Diabetes Care
American Diabetes Association

Once-Weekly Basal Insulin Fc Demonstrated Similar Glycemic Control to Once-Daily Insulin Degludec in Insulin-Naive Patients With Type 2 Diabetes: A Phase 2 Randomized Control Trial

Juliana M. Bue-Valleskey, Christof M. Kazda, Chenchen Ma, Jenny Chien, Qianyi Zhang, Emmanuel Chigutsa, William Landschulz, Axel Haupt, and Juan P. Frias

Diabetes Care 2023;46(5):1060–1067 | https://doi.org/10.2337/dc22-2396

Once-weekly basal insulin Fc (BIF) demonstrated similar glycemic control to once-daily insulin degludec in insulin-naive patients with type 2 diabetes (T2D) in this phase 2 randomized controlled trial. CGM, continous glucose monitoring.

Background

Once-weekly BIF combines a novel single-chain insulin variant with a human IgG_2 Fc domain and is designed for once-weekly subcutaneous administration for the treatment of diabetes.

Patient Population

N = 278 insulin-naive people with T2D

55% male 45% female

Mean Baseline Characteristics:

Age = 58 years

Duration of T2D = 10 years

HbA_{1c} = 8.0%

Study Design

2-week screening/lead-in

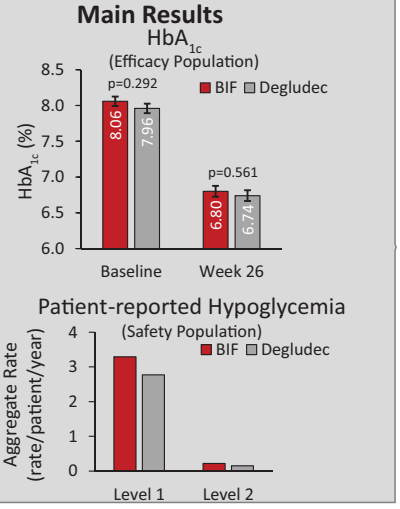
↓

26-week treatment period

BIF administered once weekly ↔ Degludec -administered once daily

- Treat-to-target fasting glucose: BIF used 101-140 mg/dL (5.6 to <7.8 mmol/L) for the first 2 weeks only; 80-100 mg/dL (4.4 to <5.6 mmol/L) was used for both treatments
- All patients underwent intermittent blinded CGM (Abbott Libre Pro)
- Assessed HbA_{1c}, fasting glucose, incidence and rate of hypoglycemia

Main Results



Conclusion

Once-weekly BIF demonstrated excellent glycemic control similar to Once-daily degludec and no difference in hypoglycemia or other safety findings in insulin-naive patients with T2D.

ARTICLE HIGHLIGHTS

- This study assessed once-weekly basal insulin Fc (BIF) as a treatment option for insulin-naive patients with type 2 diabetes (T2D).
- The research question was whether BIF is a safe and efficacious treatment for insulin-naive patients with T2D.
- BIF administered once weekly achieved similar glycemic control with similar hypoglycemia risk compared with once-daily degludec.
- BIF has the potential to safely and effectively manage glycemic control in insulin-naive patients with T2D while reducing injection burden.

Once-Weekly Basal Insulin Fc Demonstrated Similar Glycemic Control to Once-Daily Insulin Degludec in Insulin-Naive Patients With Type 2 Diabetes: A Phase 2 Randomized Control Trial

Juliana M. Bue-Valleskey,[1] Christof M. Kazda,[2] Chenchen Ma,[1] Jenny Chien,[1] Qianyi Zhang,[1] Emmanuel Chigutsa,[1] William Landschulz,[1] Axel Haupt,[1] and Juan P. Frias[3]

Diabetes Care 2023;46:1060–1067 | https://doi.org/10.2337/dc22-2396

ORIGINAL ARTICLE

OBJECTIVE

Basal insulin Fc (BIF) (insulin efsitora alfa; LY3209590), a fusion protein combining a novel single-chain insulin variant with a human IgG Fc domain, is designed for once-weekly basal insulin administration. This phase 2 study assessed the safety and efficacy of BIF versus degludec in insulin-naive patients with type 2 diabetes (T2D) previously treated with oral antihyperglycemic medications.

RESEARCH DESIGN AND METHODS

During this randomized, parallel, open-label study, 278 insulin-naive patients with T2D were randomly assigned (1:1) to receive BIF once weekly or degludec once daily over the 26-week treatment period. Both groups were titrated to fasting glucose of 80–100 mg/dL (4.4 to <5.6 mmol/L). The primary end point was HbA_{1c} change from baseline to week 26 (noninferiority margin 0.4%). Secondary end points included fasting blood glucose (FBG), six-point glucose profiles, and rate of hypoglycemia.

RESULTS

After 26 weeks of treatment, BIF demonstrated a noninferior HbA_{1c} change from baseline versus degludec, with a treatment difference of 0.06% (90% CI −0.11, 0.24; *P* = 0.56). Both BIF and degludec treatment led to significant reductions in FBG from baseline. At week 26, the between-treatment difference for BIF versus degludec was 4.7 mg/dL (90% CI 0.1, 9.3; *P* = 0.09). The rate of level 2 hypoglycemia was low and not significantly different between treatment groups (BIF 0.22 events/patient/year, degludec 0.15 events/patient/year; *P* = 0.64); there was no severe hypoglycemia. The occurrence of treatment-emergent adverse events was also similar between BIF and degludec.

CONCLUSIONS

Once-weekly BIF achieved excellent glycemic control similar to degludec, with no concerning hypoglycemia or other safety findings.

Current clinical guidelines recommend an HbA_{1c} target of <7% (53 mmol/mol) without significant hypoglycemia for adults with diabetes (1). To achieve this target,

[1]Eli Lilly and Company, Indianapolis, IN
[2]Lilly France, Neuilly sur Seine, France
[3]Velocity Clinical Research, Los Angeles, CA

Corresponding author: Juliana M. Bue-Valleskey, bue-valleskey_juliana_m@lilly.com

Received 9 December 2022 and accepted 21 February 2023

Clinical trials reg. no. NCT04450394, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.22144145.

This article is featured in podcasts available at https://diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

See accompanying article, p. 1052.

basal insulin therapy may be needed in patients with type 2 diabetes (T2D). However, there is often hesitancy to initiate and appropriately adjust insulin for people with T2D. Prior to initiation of insulin, people with T2D feel that incorporating insulin into their treatment regimen will be painful, lead to a significant time and physical burden, and represent a personal failure (2). Furthermore, for patients in whom insulin is initiated, relatively few reach their glycemic targets. Less than 30% of people with T2D reach an HbA_{1c} <7% within 12 months of treatment (3).

A once-weekly insulin regimen has the potential to overcome clinical inertia and may encourage basal insulin treatment initiation at the optimal time for patients. Additionally, a reduction in patients' mental and physical burden could improve adherence to and persistence with an insulin regimen. Results from studies with other antidiabetic agents, namely glucagon-like peptide 1 (GLP-1) agonists, indicated that a weekly treatment option improves glycemia and medication adherence compared with a once-daily option (4,5).

Two once-weekly basal insulins are currently under clinical development: basal insulin Fc (BIF) (insulin efsitora alfa; LY3209590) and insulin icodec. BIF is a fusion protein combining a novel single-chain insulin variant together with a human IgG_2 Fc domain and is designed for once-weekly subcutaneous administration. Previous phase 1 studies demonstrated that BIF has a low peak-to-trough ratio (1.14, or <15% variation in insulin concentration) and a half-life of 17 days, with a sustained decrease in fasting glucose over the course of 1 week (6). This low peak-to-trough ratio may result in more stable glucose levels both within and between days. BIF also showed effective glycemic control in a phase 2 study of people with T2D previously treated with a basal insulin (7). Icodec is a novel basal insulin analog with a half-life of ~1 week (8). Icodec was well tolerated and demonstrated effective glycemic control in phase 2 studies of insulin-naive people with T2D (9,10) and with T2D previously treated with basal insulin (11). Results from three phase 3 trials conducted in insulin-naive patients with T2D (ONWARDS 1, ONWARDS 3, and ONWARDS 5) indicated that icodec demonstrates noninferiority (and statistical superiority) in reducing HbA_{1c} compared with once-daily basal insulin analogs (12–14). The aim of the current phase 2 treat-to-target study was to assess the safety and efficacy of once-weekly BIF versus once-daily degludec in insulin-naive patients with T2D previously treated with oral antihyperglycemic medications.

RESEARCH DESIGN AND METHODS

Study Design

This study was a multicenter, randomized, parallel, open-label, comparator-controlled phase 2 trial conducted at 61 sites in Argentina, Germany, Poland, and the U.S. The study consisted of three study periods: a 2-week screening and lead-in period, a 26-week treatment period, and a 5-week safety follow-up (Supplementary Fig. 1).

The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the independent ethics committee or institutional review board at each site. All participants provided written informed consent prior to participation.

Patients

Eligible participants included insulin-naive patients with T2D previously treated with metformin alone or in combination with dipeptidyl peptidase 4 (DPP-4) and/or sodium–glucose cotransporter 2 (SGLT2) inhibitors for at least 3 months prior to screening. Patients were 18–75 years of age; had a baseline HbA_{1c} value of 7.0–9.5%, inclusive; and a BMI between 20 and 45 kg/m^2, inclusive, with no significant weight change (≥5%) in the past 3 months. Inclusion and exclusion criteria are provided in Supplementary Table 1. Patients were recruited between 1 July 2020 and 4 February 2021.

Randomization

Patients were randomly assigned 1:1 to BIF or degludec treatment groups using an interactive web-response system. The BIF group used a paper-based algorithm that provided guidance on BIF initiation and titration. Another BIF group that used a digital dosing algorithm was discontinued because of technical issues with the tool caused by missing values and data entry errors. Patients randomly assigned to the digital algorithm (n = 14) were transitioned to the BIF paper-based algorithm, and their data were included in safety analyses but excluded from efficacy analyses.

Procedures

During the screening and lead-in period, patients were trained on disease management, study diaries, and procedures. Patients were provided with a glucose meter to collect self-monitoring of blood glucose (SMBG) measurements. Patients were instructed on signs, symptoms, and treatment of hypoglycemia and to document all readings ≤70 mg/dL (<3.9 mmol/L) in the electronic diary. Patients were provided with and trained on the Libre Pro continuous glucose monitoring (CGM) system (Abbott), which was used in a blinded mode during three predefined 14-day periods: prior to weeks 0, 12, and 26.

BIF was provided as a lyophilized powder and dosed in milligrams immediately following reconstitution. One goal of the phase 2 program was to determine the international unit conversion. Rather than rely on the conventional use data derived from clamp studies to determine the unit definition for ultra–long-acting insulins, which may not be accurate for all diabetes populations (15), phase 2 data were used to determine the BIF unit definition for phase 3 development.

Patients randomly assigned to the BIF treatment received one dose of BIF once weekly during the 26-week treatment period approximately on the same day and at the same time each week (7). BIF was titrated weekly for weeks 1–12, then every 4 weeks thereafter.

BIF was administered by study personnel at the site from weeks 0 to 8. The starting dose was based on previous phase 1 studies and an interim analysis of another phase 2 study in patients with T2D previously treated with basal insulin (7), as well as from pharmacokinetics/pharmacodynamics modeling using virtual patients. The first weekly dose was based on baseline median fasting blood glucose (FBG) and body weight (details provided in the Supplementary Material) and included a one-time loading dose administered at day 0, which was a threefold increase of the estimated weekly dose. This loading dose was based on results of phase 1 studies and used to achieve steady-state concentrations more quickly and to minimize transient hyperglycemia. For weeks 9–12 and 16, either study personnel or patients could administer BIF at the site. At weeks 13–15 and 17–25, BIF could be self-administered by patients at home or by study personnel at the site. Patients randomly assigned to the

degludec treatment self-administered degludec once daily at approximately the same time each day (starting dose 10 units) using a dose algorithm with prespecified FBG tiers and dosing increments (Supplementary Material).

Both the BIF and degludec treatment groups had an FBG target of 80 to ≤100 mg/dL (4.4 to <5.6 mmol/L), used the median of at least three FBG readings in the prior week for dose adjustment, and had similar hypoglycemia criteria for dose reduction. Because of the long half-life of BIF and the potential risk of early accumulation after the loading dose, the titration target for the first 2 weeks of treatment was 101–140 mg/dL (5.6 to <7.8 mmol/L). Treatments were administered via subcutaneous injections, rotating among the left, right, upper, and lower abdominal quadrants.

Outcomes

The primary end point was the efficacy of BIF versus degludec as measured by the HbA_{1c} change from baseline to week 26. Daily FBG (prebreakfast) measurements were recorded in the patients' electronic diaries. Measurements could have been collected as often as possible, especially as needed to evaluate hypoglycemia symptoms. Additionally, two six-point SMBG assessments (before and 2 h after each meal) were performed on nonconsecutive days in the week prior to weeks 0, 3, 6, 9, 12, 16, 24, and 26.

Patients also underwent three blinded CGM sessions using the Libre Pro system in the 14-day period prior to randomization (week 0), prior to week 12, and prior to week 26. The mean percent time in range (TIR) (70–180 mg/dL [3.9–10.0 mmol/L]), time below range (<70 mg/dL [3.9 mmol/L] or <54 mg/dL [3.0 mmol/L]), and time above range (181–250 mg/dL [10.0–13.9 mmol/L]) were calculated.

Safety was monitored throughout the study, and analyses were performed on the safety population. The incidence and rate of hypoglycemia were based on the data recorded by the participant. Level 1 hypoglycemia was defined as a glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L), and level 2 hypoglycemia was defined as a glucose <54 mg/dL (3.0 mmol/L). Severe hypoglycemia (level 3) was defined as an event requiring assistance because of neurological impairment. Incidence of treatment-emergent adverse events and clinical assessments, including a physical examination, body weight, vital signs, electrocardiograms, and laboratory measures, were assessed.

Statistical Analysis

The sample size was determined such that ∼250 total randomly assigned patients, with ∼200 completers, would provide >80% statistical power to demonstrate noninferiority for the primary objective with the following assumptions: true mean difference of 0%, SD of 1.1%, noninferiority margin of 0.4% (Diabetes Control and Complications Trial [DCCT] units), and two-sided $\alpha = 0.1$. All tests of treatment effects were conducted at a two-sided $\alpha = 0.1$, and all CIs were given at a two-sided 90% level.

Efficacy analyses were conducted on the efficacy population of randomly assigned patients receiving at least one dose of study treatment, excluding those previously allocated to the discontinued BIF digital algorithm. Safety analyses were conducted on the safety population of all randomly assigned patients who took at least one dose of study treatment. Patients previously assigned to the discontinued BIF algorithm were pooled with the BIF paper-based algorithm group for the safety analysis.

The treatment efficacy estimand was used to evaluate the primary end point, which was defined as the treatment differences in the change in HbA_{1c} from baseline to week 26 for all patients who adhered to the assigned treatment and did not initiate noninsulin glucose-lowering agents during the treatment. This approach provided an estimation of the population-level treatment effect without confounding effects of other glucose-lowering agents.

The mixed models for repeated measures (MMRM) model was used with the HbA_{1c} changes at week 6, 12, 16, and 26, and the missing values were handled implicitly in the MMRM analysis under the assumption of missing at random. The MMRM model included treatment (BIF [paper-based, nondigital] algorithm, degludec), strata (country, DPP-4 [yes/no], SGLT2 [yes/no], and baseline BMI [<30, ≥30 kg/m^2]), visit, and treatment-by-visit interaction as the fixed effects and the baseline value of the dependent variable as the covariate. The HbA_{1c} is reported in the DCCT unit of percent. Other efficacy end points were analyzed using the same MMRM model with the addition term of HbA_{1c} strata (<8.5% and ≥8.5%).

The hypoglycemia event rate was calculated by the total number of patient-reported events divided by total treatment exposure. The relative rate was used for treatment comparison. The CI was estimated by an empirical method based on the delta method and assumption of log-normal distribution because the regular method with Poisson distribution may underestimate the variance, especially since the patient-reported hypoglycemia data in this insulin-naive population were sparse.

No multiplicity adjustments were conducted. Data were analyzed using SAS version 7.1 or later statistical software.

Data and Resource Availability

The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

Of the 278 randomly assigned patients, 129 were allocated to the BIF group (paper-based algorithm, efficacy population) and 135 to degludec, with a total of 143 in the BIF safety population. The BIF safety population included the 14 patients previously assigned to the discontinued BIF digital algorithm. Overall, 93.0% and 89.6% of patients in the BIF and degludec groups, respectively, completed the study (disposition shown in Supplementary Fig. 2). Discontinuations from the study were due to adverse events (two in the BIF group), death (1 in the degludec group), loss to follow-up (three in the degludec group), physician decision (1 in the degludec group), protocol deviation (two in the BIF group), and withdrawal by the patient (six in the BIF and nine in the degludec groups). The participant death was not considered related to study treatment.

Demographic and baseline characteristics were well balanced across treatments (Table 1). Approximately 55% of the patients were male, and the overall mean age was 58.3 years. The mean ± SD HbA_{1c} was 8.02 ± 0.77% (64.14 ± 8.39 mmol/mol), BMI was 32.0 ± 5.5 kg/m^2, and fasting serum glucose was 165.6 ±

Table 1—Baseline characteristics for randomly assigned patients

Characteristic	Insulin degludec (*n* = 135)	BIF Efficacy population (*n* = 129)	BIF Algorithm 2 population (*n* = 14)	BIF Pooled safety population (*n* = 143)	Total (*N* = 278)
Age, years	59.4 ± 9.1	57.4 ± 9.9	56.3 ± 8.8	57.3 ± 9.7	58.3 ± 9.5
Sex, %					
Female	43.7	45.0	64.3	46.9	45.3
Male	56.3	55.0	35.7	53.1	54.7
Ethnicity, *n* (%)					
Hispanic or Latino	59 (43.7)	61 (47.3)	8 (57.1)	69 (48.3)	128 (46.0)
Non-Hispanic or Latino	76 (56.3)	68 (52.7)	6 (42.9)	74 (51.7)	150 (54.0)
Duration of T2D, years	9.7 ± 6.0	10.6 ± 6.9	9.1 ± 5.9	10.4 ± 6.8	10.1 ± 6.4
HbA_{1c}					
%	8.0 ± 0.8	8.1 ± 0.8	8.4 ± 0.8	8.1 ± 0.8	8.0 ± 0.8
mmol/mol	63.4 ± 8.2	64.5 ± 8.4	68.1 ± 9.1	64.8 ± 8.5	64.1 ± 8.4
Fasting serum glucose					
mg/dL	160.7 ± 36.7	169.7 ± 42.0	174.5 ± 43.4	170.2 ± 42.0	165.6 ± 39.7
mmol/L	8.9 ± 2.0	9.4 ± 2.3	9.7 ± 2.4	9.5 ± 2.3	9.2 ± 2.2
Weight, kg	90.6 ± 19.6	91.3 ± 21.0	88.4 ± 19.8	91.0 ± 20.8	90.8 ± 20.2
BMI, kg/m^2	31.6 ± 5.5	32.2 ± 5.3	33.5 ± 6.3	32.3 ± 5.4	32.0 ± 5.5
Oral T2D medications, *n* (%)					
Metformin alone	74 (54.8)	76 (58.9)	11 (78.6)	87 (60.8)	161 (57.9)
Metformin, DPP-4 inhibitors	18 (13.3)	17 (13.2)	0	17 (11.9)	35 (12.6)
Metformin, SGLT2 inhibitors	29 (21.5)	25 (19.4)	2 (14.3)	27 (18.9)	56 (20.1)
Metformin, SGLT2, DPP-4 inhibitors	14 (10.4)	11 (8.5)	1 (7.1)	12 (8.4)	26 (9.4)

Data are mean ± SD unless otherwise indicated.

39.7 mg/dL (9.19 ± 2.21 mmol/L), and the mean duration of T2D was 10.1 years.

No statistically significant treatment differences in HbA_{1c} values were observed during the study (Fig. 1*A*). HbA_{1c} change from baseline to week 26 for BIF (−1.20%) was noninferior to degludec (−1.26%) with a treatment difference of 0.06% (90% CI −0.11, 0.24; *P* = 0.561). The proportion of patients achieving HbA_{1c} <7% (53 mmol/mol) was similar between treatments at week 26 (BIF 62.3% vs. degludec 68.6%; *P* = 0.353). In the subgroup analysis of patients with baseline HbA_{1c} above or below the median (7.9%), no significant treatment-by-subgroup interactions were noted. Results are summarized in Supplementary Table 2.

Based on SMBG readings, both treatments achieved significant reductions in FBG at week 26 compared with baseline (Fig. 1*B*). The treatment difference between BIF and degludec at week 26 was 4.7 mg/dL (90% CI 0.1, 9.3 [0.26 mmol/L (0.01, 0.52)]; *P* = 0.09) (Fig. 1*B*). The six-point SMBG profiles were similar between treatments for all time points and showed improvement from baseline assessments. No notable differences between treatments other than the fasting value at week 26 were observed (Fig. 2*A*).

CGM assessments were performed during three separate 14-day sessions and were prespecified exploratory objectives. Compliance was erratic, resulting in ∼60% of patients providing valid data (defined as 70% of data per day for at least 3 days for baseline and post-baseline assessments) for the session prior to week 26. Criteria for valid data were loosened to include as much data as possible, which creates the potential for bias that is likely equally distributed between treatments. With these caveats

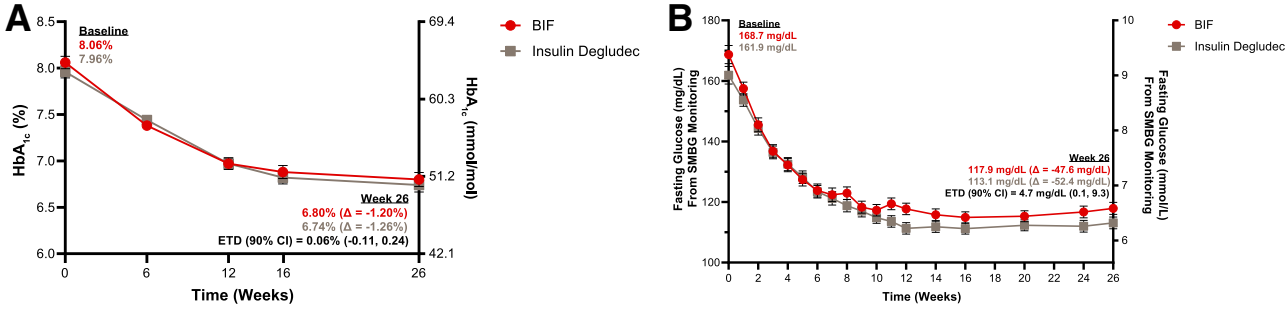


Figure 1—*A*: HbA_{1c} levels over the course of the 26-week treatment period; inset shows estimated treatment difference (ETD) (90% CI) at 26 weeks. *B*: FBG over the course of the 26-week treatment period; inset shows estimated treatment difference (90% CI) at 26 weeks. Data are least squares mean ± SE. Δ, change from baseline.

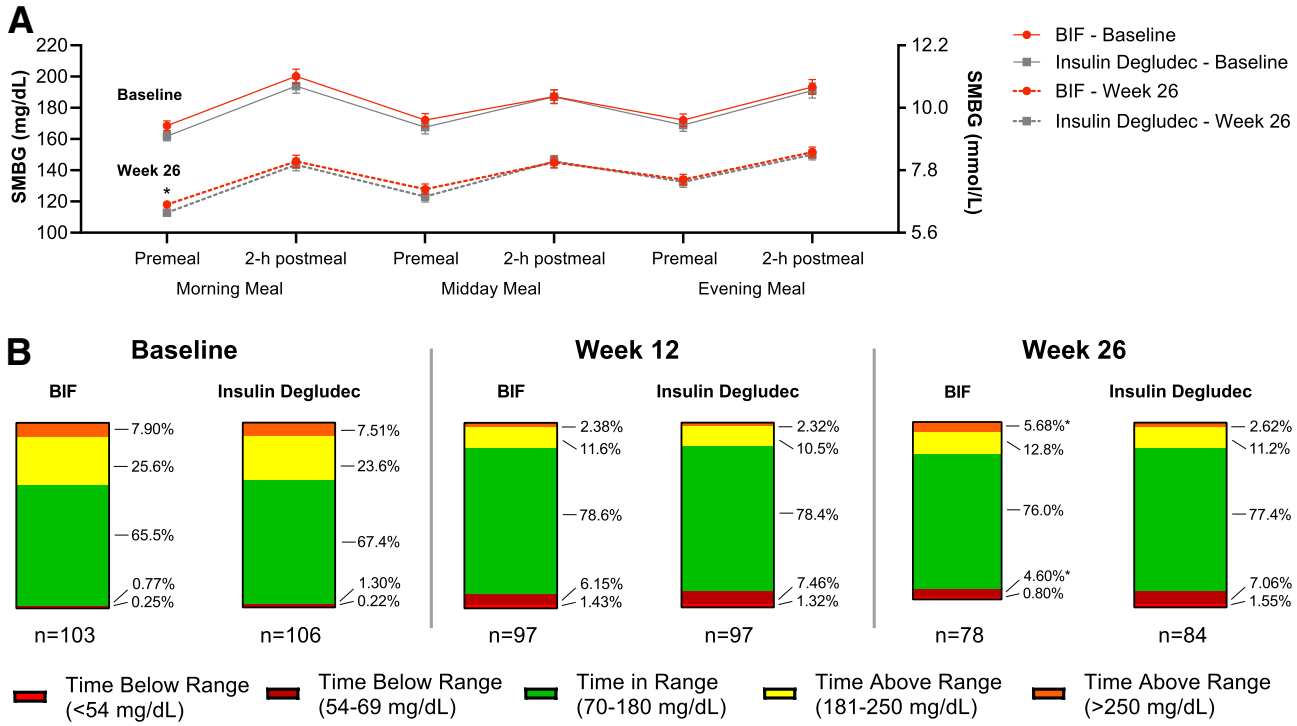


Figure 2—*A*: Glucose profile for six-point SMBG monitoring. Data are the least squares mean ± SE. *B*: TIR parameters for 24-h period collected from assessments performed at baseline and after 12 and 26 weeks of treatment. Data are least squares mean. CGM assessments at week 26 reflect ∼60% of the BIF group. *$P < 0.1$ for BIF vs. insulin degludec.

in mind, observations from TIR parameters are presented by session in Fig. 2*B*. The ambulatory glucose profiles from baseline and week 26 are presented for both treatments (Supplementary Fig. 3). Parameters describing within- and between-day variability, as summarized in Supplementary Table 3, suggest that both treatments had a similar effect on ambient glucose. Both treatments increased percent TIR over a 24-h period for the assessments prior to weeks 12 and 26 compared with baseline measures (Fig. 2*B*). On average, the BIF and degludec treatment groups had ≥75% TIR throughout the 24-h period by the end of study treatment, with BIF demonstrating a tendency for lower percent time below range (<70 mg/dL [3.9 mmol/L]).

Using patient-reported doses, increases in doses during treatment were observed for both groups (Supplementary Fig. 4); however, no statistical analyses were performed. The mean ± SD weekly insulin dose for the BIF group at baseline was 2.76 ± 1.15 mg (using a conversion factor of 35 units/mg, which corresponds to ∼97 units/week or ∼14 units/day); this was calculated as one-third of the dose at week 0 because of the loading dose. The weekly BIF dose at week 26 was 10.25 ± 6.16 mg (∼350 units/week or 51 units/day). The mean ± SD daily degludec dose was 10.42 ± 3.77 units at baseline and 45.48 ± 27.14 units at week 26. Clinical relevance of this apparent difference in estimated daily dose at end point is uncertain. Patients in both groups may have required additional time to complete titration, as median doses had not plateaued by week 26.

The hypoglycemic events summary is presented in Table 2. The rates of all documented, nocturnal, and nonnocturnal level 2 patient-reported hypoglycemia

Table 2—Patient-reported hypoglycemia (safety population)

	24-h Daily documented hypoglycemia				Nocturnal hypoglycemia (bedtime-waking)			
	n (%)	Episodes, *n*	Mean aggregate rate per patient per year	*P*[a]	*n* (%)	Episodes, *n*	Mean aggregate rate per patient per year	*P*[a]
Level 1 hypoglycemia								
BIF (*n* = 143)	52 (36.4)	229	3.29		19 (13.3)	35	0.50	
Degludec (*n* = 135)	36 (26.7)	181	2.77		17 (12.6)	51	0.78	
RR (90% CI)			1.19 (0.68, 2.08)	0.616			0.64 (0.32, 1.28)	0.290
Level 2 hypoglycemia								
BIF (*n* = 143)	8 (5.6)	15	0.22		2 (1.4)	3	0.04	
Degludec (*n* = 135)	4 (3.0)	10	0.15		3 (2.2)	4	0.06	
RR (90% CI)			1.41 (0.42, 4.75)	0.644			0.70 (0.14, 3.42)	0.714

No severe hypoglycemia (level 3: hypoglycemia requiring assistance because of neurological impairment) was reported. RR, relative rate. [a]Based on empirical variance estimation for the event rate.

from week 0 to 26 were similar between the treatments (all $P \geq 0.496$). Similarly, the rate of all documented, nocturnal, and nonnocturnal level 1 hypoglycemia from week 0 to 26 was similar between treatments (all $P \geq 0.290$). No severe hypoglycemia (level 3) was reported.

Reported adverse events were balanced between treatments (Supplementary Table 4). One death occurred in the degludec group (as a result of coronavirus 2019 pneumonia). No treatment-emergent hepatic disorders were reported, and both treatments showed reductions in hepatic enzymes with no clinically significant differences between treatments. Clinical chemistry and hematology, vital signs, and electrocardiogram assessments were unremarkable. Adverse events identified by standard Medical Dictionary for Regulatory Activities query for hypersensitivity reactions were reported more frequently with BIF (six vs. zero patients for degludec), and such events will be monitored in the phase 3 trial. Other safety measures, including cardiovascular events, injection site reactions, and immunogenicity, did not indicate any unexpected or concerning safety findings with BIF treatment compared with degludec. Additionally, no statistically significant differences ($P = 0.253$) in body weight gain were noted between BIF (2.9 kg) and degludec (2.5 kg) at week 26, with a treatment difference of 0.4 kg (90% CI −0.2, 1.1).

CONCLUSIONS

An efficacious and safe once-weekly basal insulin treatment has the potential to overcome clinical inertia and support the initiation of insulin therapy at an appropriate time for insulin-naive patients with T2D. Moreover, a basal insulin option that is simple to initiate, easy to titrate, convenient, and provides relevant glycemic improvement is essential for this patient population.

Therefore, this 26-week, phase 2, treat-to-target study assessed the efficacy and safety of BIF in insulin-naive patients with T2D against best-in-class degludec with an ambitious fasting glucose titration target of 80–100 mg/dL. Although the study used a complex dosing algorithm for BIF, both BIF and degludec achieved a mean HbA_{1c} <7% at week 26. Other glycemic parameters, such as fasting glucose, SMBG, and TIR, were all similar between the treatments and reflected notable improvements from baseline. The rate of hypoglycemia per year was very low, and there was no significant increase of documented hypoglycemia based on patient-reported events with BIF compared with degludec. Despite the theoretical hypoglycemia risk with once-weekly basal insulin treatment and limitations of the CGM data set for this study, passive collection of hypoglycemia using CGM was not concerning between treatment differences. No severe hypoglycemia was reported. Though the glycemic control end points were quite similar between treatments, interpretation of dosing information is confounded by differences in the dosing algorithms; residual uncertainty related to the current unit definition, which will not be confirmed until the end of phase 3; and the likelihood that patients in both groups may have required additional time to complete titration.

These results are consistent with results from a previous phase 2 BIF study, which demonstrated that BIF is safe and efficacious in patients with T2D suboptimally controlled with basal insulin (7). In that study, BIF demonstrated noninferior glycemic control compared with degludec as measured by HbA_{1c} change from baseline to study end point, despite higher fasting glucose targets for BIF than for degludec. Results from the current study are also comparable with those from another phase 2 study evaluating weekly basal insulin icodec in insulin-naive patients with T2D (9). With an FBG target of 70–108 mg/dL, icodec demonstrated noninferior glycemic control compared with insulin glargine. Reported rates of level 1 hypoglycemia were low. With a fasting glucose target of 80–100 mg/dL, the incidence and rate of level 1 hypoglycemia after BIF administration in the current study were also low and not significantly different than degludec. BIF's low weekly peak-to-trough ratio and long half-life may convey lower between-day glucose variability (16), which could influence hypoglycemia risk relative to day of injection and provide some flexibility with regard to the timing of the weekly injection within a range of 2–3 days; however, these hypotheses require confirmation.

BIF was well tolerated, and routine safety assessments in this study were unremarkable, but there was an imbalance in hypersensitivity reactions. Though none of these presented as systemic hypersensitivity, hypersensitivity and injection site reactions will be monitored during phase 3.

A unit definition for BIF was estimated using data from the BIF phase 1 program, but an important aim of the broader phase 2 program was to refine the unit definition based on glycemic outcomes from all relevant patient populations. Therefore, BIF was dosed in milligrams during the current study. As was done during development of basal insulin peglispro, efficacy outcomes from the phase 2 studies were used to inform a meta-analysis of a unit definition for all patient populations (15) rather than relying on a unit definition obtained from data derived from clamp studies that may not be sufficiently accurate for all intended patient populations. As all phase 2 trials are now complete, the current unit definition for weekly dosing is set at 1 mg of BIF being equivalent to 35 IU and will be confirmed when phase 3 is complete.

This study has several limitations. One limitation, common for phase 2 research, was the lack of generalizability to the broader insulin-naive T2D population. At the time of study conduct, there was limited phase 1 experience and no outpatient experience in this patient population or on a background therapy of GLP-1 analogs. With limited sample size, it was not possible to appropriately evaluate multiple concomitant medication subgroups, especially with drugs that create confounding issues from weight loss. It was therefore important to characterize a broad range of exposure/response and safety/tolerability so that BIF can be more safely and effectively studied with GLP-1 analogs and other oral agents as part of the larger, more diverse phase 3 program.

Another limitation required BIF dosing at the study site for the first 12 weeks of the study, and this lack of visit flexibility may have impacted patients' willingness to continue participation. This limitation is common across the BIF phase 2 program and is related to use of a lyophilized powder formulation, which also contributed to the lack of blinding because of differing appearance and dosage. These formulation-dependent issues will not be applicable in phase 3 when a prefilled pen formulation with dosing in international units will be used.

Compliance with collection of CGM was limited, and the system's reduced

accuracy in the hypoglycemic range limited the strength of interpretations from the CGM data. Although ~60% of patients provided valid data for the week 24–26 CGM session, improvements in the ambulatory glucose profiles were evident from baseline to week 26, which were supported by other indices of glycemic control.

The BIF dose adjustment algorithm was unusually complex compared with those commonly used with daily basal insulin because it was intended to serve as a manual, paper-based backup for dose adjustment in the event of technical issues with the digital algorithm. Despite this complexity, a potential strength of this study was the use of predefined dosing algorithms for both BIF and degludec using the same FBG target (80–100 mg/dL) for both treatments, which enabled comparisons between groups. Although the initiation and titration approaches differed between BIF (mg) and degludec (units), the titration used for degludec in this study has been used successfully in prior basal insulin studies. The results are consistent with expectations for degludec treatment in insulin-naive patients with T2D (17) and provided a robust frame of reference for the outcomes observed with weekly administration of BIF.

This phase 2 study was crucial for understanding how to dose BIF in insulin-naive patients and for determining the unit definition. The BIF dosing algorithm, albeit complex, was developed to accommodate the unique pharmacokinetics/pharmacodynamics of BIF and was not intended for the general clinical setting. It used an individualized starting dose strategy based on both body weight and FBG and a loading dose approach. This resulted in a range of BIF starting doses that was necessary to achieve an appropriate therapeutic concentration more quickly and to achieve FBG goals within the first 12–14 weeks for assessment of HbA_{1c} at 26 weeks. Ultimately, this approach resulted in effective titration to treatment target with minimal hypoglycemia risk. Data from this study will be used to develop a phase 3 dosing algorithm that is more consistent with commonly used approaches for daily basal insulin adjustment and less individualized. BIF is currently in phase 3 development, referred to as the Once Weekly Insulin Therapy (QWINT) program, and two studies are focusing on insulin-naive patients (QWINT-2 [ClinicalTrials.gov reg. no. NCT05362058] and QWINT-1 [ClinicalTrials.gov reg. no. NCT05662332]).

This study demonstrated the clinical utility and potential of BIF as a promising once-weekly basal insulin that will reduce the injection burden in insulin-naive patients with T2D. Once-weekly BIF achieved excellent glycemic control, with low rates of hypoglycemia similar to degludec titrated in a manner consistent with standard of care.

Acknowledgments. The authors thank all study participants and Kristen Syring, PhD, and Alastair Knights, PhD (Eli Lilly and Company), for medical writing assistance.

Funding. This study and medical writing assistance was funded by Eli Lilly and Company.

Duality of Interest. J.M.B.-V., C.M.K., C.M., J.C., Q.Z., E.C., W.L., and A.H. are employees and shareholders of Eli Lilly and Company. J.P.F. declares research support from Akero, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, 89bio, Eli Lilly and Company, Intercept, IONIS, Janssen, Madrigal, Metacrine, Merck, NorthSea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, and Sanofi and participation in speakers bureaus of Eli Lilly and Company and Sanofi and advisory boards or as a consultant for Akero, Altimmune, Axcella Health, Becton Dickenson, Boehringer Ingelheim, Carmot Therapeutics, Echosens, 89bio, Eli Lilly and Company, Gilead, Intercept, Metacrine, Merck, Novo Nordisk, Pfizer, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.M.B.-V., C.M.K., J.C., and A.H. conceptualized and designed the study. C.M., J.C., Q.Z., and E.C. contributed to the analysis of the data. W.L. provided trial and patient safety oversight. J.P.F. was an investigator in the trial. All authors contributed to the interpretation of the data and the critical review and final approval of the manuscript. J.M.B.-V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented orally at the 82nd Scientific Sessions of the American Diabetes Association, New Orleans, LA, 3–7 June 2022, and in poster form at the 58th Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, 19–23 September 2022.

References

1. American Diabetes Association Professional Practice Committee. 6. Glycemic targets: Standards of Medical Care in Diabetes-2022. Diabetes Care 2022;45(Suppl. 1):S83–S96

2. Stuckey H, Fisher L, Polonsky WH, et al. Key factors for overcoming psychological insulin resistance: an examination of patient perspectives through content analysis. BMJ Open Diabetes Res Care 2019;7:e000723

3. Blonde L, Brunton SA, Chava P, et al. Achievement of target A1C <7.0% (<53 mmol/mol) by U.S. type 2 diabetes patients treated with basal insulin in both randomized controlled trials and clinical practice. Diabetes Spectr 2019;32:93–103

4. 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;381:117–124

5. 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

6. Heise T, Chien J, Beals JM, et al. Pharmacokinetic and pharmacodynamic properties of the novel basal insulin fc (insulin efsitora alfa), an insulin fusion protein in development for once-weekly dosing for the treatment of patients with diabetes. Diabetes Obes Metab 2023;25:1080–90

7. Frias J, Chien J, Zhang Q, et al. Safety and efficacy of once-weekly basal insulin fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study. Lancet Diabetes Endocrinol 2023;11:158–68

8. Nishimura E, Pridal L, Glendorf T, et al. Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing. BMJ Open Diabetes Res Care 2021;9:e002301

9. Rosenstock J, Bajaj HS, Janež A, et al.; NN1436-4383 Investigators. Once-weekly insulin for type 2 diabetes without previous insulin treatment. N Engl J Med 2020;383:2107–2116

10. Lingvay I, Buse JB, Franek E, et al. A randomized, open-label comparison of once-weekly insulin icodec titration strategies versus once-daily insulin glargine U100. Diabetes Care 2021;44:1595–1603

11. Bajaj HS, Bergenstal RM, Christoffersen A, et al. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in type 2 diabetes inadequately controlled on daily basal insulin: a phase 2 randomized controlled trial. Diabetes Care 2021;44:1586–1594

12. Novo Nordisk. Novo Nordisk achieves primary objectives of ONWARDS 1 and 6 trials with once-weekly insulin icodec demonstrating superior reduction in HbA1c vs insulin glargine U100 in ONWARDS 1 [press release]. 3 June 2022. Accessed 12 January 2023. Available from https://www.globenewswire.com/news-release/2022/06/03/2455751/0/en/Novo-Nordisk-achieves-primary-objectives-of-ONWARDS-1-and-6-trials-with-once-weekly-insulin-icodec-demonstrating-superior-reduction-in-HbA1c-vs-insulin-glargine-U100-in-ONWARDS-1.html

13. Novo Nordisk. Novo Nordisk achieves primary objectives of ONWARDS 3 and 4 trials with once-weekly insulin icodec demonstrating superior reduction in HbA1c vs insulin degludec in ONWARDS 3 [press release]. 29 July 2022. Accessed 12 January 2023. Available from https://www.globenewswire.com/news-release/2022/07/29/2488672/0/en/Novo-Nordisk-achieves-primary-objectives-of-ONWARDS-3-and-4-trials-with-once-weekly-insulin-icodec-demonstrating-superior-reduction-in-HbA1c-vs-insulin-degludec-in-ONWARDS-3.html

14. Novo Nordisk. Once-weekly insulin icodec demonstrates superior reduction in HbA1c in combination with a dosing guide app versus once-daily basal insulin in people with type 2 diabetes in ONWARDS 5 phase 3a trial [press release].

3 October 2022. Accessed 12 January 2023. Available from https://www.globenewswire.com/news-release/2022/10/03/2526800/0/en/Once-weekly-insulin-icodec-demonstrates-superior-reduction-in-HbA1c-in-combination-with-a-dosing-guide-app-versus-once-daily-basal-insulin-in-people-with-type-2-diabetes-in-ONWARDS.html

15. Qu Y, Luo J, Garhyan P, Antalis CJ, Chang AM, Jacober SJ. Dose unit establishment for a new basal insulin using joint modeling of insulin dose and glycemic response. J Diabetes Sci Technol 2018;12:155–162

16. Heise T. The future of insulin therapy. Diabetes Res Clin Pract 2021;175:108820

17. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012;35:2464–2471