# 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

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## Summary

**Background** The burden of daily basal insulins often causes hesitancy and delays in the initiation of insulin therapy. Basal insulin Fc (BIF, insulin efsitora alfa), designed for once-weekly administration, is a fusion protein combining a novel single-chain insulin variant with a human immunoglobulin G (IgG) Fc domain. In this study, we explored the safety and efficacy of BIF in people with type 2 diabetes who had been previously treated with basal insulin.

**Methods** For this phase 2, 44-site (clinical research centres and hospitals), randomised, open-label, comparator-controlled, 32-week study in the USA, Puerto Rico, and Mexico, we enrolled participants with type 2 diabetes. Eligible participants had to be adults (aged ≥18 years) and to have been treated with basal insulin and up to three oral antidiabetic medicines. Participants were randomly assigned (1:1:1) to subcutaneous administration of BIF (BIF treatment group 1 [BIF-A1] or 2 [BIF-A2]) or insulin degludec. Randomisation was stratified by country, baseline $HbA_{1c}$ values (<8·5% or ≥8·5%; <69·4 or ≥69·4 mmol/mol), use of sulfonylureas (yes or no), and baseline BMI (<30 or ≥30 kg/m²). The randomisation scheme was performed using an interactive web-response system, which ensured balance between treatment groups. Different fasting glucose targets for the BIF-A1 (≤7·8 mmol/L or ≤140 mg/dL; titrated every 2 weeks), BIF-A2 (≤6·7 mmol/L or ≤120 mg/dL; titrated every 4 weeks), and degludec (≤5·6 mmol/L or ≤100 mg/dL) groups were selected. Patients randomly assigned to BIF received a one-time loading dose ranging from 1·5–3 times their calculated weekly dose. The first weekly dose was administered 1 week after the loading dose. We used interstitial fasting glucose measurements from the Dexcom G6 continuous glucose monitoring system to titrate the basal insulin. The primary measure of glycaemic control was change in $HbA_{1c}$ from baseline to week 32 for BIF. BIF was also compared with degludec (with a non-inferiority margin of 0·40%). The efficacy analysis set consisted of data from all randomised study participants who received at least one dose of the study medication and participants were analysed according to the treatment they were assigned. The safety population was the same as the efficacy analysis set. The completed trial is registered at ClinicalTrials.gov (NCT03736785).

**Findings** Between Nov 15, 2018 and Feb 18, 2020, 399 participants were enrolled and randomised to BIF-A1 (n=135), BIF-A2 (n=132), or degludec (n=132); 202 (51%) were female and 197 (49%) were male. 379 were analysed for the primary outcome (BIF-A1: n=130; BIF-A2: n=125; degludec: n=124). Mean HbA1c change from baseline to week 32, the primary outcome, was –0·6% (SE 0·1%) for BIF-A1 and BIF-A2. Degludec achieved a change from baseline of –0·7% (0·1%). The pooled BIF analysis achieved non-inferiority versus degludec for the treatment difference in HbA1c (0·1% [90% CI –0·1 to 0·3]). The hypoglycaemia (≤3·9 mmol/L or ≤70 mg/dL) event rates (hypoglycaemia events per patient per year) in the BIF groups were 25% lower than those in the degludec group (treatment ratio BIF-A1 *vs* degludec was 0·75 [0·61–0·93]; and BIF-A2 *vs* degludec was 0·74 [0·58–0·94]). BIF was well tolerated; treatment-emergent adverse events were similar across groups.

**Interpretation** Weekly BIF achieved a similar efficacy compared with degludec despite higher fasting glucose targets in the BIF groups. Higher fasting glucose targets and lower glucose variability might have contributed to lower hypoglycaemia rates for BIF compared with degludec. These findings support continued development of BIF as a once-weekly insulin treatment for people with diabetes.

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## Introduction

The treatment of type 2 diabetes frequently requires the addition of basal insulin as the disease progresses if patients do not achieve glycaemic targets.[1] Although treatment guidelines recommend that intensification of therapy with basal insulin should not be delayed,[2,3] there is often hesitation from both health-care providers and patients to initiate insulin therapy.[4–6] The perception that insulin places a substantial burden on patients, the fear of injections, the fear of the potential complications, and

## Research in context

### Evidence before this study

We searched PubMed using the terms "basal insulin", "insulin degludec", "once-weekly insulin", and "type 2 diabetes", with no date or study duration restrictions. Articles not published in English were excluded. For people with type 2 diabetes who fail to achieve their glycaemic targets, current treatment guidelines recommend that intensification of therapy with basal insulin should not be delayed. Once-weekly basal insulin Fc (BIF) is a novel fusion protein combining a single-chain insulin variant with a human immunoglobulin G (IgG) Fc domain. BIF has previously shown a flat pharmacokinetic profile, a low peak-to-trough ratio, and a sustained reduction in fasting blood glucose in phase 1 trials. Its safety profile was reported to be similar to that of daily basal insulins.

### Added value of this study

To our knowledge, this is the first randomised clinical trial to compare the efficacy and safety of a once-weekly BIF fusion protein with daily basal insulin. Treatment with weekly BIF for 32 weeks resulted in improvement in $HbA_{1c}$ compared to baseline (primary outcome). Weekly BIF treatment demonstrated non-inferiority in $HbA_{1c}$ reduction compared with treatment with daily insulin degludec, despite titrating BIF to higher fasting glucose targets than we did for degludec. Overall, the safety and tolerability profile of BIF was similar to that of insulin degludec, but with a lower rate of hypoglycaemia. The key finding was that people with type 2 diabetes who were treated with basal insulin were able to switch to BIF using a loading dose, without loss of glycaemic control, and were able to safely up-titrate the BIF dose using a simple titration algorithm.

### Implications of all the available evidence

Weekly BIF treatment resulted in stable glycaemic control in people with type 2 diabetes previously treated with basal insulin. The reduced treatment burden of once-weekly insulin compared with daily insulin has the potential to improve treatment adherence and positively affect glycaemic outcomes. These BIF data show promise for patients who require insulin treatment intensification. These findings support continued development of BIF as a once-weekly insulin treatment of diabetes.

the misconception that the need for insulin is a personal failure all contribute to this hesitancy,[6,7] which can ultimately lead to delays in insulin initiation.[8–11] Additionally, in patients who start basal insulin, adherence to daily insulin therapy has been shown to be suboptimal in real-world studies.[12]

Medication non-adherence in people with type 2 diabetes leads to poor glycaemic outcomes, specifically $HbA_{1c}$.[13–15] A retrospective meta-analysis of electronic medical records showed that only about 28% of patients with type 2 diabetes treated with once-daily basal insulin achieved a target $HbA_{1c}$ of less than 7·0% (or 53·0 mmol/mol) at 6 months and only about 27% achieved this target at 12 months.[16]

Once-weekly insulin, given that it requires less frequent injections than daily insulin, might have the potential to improve patients' self-management and health-related quality of life,[17,18] which could ultimately improve adherence and persistence with therapy. A study that compared once-weekly GLP-1 receptor agonists with once-daily GLP-1 receptor agonist therapy in people with type 2 diabetes, in which both treatments led to improvements in glycaemia,[19] showed a significant improvement in medication adherence in those receiving once-weekly GLP-1 receptor agonists.[20]

Once-weekly basal insulin Fc (BIF; also known as insulin efsitora alfa or LY3209590) is a fusion protein combining a novel single-chain variant of insulin with a human immunoglobulin G (IgG) Fc domain developed for the treatment of people with type 1 or type 2 diabetes. BIF has a half-life of 17 days, which allows for once-weekly dosing, and results in a flat pharmacokinetic profile with a peak-to-trough ratio of 1·14 at steady state.[21]

This study is the first phase 2 study of weekly BIF. Our aim was to explore the efficacy and characterise the safety profile of BIF in a 32-week study in people with type 2 diabetes who had been previously treated with basal insulin and oral antidiabetic medications.

## Methods

### Study design

This is a phase 2, multicentre, randomised, open-label, comparator-controlled study with three study periods. The study was completed at 44 sites (clinical research centres and hospitals) in the USA, Puerto Rico, and Mexico. The protocol was approved by the institutional review boards at each site and the trial was done in accordance with local regulations, the principles of the Declaration of Helsinki, the International Ethical Guidelines by the Council of International Organizations of Medical Sciences, and Good Clinical Practice guidelines. The completed trial is registered at ClinicalTrials.gov (NCT03736785), where the study protocol is available.

### Participants

To be eligible, participants had to be adults (aged ≥18 years) with type 2 diabetes and a BMI between 20 and 45 kg/m², inclusive, and an $HbA_{1c}$ value between 6·5% and 10·0% (or 47·5 and 85·8 mmol/mol), inclusive, at screening. Participants must have been treated with at least 10 units per day and less than 1·5 units/kg per day of insulin glargine, insulin detemir, or insulin degludec, with or without up to three oral

antidiabetic medications for 3 months before screening. Participants' sex was recorded by site personnel. All participants provided written informed consent.

### Randomisation and masking

Participants were randomly assigned in a 1:1:1 ratio, using a computer-generated random sequence, to receive BIF (Eli Lilly and Company; Indianapolis, IN, USA) algorithm 1 (BIF-A1 group), BIF algorithm 2 (BIF-A2 group), or insulin degludec (Novo Nordisk; Bagsværd, Denmark; degludec group). Randomisation was stratified by country, baseline $HbA_{1c}$ values (<8·5% or ≥8·5%; <69·4 or ≥69·4 mmol/mol), use of sulfonylureas (yes or no), and baseline BMI (<30 or ≥30 kg/m²). The randomisation scheme was performed using an interactive web-response system, which ensured balance between treatment groups. Site personnel could confirm that they located the correct study drug by entering a confirmation number found on the drug label into the interactive web-response system. Insulin degludec served as an unblinded active comparator.[22]

### Procedures

The study consisted of three periods: a 2-week screening period, a 32-week treatment period, and a 5-week safety follow-up period (appendix p 10). During the screening period, participants continued the same formulation and dose of the previously used insulin therapy and oral antidiabetic drugs. Oral antidiabetic medications were continued throughout the treatment period. The last dose of the participants' previous daily basal insulin was taken on day –1. The Dexcom G6 continuous glucose monitoring (CGM) system (Dexcom; San Diego, CA, USA) was used in an unblinded mode starting at randomisation (day 0) and through the entire 32-week treatment period.

See Online for appendix

Patients randomly assigned to BIF received a one-time loading dose ranging from 1·5–3 times their calculated weekly dose (appendix p 1). The loading and initial weekly doses were based on their previous daily basal insulin dose and their glycaemic control stratified by baseline $HbA_{1c}$ (using a threshold of 8·5% [or 69·4 mmol/mol]). Therefore, the loading and initial weekly dose included a correction for inadequate glucose control. We chose the loading dose on the basis of results of phase 1 studies that tried to achieve a pharmacokinetic exposure close to the steady-state exposure within the first week of dosing and to avoid transient hyperglycaemia. The first weekly dose was administered 1 week after the loading dose. The dosing of BIF in the phase 2 programme used mg steps and not insulin international units (IU), to help establish the clinically correct mg-to-IU conversion factor in all relevant populations. The conversion factor used in this study was calculated on the basis that 1 mg of BIF equals 49 IU, which would translate into a daily dose of 7 IU of a daily basal insulin.

BIF was provided as a lyophilised powder, which required reconstitution with a sterile solution (water for injection or physiological sodium chloride) before administration. BIF was then administered subcutaneously, rotating between the left and right abdominal regions; first, BIF was injected by site personnel and subsequent doses were administered by the participant. We used interstitial fasting glucose measurements from the Dexcom G6 CGM system to titrate the basal insulin. The study was a typical treat-to-target study. BIF-A1 targeted a fasting glucose concentration of less than or equal to 140 mg/dL (7·8 mmol/L) titrated every 2 weeks, and BIF-A2 targeted a fasting glucose concentration of less than or equal to 120 mg/dL (6·7 mmol/L) titrated every 4 weeks. Insulin degludec targeted a fasting glucose concentration of less than or equal to 100 mg/dL (5·6 mmol/L) titrated weekly. To ensure patient safety in the first large outpatient study with this insulin, higher blood glucose targets were chosen for BIF than for insulin degludec, as there was a theoretical risk of prolonged hypoglycaemia with a once-weekly insulin. Additionally, all patients were on an unblinded CGM system. We used a dosing algorithm modified from Riddle and colleagues[22] for insulin degludec (administered subcutaneously), and we adjusted BIF in mg increments with a similar expected pharmacodynamic response as insulin degludec.

We used the following glucose measurements throughout the study: (1) serum glucose from a central laboratory; (2) plasma glucose equivalents from self-monitored plasma glucose based on the CGM sensor; and (3) analysis of time in glucose ranges using CGM outputs. For the serum glucose analysis, we collected blood from the participants, allowed it to clot, and then we collected the serum and analysed it for glucose. Fasting plasma glucose was documented each day by the participant using the value displayed on the CGM device after wakening or using a finger-stick glucose measurement. For fasting plasma glucose, we calculated baseline, week 12, and week 32 data as the average of the 4–7 days before. Two 6-point self-monitored plasma glucose profiles (before and 2 h after the morning, midday, and evening meals) were documented on non-consecutive days. Fasting serum glucose was measured during a fasted state at baseline, and at week 6, 12, 18, 28, and 32. $HbA_{1c}$ was measured at week 0, 6, 12, 18, 28, and 32, and bodyweight was measured at week 0, 3, 6, 12, 18, 28, and 32, at about the same time in the morning after an overnight fast.

Participants had a comprehensive efficacy and safety evaluation approximately 1 week after the last dose of the study drug and a safety follow-up visit approximately 6 weeks after the last dose of the study drug. Additional visits during this 5-week follow-up period were based on clinical necessity as determined by the investigator.

### Outcomes

The primary objective of this study was to explore the efficacy of BIF in participants with type 2 diabetes in the two BIF groups. This study was not designed as a typical parallel study using between-treatment comparison as

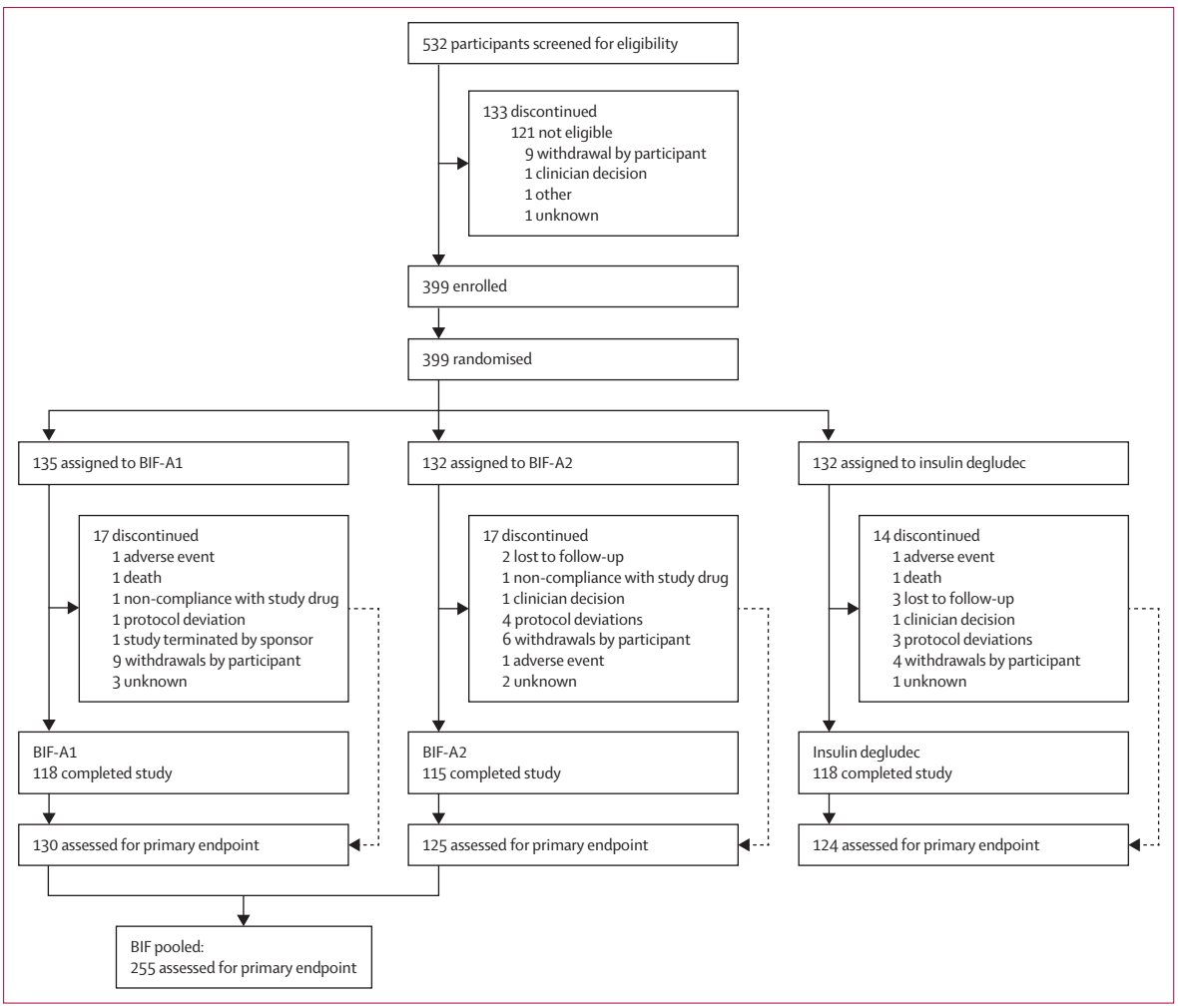


***Figure 1:*** **Trial profile**
The efficacy analysis set (N=398) included all randomised participants who received at least one dose of study drug (one participant assigned to BIF-A2 did not receive any dose). BIF-A1=once weekly basal insulin Fc algorithm 1. BIF-A2=once weekly basal insulin Fc algorithm 2.

the primary objective because all three treatment groups used different titration targets, which would confound the between-treatment comparison. $HbA_{1c}$ change from baseline to week 32 for BIF, given in DCCT (Diabetes Control and Complications Trial) units, was the primary endpoint. The non-inferiority margin compared with insulin degludec was 0·40% (DCCT units). $HbA_{1c}$ change from baseline to week 12, fasting serum glucose change from baseline to weeks 12 and 32, incidence and rate of hypoglycaemia, incidence of treatment-emergent adverse events, bodyweight change from baseline to weeks 12 and 32, time in target glucose range, and the association between insulin dose and efficacy ($HbA_{1c}$, fasting glucose) were also assessed to support the mg-to-IU conversion assessment.

Safety analyses included adverse events, clinical laboratory parameters, vital signs, and hypoglycaemia. We analysed the rate and incidence of hypoglycaemic episodes. Participants collected information about hypoglycaemic events throughout the study in their diary. Participants were trained before the treatment period about signs and symptoms of hypoglycaemia and how to treat it. Because the participants were wearing an unblinded CGM device throughout the study, all CGM hypoglycaemia alarms (at 70 mg/dL [3·9 mmol/L] and at 55 mg/dL [3·1 mmol/L]) were encouraged to be documented by the participants in their diaries. Hypoglycaemic event data were participant-reported and required a CGM reading of less than or equal to 70 mg/dL (3·9 mmol/L); there was no duration requirement for the participant-reported hypoglycaemic events. Documented hypoglycaemia was defined as an event with a plasma glucose concentration of less than or equal to 70 mg/dL (3·9 mmol/L) or less than 54 mg/dL (3·0 mmol/L) for more severe hypoglycaemia. Nocturnal hypoglycaemia was defined as any event that occurred between the participants' bedtime and waking. Participants had an

| | Insulin degludec (n=132) | BIF-A1 (n=135) | BIF-A2 (n=132) | BIF pooled (n=267) |
|---|---|---|---|---|
| Sex | | | | |
| Female | 65 (49%) | 67 (50%) | 70 (53%) | 137 (51%) |
| Male | 67 (51%) | 68 (50%) | 62 (47%) | 130 (49%) |
| Age, years | 60·8 (10·0) | 60·2 (9·9) | 59·6 (11·3) | 59·9 (10·6) |
| Weight, kg | 87·1 (20·7) | 90·6 (19·5) | 88·1 (18·9) | 89·4 (19·2) |
| Race | | | | |
| American Indian/ Alaska native | 19 (14%) | 16 (12%) | 18 (14%) | 34 (13%) |
| Asian | 6 (5%) | 4 (3%) | 5 (4%) | 9 (3%) |
| Black or African American | 10 (8%) | 16 (12%) | 10 (8%) | 26 (10%) |
| White | 94 (71%) | 97 (72%) | 97 (74%) | 194 (73%) |
| Ethnicity | | | | |
| Hispanic or Latin American ethnic origin | 73 (55%) | 67 (50%) | 78 (59%) | 145 (54%) |
| Country | | | | |
| Mexico | 21 (16%) | 21 (16%) | 19 (14%) | 40 (15%) |
| USA, including Puerto Rico | 111 (84%) | 114 (84%) | 113 (86%) | 227 (85%) |
| BMI, kg/m² | 31·8 (5·7) | 32·5 (5·9) | 32·4 (5·8) | 32·5 (5·9) |
| $HbA_{1c}$, % | 8·1 (0·9) | 8·2 (0·9) | 8·0 (0·9) | 8·1 (0·9) |
| $HbA_{1c}$, mmol/mol | 65·4 (9·6) | 66·1 (9·5) | 64·2 (9·8) | 65·2 (9·7) |
| FSG, mg/dL | 144·5 (51·0) | 140·6 (52·9) | 141·7 (47·5) | 141·2 (50·2) |
| FSG, mmol/L | 8·0 (2·8) | 7·8 (2·9) | 7·9 (2·6) | 7·8 (2·8) |
| Duration of diabetes, years | | | | |
| Mean (SD) | 15·1 (8·0) | 15·0 (8·5) | 14·1 (9·1) | 14·6 (8·8) |
| Median (IQR) | 14·7 (9·6–19·6) | 12·9 (8·6–20·5) | 12·7 (7·6–18·7) | 12·8 (7·8–19·6) |
| eGFR groups, mL/min per 1·73m² | | | | |
| ≥30 to <60 | 14 (11%) | 9 (7%) | 9 (7%) | 18 (7%) |
| ≥60 to <90 | 56 (42%) | 48 (36%) | 61 (46%) | 109 (41%) |
| ≥90 | 62 (47%) | 78 (58%) | 62 (47%) | 140 (52%) |
| Sulfonylureas treatment at study entry, yes | 36 (27%) | 43 (32%) | 37 (28%) | 80 (30%) |

Data are n (%) or mean (SD), unless otherwise stated. BIF-A1=once weekly basal insulin Fc algorithm 1. BIF-A2=once weekly basal insulin Fc algorithm 2. eGFR=estimated glomerular filtration rate. FSG=fasting serum glucose.

***Table 1:*** **Demographics and baseline characteristics of the randomised population**

efficacy and safety evaluation after 32 weeks of treatment exposure and a safety follow-up about 5 weeks after week 32.

### Statistical analysis

The sample size calculation was based on the secondary objective as basing the calculation on the between-group analysis is a more conservative approach and would provide more power to the within-group analyses. 375 randomised participants in 1:1:1 ratio, with about 300 completing the study (100 per treatment group), would provide 90% statistical power to demonstrate the non-inferiority (with a margin of 0·40%) of pooled BIF to insulin degludec for the change in $HbA_{1c}$ from weeks 0 to 32, with assumptions of no difference between treatment, an SD of 1·1%, at a two-sided alpha level of 0·1, and a 20% dropout rate in 32 weeks. The upper bound of the CI was used to establish non-inferior $HbA_{1c}$ change from baseline. The non-inferiority margin was based on US Food and Drug Administration guidance.[23]

The efficacy analysis set consisted of data from all randomised study participants who received at least one dose of the study medication (efficacy analysis set), excluding data after using rescue medication or stopping study medication. Participants were analysed according to the treatment they were assigned. The safety population was the same as the efficacy analysis set, and safety analyses included all data up to the end of the study.

The primary efficacy measure was analysed by a mixed-model repeated measures (MMRM) model using data from the efficacy analysis set. The MMRM model included treatment, country, BMI strata, sulfonylureas use at baseline, visit, and treatment-by-visit interaction as fixed effects and baseline $HbA_{1c}$ as a covariate (appendix p 5). For the MMRM model, the missing data were handled implicitly and thus no other imputation was conducted.

For other continuous variables, including the CGM measures, we used either an MMRM model or analysis of covariance to evaluate the treatment impact. For the binary variables, we used Fisher's exact test or a logistic regression model for treatment comparison. The hypoglycaemia event rates were analysed by a negative binomial regression model and we used the event rate ratio for treatment comparisons.

No multiplicity adjustment was done for this study because this is a phase 2 study with a fairly small number of participants. In total, two interim analyses were pre-planned and performed during the course of the trial. One interim analysis was of select safety, efficacy, and pharmacokinetic data after 50% of study participants had completed 6 weeks of treatment and a subsequent interim analysis was done when all study participants completed 12 weeks of treatment. The data from these interim analyses were not shared with investigators and only used internally by the sponsor to ascertain the safety and efficacy of the algorithms and to plan for future studies. No changes to the protocol resulted from these interim analyses.

The primary estimand supports the interpretation of the treatment efficacy effect as participants adhere to study treatment and is free from the confounding effect of rescue medications. The attributes of the estimand were: (1) treatment: randomised treatment; (2) population: all randomised study participants with at least one dose of study medication (BIF or insulin degludec); (3) intercurrent event handling: treatment discontinuation for any reason and initiation of rescue medication were both handled according to the missing-at-random assumption; (4) variable of interest: $HbA_{1c}$ change from baseline to week 32; (5) summary measure: least-squares mean.

The investigator was responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data. An electronic data capture system was used for the

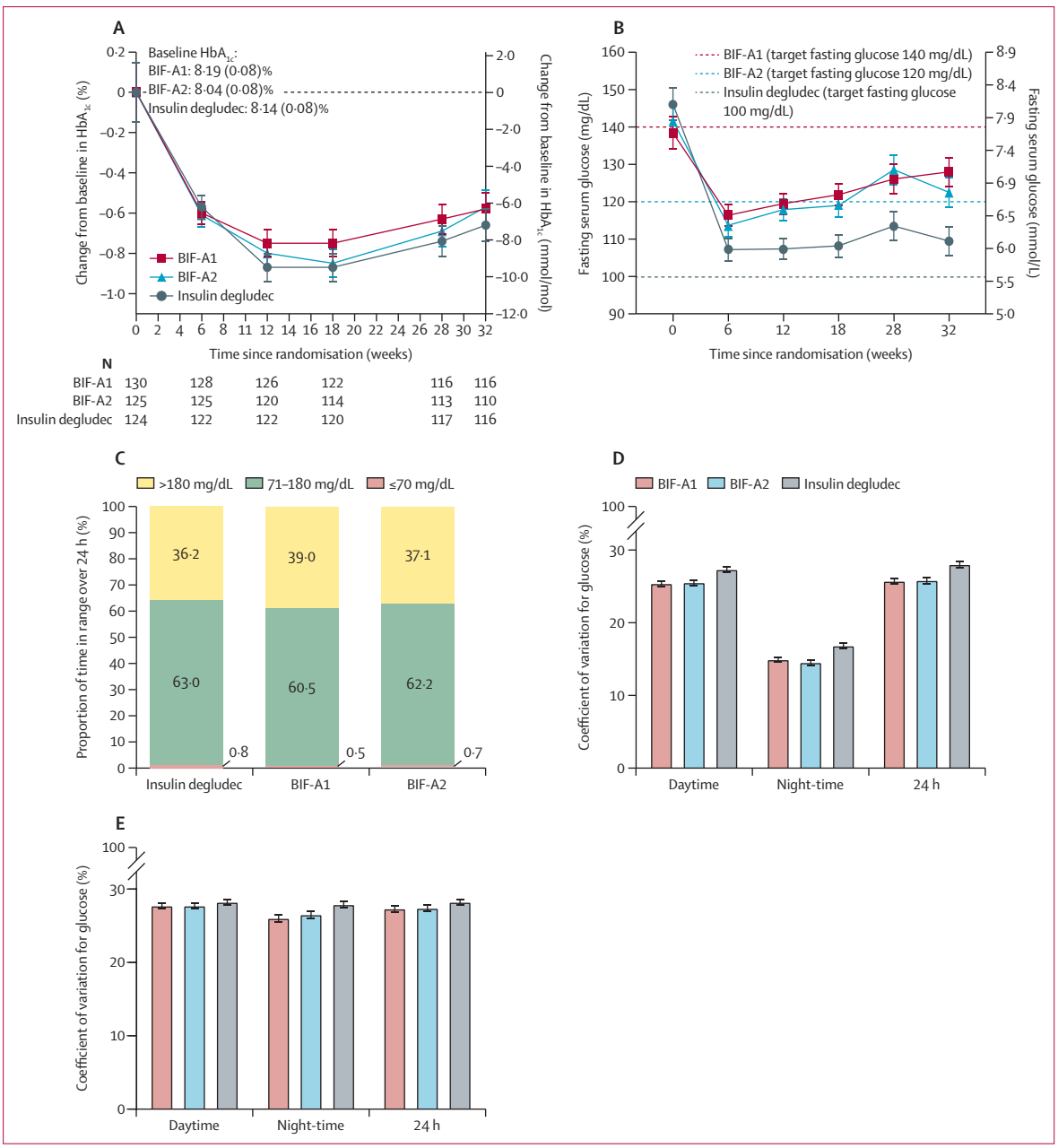


***Figure 2:*** **Glycaemic control**

Data are least-squares mean (SE), unless otherwise stated. (A) $HbA_{1c}$ values over time from the MMRM analysis. All treatment groups had a significant change from baseline at every timepoint (p<0·001). (B) Fasting serum glucose values over time from the MMRM analysis. (C) Proportion of the 24-h period in hypoglycaemic (≤70 mg/dL), hyperglycaemic (>180 mg/dL), and target (71–180 mg/dL) blood glucose range between week 0 and 32. (D) Within-day glycaemic variability from CGM values for baseline to week 32 from an analysis of covariance. (E) Between-day glycaemic variability from CGM values for baseline to week 32 from an analysis of covariance. BIF-A1=once weekly basal insulin Fc algorithm 1. BIF-A2=once weekly basal insulin Fc algorithm 2. CGM=continuous glucose monitoring. MMRM=mixed-model repeated measures.

collection of data. Statistical analysis was completed using SAS Enterprise, version 7.1 or above.

### Role of the funding source

The funder of the study was involved in the study design, data collection, data review, data analysis, and drafting of the report (by providing medical writing support).

## Results

Between Nov 15, 2018 and Feb 18, 2020, 532 study participants with type 2 diabetes were screened, and 399 were randomised (figure 1). Of the 399 participants, 135 were randomised to the BIF-A1 group, 132 were randomised to the BIF-A2 group, and 132 were randomised to the insulin degludec group. 48 participants

| | Insulin degludec (n=124) | BIF-A1 (n=130) | BIF-A2 (n=125) | BIF pooled (n=255) |
|---|---|---|---|---|
| **Primary analyses** | | | | |
| $HbA_{1c}$, % | | | | |
| Baseline | 8·1 (0·1) | 8·2 (0·1) | 8·0 (0·1) | 8·1 (0·1) |
| Change from baseline at week 32 | −0·7 (0·1) | −0·6 (0·1) | −0·6 (0·1) | −0·6 (0·1) |
| Difference in change from baseline *vs* insulin degludec (90% CI) | NA | 0·1 (−0·1 to 0·3) | 0·1 (−0·1 to 0·3) | 0·1 (−0·1 to 0·3) |
| $HbA_{1c}$, mmol/mol | | | | |
| Baseline | 65·5 (0·9) | 66·1 (0·9) | 64·4 (0·9) | 65·2 (0·6) |
| Change from baseline at week 32 | −7·2 (0·9) | −6·3 (0·9) | −6·2 (0·9) | −6·2 (0·7) |
| Difference in change from baseline *vs* insulin degludec (90% CI) | NA | 0·9 (−1·2 to 3·1) | 1·0 (−1·1 to 3·2) | 1·0 (−0·9 to 2·8) |
| **Secondary analyses** | | | | |
| Fasting plasma glucose by SMPG, mg/dL | | | | |
| Baseline | 148·8 (3·5) | 149·8 (3·4) | 147·2 (3·5) | 148·5 (2·5) |
| Change from baseline at week 32 | −32·7 (2·0) | −16·8 (2·0) | −17·3 (2·1) | −17·0 (1·4) |
| Difference in change from baseline *vs* insulin degludec (90% CI) | NA | 15·9 (11·2 to 20·6) | 15·4 (10·7 to 20·2) | 15·7 (11·6 to 19·8) |
| Fasting plasma glucose by SMPG, mmol/L | | | | |
| Baseline | 8·3 (0·1) | 8·3 (0·2) | 8·2 (0·2) | 8·3 (0·1) |
| Change from baseline at week 32 | −1·8 (0·1) | −0·9 (0·1) | −1·0 (0·1) | −0·9 (0·1) |
| Difference in change from baseline *vs* insulin degludec (90% CI) | NA | 0·9 (0·6 to 1·1) | 0·9 (0·6 to 1·1) | 0·9 (0·6 to 1·1) |
| Proportion of participants achieving $HbA_{1c}$ <7%, n (%) | | | | |
| Baseline | 14 (11%) | 11 (8%) | 11 (9%) | 22 (9%) |
| Change from baseline at week 32 | NA | NA | NA | NA |
| Odds ratio (90% CI) week 32 *vs* insulin degludec | NA | 1·5 (0·9 to 2·6) | 1·0 (0·6 to 1·8) | 1·3 (0·8 to 2·0) |
| Bodyweight, kg | | | | |
| Baseline | 87·1 (1·7) | 90·6 (1·7) | 88·2 (1·7) | NA |
| Change from baseline at week 32 | 2·0 (0·3) | 1·0 (0·3) | 1·0 (0·3) | NA |
| Difference in change from baseline *vs* insulin degludec (90% CI) | NA | −1·0 (−1·7 to −0·2) | −1·0 (−1·8 to −0·2) | NA |

Data are least-squares mean (SE) or n (%). BIF-A1=once weekly basal insulin Fc algorithm 1. BIF-A2=once weekly basal insulin Fc algorithm 2. CGM=continuous glucose monitoring. NA=not applicable. SMPG=self-monitored plasma glucose.

***Table 2:*** **Measures of efficacy from randomisation to week 32 for the participants with at least one dose of study medication**

discontinued after randomisation, most of them due to participant withdrawal. The baseline characteristics were well balanced across treatment groups. Overall, the mean age was 60·2 years (SD 10·4) and 202 (51%) were female (table 1). Mean BMI was 32·2 kg/m² (SD 5·8). Mean $HbA_{1c}$ at baseline was 8·1% (SD 0·9; or 65·2 mmol/mol [9·6]), and mean fasting serum glucose was 142·3 mg/dL (SD 50·4; or 7·9 mmol/L [2·8]). The mean daily basal insulin dose at randomisation was similar between treatment groups (about 39 IU).

The three treatment groups showed improvements in $HbA_{1c}$ from baseline to week 32 (figure 2A; table 2). The treatment difference for $HbA_{1c}$ change from baseline between pooled BIF and insulin degludec groups was 0·1% (90% CI −0·1 to 0·3); pooled BIF achieved non-inferiority versus insulin degludec. BIF-A1 and BIF-A2 also demonstrated non-inferiority against insulin degludec for change in $HbA_{1c}$ from baseline to week 32, on the basis of the 0·40% non-inferiority margin. There were no significant differences in $HbA_{1c}$ between either BIF treatment and insulin degludec at any timepoint during the 32-week treatment period. Furthermore, the proportion of patients who achieved an $HbA_{1c}$ concentration of less than 7·0% (or 53 mmol/mol) was similar across the three treatment groups from baseline to week 32 (table 2).

The three treatment groups showed an improvement in fasting serum glucose at week 32 compared with baseline (figure 2B), and each group was within approximately 10 mg/dL of the pre-specified fasting glucose target at week 32. Both BIF-A1 and BIF-A2 had significantly higher fasting serum glucose values than insulin degludec at week 12 and week 32, reflecting the difference in fasting glucose targets of the three treatment groups. Furthermore, there were significant differences in change from baseline fasting serum glucose between the BIF groups and insulin degludec (BIF-A1 *vs* insulin degludec=18·5 mg/dL [9·1–27·8]; BIF-A2 *vs* insulin degludec=13·0 mg/dL [3·4–22·5]). However, there was no difference in fasting serum glucose between the two BIF treatment groups.

BIF-A1 and BIF-A2 had significantly higher glucose values before the morning meal (treatment difference=0·86 mmol/L [0·60–1·11] and 0·84 mmol/L [0·58–1·10]; p≤0·001;) and 2 h after the morning meal

(treatment difference = 0·94 mmol/L [0·38–1·50]; p=0.006 and 1·03 [0·46–1·60]; p=0·003) compared with insulin degludec during the 6-point self-monitored plasma glucose profile at week 32, reflecting the difference in fasting glucose targets (appendix p 11). The glucose values at all other timepoints were similar across the treatment groups.

The CGM data revealed that the proportion of a 24-h time period spent in range (71–180 mg/dL or 3·9–10·0 mmol/L), in hyperglycaemia (>180 mg/dL or >10·0 mmol/L), and in hypoglycaemia (≤70 mg/dL or ≤3·9 mmol/L) was similar for the three treatments during the 32-week treatment period (figure 2C). During the 24-h period, less than 1% was spent in hypoglycaemia and more than 60% was spent in range for all three treatment groups. People in the BIF-A1 group spent significantly less time in hypoglycaemia (≤70 mg/dL; 3·9 mmol/L) during the night time (0000 h to 0600 h) compared with insulin degludec for the 32-week treatment period (treatment difference=–0·46% [–0·74 to –0·18]; p=0·008). There were no significant differences during the daytime. Similarly, there were no treatment differences in time spent in the hypoglycaemic range of less than 54 mg/dL (3·0 mmol/L) at any period.

Within-day glycaemic variability, as measured by CGM (coefficient of variation for glucose [%]), was significantly lower during the daytime, night-time, and 24-h periods for BIF-A1 and BIF-A2 than for insulin degludec, and BIF-A1 and BIF-A2 had significantly less between-day glycaemic variability during the night-time period than did insulin degludec (figure 2D–E; appendix pp 6–7).

The change from the first weekly dose to the week 32 dose was 9·26 mg to 9·17 mg for BIF-A1 and 8·71 mg to 9·02 mg for BIF-A2, whereas the daily dose in the insulin degludec group changed from 39·03 IU to 56·58 IU from baseline to week 32.

People in the BIF-A1 and BIF-A2 groups had significantly smaller increases in bodyweight from baseline to week 32 (1·0 kg) compared with those in the insulin degludec group (2·0 kg); BIF-A1 *vs* insulin degludec=–1·0 kg [90% CI –1·7 to –0·2]; p=0·037; BIF-A2 *vs* insulin degludec=–1·0 kg [–1·8 to –0·2], p=0·035; table 2).

The mean exposure to study medication for each group was 208·7 days for BIF-A1, 207·3 days for BIF-A2, and 205·8 days for insulin degludec. 352 (88%) of 398 total participants who received at least one dose of study drug were exposed to the study drug for at least 183 days. The exposure in total person-years for each group was 77·2 person-years for BIF-A1, 74·3 person-years for BIF-A2, and 74·4 person-years for insulin degludec. Overall, there were six participants with treatment-emergent anti-drug antibodies (two in the BIF-A1 group; three in the BIF-A2 group; one in the insulin degludec group; appendix p 8).

BIF, as with all weekly administered drugs, has a weekly and not a daily peak-to-trough profile. Therefore, it is important to analyse the time spent in hypoglycaemia as a function of day post-injection of BIF. Results showed that the time spent in hypoglycaemia (<54 and ≤70 mg/dL; <3·0 and ≤3·9 mmol/L), as measured by CGM, was similar across all 7 days after BIF administration (appendix p 12).

The event rates of all documented hypoglycaemia (≤70 mg/dL [≤3·9 mmol/L]) were about 25% lower and those for nocturnal hypoglycaemia were at least 33% lower from baseline to week 32 for BIF-A1 and BIF-A2 compared with insulin degludec; the event rate ratios for these categories of level 1 hypoglycaemia were significantly lower for BIF-A1 and BIF-A2 *vs* insulin degludec. The event rate (events per patient per year) for all documented level 2 hypoglycaemia (<54 mg/dL [<3·0 mmol/L]) was 2·2 for BIF-A1, 2·4 for BIF-A2, and 3·0 for insulin degludec. These differences did not reach statistical significance. The event rate ratios for level 1 non-nocturnal and all categories of level 2 hypoglycaemia (ie, non-nocturnal, nocturnal, 24-h) were consistently lower for BIF than for insulin degludec but were not statistically significant (table 3).

| | BIF-A1 (n=135) | BIF-A2 (n=131) | Insulin degludec (n=132) |
|---|---|---|---|
| **Documented 24-h hypoglycaemia (≤70 mg/dL; ≤3·9 mmol/L)** | | | |
| Incidence | 124 (91·85%) | 117 (89·31%) | 117 (88·64%) |
| Event rate | 23·0 | 22·5 | 30·5 |
| Event rate ratio (90% CI) | 0·75 (0·61–0·93) | 0·74 (0·58–0·94) | .. |
| **Documented nocturnal hypoglycaemia (≤70 mg/dL; ≤3·9 mmol/L)** | | | |
| Incidence | 105 (77·78%) | 88 (67·18%) | 105 (79·55%) |
| Event rate | 7·6 | 6·5 | 11·4 |
| Event rate ratio (90% CI) | 0·67 (0·52–0·85) | 0·57 (0·43–0·74) | .. |
| **Documented non-nocturnal hypoglycaemia (≤70 mg/dL; ≤3·9 mmol/L)** | | | |
| Incidence | 119 (88·15%) | 107 (81·68%) | 113 (85·61%) |
| Event rate | 15·0 | 16·2 | 19·0 |
| Event rate ratio (90% CI) | 0·79 (0·62–1·02) | 0·86 (0·65–1·12) | .. |
| **Documented 24-hr hypoglycaemia (<54 mg/dL; <3·0 mmol/L)** | | | |
| Incidence | 66 (48·89%) | 68 (51·91%) | 76 (57·58%) |
| Event rate | 2·2 | 2·4 | 3·0 |
| Event rate ratio (90% CI) | 0·72 (0·50–1·04) | 0·78 (0·48–1·26) | .. |
| **Documented nocturnal hypoglycaemia (<54 mg/dL; <3·0 mmol/L)** | | | |
| Incidence | 39 (28·89%) | 32 (24·43%) | 46 (34·85%) |
| Event rate | 1·0 | 0·8 | 1·2 |
| Event rate ratio (90% CI) | 0·83 (0·53–1·29) | 0·67 (0·43–1·05) | .. |
| **Documented non-nocturnal hypoglycaemia (<54 mg/dL; <3·0 mmol/L)** | | | |
| Incidence | 45 (33·33%) | 52 (39·69%) | 56 (42·42%) |
| Event rate | 1·2 | 1·5 | 1·8 |
| Event rate ratio (90% CI) | 0·66 (0·42–1·01) | 0·79 (0·46–1·37) | .. |

Incidence data are reported as the number of participants (proportion of participants [%]). Event rate data are presented as events per patient per year. Event rate ratio is the ratio of the BIF event rate to the insulin degludec event rate and is presented as the ratio (90% CI). Documented hypoglycaemia is defined as an event associated with a plasma glucose concentration of less than or equal to 70 mg/dL (≤3·9 mmol/L) or less than 54 mg/dL (<3·0 mmol/L). Nocturnal hypoglycaemia is defined as any event that occurs between the participants bedtime and waking. BIF-A1=once weekly basal insulin Fc algorithm 1. BIF-A2=once weekly basal insulin Fc algorithm 2.

***Table 3:*** **Hypoglycaemic events from randomisation to week 32**

| | Insulin degludec (n=132) | BIF-A1 (n=135) | BIF-A2 (n=131) | BIF pooled (n=266) |
|---|---|---|---|---|
| **Adverse events** | | | | |
| Serious adverse event | 10 (8%) | 7 (5%) | 8 (6%) | 15 (6%) |
| Treatment-emergent adverse event | 74 (56%) | 79 (59%) | 87 (66%) | 166 (62%) |
| Treatment-emergent adverse event related to study treatment | 6 (5%) | 8 (6%) | 16 (12%) | 24 (9%) |
| **Adverse event of special interest** | | | | |
| Administration site conditions | 1 (1%) | 1 (1%) | 4 (3%) | 5 (2%) |
| Hypersensitivity events | 3 (2%) | 4 (3%) | 10 (8%) | 14 (5%) |
| Major cardiovascular events | 3 (2%) | 1 (1%) | 1 (1%) | 2 (1%) |
| Severe hypoglycaemia | 0 | 0 | 2 (2%) | 2 (1%) |

Data are n (%). The safety analysis population consisted of all randomised participants with at least one dose of study medication (n=398). BIF-A1=once weekly basal insulin Fc algorithm 1. BIF-A2=once weekly basal insulin Fc algorithm 2.

*Table 4:* **Adverse events from randomisation to week 32**

Two severe hypoglycaemic events were reported in the BIF-A2 group. No severe hypoglycaemic events were reported in the BIF-A1 or insulin degludec groups. Both participants recovered quickly and without sequelae after ingesting oral carbohydrates. BIF was well tolerated with no clinically significant changes in clinical laboratory evaluations, vital signs, or electrocardiograms. Reported treatment-emergent adverse events were similar across the three treatment groups (table 4). The most frequently reported treatment-emergent adverse events were upper respiratory tract infections (7%) and diarrhoea (5%). Overall, 33 treatment-emergent serious adverse events were reported by 25 participants; there were no significant differences between treatments. Six confirmed deaths and non-fatal cardiovascular adverse events (two cardiovascular deaths [one in the BIF-A1 group and one in the insulin degludec group], three myocardial infarctions and percutaneous coronary interventions [two in the BIF-A2 group and one in the insulin degludec group], and one stroke [in the insulin degludec group]) were reported. None of the deaths were considered related to the treatment. Six participants reported treatment-emergent injection site reactions; the incidence of the events was similar across the three treatment groups.

Liver enzymes and standard safety laboratories were monitored from randomisation to the end of the study. There were no significant treatment differences in the percent change from baseline to week 32 for alkaline phosphatase, aspartate transaminase, and bilirubin or other safety laboratory values (appendix p 8). No cases of liver alanine aminotransferase elevations more than 3 times the upper limit of normal were detected during the study. All markers of peripheral insulin action (ie, free fatty acids and triglycerides), as well as other lipid parameters, showed a similar pattern for the three study groups. No other unusual laboratory findings were observed.

## Discussion

This is the first treat-to-target, basal-switch study comparing the efficacy and safety of BIF with insulin degludec in people with type 2 diabetes who had been previously treated with basal insulin. Treatment with BIF for 32 weeks resulted in improvement in glycaemic control compared to baseline as measured by change in $HbA_{1c}$ (primary outcome). BIF demonstrated non-inferiority in $HbA_{1c}$ change compared with insulin degludec. Time in range and proportion of patients reaching the target of less than 7% were also similar between the BIF and degludec groups, suggesting no clinically relevant difference in glycaemic control. All insulins were successfully titrated towards their given fasting glucose targets, with insulin degludec achieving the lowest fasting serum glucose value. The risk of documented and nocturnal hypoglycaemia was significantly lower with BIF than with insulin degludec. Furthermore, the similar time spent with hypoglycaemia across all 7 days after BIF administration is in line with the low peak-to-trough ratio of 1·14.[21] The within-day and between-day (night-time) glycaemic variability of BIF were both significantly lower than that of insulin degludec.

BIF is the second once-weekly insulin in development and has shown clinical utility for the treatment of people with diabetes, with a similar efficacy and safety profile as insulin degludec. Another study also used a loading dose approach with insulin icodec and showed an improvement in time in range, as measured by CGM, compared with insulin glargine in a similar patient population.[24] However, the fasting glucose target of 130 mg/dL (7·2 mmol/L) for insulin glargine used in the insulin icodec study was higher than the stricter target of 100 mg/dL (5·6 mmol/L) used for insulin degludec in this trial. Another study in patients initiating insulin therapy with a target pre-breakfast blood glucose target of 70–108 mg/dL (3·9–6·0 mmol/L) reported similar glycaemic control between insulin icodec and insulin glargine.[25] However, an odds ratio of 1·84 for hypoglycaemic events and 1·70 for clinically significant hypoglycaemia was reported favouring insulin glargine over insulin icodec. It is reassuring that there were no observed cases of persistent prolonged hypoglycaemia in the insulin icodec trials.

There are similarities and differences between BIF and insulin icodec. Both insulins benefit from a loading dose, at least in patient populations previously treated with insulin, to avoid transient hyperglycaemia and to reach a pharmacokinetic steady state within days. It seems that higher fasting glucose target ranges provide a safety margin and still achieve glycaemic efficacy similar to daily basal insulins. Furthermore, daily insulin fluctuations, which are seen with current daily basal insulins, should be minimised by both weekly insulin compounds.[26] However, the two weekly insulins are very different molecules. Insulin icodec is an acylated insulin with a half-life of 8 days (196 h), while BIF is an Fc fusion protein with

a longer half-life of 17 days.[21,25,27] Thus, loading doses will be different for these two weekly insulins. For insulin icodec, the loading dose was 2 times that of the pre-trial weekly insulin dose, while BIF seems to work well with a 3-times higher loading dose. BIF has a weekly peak-to-trough ratio of 1·14.[21] Thus, BIF has a stable pharmacokinetic profile during all days of the week with just 14% more insulin action at the maximum observed concentration ($C_{max}$) day.[21] The low peak-to-trough ratio might have led to the favourable hypoglycaemia profile seen in this study. There was no increase of hypoglycaemia on a specific day after injection of BIF, and, as expected for a weekly insulin, BIF improved glycaemic variability (within-day and between-day) compared with insulin degludec.

However, the interpretation of the presented data has limitations. As insulin degludec has been titrated to a stricter fasting glucose target, the differences in fasting glucose achieved and rate of hypoglycaemia observed must be interpreted with this stricter target in mind. Larger, phase 3 studies are needed to evaluate whether such a benefit could be realised with the same fasting glucose target. However, the higher fasting glucose targets were necessary as the safety of participants for this first, large, outpatient trial was of utmost importance. Notably, BIF fasting serum glucose values at week 32 were still within the American Diabetes Association-recommended fasting glucose range,[2] and glycaemic control improved from baseline. Additionally, the primary outcome was the change in $HbA_{1c}$ from baseline to week 32 within the BIF groups, to assess the efficacy of the two different dosing algorithms, not the comparison between BIF and the comparator (insulin degludec). Furthermore, patients in the insulin degludec group might have benefited from the investigators having more experience with daily insulin titration in contrast to the novel weekly dosing. The patient population was limited geographically to the USA, Mexico, and Puerto Rico, potentially limiting the generalisability of the study.

Another limitation was that this study could not be blinded since the exact mg-to-IU conversion for BIF was not yet available at the start of the trial. BIF was not titrated with IU but with mg increments. The increments were chosen to be similar to the dose increment of insulin degludec but were not precisely defined. This approach was taken because a unit definition for ultra-long-acting insulins, based on phase 1 data derived from clamp studies, might not be accurate for all patient populations. Therefore, one objective of the phase 2 studies, including this one, was to inform a meta-analysis of a unit definition for the phase 3 trials. This type of analysis was previously performed for basal insulin peg lipsro with good accuracy.[28] Finally, although two pre-planned interim analyses were performed during the trial, the results were strictly retained at the sponsor level and not communicated to the study sites. Therefore, the study conduct was not affected by the interim analyses, and so no impact on the overall quality of the study data was expected.

The study also had strengths. It included a large type 2 diabetes population with a diverse and equally distributed oral antidiabetic medicine background, including sulfonylureas. Furthermore, the long duration of the study enabled both insulins to reach the target fasting glucose levels. As a quality parameter in this study, insulin degludec achieved a very strict fasting glucose target of less than 110 mg/dL (6·1 mmol/L), which is in line with other sponsor-conducted research with insulin degludec.[29] Finally, the use of CGM for all participants throughout the duration of the trial allowed for a detailed assessment of glycaemic control and hypoglycaemia, and minimised reporting bias of hypoglycaemic episodes. All groups of this study had a much higher hypoglycaemia reporting rate than did those for studies without CGM.[30,31]

The presented safety data indicate that there is no increased risk with BIF treatment compared with insulin degludec. No difference in the occurrence of treatment-emergent antidrug antibodies was observed between the BIF and insulin degludec groups, which is consistent with this well established time extension platform previously used with dulaglutide.

In conclusion, in people with type 2 diabetes previously treated with basal insulin, once-weekly BIF did not show meaningful differences from once-daily insulin degludec in terms of safety and efficacy. The findings suggest that weekly insulin dosing is a viable option for this patient population and might provide the benefit of more stable glycaemic control with reduced treatment burden. Further phase 2 studies were conducted to evaluate BIF in people with type 1 diabetes (NCT04450407) or type 2 diabetes (insulin-naive patients; NCT04450394) compared with insulin degludec with a strict glycaemic target of 100 mg/dL (5·6 mmol/L). Together, these studies informed a large, phase 3 programme, entitled Once Weekly Insulin Therapy (QWINT), that is currently underway.

#### Contributors

JC, AH, and CK conceptualised and designed the study. JF was an investigator in the trial. PW and WL provided trial and patient safety oversight. JC, QZ, and EC contributed to the analysis of the data. JF, JC, QZ, KS, AH, and CK contributed to the interpretation of the data. KS, AH, and CK contributed to manuscript writing. QZ and CK had full access to and verified all the study data and were responsible for the decision to submit for publication. All authors contributed to the critical review and final approval of the manuscript. All authors affirm the accuracy and completeness of the data and attest to the fidelity of the trial to the protocol.

#### Declaration of interests

JF declares research support from Allergan, AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly and Company, Intercept, Janssen, Madrigal, Metacrine, Merck, NorthSea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, Sanofi, and Theracos. JF is also on the speaker bureau from Merck and Sanofi and has participated in advisory boards or as a consultant for Altimmune, Axcella Health, Boehringer Ingelheim, Coherus Therapeutics, Echosens, 89bio, Eli Lilly and Company, Gilead, Intercept, Merck, Novo Nordisk, and Sanofi. JC, QZ, EC, WL, KS, PW, AH, and CK are all employees of Eli Lilly and Company. JC, QZ, EC, WL, PW, AH, and CK are shareholders of Eli Lilly and Company

### Data sharing

Anonymised participant data obtained or analysed during the current study are available from the corresponding author upon reasonable request. Proposals will be reviewed and approved by the sponsor and investigator on the basis of scientific merit. After approval of a proposal, data can be shared through secure online platforms after a data access agreement is signed. All data will be made available for a minimum of 5 years from the end of the trial. The study protocol is available online at ClinicalTrials.gov (NCT03736785).

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