More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial

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OBJECTIVE

To compare insulin glargine 300 units/mL (Gla-300) versus insulin degludec 100 units/mL (IDeg-100) in this first head-to-head randomized controlled trial.

RESEARCH DESIGN AND METHODS

BRIGHT (NCT02738151) was a multicenter, open-label, active-controlled, two-arm, parallel-group, 24-week, noninferiority study in insulin-naive patients with uncontrolled type 2 diabetes. Participants were randomized 1:1 to evening dosing with Gla-300 (*N* = 466) or IDeg-100 (*N* = 463), titrated to fasting self-monitored plasma glucose of 80–100 mg/dL. The primary end point was HbA_{1c} change from baseline to week 24. Safety end points included incidence and event rates of hypoglycemia.

RESULTS

At week 24, HbA_{1c} improved similarly from baseline values of 8.7% (72 mmol/mol) in the Gla-300 group and 8.6% (70 mmol/mol) in the IDeg-100 group to 7.0% (53 mmol/mol)—least squares mean difference −0.05% (95% CI −0.15 to 0.05) (−0.6 mmol/mol [−1.7 to 0.6])—demonstrating noninferiority of Gla-300 versus IDeg-100 ($P < 0.0001$). Hypoglycemia incidence and event rates over 24 weeks were comparable with both insulins, whereas during the active titration period (0–12 weeks) the incidence and rate of anytime (24-h) confirmed hypoglycemia (≤70 and <54 mg/dL) were lower with Gla-300. Both insulins were properly titrated and exhibited no specific safety concerns.

CONCLUSIONS

Gla-300 and IDeg-100 provided similar glycemic control improvements with relatively low hypoglycemia risk. Hypoglycemia incidence and rates were comparable with both insulins during the full study period but lower in favor of Gla-300 during the titration period. The choice between these longer-acting basal insulins may be determined by factors such as access and cost, alongside clinical considerations.

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Long-acting basal insulin analogs represented a significant advance in the management of diabetes, providing longer duration of action, flatter action profiles (1), and less day-to-day variability than NPH insulin, with lower risk for hypoglycemia (1). Basal insulin analogs contributed to an important translational clinical advancement in the treatment of patients with type 2 diabetes, allowing for the development of the treat-to-target concept (2) that could be facilitated more easily with these longer-acting basal insulin analogs with less hypoglycemia. Currently, basal insulin analogs are increasingly used not only by endocrinologists but also by general practitioners.

Further pharmacokinetic/pharmacodynamic (PK/PD) improvements have been made with the even longer-acting second-generation basal insulin analogs insulin degludec 100 units/mL (IDeg-100) and insulin glargine 300 units/mL (Gla-300) (3–5), which have smoother PK/PD profiles than insulin glargine 100 units/mL (Gla-100) with lower variability (3,5). The BEGIN and EDITION clinical trial development programs for IDeg-100 and Gla-300, respectively, demonstrated similar HbA_{1c} reductions to Gla-100 but with less hypoglycemia in people with type 2 diabetes (6,7). However, direct clinical comparisons between these two second-generation basal insulin analogs are unavailable, except for two head-to-head PK/PD insulin clamp comparisons in type 1 diabetes (8,9) that showed conflicting results.

Here we report on the BRIGHT study, the first head-to-head randomized clinical trial designed to compare the efficacy and safety of Gla-300 with IDeg-100 in participants with type 2 diabetes inadequately controlled with oral agents with or without glucagon-like peptide 1 receptor agonists (GLP-1 RAs).

RESEARCH DESIGN AND METHODS

Study Design and Participants

BRIGHT (reg. no. NCT02738151, ClinicalTrials.gov) was a multicenter (158 sites, 16 countries), open-label, randomized, active-controlled, two-arm, parallel-group, 24-week noninferiority study in adult participants with uncontrolled type 2 diabetes (HbA_{1c} ≥7.5% [≥58 mmol/mol] and ≤10.5% [≤91 mmol/mol] at screening) on oral agents, including sodium–glucose cotransporter 2 (SGLT2) inhibitors, with or without GLP-1 RAs. Exclusion criteria included current or previous use of insulin, initiation of new glucose-lowering medications and/or weight-loss drug in the last 3 months before screening; BMI <25 kg/m^2 or >40 kg/m^2, end-stage renal disease, any contraindication to IDeg-100 or Gla-300, and history of hypersensitivity to the active substance or to any of the excipients of IDeg-100 or Gla-300. A full list of inclusion and exclusion criteria are presented in Supplementary Table 1.

All participants provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice.

Randomization and Treatment

The randomization scheme was provided by the study statistician to an interactive response technology (IRT) system, which then generated the patient randomization list and allocated treatment arms to the patients accordingly. At the screening visit the investigator contacted the IRT center to receive the patient number. Treatment kits were allocated using the centralized IRT system, requiring the investigator to contact the centralized IRT system and provide patient-specific details.

Eligible participants were randomized 1:1 to receive Gla-300 or IDeg-100 and were stratified by HbA_{1c} level (<8.0%, ≥8.0% [<64 mmol/mol, ≥64 mmol/mol]) and sulfonylurea (SU) or glinide use (yes, no) at screening. Gla-300 and IDeg-100 were self-administered by subcutaneous injection once daily between 1800 h and 2000 h throughout the study period. Starting doses, as per labeling, were 0.2 units/kg for Gla-300 and 10 units for IDeg-100 and were titrated to achieve glycemic targets according to the same titration algorithm (Supplementary Table 2). Doses were adjusted at least weekly, but not more often than every 3 days, targeting a fasting self-monitored plasma glucose (SMPG) of 80–100 mg/dL while avoiding hypoglycemia. The "active" titration period was 0–12 weeks, during which time achievement of the fasting SMPG target was aimed for. During weeks 13–24, dose titrations were still allowed. Dose adjustments (−2, 0, +2, +4, or +6 units) were based on median fasting SMPG values from the last three measurements, including the day of titration. Background therapies were not changed during the study unless safety concerns necessitated dose reduction or discontinuation.

End Points

The primary end point was the change in HbA_{1c} from baseline to week 24. Secondary efficacy end points included change in fasting plasma glucose (FPG), fasting SMPG, and eight-point SMPG profiles from baseline to week 24; change in variability of 24-h SMPG, based on eight-point profiles; percentage of participants reaching target HbA_{1c} <7.0% (<53 mmol/mol) at week 24; and percentage of participants reaching target HbA_{1c} <7.0% (<53 mmol/mol) at week 24 without confirmed hypoglycemia (≤70 mg/dL and <54 mg/dL) during the 24-week treatment period.

Safety end points included the incidence and event rates of hypoglycemia during the 24-week on-treatment period, the active titration period (weeks 0–12), and the maintenance period (weeks 13–24). Documented symptomatic hypoglycemia was defined as an event that was symptomatic with a confirmatory blood glucose reading (≤70 mg/dL or <54 mg/dL). Severe hypoglycemia was defined as an event requiring assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions. Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤70 mg/dL or <54 mg/dL) and severe events, if any. Hypoglycemia that occurred between 0000 h and 0559 h was defined as nocturnal. Other safety outcomes included body weight and adverse events (AEs). Change in basal insulin dose was also assessed, although this was not a prespecified end point.

Data Analysis and Statistics

Sample size calculations were made using nQuery Advisor software version 7.0 (Cork, Ireland). Analyses were performed using SAS version 9.4 (Cary, NC).

A sample size of 920 randomized participants was chosen to ensure with at least 90% power that the upper bound of the two-sided 95% CI of the adjusted mean difference in HbA_{1c} change from

baseline between Gla-300 and IDeg-100 would not exceed a noninferiority margin of 0.3%, assuming a common SD of 1.4% with a one-sided test at the 2.5% significance level and a true difference of 0.0%. If noninferiority was achieved, superiority was tested according to a hierarchical procedure.

All efficacy end points were assessed in the intention-to-treat (ITT) population (all randomized participants who received at least one dose of study insulin, analyzed according to the treatment group allocated by randomization). Safety end points were analyzed in the safety population (all randomized patients who received at least one dose of study insulin, according to the treatment actually received). The primary end point, change in HbA_{1c} during the 24-week on-treatment period, was analyzed by a mixed-effect model with repeated measures (MMRM), using the missing at random framework, with fixed categorical effects of treatment, visit, treatment-by-visit interaction, randomization strata of SU or glinide use at screening (yes, no), and the continuous fixed covariates of baseline efficacy parameter value and baseline efficacy parameter value-by-visit interaction. Sensitivity analyses were conducted for the primary end point using all available postbaseline HbA_{1c} values, regardless of study treatment discontinuation and rescue therapy initiation (deviations); the per-protocol population (a subset of the ITT population without deviations); and multiple imputation (missing at random, penalized) and tipping point analyses in order to assess the robustness of primary efficacy analysis results with regard to missing HbA_{1c} at week 24.

All continuous secondary efficacy end points were analyzed using the same MMRM approach, with the additional randomization strata of HbA_{1c} at screening. Binary efficacy end points were assessed during the 24-week on-treatment period and before any rescue treatment, analyzed using a logistic regression model adjusted on randomization strata. For participants who discontinued study treatment prematurely or for those who received rescue therapy during the 24-week on-treatment period, time windows were applied to retrieve assessments performed at premature end-of-treatment and prerescue visits for the MMRM analyses. No multiplicity adjustments were made on secondary efficacy variables; only 95% CIs were reported.

For safety end points, proportion of participants experiencing ≥1 hypoglycemic event was analyzed using logistic regression, including randomization strata as covariates. Hypoglycemic event rates were analyzed using an overdispersed Poisson regression model adjusted on randomization strata. AEs were coded using MedDRA.

RESULTS

Baseline Characteristics

Participants (N = 929) were randomized into the Gla-300 (N = 466) and IDeg-100 (N = 463) treatment arms, and the ITT population included 462 participants in each treatment arm (Supplementary Fig. 1). Overall, 99.5% of the randomized population received treatment, with 94.2% completing the 24-week treatment period.

At baseline, the most commonly used noninsulin antihyperglycemic drugs were metformin (91.5%) and SU (65.7%) and, overall, characteristics were similar in both treatment arms (Table 1).

Glycemic Control

Mean (± SD) HbA_{1c} at baseline was 8.7 ± 0.8% (72 ± 9 mmol/mol) and 8.6 ± 0.8% (70 ± 9 mmol/mol) in the Gla-300 and IDeg-100 groups, respectively, decreasing to 7.0 ± 0.8% (53 ± 9 mmol/mol) and 7.0 ± 0.8% (53 ± 8 mmol/mol) by week 24 (Fig. 1*A* and Table 2). Least squares (LS) mean change (± SE) in HbA_{1c} from baseline to week 24 was −1.64 ± 0.04% (−18.0 ± 0.4 mmol/mol) for Gla-300 and −1.59 ± 0.04% (−17.4 ± 0.4 mmol/mol) for IDeg-100, with a LS mean difference for Gla-300 versus IDeg-100 of −0.05% (95% CI −0.15 to 0.05) (−0.6 mmol/mol [−1.7 to 0.6]), demonstrating noninferiority of Gla-300 versus IDeg-100 ($P < 0.0001$) for the primary end point. Superiority of Gla-300

Table 1—Baseline characteristics (randomized population)

Baseline characteristics	Gla-300 (N = 466)	IDeg-100 (N = 463)	Total (N = 929)
Age, years	60.6 ± 9.6	60.5 ± 9.8	60.5 ± 9.7
Sex (% male/female)	53/47	54/46	54/46
BMI, kg/m^2	31.7 ± 4.3	31.3 ± 4.4	31.5 ± 4.4
Known type 2 diabetes duration, years	10.5 ± 6.1	10.7 ± 6.5	10.6 ± 6.3
HbA_{1c}			
%	8.71 ± 0.83	8.57 ± 0.80	8.64 ± 0.82
mmol/mol	71.7 ± 9.1	70.2 ± 8.7	70.9 ± 9.0
HbA_{1c} randomization strata			
<8.0% (<64 mmol/mol)	86 (18.5)	85 (18.4)	171 (18.4)
≥8.0% (≥ 64 mmol/mol)	380 (81.5)	378 (81.6)	758 (81.6)
FPG, mg/dL	191 ± 49	182 ± 51	186 ± 51
Fasting SMPG, mg/dL	178 ± 40	172 ± 38	175 ± 39
eGFR, mL/min/1.73 m^2	92.4 ± 26.8	90.8 ± 26.0	91.6 ± 26.4
Number of prior noninsulin antihyperglycemic agents used			
0	0 (0.0)	1 (0.2)	1 (0.1)
1	70 (15.0)	65 (14.0)	135 (14.5)
2	179 (38.4)	187 (40.4)	366 (39.4)
>2	217 (46.6)	210 (45.4)	427 (46.0)
Prior noninsulin antihyperglycemic treatment (%)			
Metformin	91.8	91.1	91.5
SUs	64.6	66.7	65.7
Glinides	2.6	1.9	2.3
Thiazolidinediones	4.5	5.2	4.8
DPP-4 inhibitors	26.0	22.9	24.4
SGLT2 inhibitors	13.3	13.4	13.3
GLP-1 RAs	9.9	14.0	11.9
α-Glucosidase inhibitors	1.9	1.5	1.7
Other	0.2	0.2	0.2

Data are presented as mean ± SD or n (%) unless otherwise stated. DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate.

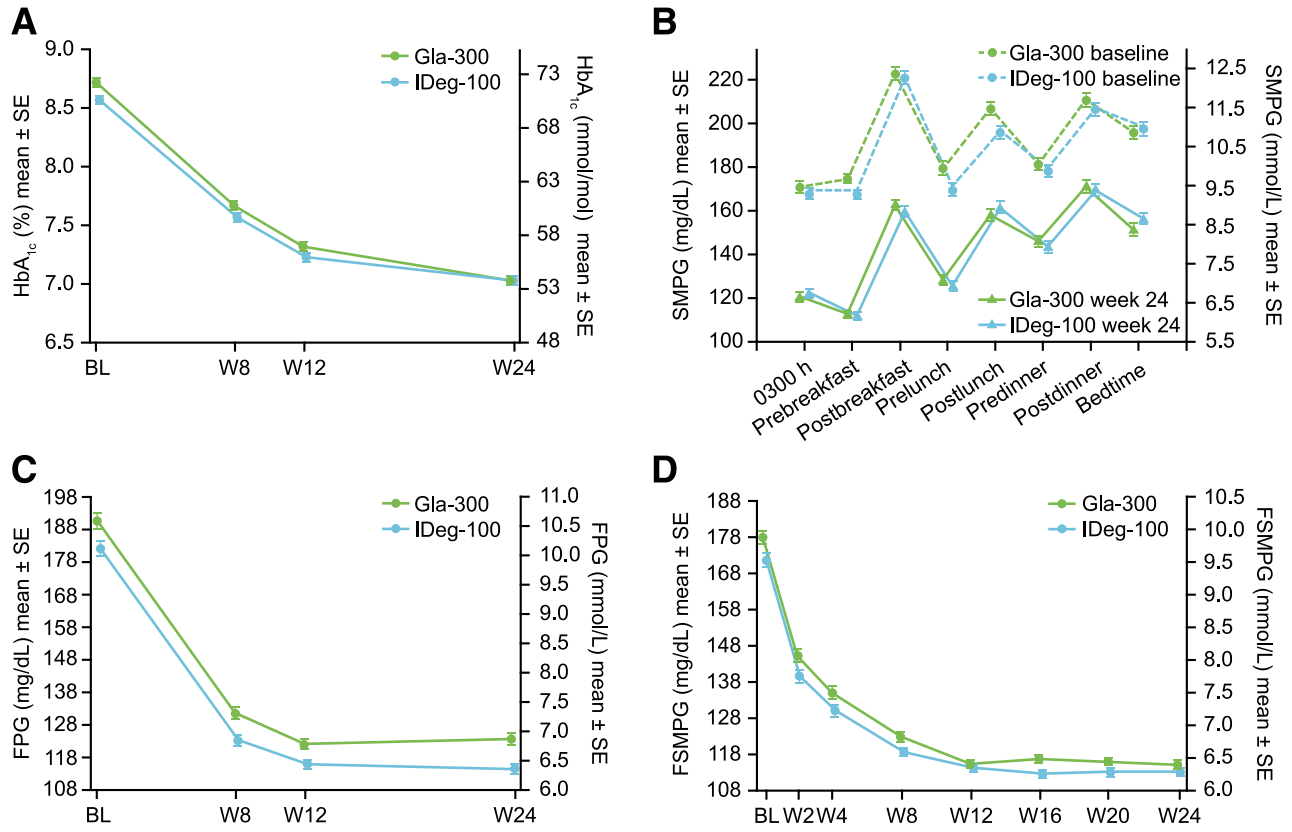

Figure 1—HbA_{1c} levels (*A*), eight-point SMPG profiles (*B*), FPG levels (*C*), and fasting SMPG levels (*D*) over 24 weeks of treatment, ITT population. BL, baseline; FSMPG, fasting SMPG; W, week. (A high-quality color representation of this figure is available in the online issue.)

versus IDeg-100 was not demonstrated. Robustness of the primary analysis was supported by the results of sensitivity analyses to assess the impact of missing data, including a per-protocol analysis (not shown). Furthermore, no evidence of heterogeneity of treatment effect according to randomization strata of SU or glinide use (yes, no) was observed (P = 0.626, data not shown).

The proportions of participants who reached HbA_{1c} target <7.0% (<53 mmol/mol), or HbA_{1c} target <7.0% (<53 mmol/mol) without confirmed hypoglycemia (≤70 mg/dL or <54 mg/dL) at any time of day (24 h), at week 24 were comparable between treatment arms (Table 2).

Mean FPG and fasting SMPG at baseline and week 24 are presented in Table 2 and Fig. 1*C* and *D*. The LS mean difference in FPG change from baseline to week 24 was 7.7 mg/dL (95% CI 2.7–12.7) for Gla-300 versus IDeg-100. The LS mean difference in fasting SMPG change from baseline to week 24 was 1.1 mg/dL [95% CI −1.9 to 4.1] for Gla-300 versus IDeg-100. The eight-point fasting SMPG profiles appeared similar with Gla-300 and IDeg-100 by week 24 (Fig. 1*B*). Mean coefficient of variation for eight-point profiles (24-h SMPG), expressing within-day plasma glucose variability, was comparable for Gla-300 and IDeg-100 at baseline (22.5% and 23.4%, respectively) and at week 24 (27.6% and 28.0%, respectively).

Hypoglycemia

Anytime (24-h) Hypoglycemia

The incidence of confirmed hypoglycemia (≤70 mg/dL) at any time of day (24 h) during the 24-week on-treatment period was comparable with Gla-300 and IDeg-100, being 66.5% and 69.0% (odds ratio [OR] 0.88 [95% CI 0.66–1.17]. There was also no difference between treatments in the incidence of confirmed hypoglycemia at the <54 mg/dL threshold over 24 weeks (Fig. 2). Patients using SUs or glinides at screening were more likely to experience hypoglycemia than those who were not, but no evidence of heterogeneity of treatment effect according to randomization strata of SU or glinide use (yes, no) was observed for the incidence of confirmed hypoglycemia (≤70 mg/dL and <54 mg/dL) (P > 0.05, data not shown). The event rate of confirmed hypoglycemia (≤70 mg/dL) at any time of day during the 24-week on-treatment period was comparable with Gla-300 and IDeg-100, with 9.3 and 10.8 events per patient-year, respectively (rate ratio [RR] 0.86 [95% CI 0.71–1.04]) (Fig. 2). A comparable rate of confirmed hypoglycemia (<54 mg/dL) was also observed with Gla-300 and IDeg-100 (0.6 versus 0.9 events per patient-year, RR 0.69 [95% CI 0.45–1.08]) (Fig. 2). However, for both incidence and rates, the direction of effect was in favor of Gla-300 for confirmed hypoglycemia (defined by either glycemic threshold) over 24 weeks (Fig. 2).

During the first 12 weeks, incidence and event rates of confirmed hypoglycemia (≤70 mg/dL and <54 mg/dL) were lower with Gla-300 versus IDeg-100 (Fig. 2). Incidence and event rates of confirmed hypoglycemia (≤70 mg/dL and <54 mg/dL) were comparable in both treatment groups during weeks 13–24 (Fig. 2).

The results for anytime (24-h) documented symptomatic hypoglycemia were similar to those for confirmed hypoglycemia (data not shown).

Table 2—Glycemic control (ITT population)

Efficacy parameters	Gla-300 (N = 462)	IDeg-100 (N = 462)
HbA_{1c}		
Baseline		
%	8.72 ± 0.83	8.57 ± 0.80
mmol/mol	71.8 ± 9.1	70.2 ± 8.8
Week 24		
%	7.03 ± 0.79	7.03 ± 0.77
mmol/mol	53.3 ± 8.6	53.3 ± 8.4
LS mean change from baseline to week 24 ± SE		
%	−1.64 ± 0.04	−1.59 ± 0.04
mmol/mol	−18.0 ± 0.4	−17.4 ± 0.4
LS mean difference (95% CI)		
%	−0.05 (−0.15 to 0.05)[a]	
mmol/mol	−0.6 (−1.7 to 0.6)[a]	
Patients who reached HbA_{1c} target <7.0% (<53 mmol/mol), n (%)	225 (48.7)	206 (44.6)
OR (95% CI)	1.19 (0.91–1.54)	
Patients who reached HbA_{1c} target without confirmed (≤70 mg/dL) hypoglycemia, n (%)	62 (13.4)	60 (13.0)
OR (95% CI)	1.05 (0.71–1.55)	
Patients who reached HbA_{1c} target without confirmed (<54 mg/dL) hypoglycemia, n (%)	194 (42.0)	175 (37.9)
OR (95% CI)	1.20 (0.92–1.57)	
FPG, mg/dL		
Baseline	190.60 ± 49.36	182.12 ± 51.68
Week 24	123.76 ± 40.60	114.54 ± 33.23
LS mean change from baseline to week 24 ± SE	−63.47 ± 1.956	−71.16 ± 1.977
LS mean difference (95% CI)	7.68 (2.71–12.65)	
Fasting SMPG, mg/dL		
Baseline	177.85 ± 40.49	171.65 ± 38.16
Week 24	115.21 ± 23.66	113.29 ± 20.65
LS mean change from baseline to week 24 ± SE	−58.11 ± 1.21	−59.18 ± 1.22
LS mean difference (95% CI)	1.08 (−1.94 to 4.10)	

Baseline and week 24 values are mean ± SD. [a]Primary end point; $P < 0.0001$ for noninferiority (noninferiority margin 0.3%).

Nocturnal (0000–0559 h) Hypoglycemia

The incidence of nocturnal (0000–0559 h) confirmed hypoglycemia (≤70 mg/dL) during the 24-week on-treatment period was comparable with both treatments: 28.6% with Gla-300 and 28.8% with IDeg-100 (OR 0.99 [95% CI 0.74–1.32]). No difference between treatments over 24 weeks was seen in the incidence of confirmed hypoglycemia at the <54 mg/dL threshold (Fig. 2). The event rates of nocturnal confirmed hypoglycemia (≤70 mg/dL) during the 24-week period were comparable with Gla-300 and IDeg-100, being 1.8 and 2.3 events per patient-year, respectively (RR 0.81 [95% CI 0.58–1.12]) (Fig. 2). Event rates of nocturnal confirmed hypoglycemia (<54 mg/dL) during the 24-week period were also comparable with Gla-300 and IDeg (Fig. 2).

When analyzing hypoglycemia by study period (Fig. 2), the incidence of nocturnal confirmed hypoglycemia (≤70 and <54 mg/dL) was comparable across treatment groups during the first 12 weeks. During this period, the rate of confirmed nocturnal hypoglycemia (≤70 mg/dL) was lower with Gla-300 than with IDeg, at 1.4 and 2.2 events per patient-year, respectively (RR 0.65 [95% CI 0.43–0.98]), whereas the rate of confirmed nocturnal hypoglycemia (<54 mg/dL) was comparable with both treatments.

For nocturnal (0000–0559 h) documented symptomatic hypoglycemia, similar results as for confirmed hypoglycemia were observed (data not shown).

Severe Hypoglycemia

Overall, during the 24-week study, only 1 participant (female, 49 years old, treated with metformin) experienced severe hypoglycemia. This single event was reported in the Gla-300 group during the 13–24-week period and was due to the patient skipping her evening meal and not reducing her insulin dose after a nonsevere event 2 days earlier.

Insulin Dose

The mean daily insulin dose (± SD) on day 1 was 16.9 ± 4.4 units (0.19 ± 0.04 units/kg) for Gla-300 and 10.2 ± 1.9 units (0.12 ± 0.04 units/kg) for IDeg-100. At week 24, the mean daily dose was 50.5 ± 25.6 units (0.54 ± 0.26 units/kg) for Gla-300 and 39.2 ± 23.3 units (0.43 ± 0.24 units/kg) for IDeg-100 (Supplementary Fig. 2*A*). The mean dose increases from baseline to week 24 were 33.6 ± 24.4 units (0.36 ± 0.25 units/kg) and 29.1 ± 23.3 units (0.31 ± 0.24 units/kg) for Gla-300 and IDeg-100, respectively (Supplementary Fig. 2*B*).

Body Weight

Mean (± SD) body weight increased from baseline (90.6 ± 16.1 kg and 88.7 ± 15.9 kg in the Gla-300 and IDeg-100 groups, respectively) to week 24 (92.5 ± 16.6 and 91.4 ± 16.7 kg), an absolute mean increase of 2.0 ± 3.8 kg with Gla-300 and 2.3 ± 3.6 kg with IDeg-100 (Supplementary Fig. 3). LS mean difference in body weight change for Gla-300 versus IDeg-100 was −0.33 kg (95% CI −0.81 to 0.15).

AEs

Overall, 202 (43.7%) and 221 (47.8%) participants in the Gla-300 and IDeg-100 groups, respectively, reported AEs during the 24-week study period. Serious AEs were reported in 21 (4.5%) and 20 (4.3%) participants, respectively. Four (0.9%) participants in the Gla-300 group and 5 (1.1%) in the IDeg-100 group reported an AE that led to permanent discontinuation of the investigational drug. One death occurred in the Gla-300 group, due to adenocarcinoma of the colon. Injection site reactions occurred in 1.7% (n = 8) and 1.3% (n = 6) participants in the Gla-300 and IDeg-100 groups, respectively.

CONCLUSIONS

To date, head-to-head comparisons between Gla-300 and IDeg-100 have relied on PK/PD studies in type 1 diabetes and indirect trial-level meta-analyses (3,4,10,11). The BRIGHT study is the first head-to-head trial investigating the clinical efficacy and safety of these two second-generation, longer-acting basal insulin analogs. In this population of insulin-naive patients with uncontrolled long-standing type 2 diabetes on multiple oral antihyperglycemic drugs with or without GLP-1 RAs, Gla-300 was similar

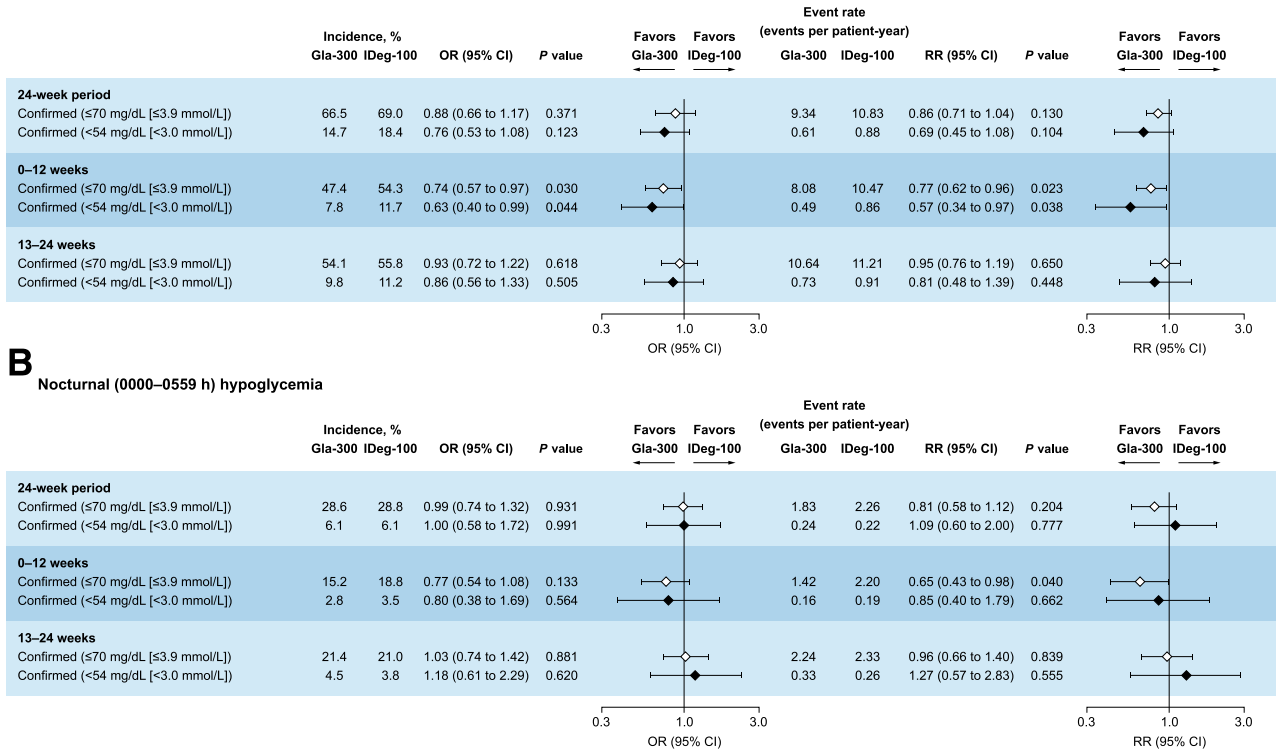

Figure 2—Hypoglycemia at any time of day (24 h) (*A*) or during the nocturnal period (0000–0559 h) (*B*), safety population. Nominal *P* values are provided.

to IDeg-100 in terms of HbA_{1c} reduction (from an overall mean 8.6% [71 mmol/mol] at baseline to 7.0% [53 mmol/mol] at week 24). Furthermore, similar proportions of participants in the Gla-300 and IDeg-100 groups achieved HbA_{1c} target <7.0% (<53 mmol/mol) without confirmed hypoglycemia (≤70 mg/dL and <54 mg/dL). Hypoglycemia incidence and rates were generally low, although slightly higher than in the insulin-naive population in the EDITION 3 study comparing Gla-300 versus Gla-100 (where, in contrast with the BRIGHT study, SUs and glinides were discontinued) (12). Most notably, only one severe hypoglycemic event occurred during the entire 24-week trial, attesting to the safety of both these longer-acting basal insulins, which can allow stricter glycemic goals when properly initiated and titrated.

At study end, FPG values were fairly similar with IDeg-100 and Gla-300, although there was a greater reduction from baseline with IDeg-100 than Gla-300 (Fig. 1*C*). In contrast, fasting SMPG was higher at baseline with Gla-300 but decreased similarly compared with IDeg-100 and was no different at study end (Fig. 1*D*). The reasons for the small discrepancy between FPG and fasting SMPG are not clear but may reflect differences in how and when samples for FPG and fasting SMPG were taken; FPG sampling and analysis was performed during on-site visits, while fasting SMPG was usually sampled and tested when participants awoke and prior to breakfast, with mean values from the previous 7 days used in the analysis for each relevant time point. Furthermore, the fasting SMPG results may be of more clinical relevance, given that these values guided insulin titration (as per protocol) during the study. Nevertheless, these findings are consistent with results from trial-level meta-analyses indirectly comparing the EDITION and BEGIN clinical trial programs, which showed a discrepancy between the FPG and fasting SMPG change for Gla-300 and IDeg-100 versus Gla-100 (13).

Of note, within-day variability of 24-h SMPG (based on the eight-point SMPG profiles) in BRIGHT was comparable within the Gla-300 and IDeg-100 groups at baseline and week 24, indicating no difference in within-day intrasubject variability between these two second-generation basal insulins. The increase in intrasubject variability from baseline to week 24 was minimal, suggesting that both longer-acting basal insulins reduce blood glucose levels smoothly in type 2 diabetes. Further analyses will be conducted to assess whether day-to-day differences in glucose variability, if any, exist between Gla-300 and IDeg-100 in patients with type 2 diabetes in clinical practice.

Hypoglycemia incidence and rates were comparable between the insulins over the entire 24-week treatment period. However, lower incidence and annualized rates of anytime (24-h) confirmed hypoglycemia (≤70 and <54 mg/dL) were observed with Gla-300 versus IDeg-100 during the initial titration period (0–12 weeks), despite this time also being the period with the highest increase in insulin doses and greatest drop in fasting SMPG and HbA_{1c}. During the 13–24-week period, when there were smaller changes in insulin dose, the incidence and rates of confirmed hypoglycemia were comparable

in both treatment groups. The finding of less hypoglycemia with Gla-300 versus IDeg-100 during the time of more intensive insulin titration could help to build patient confidence to initiate and properly titrate their basal insulin with less fear of hypoglycemia. Similar HbA_{1c} improvement accompanied by less hypoglycemia is consistent with studies of basal insulin analogs versus the "standard comparator" in insulin-naive type 2 diabetes (2,14). Additional studies (real-world evidence and/or randomized controlled) comparing Gla-300 and IDeg-100 in more advanced type 2 diabetes are needed to determine whether the difference between the two insulins observed in the current study also applies to patients at higher risk of hypoglycemia (such as those on long-term basal or basal-bolus insulin treatment).

The reduced rates of certain categories of hypoglycemia with Gla-300 compared with IDeg-100 may reflect PK/PD differences. Despite the limitations of available PK/PD studies in type 1 diabetes (8,9), it appears from steady-state PD profiles (8,9) that IDeg-100 has a tendency for greater glucose-lowering activity between 8 and 12 h postdosing compared with Gla-300. Given the evening injection time, this might explain, at least in part, the slightly higher rates of nocturnal hypoglycemia ($\leq$70 mg/dL) with IDeg-100 observed during this study. However, PK/PD studies in type 2 diabetes are needed to more specifically characterize similarities and differences between Gla-300 and IDeg-100, not only with evening but also with morning dosing.

The mean starting dose of Gla-300 was higher by 0.07 units/kg than the dose of IDeg-100, as per label instructions (0.2 units/kg for Gla-300 and 10 units for IDeg-100), and remained higher throughout the study. At week 24 the Gla-300 insulin dose was higher by 0.11 units/kg than the IDeg-100 dose, an increase in the mean dose difference by 0.04 units/kg compared with baseline. This difference was to be expected, given the similar doses observed between IDeg-100 and Gla-100 in the BEGIN trials (15) and the higher doses of Gla-300 versus Gla-100 in the EDITION trials (7). The dose difference is not due to a lower potency of Gla-300, since the mechanism of action and metabolism (generation of the active metabolite M1) is the same as that of Gla-100 (16), and Gla-300 has the same potency as both regular human insulin and Gla-100 after intravenous administration (17,18). The greater dose of Gla-300 after subcutaneous injection is needed to compensate for its lower bioavailability owing to the longer residence time of its microprecipitates in the subcutaneous space and subsequent local degradation by tissue proteases. This interpretation is indirectly favored by the fact that the slightly higher Gla-300 dose in BRIGHT did not translate into increased hypoglycemia risk nor greater weight gain; in fact, the trends, if any, were in the opposite direction, in line with the EDITION studies in people with type 2 diabetes (7).

The strengths of this study include the head-to-head, randomized trial design, which was powered to assess the primary HbA_{1c} end point. The study was conducted effectively, with systematic, proper insulin titration, and with most participants (who had similar baseline characteristics) completing the treatment period. The open-label design was a limitation, but it was unavoidable owing to the difficulty in blinding trial participants to the identity of the two basal insulin analog pens. This may have introduced a bias if users or investigators perceived either insulin as "more effective" or "safer" than the other. Furthermore, the study may be limited by the relatively short 24-week duration, and assessing outcomes over a longer follow-up period would be of interest.

This head-to-head study of Gla-300 versus IDeg-100 in insulin-naive individuals with type 2 diabetes demonstrated that both second-generation longer-acting basal insulin analogs were associated with comparable reductions in HbA_{1c}, glucose profiles, and fasting SMPG. Comparable glycemic control was achieved alongside similarly low overall incidence and rates of hypoglycemia in both insulin groups throughout the treatment period. However, Gla-300 was associated with lower incidence and rates of anytime (24-h) confirmed hypoglycemia ($\leq$70 and $<$54 mg/dL) than IDeg-100 during the 0–12-week period when most of the insulin dose titration and plasma glucose reduction occurred. Gla-300 was also associated with a lower rate of nocturnal (0000–0559 h) confirmed hypoglycemia ($\leq$70 mg/dL) during the initial titration period. The overall safety profiles for Gla-300 and IDeg-100 were similar, and both insulins were well tolerated with no specific safety concerns. This trial is the first to identify hypoglycemia risk reduction for Gla-300 versus IDeg-100. Notably, there was only one episode of severe hypoglycemia, suggesting that reducing severe hypoglycemia risk need not necessarily be a factor in the decision-making process for selecting these longer-acting basal insulins in treatment of insulin-naive patients with type 2 diabetes. Moreover, given that there are more similarities than differences in efficacy and safety between these two second-generation basal insulin analogs, it is suggested that selection of which to use in clinical practice should be determined not just by the evaluation of clinical factors but mainly by practical factors such as access and cost.

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Appendix

Participating Physicians. *Bulgaria*: Zdravko Kamenov, Malina Petkova, and Nataliya Dzhermanova-Temelkova. *Croatia*: Dubravka Jurisic Erzen, Sanja Klobucar Majanovic, and Lea Smircic Duvnjak. *Czech Republic*: Juraj Divinec, Milan Kvapil, Renata Golanova, Renata Vodickova, Sabina Palova, Dagmar Bartaskova, Martin Prazny, and Marek Honka. *Denmark*: Hans Perrild, Ulrik Pedersen-Bjergaard, Soeren Gregersen, and Knud Yderstraede. *France*: Bertrand Cariou, Gerard Fradet, Didier Gouet, Samy Hadjaj, Anne-Marie Guedj, and Pierre Serusclat. *Greece*: Ioannis Doupis, Nikolaos Tentolouris, Andreas Melidonis, and Nikolaos Papanas. *Hungary*: Gyorgy Jermendy, Adam Tabak, Judit Rapi, and Albert Szocs. *Israel*: Naim Shehadeh, Jacob Ilani, Muhammad Sabbah, Rosane Abramof-Ness, Julio Wainstein, Muhammad Sheikh Ahmad, and Victor Vishlitzky. *Italy*: Carlo Giorda, Fabio Broglio, Francesco Giorgino, Paola D'Angelo, Giorgio Sesti, Agostino Consoli, Raffaele Napoli, Enzo Bonora, Stefano Genovese, Piermarco Piatti, Paolo Pozzilli, and Matteo Bonomo. *Romania*: Eduard Adamescu, Anca Cerghizan, Adriana Cif, Dana Cosma, Carmen Crisan, Brindusa Cofaru, Ioana Ferariu, Ana-Maria Mateescu, Annamaria Bodo, Adriana Onaca, Mihai Pena, Delia Reurean-Pintilei, and Cristian Serafinceanu. *Serbia*: Nebojsa Lalic, Radivoj Kocic, and Milica Pesic. *Slovakia*: Zbynek Schroner, Emil Martinka, Martina Merciakova, Dasa Skripova, and Edita Fedurcova. *Sweden*: Margareta Hellgren and Magnus Londahl. *Switzerland*: Bernd Schultes and Gottfried Rudofsky. *U.K.*: Ahmed Yousseif, Jeffrey Stephens, Andrew Gough, Stonny Joseph, Chinnusamy Ravikumar, and Ajith George. *U.S.*: Michael Dempsey, George Dailey, Dama Alexander Ziworitin, Mark Benson, Michael Reeves, Julio Rosenstock, Deirdre McMullen, Carl Meisner, Azazuddin Ahmed, Vanita Aroda, Ronald Brazg, Juan Pablo Frías, Sumana Gangi, Lenita Hanson, Richard Jackson, Michael Jardula, Wynter Kipgen, Milton Wong, Charles Lovell, Charles Lunn, Jose Mandry, Caroline Mbogua, Michael Oliver, Marina Raikhel, Preet Randhawa, Jackson Rhudy, Jay Sandberg, Luis Soruco, Faizullah Syed, Ronald Watts, Michelle Zaniewski-Singh, Ahmed Arif, Brian Webster, Darron Molter, Samer Nakhle, Rakesh Patel, Normam Fishman, Peter Winkle, Aron Schlau, Dale Allison, Robert Strzinek, Lawrence Alwine, Jamal Hammoud, Michael Robinson, John Earl, Jeffrey Green, Isam Marar, Stephen Smith, Dan Streja, Ernie Riffer, Ronald Mayfield, Adeniyi Olabiyi Odugbesan, Thad Riley, Louis Chaykin, Lisa Cohen, Charles Debusk, Bernard Grunstra, Sanford Plevin, Jeffrey Unger, Jonathan Wilson, Randall Huling Jr., John Reed, Richard Sachson, Alan Schwartz, Paul Wakefield, Salil Nadkarni, C. Wilson Sofley, Douglas Denham, Jack Whalen, Kathleen Jones, Sandra Weber, Udaya Kabadi, and Anuj Bhargava.

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