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Novel Once-Weekly Basal Insulin Fc Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes

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Novel Once-Weekly Basal Insulin Fc (BIF) Achieved Similar Glycemic Control With a Comparable Safety Profile Versus Insulin Degludec in Patients with Type 1 Diabetes (T1D)

Background

Once-weekly BIF combines a novel single-chain insulin variant with a human IgG2 Fc domain and is designed for once-weekly subcutaneous administration for the treatment of diabetes.

Patient Population

N = 266 people with T1D

62% male 38% female

Mean Baseline Characteristics:

Age = 46 years

Duration of T1D = 22 years

Baseline HbA_{1c} = 7.5%

Study Design

2-week screening/lead-in

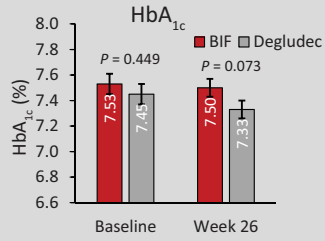
26-week treatment period

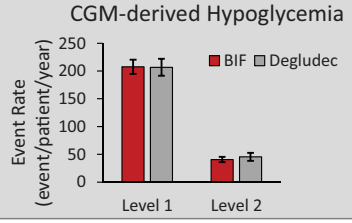
BIF administered once weekly

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 unblinded CGM (Dexcom G6)
- Assessed HbA_{1c}, fasting glucose, incidence and rate of hypoglycemia

Main Results





Conclusion

Once-weekly BIF demonstrated similar glycemic control compared with once-weekly degludec and no difference in hypoglycemia or other safety findings in patients with T1D.

ARTICLE HIGHLIGHTS

- Once-weekly basal insulin Fc (BIF) was administered as treatment for patients with type 1 diabetes (T1D).
- We wanted to determine if BIF is safe and efficacious for patients with T1D.
- BIF demonstrated similar glycemic control to daily insulin degludec, without increasing the risk of hypoglycemia in patients with T1D.
- BIF has the potential to safely and effectively provide glycemic control while reducing the injection burden in T1D.

Novel Once-Weekly Basal Insulin Fc Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes

Christof M. Kazda,[1] Juliana M. Bue-Valleskey,[2] Jenny Chien,[2] Qianyi Zhang,[2] Emmanuel Chigutsa,[2] William Landschulz,[2] Paula Wullenweber,[2] Axel Haupt,[2] and Dominik Dahl[3]

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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 safety and efficacy of BIF versus degludec in 265 patients with type 1 diabetes (T1D) using multiple daily injections.

RESEARCH DESIGN AND METHODS

During this randomized, parallel, open-label study, patients with T1D were randomized (1:1) to receive BIF once weekly or degludec once daily over the 26-week treatment period. Both groups were titrated to a fasting glucose level of 80–100 mg/dL. The primary end point was HbA_{1c} change from baseline to week 26 (noninferiority margin, 0.4%). Secondary end points included percent time in range (TIR) (70–180 mg/dL), continuous glucose monitoring (CGM) fasting glucose (FG) level, and rate of hypoglycemia.

RESULTS

After 26 weeks, patients receiving BIF had noninferior HbA_{1c} change from baseline versus those receiving degludec, with a statistically significant treatment difference of 0.17% (90% CI 0.01, 0.32; *P* = 0.07) favoring the comparator. Percent TIR was similar for patients in the BIF (56.1%) and degludec (58.9%; *P* = 0.112) groups at week 26. FG values were significantly higher for patients receiving BIF (158.8 mg/dL) versus degludec (143.2 mg/dL; *P* = 0.003). Rates of CGM-derived hypoglycemia were not statistically significantly different for BIF and degludec over 24 h for level 1 (*P* = 0.960) or level 2 (*P* = 0.517) hypoglycemia during the treatment period. Occurrence of serious adverse events was similar between the BIF and degludec groups.

CONCLUSIONS

Once-weekly BIF demonstrated noninferior glycemic control to once-daily degludec (treatment difference: 0.17% favoring degludec) and no difference in hypoglycemia or other safety findings in patients with T1D.

Patients with type 1 diabetes (T1D) require insulin therapy to control glycemia. However, only 21% of adults with T1D reached the American Diabetes Association

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target HbA_{1c} level of 7% between 2016 and 2018 (1,2). Innovations in the treatment of diabetes, such as continuous glucose monitoring (CGM) have led to improvements in HbA_{1c} (3,4). Advances in insulin delivery, like continuous subcutaneous insulin infusion, helped to further ease the significant emotional and physical burden of diabetes management and improve glycemic control (5). Despite these advances, further improvement is still necessary. One potential advancement is once-weekly basal insulin. For people with T1D treated with multiple daily basal injections, a once-weekly basal insulin would lead to the reduction from 365 basal insulin injections to 52 over the course of a year.

Basal Insulin Fc (BIF; LY3209590, insulin efsitora alfa) is a fusion protein combining a novel single-chain insulin variant with a human IgG2 Fc domain and designed for once-weekly administration (6). Previous phase 1 studies indicated that BIF has a low weekly peak to trough ratio (1.14, or $<$15% variation in insulin concentration) and half-life of 17 days (7). This low peak to trough ratio may result in more stable glucose levels both within and between days.

An effective once-weekly basal insulin would need to provide predictable pharmacokinetic and pharmacodynamic profiles without increasing the risk of hypoglycemia for patients with diabetes. Recently, a phase 2 study of patients with type 2 diabetes (T2D) previously treated with basal insulin indicated that BIF is safe and efficacious as a once-weekly treatment (8). In fact, BIF demonstrated noninferior glycemic control versus daily insulin degludec as measured by HbA_{1c} change from baseline to treatment end point.

The aim of the present phase 2 treat-to-target study was to assess the safety and efficacy of weekly BIF versus daily insulin degludec in patients with T1D previously treated with multiple daily basal injections.

RESEARCH DESIGN AND METHODS

Research Design

This was a multicenter, randomized, parallel, open-label, comparator-controlled phase 2 study conducted at 49 sites in Spain, Austria, Germany, Puerto Rico, and the U.S. The study consisted of three study periods: a 2-week lead-in period, a 26-week treatment period, and 5-week safety follow-up (Supplementary Fig. 1).

The trial was conducted in accordance with the principles of the Declaration of Helsinki guidelines and Good Clinical Practice guidelines. The trial was approved by independent ethics committees or institutional review boards at each site. All patients provided written, informed consent prior to participation. The trial is registered on clinicaltrials.gov (NCT04450407).

Patients

Eligible patients included people with T1D treated with multiple daily basal injections for at least 3 months prior to screening. Patients were adults (aged $\geq$18 years) who had a diagnosis of T1D and with a fasting C-peptide level $\leq$0.30 nmol/L; an HbA_{1c} value of 5.6% to 9.5%, inclusive; and a BMI $\leq$35 kg/m^2 with no substantial weight change ($\geq$5%) in the past 3 months. Patients were treated with a stable regimen of glargine (U-100 or U-300), detemir, or degludec (U-100 or U-200) as basal insulin and a stable regimen of lispro, aspart, FiAsp, or glulisine as bolus insulin. Inclusion and exclusion criteria are listed in Supplementary Table 1. Patients were recruited between 6 July 2020, and 22 January 2021.

Randomization

Patients were randomized 1:1 to BIF or degludec treatment groups, using an interactive web-response system. Those patients assigned to the BIF group followed a paper-based algorithm that provided guidance on BIF dosing initiation and titration. An additional BIF group that used a digital algorithm was discontinued because of technical issues leading to an unacceptable number of missing values and wrong data entries. Patients randomized to this BIF digital algorithm group (n = 16) were transitioned to the BIF paper algorithm, and the patients' data were included in the safety analysis but excluded from the efficacy analyses.

Procedures

During the screening and lead-in period, patients were trained on disease monitoring and management, study diaries, and study procedures. Patients were provided with and trained on an unblinded Dexcom G6 CGM device with set hypoglycemic alerts. The device was activated at week 1 to collect baseline CGM data.

BIF was provided to study sites as a lyophilized powder and was dosed in milligrams immediately after reconstitution. One goal of the phase 2 development program was to determine the appropriate IU conversion (from milligrams to IU) and to optimize the titration algorithm. Because conventional use of phase 1 data derived from clamp studies to determine the unit definition for ultra-long-acting insulins may not be accurate for all patient populations (9), phase 2 data were used for to determine the BIF unit definition for phase 3 development.

Patients randomized to the BIF treatment arm received one dose of BIF once weekly during the 26-week treatment period. Dose adjustments (details provided in the Supplementary Material) were based on the median fasting glucose level from CGM measurements obtained on at least 3 days during the previous week using a paper-based algorithm similar to the established Riddle algorithm (10). BIF was titrated weekly for weeks 1–12, then every 4 weeks through the end of the treatment period.

BIF was administered by site personnel at the site from weeks 0 to 8. The first BIF dose was a one-time loading dose administered on day 0, which was a threefold increase of the estimated weekly dose. This loading-dose approach was chosen on the basis of results of phase 1 studies to achieve steady-state concentrations more quickly and to avoid transient hyperglycemia. This first dose was calculated on the basis of baseline median fasting glucose level and the previously used dose of daily basal insulin (details provided in the Supplementary Material). For weeks 9–12 and 16, either study personnel or patients could administer BIF at the site. At weeks 13, 14, 15, and 17–25, BIF could be self-administered by patients at home or by study personnel at the site. Doses were administered on approximately the same day and at approximately the same time each week.

Patients randomized to the degludec treatment group self-administered degludec once daily (based on a modified Riddle algorithm [10]; details provided in the Supplementary Material) at approximately the same time each day. The modification of this algorithm was based on internal modeling with the

goal to optimize efficacy of the titration without increasing hypoglycemia risk.

Both BIF and degludec treatment groups had a fasting glucose target of 80–100 mg/dL (4.4 to <5.6 mmol/L), and the treatments were administered via subcutaneous injections, rotated among the left, right, upper, and lower abdominal quadrants. 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.

Patients continued their rapid-acting insulin treatment throughout the study. Investigators were responsible for adapting mealtime and correction bolus dosing according to standards of medical care.

Outcomes

The primary end point was to compare the efficacy of BIF with degludec as measured by the HbA_{1c} change from baseline to week 26. Daily fasting (pre-breakfast) glucose measurements were recorded by the patients in the eDiary using the value displayed on their CGM device. Additionally, two six-point glucose assessments from CGM were documented on nonconsecutive days in the week prior to weeks 0, 6, 12, 16, and 26. Glycemic variability was assessed by between- and within-day SD and coefficient of variation of the six-point glucose assessments. Fasting serum glucose level was measured at baseline and weeks 6, 12, 16, 24, and 26 via a central laboratory. The mean percent time patients spent in glucose ranges also was calculated.

Safety was monitored throughout the study. The incidence and rate of CGM-derived hypoglycemia, defined as a glucose value meeting the respective hypoglycemia threshold for at least three consecutive CGM readings (15 min), were assessed using the CGM database. Patient-reported, documented hypoglycemia was defined as any CGM reading <70 mg/dL and was based on the data recorded by the patients. Patients were encouraged to record hypoglycemia in their eDiary any time they experienced signs or symptoms regardless of glucose reading. Additionally, the incidence of treatment-emergent adverse events and clinical assessments, including physical examination, body weight, vital signs, electrocardiograms, and laboratory measures, were assessed.

Statistical Analysis

The sample size was determined such that a total of approximately 238 randomized patients, with approximately 190 completers, would provide >80% statistical power to demonstrate noninferiority for the primary objective with the following assumptions: true mean difference = 0%, SD of 1.1%, noninferiority margin of 0.4% (Diabetes Control and Complications Trial unit), and using two-sided α level of 0.1. All tests of treatment effects were conducted at a two-sided α level of 0.1, and all CIs are given at a two-sided 90% level.

Efficacy analyses were conducted on the efficacy population, which included randomized patients who took at least one dose of the study treatment and excluding those patients previously randomized to the discontinued BIF digital algorithm. The safety analysis was conducted on the safety population, which included all randomized patients who took at least one dose of study treatment.

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 during the study. The analysis data included data up to the discontinuation of study treatment.

The mixed-model repeated measures (MMRM) model was used with the HbA_{1c} changes at weeks 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 algorithm; degludec), country, visit, and treatment by visit interaction as fixed effects and the baseline value of the dependent variable as the covariate. Other efficacy measures were analyzed using the same MMRM model with the addition term of HbA_{1c} strata (<8.5%, ≥8.5%). The hypoglycemia event rates were analyzed by a negative binomial regression model.

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

Data and Resource Availability

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

RESULTS

Of the 266 patients with T1D who were randomized in this trial, 124 were randomized to the BIF paper-based algorithm and 126 were randomized to receive degludec. There were 139 patients included in the BIF-pooled arm (i.e., the safety population), including an additional 16 patients originally assigned to the discontinued BIF digital algorithm. Overall, 240 patients completed the study; 87.1% of patients randomized to BIF and 93.7% randomized to degludec completed the study. Patient disposition is provided in Supplementary Fig. 2.

Demographic and baseline characteristics were well balanced across both groups (Table 1). Approximately 62% of patients were male and the overall mean age of patients was 46.4 years. The mean ± SD HbA_{1c} was 7.49% ± 0.85% (58.4 ± 9.3 mmol/mol), BMI was 27.4 ± 4.0 kg/m^2 and the mean duration of diabetes was 22.1 ± 13.5 years. The mean daily basal insulin dose at randomization was similar between treatment arms (approximately 27 IU).

HbA_{1c} values over time are presented in Fig. 1*A*. With the treatment difference of 0.17% and the 90% CI of 0.01–0.32 for BIF versus insulin degludec, the change in HbA_{1c} from baseline to week 26 for BIF (0.04%) was noninferior to degludec (−0.13%), based on the prespecified noninferiority margin of 0.4%. The HbA_{1c} change from baseline to week 26 was significantly smaller for the BIF treatment compared with the degludec group ($P = 0.073$). The proportion of patients who achieved HbA_{1c} <7% was similar between treatment groups at week 26 (BIF 31.3% vs. degludec 37.1%; $P = 0.595$).

Fasting serum glucose values, assessed by a central laboratory, showed significant reductions at weeks 6, 12, 16, 24, and 26 for degludec ($P \leq 0.03$), whereas BIF fasting serum glucose levels remained similar over the treatment period (Supplementary Fig. 3). There was no statistically significant difference for change from baseline for fasting serum glucose (by the central laboratory) between treatment groups at week 26 (10.8 mg/dL [90% CI −1.9, 23.5]; $P = 0.161$). However, fasting glucose values as measured by CGM were significantly higher for the BIF group compared with the degludec group over the 26-week treatment period (Fig. 1*B*). The six-point glucose profiles demonstrated that glucose

Table 1—Baseline characteristics for randomized patients

Characteristic	Insulin degludec (*n* = 126)	BIF			Total (*N* = 265)
		Efficacy population (*n* = 123)	Algorithm 2 population (*n* = 16)	Pooled safety population (*n* = 139)	
Age, years	47.4 (13.7)	44.4 (14.9)	53.4 (16.3)	45.5 (15.3)	46.4 (14.5)
Female/male, %	38.1/61.9	39.8/60.2	25.0/75.0	38.1/61.9	38.1/61.9
Ethnicity, *n* (%)					
Hispanic or Latino	10 (7.9)	22 (17.9)	5 (31.3)	27 (19.4)	37 (14.0)
Non-Hispanic or Latino	116 (92.1)	100 (81.3)	11 (68.8)	111 (79.9)	227 (85.7)
Duration of diabetes years	22.3 (13.9)	21.7 (13.3)	23.9 (11.8)	22.0 (13.1)	22.1 (13.5)
HbA_{1c}, %	7.5 (0.9)	7.5 (0.9)	7.6 (0.7)	7.5 (0.8)	7.5 (0.9)
HbA_{1c}, mmol/mol	57.9 (9.5)	58.6 (9.3)	60.0 (7.6)	58.8 (9.1)	58.4 (9.3)
Fasting serum glucose, mg/dL	159.3 (67.1)	165.5 (68.4)	164.6 (66.4)	165.4 (67.9)	162.5 (67.5)
Fasting serum glucose, mmol/L	8.8 (3.7)	9.2 (3.8)	9.1 (3.7)	9.2 (3.8)	9.0 (3.7)
Weight, kg	82.0 (15.1)	81.0 (15.9)	83.9 (17.4)	81.3 (16.0)	81.6 (15.6)
BMI, kg/m^2	27.2 (4.1)	27.5 (4.0)	27.9 (4.1)	27.5 (4.0)	27.4 (4.0)
Basal insulin at baseline, *n* (%)					
Insulin degludec	58 (46.0)	52 (42.3)	4 (25.0)	56 (40.3)	114 (43.0)
Insulin detemir	4 (3.2)	5 (4.1)	0	5 (3.6)	9 (3.4)
Insulin glargine	64 (50.8)	66 (53.7)	12 (75.0)	78 (56.1)	142 (53.6)
eGFR group ($mL/min/1.73m^2$), *n* (%)					
≥30 to <60	3 (2.4)	4 (3.3)	0	4 (2.9)	7 (2.6)
≥60 to <90	44 (34.9)	33 (26.8)	9 (56.3)	42 (30.2)	86 (32.5)
≥90	79 (62.7)	86 (69.9)	7 (43.8)	94 (66.9)	172 (64.9)

Mean (SD) for continuous variables. eGFR, estimated glomerular filtration rate.

values were similar across both treatment groups for all other time points at baseline and week 26, except the statistically significantly higher CGM-based fasting glucose level for the BIF group compared with the degludec group at week 26 (Fig. 1*C*). There were no statistically significant differences between treatment groups for any glycemic variability measurements derived from CGM at week 26 (Supplementary Table 2).

There was no statistically significant difference in the percentage of TIR (70 to 180 mg/dL [3.9 to 10.0 mmol/L]) during the 24-h period or during the nighttime (midnight to 0600) between treatments at week 26. For the daytime period (0600 to 2400), patients in the BIF group spent a significantly smaller percentage of TIR compared with patients in the insulin degludec group at week 26 (least squares mean [LSM] −3.4% [90% CI −6.4, −0.5]; $P = 0.058$). At week 26, there were no statistically significant differences between BIF and insulin degludec in the percentage of time below range (≥54 and <70 mg/dL [3.0 to 3.9 mmol/L]), time below range (<54 mg/dL [3.0 mmol/L]), or time above range (181 to 250 mg/dL [10.1 to 13.9 mmol/L]) during the daytime, nighttime, and 24-h periods. Stable ambulatory glucose profiles from baseline to end point were observed for both treatment groups (Supplementary Fig. 4).

In the BIF arm, the weekly basal insulin dose remained stable after the initial loading dose (Supplementary Fig. 5*A*). Similarly, a significant basal insulin dose change was not observed in the degludec group from baseline during the 26-week treatment period. Daily rapid-acting insulin doses did not show statistically significant differences between treatments at baseline, week 12, or week 26 (Supplementary Fig. 5*B*). The use of rapid-acting insulin steeply increased in weeks 1 and 2 of BIF dosing as compared with insulin degludec. This was a compensatory increase in rapid-acting insulin use due to underdosing of BIF with the loading dose. When analyzed by meal, rapid-acting insulin doses showed a significant difference in change from baseline to week 26 between the BIF group and the degludec group for morning, midday, and evening meals. Patients in the BIF group had higher use of rapid-acting insulin doses at the morning meal and lower use of rapid-acting insulin administered at the midday and evening meals compared with the degludec group, which led to similar total rapid-acting dose between the treatment groups at week 26.

Patient-reported hypoglycemia rates showed the same between-treatment results as compared with CGM-derived events (Supplementary Table 3). Three severe hypoglycemic events were reported: 1 in the BIF group and 2 in the degludec group. Two of these events were treated with food and the patients recovered. The third event was self-treated with an energy drink and then the patient went to the emergency room with a blood glucose reading of 228 mg/dL. The patient recovered rapidly and was released. For the rates of CGM-derived hypoglycemia from weeks 0 to 26, there were no statistically significant differences observed between the BIF and degludec groups during the daytime, nighttime, or 24-h periods for level 1 (≥54 and <70 mg/dL) or level 2 (<54 mg/dL) hypoglycemia (Table 2). Furthermore, the duration of time in the hypoglycemic range over a 24-h period was similar for the BIF and degludec groups for level 1 (BIF: 28.4 min;

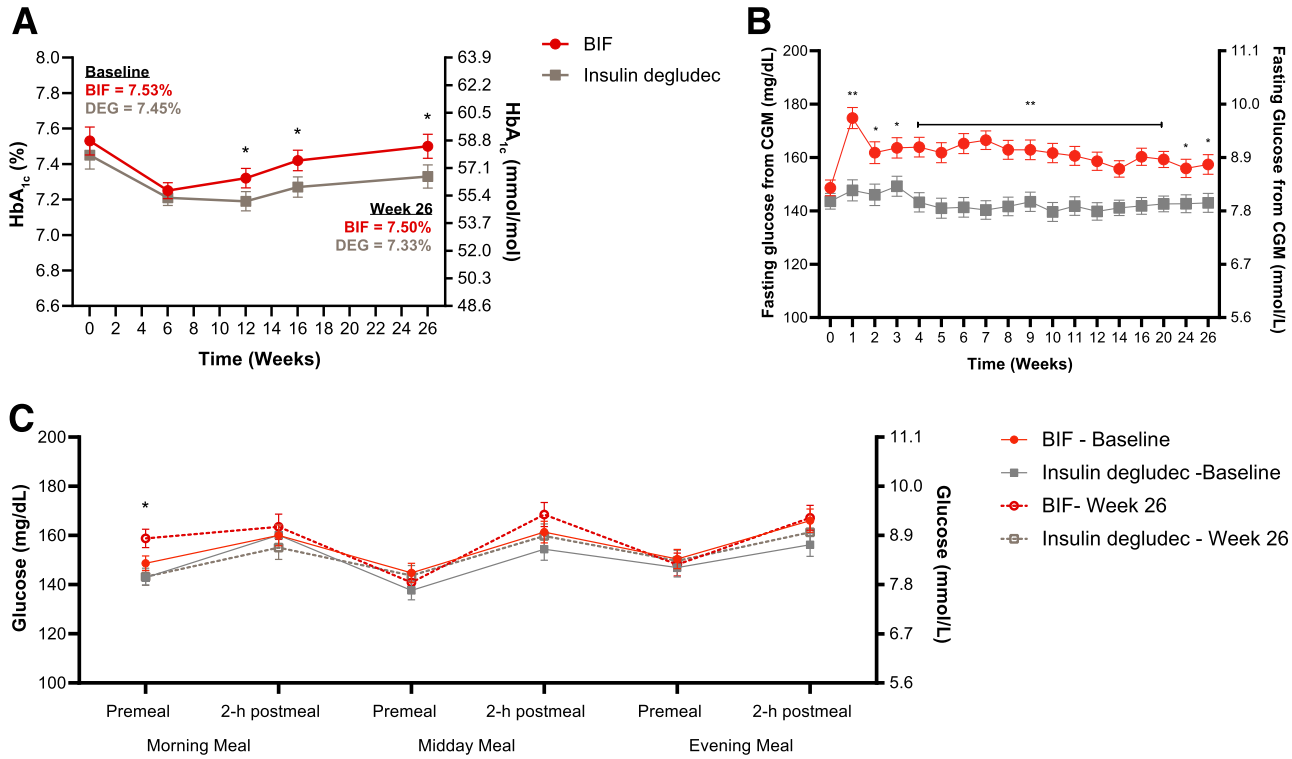

Figure 1—*A*: HbA_{1c} levels over the course of the 26-week treatment period. *B*: Fasting glucose based on CGM over the course of the 26-week treatment period. *C*: Six-point CGM-based glucose profiles at baseline and week 26. Data are presented as LSM ± SE. *$P < 0.1$ for BIF vs. insulin degludec. DEG, degludec.

degludec: 32.0 min; $P = 0.371$) and level 2 (BIF: 7.46 min; degludec: 7.89 min; $P = 0.816$) hypoglycemia. Duration of time in levels 1 and 2 hypoglycemic ranges over the 24-h period for BIF was independent of the day postinjection. No prolonged or repeated hypoglycemia events were observed.

Overall, BIF was well tolerated. The incidence and reporting of treatment-emergent adverse events were 59% and 46% for BIF and degludec, respectively (Supplementary Table 4). The imbalance was driven by injection-site reactions (BIF: $n = 8$; degludec, $n = 2$), but no statistically significant difference was observed ($P = 0.107$). This is a frequent finding with lyophilized powder formulations needing reconstitution before injection with a traditional syringe. The formulation for phase 3 will be delivered as a solution in a prefilled pen device to improve local tolerability. Another imbalance was observed for hypersensitivity reactions (reported by 4% of patients receiving degludec and 6.5% of patients receiving BIF). These reactions were not directly related to the time of injection and were rather unspecific in nature. Other safety data, including vital signs, clinical chemistry, hematology, and electrocardiogram assessments, did not differ between BIF treatment and insulin degludec. Additionally, there was a statistically significant difference in body weight gain between BIF (0.1 kg) and degludec (0.6 kg) at week 26 ($P = 0.028$), favoring BIF.

No statistically significant treatment differences in the percentage change from baseline to the end of the study for liver function tests were observed. A statistically significant treatment difference was observed in the percent change from baseline to the study end point for alkaline phosphatase between BIF (2.27%; SE 1.278) and degludec (−1.18%; SE 1.302; $P = 0.060$). Although a correlation between mean fasting serum glucose level and elevations in alkaline phosphatase has been reported (11), the observed changes are within the range of physiologic variability. Overall, one patient from each treatment group (0.8%) experienced at least one potential treatment-emergent hepatic disorder event by narrow search terms.

CONCLUSIONS

Simple, efficacious, once-weekly basal insulins have the potential to substantially lessen the patient burden of insulin therapy. However, patients with T1D are more vulnerable to inadequate basal insulin dosing than are patients with T2D, because of the former's lack of endogenous insulin production. Therefore, transitioning from a daily to a weekly basal insulin would need to be precise, and the ratio of basal to bolus insulin may need to be changed as the basal insulin coverage is adjusted with the new therapy. This 26-week, treat-to-target study was conducted using a conservative BIF titration algorithm to assess efficacy and safety in people with T1D. The study was designed prior to the results were available of the phase 2 study in patients with T2D previously treated with basal insulin (8).

Despite the challenges of transitioning a patient with T1D to a once-weekly basal insulin, BIF demonstrated an absolute treatment difference in HbA_{1c} change from baseline to week 26 of 0.17% ($P = 0.073$), compared with once-daily degludec, which was within the predefined noninferiority margin. The initial increase and continued small elevation (10–14 mg/dL) of the fasting glucose levels in the BIF study arm show that the experimental

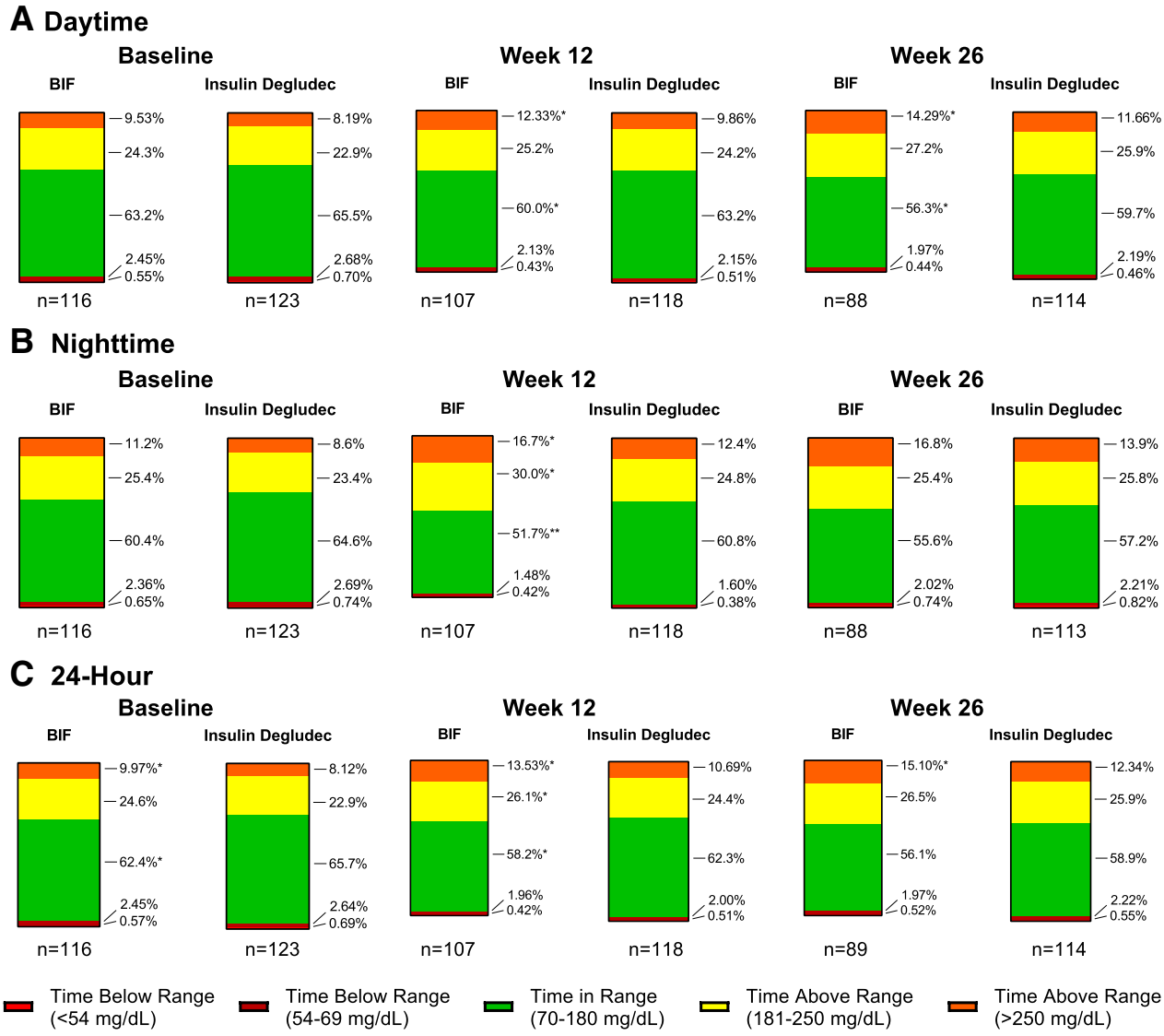

Figure 2—TIR parameters for 24-h period collected from assessments performed at baseline and after 12 and 26 weeks of treatment during the (*A*) daytime, (*B*) nighttime, and (*C*) 24-h period. Nighttime was defined as midnight to 0600. Data are presented as LSM ±SE. *$P < 0.1$ for BIF vs. insulin degludec; **$P < 0.001$ for BIF vs. insulin degludec.

treatment algorithm overestimated the potency of the novel weekly insulin and led to an insufficient up-titration. Retrospectively, when using all available pharmacokinetic and pharmacodynamic data from the phase 2 program, it became evident that BIF was initially underdosed by approximately 30% in this study. This resulted in an initial period of hyperglycemia and a compensatory increase in rapid-acting insulin to manage glycemia in the first couple of weeks. The titration algorithm was likely too conservative to efficiently compensate for the initial period of underdosing, because it had both

Table 2—CGM-derived hypoglycemia

	All hypoglycemia (24-h daily)			Nighttime hypoglycemia (midnight to 0600 h)			Daytime hypoglycemia (0600 to 2400 h)		
Hypoglycemia	*n* (%)	Event rate* (SE)	*P* value	*n* (%)	Event rate* (SE)	*P* value	*n* (%)	Event rate* (SE)	*P* value
Level 1									
BIF (*n* = 116)	116 (100)	207.6 (12.86)	0.960	113 (97.4)	40.1 (3.18)	0.604	116 (100)	170.8 (10.71)	0.623
Degludec (*n* = 123)	123 (100)	206.7 (15.22)		115 (93.5)	42.6 (3.82)		122 (99.2)	163.0 (11.88)	
Level 2									
BIF (*n* = 116)	108 (93.1)	40.7 (4.67)	0.517	84 (72.4)	11.3 (1.55)	0.450	101 (87.1)	29.2 (3.53)	0.227
Degludec (*n* = 123)	106 (86.2)	45.5 (7.19)		70 (56.9)	9.8 (1.69)		105 (85.4)	36.4 (5.63)	

*Rate per patient per year.

small dose increments (increases) and stringent hypoglycemia triggers for dose reduction. Despite this, glycemic control was only marginally different compared with degludec and reassuring that weekly insulin may also be a treatment option for T1D. Patients randomized to the degludec arm also did not achieve the target fasting glucose of 100 mg/dL. This was based on the stringent hypoglycemia criteria of the titration algorithm, which were similar in both treatment arms. The basis for the selection of such conservative titration algorithms was another 26-week treat-to-target study comparing degludec with detemir using a very aggressive titration algorithm with a fasting glucose target of 70–89 mg/dL and no mandatory basal insulin reductions for hypoglycemic events (12). Despite this aggressive algorithm, the mean end point HbA_{1c} with degludec was 7.3%, and 10.6% of participants experienced a severe hypoglycemic event during the trial. We considered such an aggressive algorithm as inappropriate for the first outpatient study with BIF.

There was no difference in incidence of hypoglycemia observed between BIF and degludec on the basis of patient-reported or CGM-derived measures. Although three severe hypoglycemic events were reported, no prolonged, repetitive hypoglycemic events were observed. Therefore, the hypothetical increased risk of hypoglycemia with a once-weekly insulin was not observed in this study when compared with current daily basal insulin. Insulin icodec, a once-weekly basal insulin currently finishing a phase 3 program, demonstrated noninferior efficacy compared with once-daily basal insulins, but there were statistically significant higher estimated rates of severe or clinically significant hypoglycemia in patients with T1D (13). The low weekly peak to trough ratio of BIF (1.14 (7)) may contribute to the comparable hypoglycemia rates between BIF and the best-in-class daily basal insulin, degludec (14). The daily fluctuations of insulin action of BIF are less pronounced compared with degludec. Within a week, the peak insulin concentration of BIF is spread over the course of days compared with the peak of a daily insulin, which is spread over a day. In the case of BIF, only 14% higher insulin concentrations are observed during the peak of the time-action profile compared with the injection day (7).

BIF was dosed in milligrams during this study because the unit conversion was not yet defined at the time the study was conducted. One aim of the full phase 2 program was to determine a unit definition that fits all patient populations and is based on the glycemic efficacy as measured by change in HbA_{1c} from baseline. As was done during development of basal insulin peg lispro, efficacy outcomes from the phase 2 studies were used to inform a meta-analysis of a unit definition for all patient populations (9) rather than relying on a unit definition obtained from data derived from clamp studies and phase 1 data. Such early data from phase 1 may not be sufficiently accurate for all intended patient populations and, for the present study, have shown an overestimation of potency based on our preliminary unit definition in phase 1. The unit definition of BIF has now been determined to be 35 IU weekly/mg for the formulation used in the phase 3 program.

A trend for more injection-site reactions and hypersensitivity reactions for BIF versus degludec was observed in this study using the lyophilized powder formulation of BIF. Injection-site reactions and hypersensitivity reactions will be monitored in our phase 3 program.

This study was limited by several factors. The study was open-label, which may have led to treatment bias. Also, as described above, BIF was underdosed during the study, which may have led to some glucose instability and small differences in HbA_{1c} between the study treatments. These small differences may have affected the hypoglycemia frequency, too. The requirement of BIF dosing at the site for the first 12 weeks of the study and the consecutive lack of visit interval flexibility may have influenced patients' willingness to continue the study when randomized to the BIF arm. Finally, the technical difficulties with the digital BIF algorithm led to its discontinuation.

However, the study strengths include the use of CGM with alarms throughout the study to mitigate risk for this population. Also, the same, strict target glucose of 100 mg/dL and predefined dosing algorithms for both treatment arms enabled easy comparison between groups.

Patients with T1D will still be a challenging population to transition from daily to weekly basal insulin therapy; however, BIF can potentially ease patient burden by reducing the number of basal insulin injections from 365 to 52 per year. The results of this trial were reassuring that, for some patients with T1D, weekly insulin may be a favorable treatment option. This phase 2 trial enabled us to improve the BIF algorithm in T1D using a meta-analysis of all pharmacokinetic and pharmacodynamic data from the phase 1 and phase 2 studies and have more certainty of the unit definition. In addition, we performed intensive pharmacokinetic and pharmacodynamic modeling in virtual patients with T1D to optimize the titration algorithm to improve glycemic outcomes without significantly increasing the risk for hypoglycemia. Those learnings are now implemented in the phase 3 trial for BIF in T1D (clinicaltrials.gov identifier NCT05463744) as part of the Once Weekly Insulin Therapy (QWINT) program.

In conclusion, once-weekly BIF demonstrated similar glycemic control compared with once-daily degludec and no difference in hypoglycemia or other safety findings in patients with T1D. These results suggest that BIF may be effectively used by patients with T1D and reduce patient burden.

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the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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