QW] insulin therapy) phase 3 program evaluated efsitora as compared with once-daily insulin degludec (degludec) or insulin glargine U100 (glargine) across a range of patients with diabetes.[5] In the QWINT-2 trial involving adults with type 2 diabetes who had not previously received insulin therapy, once-weekly efsitora, administered in a standard flexible dosing regimen, showed improvements in glycemic control and rates of clinically meaningful hypoglycemia that were similar to those with degludec.[6]

The current trial, QWINT-1, investigated the efficacy and safety of once-weekly efsitora in a straightforward, fixed-dose regimen, administered with the use of autoinjectors containing a single fixed dose, as compared with once-daily glargine in a flexible dosing regimen, both in combination with noninsulin glucose-lowering agents, in adults with type 2 diabetes who had not previously received insulin.

Methods

Trial Design

This phase 3, open-label, treat-to-target, randomized, controlled trial was conducted at 71 sites in Argentina, Mexico, and the United States. The trial comprised a 3-week screening and lead-in period, a 52-week treatment period, and a 5-week safety follow-up period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference for Harmonisation. The protocol was approved by the institutional review board at each site and is available with the statistical analysis plan at NEJM.org. All the patients provided written informed consent.

The sponsor (Eli Lilly) designed the trial and conducted site monitoring, data collation, and data analysis. The investigators were responsible for data collection; all the authors had access to the data and the data analysis. The first draft of the manuscript was written by the first author and authors employed by the sponsor. The authors critically reviewed the manuscript, approved the manuscript submission for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Adults (≥18 years of age) with type 2 diabetes who had not previously received insulin and who had a glycated hemoglobin level of 7.0 to 10.0% and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 45.0 or lower were eligible to participate in the trial if they had received stable treatment with one to three noninsulin glucose-lowering agents for at least 3 months before screening. Full inclusion and exclusion criteria are provided in Table S1.

Procedures

Participants were randomly assigned in a 1:1 ratio, with the use of an interactive Web-response system, to receive efsitora or glargine. Randomization was stratified according to country, glycated hemoglobin level at screening (<8% or ≥8%),

and the use of glucagon-like peptide-1 (GLP-1) receptor agonist (yes or no). Participants continued treatment with stable doses of noninsulin glucose-lowering agents during the lead-in and treatment periods, although dose adjustments were allowed for safety or because of the risk of hypoglycemia.

Treatment with efsitora was started at a fixed weekly dose of 100 U, administered subcutaneously with a single-dose 0.5-ml prefilled pen injector (autoinjector). The dose could be escalated after 4 weeks, as needed, to the next higher weekly dose of 150, 250, or 400 U, administered with the use of corresponding single-dose 0.5-ml autoinjectors (Fig. 1). The fixed doses of efsitora were determined on the basis of simulation outputs, input from experts on treat-to-target strategies in patients with diabetes, and data analytics on real-world insulin doses used. Dose adjustments were based on the median of the three most recent fasting blood glucose values in the preceding 7 days to achieve a target of 80 to 130 mg per deciliter (4.4 to 7.2 mmol per liter) (Tables S2 and S3A) or in response to hypoglycemia (Table S4A). After receiving efsitora at a fixed dose of 400 U for at least 4 weeks, participants who still

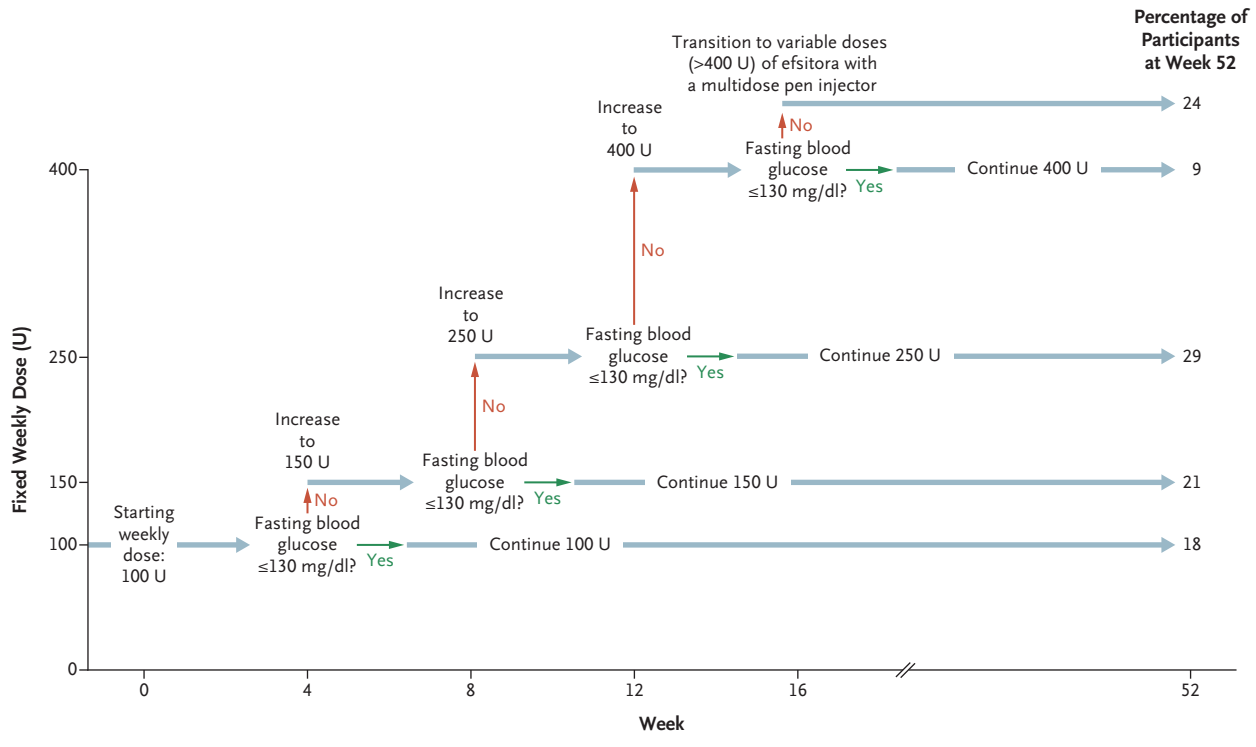

Figure 1. Fixed-Dose Regimen for Efsitora

Shown are the percentages of participants receiving each fixed dose of efsitora, as well as variable doses of efsitora administered with the multidose pen injector, at week 52. Percentages may not total 100 because of rounding. Participants continued to receive their assigned weekly dose until the next fasting blood glucose assessment indicated that a dose increase was needed. Dose assessments occurred every 4 weeks for the first 16 weeks and then at each scheduled visit thereafter (at least every 4 weeks) and were permitted only after the participant had received a given dose for at least 4 weeks. Dose reduction due to hypoglycemia could occur at any time if a participant met at least one of the following criteria: at least three hypoglycemic events with a glucose level of 70 mg per deciliter or less (≤3.9 mmol per liter), any hypoglycemic event with a glucose level of less than 54 mg per deciliter (<3.0 mmol per liter), any nocturnal hypoglycemic event with a glucose level of 70 mg per deciliter or less, or any severe hypoglycemic event (level 3; requiring assistance for treatment) in the preceding 7 days. Fixed-dose reescalation of efsitora was not permitted through the remainder of the trial if the fixed dose had previously been reduced owing to hypoglycemia. If participants were transitioned to variable doses of efsitora, administered with the multidose pen injector (KwikPen), a dose reduction of 40 U was implemented; if participants were receiving the fixed dose of 100 U, treatment was discontinued.

had a median fasting glucose level greater than 130 mg per deciliter and did not meet the criteria for hypoglycemia transitioned to treatment with efsitora at variable doses above 400 U, administered with a multidose pen injector (KwikPen) (Tables S3B and S4B). Assessments for dose adjustments of efsitora were conducted every 4 weeks for the first 16 weeks of treatment; additional assessments were allowed at each scheduled trial visit or at least every 4 weeks thereafter. If a dose reduction of a fixed dose of efsitora occurred owing to hypoglycemia, dose reescalation was not permitted through the remainder of the trial.

Glargine (100 U per milliliter) was administered with a prefilled multidose pen injector at a starting daily dose of 10 U that was subsequently adjusted on a weekly basis according to a traditional dosing algorithm to achieve the target blood glucose of 80 to 130 mg per deciliter (Table S3C) and also in response to hypoglycemia (Table S4C). Participants in both groups received a blood glucose meter to monitor their glucose levels (a minimum of three times per week) and guide insulin adjustments and to monitor for hypoglycemia.

END POINTS

The primary end point was the change in the glycated hemoglobin level from baseline to week 52 with a goal of determining whether efsitora was noninferior to glargine. The multiplicity-adjusted secondary end point was the change in the glycated hemoglobin level from baseline to week 52 with a goal of determining whether efsitora was superior to glargine. Other secondary efficacy end points included the change from baseline to week 52 in the fasting blood glucose level, as measured by participant-monitored blood glucose tests; the insulin dose at week 52; and the change from baseline to week 52 in the Treatment-Related Impact Measure–Diabetes (TRIM-D) total score (on a scale of 0 to 100, with higher scores indicating better functioning and greater well-being).

Safety end points included the incidence and rate of overall and nocturnal combined clinically significant (level 2; glucose level, <54 mg deciliter [<3.0 mmol per liter]) or severe (level 3; requiring assistance for treatment) hypoglycemia events during the treatment period and the change from baseline to week 52 in body weight. Adverse events and serious adverse events were recorded throughout the trial. An independent external data monitoring committee periodically reviewed unblinded safety data. An independent external committee whose members were unaware of the treatment-group assignments adjudicated all deaths and major cardiovascular events.

STATISTICAL ANALYSIS

The primary hypothesis was that efsitora would be noninferior to glargine with respect to the change in the glycated hemoglobin level from baseline to week 52. A noninferiority margin of 0.4 percentage points was determined on the basis of statistical and clinical perspectives and consistency with regulatory guidance. A gatekeeper approach was used to control for the type I error rate for testing the primary end point and the gated secondary end point.[7] We estimated that with 670 participants enrolled and with 568 completing the 52-week trial period, the trial would have at least 99% power to show the noninferiority of efsitora to glargine, as determined by the upper limit of a two-sided 95% confidence interval, with respect to the change in the glycated hemoglobin level from baseline to week 52, under the following assumptions: a noninferiority margin of 0.4 percentage points, no true difference between treatment groups, a standard deviation of 1.1 percentage points, and withdrawal of 15% of the patients. No multiplicity adjustments were made for evaluating other secondary and exploratory end points or for safety assessments; hypothesis testing was not conducted, and the widths of confidence intervals were not adjusted for multiplicity.

All randomly assigned participants who had received at least one dose of efsitora or glargine were included in the efficacy and safety analyses. Participants who discontinued treatment because of inadvertent enrollment were excluded from efficacy analyses. Two estimands — the treatment-regimen estimand and the efficacy estimand — were used to assess treatment efficacy. The treatment-regimen estimand (intention-to-treat analysis) represents the treatment effect in all eligible participants, regardless of adherence to the trial regimen or the use of rescue medication. The efficacy estimand represents the treatment effect in all eligible participants who had adhered to the trial intervention without using rescue medication. Results from the treatment-regimen estimand (provided in the main text) and efficacy estimand (shown in the Supplemen-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Efsitora (N=397)	Glargine (N=398)	Total (N=795)
Female sex — no. (%)	194 (48.9)	203 (51.0)	397 (49.9)
Age — yr	56.4±10.0	56.2±9.7	56.3±9.8
Race or ethnic group — no./total no. (%)†‡			
White	270/396 (68.2)	272/397 (68.5)	542/793 (68.3)
American Indian	106/396 (26.8)	107/397 (27.0)	213/793 (26.9)
Black	13/396 (3.3)	10/397 (2.5)	23/793 (2.9)
Asian	3/396 (0.8)	6/397 (1.5)	9/793 (1.1)
Hispanic or Latin American ethnic group — no. (%)†			
Yes	338 (85.1)	336 (84.4)	674 (84.8)
No	59 (14.9)	61 (15.3)	120 (15.1)
Body weight — kg	89.3±19.2	85.5±19.7	87.4±19.6
Body-mass index	32.5±5.8	31.3±6.1	31.9±6.0
Duration of diabetes — yr	9.2±6.6	9.6±6.9	9.4±6.7
Baseline glycated hemoglobin level — %	8.20±0.91	8.27±1.07	8.24±0.99
Fasting serum glucose level — mg/dl	161±48	161±52	161±50
Estimated GFR — no. (%)			
≥90 ml/min/1.73 m^2	258 (65.0)	270 (67.8)	528 (66.4)
≥60 to <90 ml/min/1.73 m^2	117 (29.5)	101 (25.4)	218 (27.4)
≥30 to <60 ml/min/1.73 m^2	20 (5.0)	26 (6.5)	46 (5.8)
<30 ml/min/1.73 m^2	2 (0.5)	1 (0.3)	3 (0.4)
Noninsulin glucose-lowering agents — no. (%)			
Metformin	373 (94.0)	370 (93.0)	743 (93.5)
DPP-4 inhibitor	126 (31.7)	121 (30.4)	247 (31.1)
SGLT2 inhibitor	85 (21.4)	91 (22.9)	176 (22.1)
GLP-1 receptor agonist	39 (9.8)	38 (9.5)	77 (9.7)
Thiazolidinedione	21 (5.3)	20 (5.0)	41 (5.2)
Number of noninsulin glucose-lowering agents — no. (%)			
1	190 (47.9)	195 (49.0)	385 (48.4)
2	167 (42.1)	164 (41.2)	331 (41.6)
3	40 (10.1)	39 (9.8)	79 (9.9)

* Plus–minus values are means ±SD. To convert the values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50. To convert the values for glucose to millimoles per liter, multiply by 0.05551. Percentages may not total 100 because of rounding. DPP-4 denotes dipeptidyl peptidase 4, GFR glomerular filtration rate, GLP-1 glucagon-like peptide-1, and SGLT2 sodium–glucose cotransporter 2.
† Race and ethnic group were reported by the participants. The definition of American Indian includes having origins in any of the original peoples of North or South America (including Central America) and maintaining a tribal affiliation or community attachment; all participants who selected the American Indian category were from Mexico.
‡ One participant in the efsitora group and one participant in the glargine group did not report race or ethnic group.

tary Appendix) are reported for the primary end point and the gated secondary end point, and results from the efficacy estimand are reported for other end points unless stated otherwise.

Continuous end points, including the primary end point, were analyzed with the use of an analysis of covariance model (treatment-regimen estimand) and a mixed model for repeated measures (efficacy estimand). The analysis of covariance model included treatment, randomization

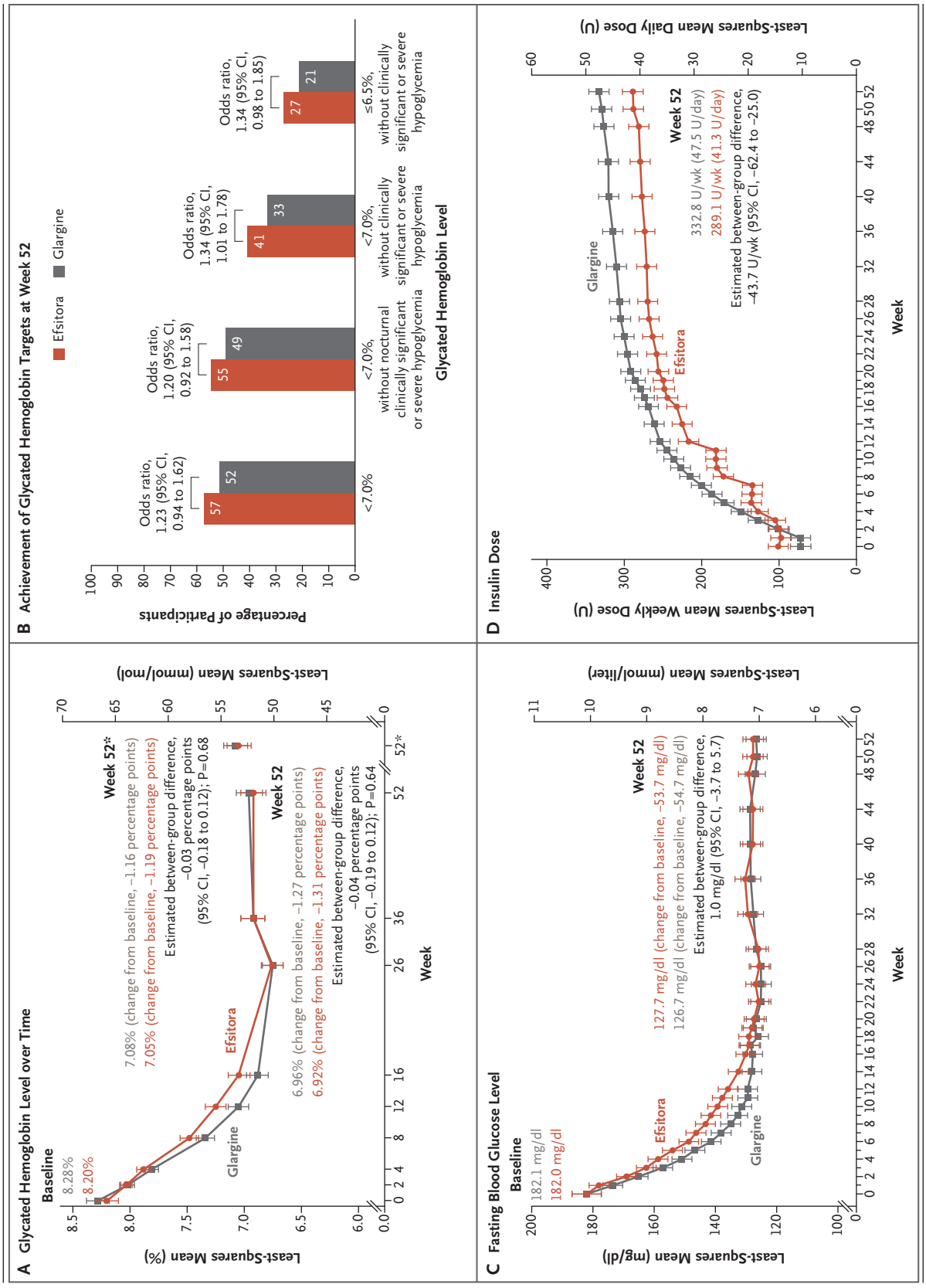

Figure 2 (facing page). Efficacy Outcomes among Participants Who Received Once-Weekly Efsitora or Once-Daily Glargine.

Panel A shows the least-squares mean glycated hemoglobin level over time among all eligible participants who had adhered to the trial intervention without using rescue medication (efficacy estimand), as well as the least-squares mean glycated hemoglobin level at week 52 among all eligible participants, regardless of adherence to the trial regimen or the use of rescue medication (treatment-regimen estimand; data indicated with an asterisk). Panel B shows the estimated percentage of participants who reached a glycated hemoglobin level below 7.0%, a level below 7.0% without nocturnal clinically significant hypoglycemia (level 2; glucose level, <54 mg per deciliter) or severe hypoglycemia (level 3; requiring assistance for treatment), a level below 7.0% without clinically significant or severe hypoglycemia, and a level of 6.5% or less without clinically significant or severe hypoglycemia (treatment-regimen estimand). Panel C shows the least-squares mean fasting blood glucose level measured by participant-monitored blood glucose tests over time (efficacy estimand). Fasting blood glucose values were derived on the basis of the participant-assigned fasting time point or the first reading between 5 a.m. and 10 a.m. if the assigned fasting time point was missing. Panel D shows the weekly and daily least-squares mean insulin dose over time (efficacy estimand). In Panels A, C, and D, the I bars indicate 95% confidence intervals; the widths of the confidence intervals were not adjusted for multiplicity. To convert values for glucose to millimoles per liter, multiply by 0.05551.

strata (country and GLP-1 receptor agonist use [yes or no]), and baseline value of the dependent variable. Missing measures were imputed by multiple imputation. Further details are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

The trial was conducted between January 14, 2023, and July 17, 2024. Of the 1148 participants who underwent screening, 795 were randomly assigned to receive efsitora (397 participants) or glargine (398 participants). A total of 44 participants (11.1%) permanently discontinued efsitora, and 42 (10.6%) permanently discontinued glargine (Fig. S2).

The demographic and baseline characteristics of the participants were broadly similar in the two treatment groups (Table 1). Overall, 397 participants (49.9%) were women. The mean age of the participants was 56.3 years, the mean duration of diabetes was 9.4 years, and the mean BMI was 31.9. The mean body weight was higher in the efsitora group than in the glargine group (89.3 vs. 85.5 kg), as was the BMI (32.5 vs. 31.3). The most common antihyperglycemic medication that participants were receiving at baseline was metformin (743 participants [93.5%]); 77 participants (9.7%) were receiving GLP-1 receptor agonists.

EFFICACY END POINTS

The mean glycated hemoglobin level decreased from 8.20% at baseline to 7.05% at week 52 with efsitora (least-squares mean change, −1.19 percentage points) and from 8.28% to 7.08% with glargine (least-squares mean change, −1.16 percentage points) (Fig. 2A and Fig. S3); the estimated between-group difference of −0.03 percentage points (95% confidence interval [CI], −0.18 to 0.12) showed the noninferiority of efsitora to glargine, but superiority was not shown (P=0.68). Subgroup analyses according to GLP-1 receptor agonist use at randomization (yes or no) and insulin dose (>400 U at any time or ≤400 U) did not show any notable differential treatment effects (Table S5).

The estimated percentages of participants reaching a glycated hemoglobin level of less than 7.0% at week 52 were 57% in the efsitora group and 52% in the glargine group (Fig. 2B). The mean fasting blood glucose level, as measured by the participants, decreased from 182.0 mg per deciliter (10.1 mmol per liter) at baseline to 127.7 mg per deciliter (7.1 mmol per liter) at week 52 with efsitora and from 182.1 mg per deciliter (10.1 mmol per liter) to 126.7 mg per deciliter (7.0 mmol per liter) with glargine (Fig. 2C). Fasting serum glucose levels measured at a central laboratory are shown in Figure S5.

At week 52, the mean total weekly insulin dose was 289.1 U per week (41.3 U per day) with efsitora and 332.8 U per week (47.5 U per day) with glargine (estimated between-group difference, −43.7 U per week; 95% CI, −62.4 to −25.0) (Fig. 2D). Similar trends in the insulin dose with adjustment for body weight were observed; the daily insulin dose at week 52 was 0.4 per kilogram of body weight with efsitora and 0.5 U per kilogram with glargine (Fig. S6). The percentages of efsitora-treated participants who used each fixed dose and the multidose pen injector with flexible dose capabilities are shown in Figure S7. At week 52, 76% of participants (229 of 300) treated with

Table 2. Hypoglycemic Episodes.*

Variable	Efsitora (N=397)		Glargine (N=398)		Estimated Rate Ratio (95% CI)†
	No. of Participants (%)	No. of Episodes (Events/PYE)	No. of Participants (%)	No. of Episodes (Events/PYE)	
Overall hypoglycemic episodes					
Hypoglycemia alert‡	222 (55.9)	1120 (3.08)	241 (60.6)	1400 (3.65)	0.85 (0.66–1.08)
Clinically significant hypoglycemia‡	103 (25.9)	174 (0.50)	118 (29.6)	331 (0.88)	0.57 (0.39–0.84)
Severe hypoglycemia§	1 (0.3)	1 (<0.01)	1 (0.3)	1 (<0.01)	1.01 (0.06–16.17)
Combined clinically significant or severe hypoglycemia‡	103 (25.9)	175 (0.50)	119 (29.9)	332 (0.88)	0.57 (0.39–0.84)
Nocturnal hypoglycemic episodes‡¶	14 (3.5)	17 (0.05)	20 (5.0)	31 (0.08)	0.58 (0.28–1.23)
Nonnocturnal hypoglycemic episodes ‡¶	97 (24.4)	158 (0.46)	111 (27.9)	301 (0.80)	0.57 (0.38–0.85)

* Levels of severity include hypoglycemia alert (level 1; glucose level, <70 to ≥54 mg per deciliter), clinically significant hypoglycemia (level 2; glucose level, <54 mg per deciliter), and severe hypoglycemia (level 3; requiring assistance for treatment). PYE denotes participant-year of exposure.
† The widths of the confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing.
‡ Rate and estimated rate ratio were estimated with the use of a negative binomial model.
§ Rate was calculated as the number of episodes divided by total exposure. Estimated rate ratio was calculated using empirical variance estimation.
¶ Hypoglycemic episodes were combined clinically significant or severe hypoglycemia. Nocturnal episodes were those occurring between midnight and 6 a.m.

efsitora continued to receive one of the fixed doses, and 24% (71 of 300) had transitioned to treatment with efsitora in variable doses, administered with the use of a multi-dose pen injector. Participants receiving fixed doses of efsitora appeared to reach the fasting glycemic goal (<130 mg per deciliter) with fewer dose increases than those receiving glargine with traditional sliding-scale dose adjustments (mean dose increases, 3.4 vs. 9.3; median, 2 vs. 8). The least-squares mean change from baseline to week 52 in the TRIM-D total score was 15.4 points with efsitora and 13.9 points with glargine (estimated between-group difference, 1.56 points; 95% CI, −0.13 to 3.25) (Fig. S8).

SAFETY AND ADVERSE EVENTS

The numbers and rates of overall, nocturnal, and nonnocturnal hypoglycemia events during the treatment period are shown in Table 2. One episode of severe hypoglycemia occurred in each treatment group. The observed rate of combined clinically significant or severe hypoglycemia was 43% lower in the efsitora group than in the glargine group (0.50 vs. 0.88 events per participant-year of exposure), with an estimated rate ratio of 0.57 (95% CI, 0.39 to 0.84). Four participants in the glargine group had more than 10 events of combined clinically significant or severe hypoglycemia, whereas no participants in the efsitora group had more than 10 such events. The rate of combined clinically significant or severe nocturnal hypoglycemia was 0.05 events per participant-year of exposure in the efsitora group and 0.08 events per participant-year of exposure in the glargine group (estimated rate ratio, 0.58; 95% CI, 0.28 to 1.23). Rates of hypoglycemia during prespecified periods and rates in subgroups of participants using or not using GLP-1 receptor agonists are shown in Tables S6 and S7, respectively.

The percentage of participants reaching a glycated hemoglobin level of less than 7.0% without clinically significant or severe hypoglycemia was 41% with efsitora (160 of 392 participants) and 33% with glargine (130 of 391). The trial protocol required that participants who met hypoglycemic criteria for dose reduction while receiving the 100 U dose of efsitora discontinue the trial drug; five participants (1.3%) discontinued efsitora for this reason.

Table 3. Summary of Adverse Events.

Event	Efsitora (N=397)	Glargine (N=398)
Adverse events — no. of participants (%)		
Any adverse event	238 (59.9)	259 (65.1)
Serious adverse event	26 (6.5)	21 (5.3)
Adverse events of interest — no. of participants (%)		
Hypersensitivity event	6 (1.5)	10 (2.5)
Injection-site reaction	7 (1.8)	6 (1.5)
Medication errors, including misuse and abuse*	1 (0.3)	0
Adjudicated events — no. of participants		
Death	3†	3‡
Acute coronary syndrome		
Heart failure	1	0
Myocardial infarction	2	2
Coronary revascularization		
Percutaneous coronary intervention	4	4
Coronary-artery bypass graft	2	0
Cerebrovascular events		
Transient ischemic attack	1	1
Stroke	3	0

* Shown are adverse events involving medication errors that met the criteria for an important protocol deviation indicative of a multiple dose. These events are considered to be important protocol deviations and of special interest because of their potential to affect a participant's safety. No medication errors that were consistent with misuse or abuse were reported.
† The deaths were due to acute myocardial infarction, congestive heart failure, and sepsis.
‡ The deaths were due to acute myocardial infarction, pulmonary edema, and septic shock.

Overall, 238 of 397 participants (59.9%) in the efsitora group and 259 of 398 (65.1%) in the glargine group reported an adverse event (Table 3). Serious adverse events were reported by 26 participants (6.5%) in the efsitora group and by 21 (5.3%) in the glargine group (Table S8). Three deaths occurred in each treatment group. No deaths were considered by the investigators to be related to efsitora or glargine. The least-squares mean change from baseline to week 52 in body weight was 3.9 kg with efsitora and 3.3 kg with glargine (estimated between-group difference, 0.57 kg; 95% CI, 0.05 to 1.10) (Fig. S9).

DISCUSSION

In this phase 3 trial involving participants with type 2 diabetes who had not previously received insulin, treatment with once-weekly efsitora in a fixed-dose regimen for 52 weeks resulted in an improvement from baseline in glycemic control and in a reduction in the glycated hemoglobin level that was similar to that with once-daily glargine. Among the participants assigned to receive efsitora, 76% were still receiving one of the fixed doses at week 52, a finding that suggests that the majority of people with type 2 diabetes requiring insulin for the first time may be adequately covered by the four doses evaluated in the present trial. This straightforward fixed-dose regimen of once-weekly efsitora, which mimics the approach used for once-weekly incretin-based therapies, may simplify treatment and lead to a lower injection burden than that with the traditional sliding-scale dose adjustments of once-daily insulin therapies. The fixed-dose regimen might have the potential to reduce the clinical inertia often observed with starting and intensifying insulin therapy.

During the trial, the reduction in the glycated

hemoglobin level was similar with efsitora and glargine, with levels reaching less than 7.0% in each of the two groups, and was accompanied by low rates of hypoglycemia. The rates of combined clinically significant and severe hypoglycemia were less than 1 event per participant-year of exposure in both groups, including during the first 16 weeks of the treatment period (during which most of the dose increases of efsitora occurred), and were lower in the efsitora group than in the glargine group. However, if a fixed dose of efsitora was reduced owing to hypoglycemia, dose reescalation was not permitted subsequently. Another phase 3 trial involving participants with type 2 diabetes who had not previously received insulin (QWINT-2), which investigated efsitora using a traditional flexible dosing regimen with weekly dose adjustments, showed low rates of combined clinically significant and severe hypoglycemia among participants receiving efsitora (<1 hypoglycemic event per participant-year of exposure) but slightly higher rates than those in the group receiving degludec.[6] Similarly, in two other phase 3 trials involving participants who had not previously received insulin, treatment with once-weekly insulin icodec, with dose adjustments made weekly, was associated with slightly higher rates of combined clinically significant and severe hypoglycemia than treatment with once-daily basal insulin (glargine in one of the trials and degludec in the other); however, the observed rates of hypoglycemia were low overall (<1 hypoglycemic event per participant-year of exposure in all groups).[8,9] In patients starting insulin for the first time, once-weekly efsitora, administered in a fixed-dose regimen, with dose adjustments made every 4 weeks, was noninferior to once-daily basal insulin in improving glycemic control without increasing hypoglycemic risk.

Although the majority of participants continued to receive the fixed doses throughout the trial, 24% transitioned to treatment with variable doses of efsitora, administered with a multidose pen injector. The trial required that participants switch to the multidose pen injector for doses higher than 400 U if their fasting blood glucose level did not reach the target of 80 to 130 mg per deciliter after 4 weeks of treatment with a fixed dose of 400 U. It is conceivable that fewer participants may have switched to variable doses with the multidose pen injector if the criteria had been based on the glycated hemoglobin level instead of the fasting blood glucose level; this strategy would have allowed for continued reductions in the glycated hemoglobin level in participants receiving the fixed dose of 400 U and potentially no need to switch to the multidose pen. Of note, the observed reductions in the glycated hemoglobin level were similar among participants receiving efsitora at doses of 400 U or less (i.e., fixed doses) and at doses higher than 400 U (i.e., variable doses).

At week 52, the mean total weekly dose was 44 U lower in the efsitora group than in the glargine group. Efsitora, administered in a fixed-dose regimen, provided glucose-lowering effects similar to those of glargine, with fewer dose increases needed. The fixed-dose regimen of efsitora decreased the number of multiple small dose adjustments seen with daily basal insulin therapies. These multiple adjustments are a possible burden for clinicians and patients that may result in therapeutic inertia and contribute to suboptimal glycemic control).[10] Many patients and prescribers are reluctant to initiate insulin therapy because of the perceived fear and treatment burden.[11,12] The simple, fixed-dose regimen of once-weekly efsitora evaluated in this trial could make initiating and managing insulin therapy for type 2 diabetes easier for clinicians and patients.

The body weight at baseline was higher among participants in the efsitora group than among those in the glargine group, and the weight gain during the trial was slightly greater in the efsitora group. The modest weight gain was consistent with participants starting basal insulin with improved glucose control.[13]

Taking the results of the present trial together with findings from the QWINT-2 trial (in which degludec was the comparator),[6] both a fixed-dose regimen and a variable-dose regimen using traditional dosing algorithms have been shown to have glucose-lowering effects and were associated with low rates of hypoglycemia. The time to achieve a blood glucose level in the target range with efsitora was slightly longer in the QWINT-1 trial than in the QWINT-2 trial, most likely because of the absence of a starting one-time loading dose in QWINT-1 and differences in the dosing algorithms (dose increases were allowed every 4 weeks with the fixed-dose regimen in the QWINT-1 trial as compared with weekly dose increases in the QWINT-2 trial); however, the differences observed in the change in the fasting blood glucose and

glycated hemoglobin levels were minimal. Despite these differences, the convenience and simplicity of the fixed-dose approach might outweigh the slower glucodynamic response for many patients, which may make fixed dosing for efsitora a valuable option in clinical practice.

Strengths of this trial included a large, multinational participant population that was generally representative of persons with type 2 diabetes (Table S9). A range of noninsulin glucose-lowering agents were permitted, which is reflective of real-world clinical practice; however, the use of sulfonylureas was not permitted. The trial had good participant retention and well-balanced treatment groups. The investigation of participant experience, with the use of participant-reported outcomes such as the TRIM-D total score, also strengthened the trial.

The trial has certain limitations. The trial had an open-label design, which could introduce bias; however, given that the injection devices and dosing frequency were different for efsitora and glargine, blinding was not feasible. In order to lower patient burden, continuous glucose monitoring was not performed; currently only 10 to 20% of persons with type 2 diabetes use continuous glucose monitoring.[14] In addition, prohibiting reescalation of efsitora fixed doses after a dose reduction due to hypoglycemia does not reflect usual clinical practice, but it was considered a necessary trade-off to minimize analytic complexity and for participant safety. Even with the inability to rechallenge participants requiring higher doses, meaningful glycemic control with minimal hypoglycemia risk was achieved in the efsitora group.

In this trial involving participants with type 2 diabetes who had not previously received insulin, once-weekly efsitora administered in a fixed-dose regimen was noninferior to once-daily glargine in reducing glycated hemoglobin levels at 52 weeks.

Supported by Eli Lilly.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the trial participants, and Juliana Bue-Valleskey (Eli Lilly) for clinical trial design and technical consultation.

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