Received: 15 July 2019 | Revised: 11 October 2019 | Accepted: 21 October 2019

DOI: 10.1111/dom.13901

ORIGINAL ARTICLE

WILEY

Similar glycaemic control and less hypoglycaemia during active titration after insulin initiation with glargine 300 units/mL and degludec 100 units/mL: A subanalysis of the BRIGHT study

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Funding information
This work was supported by Sanofi, Paris, France.

Abstract

Aim: To further investigate glycaemic control and hypoglycaemia in BRIGHT, focusing on the titration period.

Materials and Methods: BRIGHT was a multicentre, open-label, randomized, active-controlled, two-arm, parallel-group, 24-week study in insulin-naïve patients with uncontrolled type 2 diabetes initiated on glargine 300 U/mL (Gla-300) (N = 466) or degludec (IDeg-100) (N = 463). Predefined efficacy and safety outcomes were investigated during the initial 12-week titration period. In addition, patients' characteristics and clinical outcomes were assessed descriptively, stratified by confirmed (≤3.9 mmol/L) hypoglycaemia incidence during the initial titration period.

Results: At week 12, HbA1c was comparable between Gla-300 (7.32%) and IDeg-100 (7.23%), with similar least squares (LS) mean reductions from baseline (−1.37% and −1.39%, respectively; LS mean difference of 0.02; 95% confidence interval: −0.08 to 0.12). Patients who experienced hypoglycaemia during the initial titration period had numerically greater HbA1c reductions by week 12 than patients who did not (−1.46% vs. −1.28%), and higher incidence of anytime (24 hours; 73.3% vs. 35.7%) and nocturnal (00:00–06:00 hours; 30.0% vs. 11.9%) hypoglycaemia between weeks 13–24.

Conclusions: The use of Gla-300 resulted in similar glycaemic control as IDeg-100 during the initial 12-week titration period of the BRIGHT study, when less anytime (24 hours) hypoglycaemia with Gla-300 versus IDeg-100 has been reported. Experiencing hypoglycaemia shortly after initiating Gla-300 or IDeg-100 may be associated with hypoglycaemia incidence in the longer term, potentially impacting glycaemic management.

KEYWORDS

basal insulin, clinical trial, glycaemic control, hypoglycaemia, randomized trial, type 2 diabetes.

1 | INTRODUCTION

Many people with type 2 diabetes may eventually benefit from insulin therapy when attempting to achieve recommended glycaemic targets.[1] Initiation of insulin is often delayed, and even after initiation, appropriate titration is often not achieved.[2] Several patient- and healthcare professional-related barriers contribute to this therapeutic inertia, including fear of hypoglycaemia, weight gain and burdensome treatment regimens.[2-5]

The initial titration period (typically the first 12 weeks after initiation) is particularly important as it is the time when the greatest insulin dose change and glycaemic lowering occurs in clinical trials.[6] Previous real-world studies have also shown that active titration of basal insulin (BI) typically occurs during the first 12 weeks, after which there is little further titration.[7] Therefore, reducing the risk of hypoglycaemia during this period may be particularly beneficial,[6] as both randomized controlled trials and real-world evidence have shown an association between experiencing hypoglycaemia soon after initiating BI therapy and a higher risk of hypoglycaemia and BI discontinuation in the longer term.[8-10] In addition, reducing hypoglycaemia during the titration period may increase confidence to up-titrate BI. This is important because failure to reach an HbA1c of <7.0% by 3 months is associated with an increased risk of failing to achieve this target at 24 months.[8]

The second-generation BI analogues insulin glargine 300 U/mL (Gla-300) and insulin degludec (IDeg) may help overcome such barriers, by providing similar HbA1c reductions compared with the first-generation BI analogue glargine 100 U/mL (Gla-100), but with less hypoglycaemia in people with type 2 diabetes.[11,12]

In a meta-analysis of the phase 3 type 2 diabetes EDITION trials for Gla-300, improvements in confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia, at any time of day (24 hours) and during the night (00:00 to 05:59 hours), with Gla-300 versus Gla-100, were particularly marked during the titration period (baseline to week 8) compared with the maintenance period (week 8 to week 24).[12] In a meta-analysis of the phase 3 type 2 diabetes BEGIN trials, IDeg was associated with significantly lower rates of anytime (24 hours) and nocturnal (0:00–06:00 hours) confirmed (<3.1 mmol/L [<56 mg/dL]) hypoglycaemia versus Gla-100 during the overall study period, but there was no difference in hypoglycaemia rates during the titration period (week 0 to 15 weeks).[11]

BRIGHT was the first head-to-head randomized clinical trial designed to compare the efficacy and safety of Gla-300 and IDeg 100 units/mL (IDeg-100) in insulin-naïve people with type 2 diabetes.[13] The results of the primary analysis from the full 24-week period showed similar improvements in glycaemic control with Gla-300 and IDeg-100, with comparable incidence and rates of hypoglycaemia. Likewise, there were comparable incidence and rates of hypoglycaemia during the maintenance period (weeks 13–24). However, the incidence and rates of anytime (24 hours) confirmed (≤3.9 mmol/L [≤70 mg/dL] or <3.0 mmol/L [<54 mg/dL]) hypoglycaemia and the rate of nocturnal (00:00 to 06:00 hours) confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia favoured Gla-300 during the initial 12-week titration period. The present analyses were therefore conducted to attempt to explain the between-treatment hypoglycaemia difference seen in the first 12 weeks of BRIGHT, by providing a detailed evaluation of efficacy and safety of Gla-300 versus IDeg-100 during this active titration period, as well as to explore the impact of hypoglycaemia events occurring soon after BI initiation.

2 | METHODS

2.1 | Study design and participants

The full details of the BRIGHT study design and methodology have been reported previously.[13] BRIGHT (NCT02738151) was a multicentre, open-label, randomized, active-controlled, two-arm, parallel-group, 24-week, non-inferiority, treat-to-target trial in insulin-naïve adults (aged ≥18 years) with uncontrolled type 2 diabetes at screening, on oral agents with or without a glucagon-like peptide-1 receptor agonist at a stable dose for at least 3 months. Participants were randomized 1:1 to evening dosing (18:00 to 20:00 hours) with Gla-300 (N = 466) or IDeg-100 (N = 463), at a starting dose of 0.2 units/kg and 10 units, respectively, as per label instructions. Gla-300 and IDeg-100 were titrated to target a fasting self-monitored plasma glucose (SMPG) of 4.4–5.6 mmol/L (80–100 mg/dL), according to the same titration algorithm (Table S1). The dose was adjusted at least weekly, but no more than every 3 days, to the target fasting SMPG while avoiding hypoglycaemia. Dose adjustments were based on median fasting SMPG values from the last three measurements, including the day of titration. The active titration period was 0–12 weeks, during which time the aim was to achieve the fasting SMPG target. Thereafter, dose adjustments were made in order to maintain this fasting SMPG. Background therapies were not changed during the study unless safety concerns necessitated dose reduction or discontinuation. All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice.

2.2 | Outcomes

The primary endpoint in BRIGHT was change in HbA1c from baseline to week 24, the results of which have been reported previously.[13] Briefly, non-inferiority of Gla-300 versus IDeg-100 was shown in HbA1c with a least squares (LS) mean difference of −0.05% (95% confidence interval [CI]: −0.15 to 0.05) (−0.6 mmol/mol [−1.7 to 0.6]) ($P < 0.0001$).

In terms of *prespecified* secondary efficacy outcomes, this analysis of BRIGHT examined the change from baseline to week 12 in HbA1c, fasting plasma glucose (FPG) and fasting SMPG, as well as 24-hour plasma glucose based on eight-point SMPG. The percentage of participants reaching target HbA1c of <7.0% (53 mmol/mol) at week 12 and the percentage of participants reaching target HbA1c of <7.0% (53 mmol/mol) at week 12 without confirmed (≤3.9

and <3.0 mmol/L [≤70 and <54 mg/dL]) hypoglycaemia during the 12-week titration period were also examined. Confirmed hypoglycaemia was defined as any hypoglycaemic event (symptomatic or asymptomatic) confirmed by a plasma glucose value of ≤3.9 or <3.0 mmol/L (≤70 or <54 mg/dL), including severe events (defined as requiring assistance from another person to administer carbohydrate, glucagon or other resuscitative actions). Hypoglycaemia was defined by the time of occurrence as anytime (24 hours) or nocturnal (00:00 to 06:00 hours). The safety outcome assessed in this analysis was the incidence of confirmed hypoglycaemia (as defined above) by time of day during the 12- and 24-week study periods.

Additional exploratory *post hoc* efficacy endpoints included the percentage of participants reaching target fasting SMPG at week 12 without confirmed (≤3.9 and <3.0 mmol/L [≤70 and <54 mg/dL]) hypoglycaemia during the 12-week titration period. Fasting SMPG targets analyzed followed the American Diabetes Association (ADA)-recommended target of ≤7.2 mmol/L (≤130 mg/dL), and the upper threshold of the BRIGHT titration target of ≤5.6 mmol/L (≤100 mg/dL). This study also examined patient characteristics (including age, body mass index [BMI], renal function, diabetes duration and sulphonylurea [SU] use) and clinical outcomes (including HbA1c change, variability of fasting SMPG [determined using the coefficient of variation — standard deviation/mean × 100 — of ≥3 fasting SMPG measurements over 7 days prior to a visit] and hypoglycaemia incidence during weeks 13–24) according to the occurrence of confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the initial 12-week titration period. Additional safety outcomes included body weight and BI dose.

2.3 | Data analysis and statistics

Safety endpoints were analyzed in the safety population (all randomized participants who received at least one dose of study insulin, according to the treatment actually received). All continuous secondary efficacy endpoints were 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 HbA1c at screening, randomization strata of SU or glinide use at screening (Yes; No), and the continuous fixed covariates of baseline efficacy variable value and baseline efficacy variable value-by-visit interaction. Binary efficacy endpoints were assessed during the 12-week period 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 12-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 endpoints, the percentage of participants experiencing ≥1 hypoglycaemic event was analyzed using logistic regression, including randomization strata as covariates. Hypoglycaemic event rates were analyzed using an over-dispersed Poisson regression model adjusted on randomization strata. Exploratory endpoints, as well as insulin dose and body weight, were assessed for descriptive purposes only. Adverse events were coded using MedDRA.

3 | RESULTS

3.1 | Patient characteristics

Overall, 929 patients were randomized to the Gla-300 (n = 466) and IDeg-100 (n = 463) treatment arms, with 462 patients in each arm making up the intention-to-treat population. Baseline characteristics were similar between treatment arms (Table S2) and have been reported previously.[13]

During the 12-week titration period, use of non-insulin antihyperglycaemic treatments, including SUs, remained largely the same and similar between treatment groups compared with usage at baseline (Table S3).

3.2 | Glycaemic control

The LS mean (SE) HbA1c reduction from baseline to week 12 was similar for Gla-300 and IDeg-100, being −1.37 (0.04) and −1.39 (0.04), respectively, with a LS mean difference of 0.02% (95% CI: −0.08 to 0.12) (Table 1 and Figure 1).

The percentage of patients who achieved an HbA1c target of <7.0% at week 12 with Gla-300 (34.6%) and IDeg-100 (36.2%) was similar (odds ratio [95% CI]: 0.94 [0.71 to 1.23]) (Table 1). Likewise, the percentage of patients who achieved an HbA1c of <7.0% at week 12, without confirmed (≤3.9 or <3.0 mmol/L [≤70 or <54 mg/dL]) hypoglycaemia at any time of day, was similar with Gla-300 versus IDeg-100 (Table 1). Of the patients achieving an HbA1c of <7.0% at week 12, 82.5% of the patients in the Gla-300 group and 79.6% of the patients in the IDeg-100 group also achieved this target at week 24.

Mean FPG and fasting SMPG at baseline and week 12 are presented in Figure 1 and Table 1. The LS mean (95% CI) difference between Gla-300 and IDeg-100 in FPG change from baseline to week 12 was 0.25 (0.00 to 0.49) mmol/L. The LS mean (95% CI) difference between Gla-300 and IDeg-100 in fasting SMPG change from baseline to week 12 was −0.00 (−0.17 to 0.16) mmol/L. Eight-point fasting SMPG profiles were similar between Gla-300 and IDeg-100 at baseline and at week 12 (Figure 1).

The percentage of patients achieving the ADA-recommended fasting SMPG target of ≤7.2 mmol/L (≤130 mg/dL) without confirmed (≤3.9 and <3.0 mmol/L [≤70 and <54 mg/dL]) hypoglycaemia was similar between Gla-300 (34.8% and 68.6%) and IDeg-100 (31.4% and 68.4%) at week 12 (Figure 2A). By comparison, the percentage of patients achieving fasting SMPG target of ≤5.6 mmol/L (≤100 mg/dL) (the upper limit of the titration target for BRIGHT) without confirmed (≤3.9 and <3.0 mmol/L [≤70 and <54 mg/dL]) hypoglycaemia was lower than achievement of the ADA-recommended target, but still similar between treatment groups (Figure 2B).

TABLE 1 Glycaemic control during the initial titration period

Outcomes	Gla-300 (N = 462)	IDeg-100 (N = 462)
HbA1c, %		
Baseline	8.72 ± 0.83	8.57 ± 0.80
Week 12	7.32 ± 0.83	7.23 ± 0.79
LS mean change from baseline to week 12 ± SE	−1.37 ± 0.04	−1.39 ± 0.04
LS mean difference (95% CI)	0.02 (−0.08 to 0.12)	
Patients who reached HbA1c target <7.0% at week 12, n (%)	160 (34.6)	167 (36.2)
OR (95% CI) Gla-300 versus IDeg-100	0.94 (0.71 to 1.23)	
Patients who reached HbA1c target without confirmed (≤3.9 mmol/L) hypoglycaemia at any time of day	76 (16.5)	63 (13.6)
OR (95% CI) Gla-300 versus IDeg-100	1.26 (0.87 to 1.82)	
Patients who reached HbA1c target without confirmed (<3.0 mmol/L) hypoglycaemia at any time of day	145 (31.4)	150 (32.5)
OR (95% CI) Gla-300 versus IDeg-100	0.95 (0.72 to 1.26)	
FPG, mmol/L		
Baseline	10.58 ± 2.74	10.11 ± 2.87
Week 12	6.79 ± 1.99	6.44 ± 1.87
LS mean change from baseline to week 12 ± SE	−3.64 ± 0.10	−3.89 ± 0.10
LS mean difference (95% CI)	0.25 (0.00 to 0.49)	
Fasting SMPG, mmol/L		
Baseline	9.87 ± 2.25	9.53 ± 2.12
Week 12	6.41 ± 1.35	6.36 ± 1.36
LS mean change from baseline to week 12 ± SE	−3.26 ± 0.07	−3.25 ± 0.07
LS mean difference (95% CI)	−0.00 (−0.17 to 0.16)	

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; OR, odds ratio; SD, standard deviation; SE, standard error; SMPG, self-monitored plasma glucose.
Note: Data are mean ± SD unless otherwise specified.

3.3 | Hypoglycaemia

During the 12-week titration period, descriptive analysis of the incidence of confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia by time of day showed a peak of events at 06:00–08:00 hours, with numerically fewer events for Gla-300 than IDeg-100, generally consistent with the results from the 13–24-week maintenance period and the full 24-week study period for both ≤3.9 and <3.0 mmol/L (≤70 and <54 mg/dL) definitions of hypoglycaemia (Figure 3). The incidence of confirmed (≤3.9 and <3.0 mmol/L [≤70 and <54 mg/dL]) hypoglycaemia from 04:00 to 20:00 hours was numerically lower with Gla-300 versus IDeg-100 during the 12-week titration period.

3.4 | Impact of early hypoglycaemia

Overall, 219 (47.4%) and 251 (54.3%) patients experienced confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the initial 12-week titration period in the Gla-300 and IDeg-100 arms, respectively. The number of patients who experienced confirmed (<3.0 mmol/L [<54 mg/dL]) hypoglycaemia with Gla-300 and IDeg-100 during the initial 12-week titration period was 36 (7.8%) and 54 (11.7%).

HbA1c reductions from baseline to week 12 were numerically greater in patients who had experienced confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the initial 12-week titration period than in patients who had not, for both Gla-300 and IDeg-100 (Table 2). However, by week 24, HbA1c reductions from baseline were similar regardless of hypoglycaemia occurrence during the 12-week titration period.

The increase in variability of fasting SMPG from baseline to week 12 was also greater in patients who had experienced confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the titration period than in patients who had not, for both Gla-300 and IDeg-100 (Table 2).

In the overall cohort, the incidence of confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia at any time of day (24 hours) or during the night (00:00 to 06:00 hours) during weeks 13–24 was lower in patients who had not experienced hypoglycaemia within the initial 12-week titration period (Table 2).

Patients who experienced hypoglycaemia within the first 12 weeks tended to be older, had lower BMI, lower renal function, longer duration of diabetes and were more likely to be using SUs at baseline, compared with patients who had no hypoglycaemia (Table 2). The incidence of anytime (24 hours) confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the 12-week titration period was similar between Gla-300 and IDeg-100 across patients stratified according to age, BMI, duration of diabetes and SU use (Table S4). A treatment-by-subgroup interaction was observed across patients stratified according to renal function ($P = 0.0461$).

3.5 | Insulin dose and body weight

Mean (SD) daily insulin doses at baseline were 0.19 (0.04) U/kg and 0.12 (0.04) U/kg for Gla-300 and IDeg-100, respectively (a difference of 0.07 U/kg). At week 12, mean daily doses were 0.48 (0.21) U/kg and 0.37 (0.20) U/kg for Gla-300 and IDeg-100, respectively (a difference of 0.11 U/kg), corresponding to mean dose increases of 0.29 (0.20) U/kg for Gla-300 and 0.26 (0.20) U/kg for IDeg-100 (Figure S1). Analysis of the number of insulin dose adjustments showed no obvious pattern of differences between treatment groups (Figure S2). Mean (SD) body weight increased from 90.6 (16.1) kg and 88.7 (15.9) kg in the Gla-300 and IDeg-100 groups, respectively, at baseline to 91.8 (16.3) kg and 90.1 (16.2) kg, a change of 1.3 kg in both groups. The LS mean difference in body weight change from baseline for Gla-300 versus IDeg-100 was −0.04 kg (95% CI: −0.37 to 0.29).

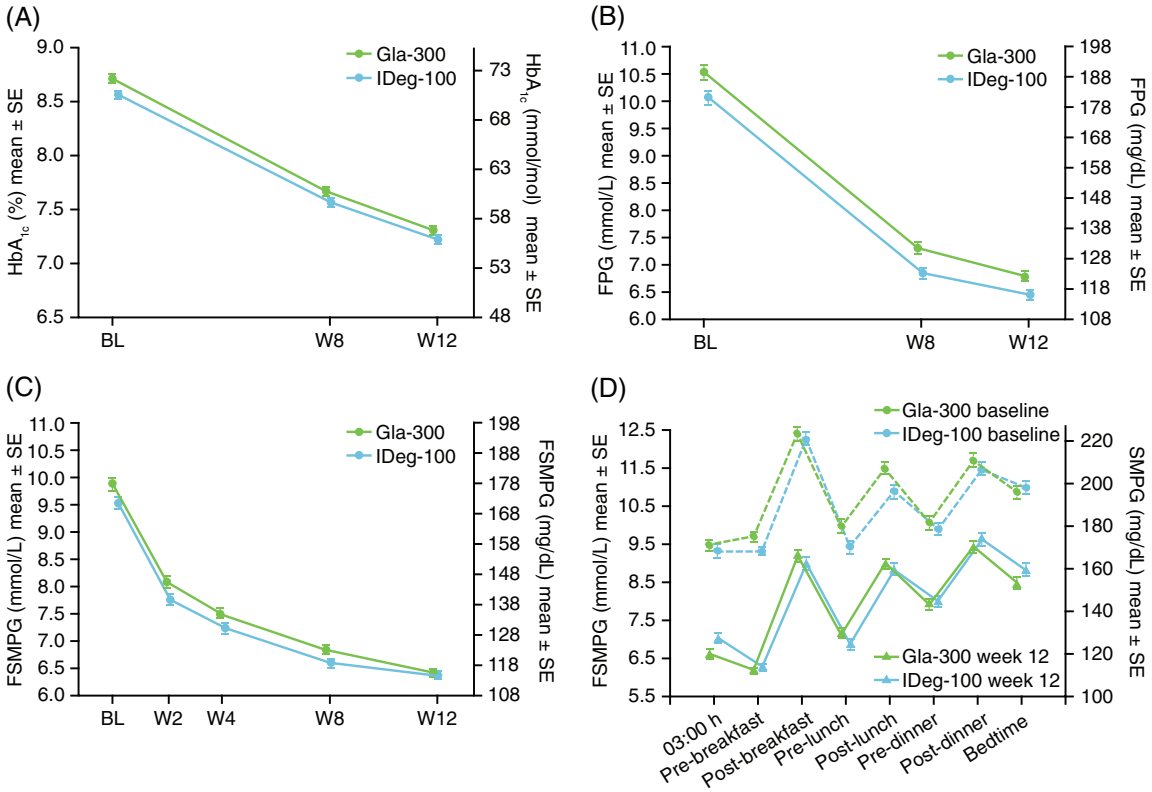

FIGURE 1 (A) HbA1c levels, (B) fasting plasma glucose (FPG) levels, (C) fasting self-monitored plasma glucose (FSMPG) levels and (D) eight-point self-monitored plasma glucose (SMPG) profiles over 12 weeks of treatment (titration period). SE, standard error.

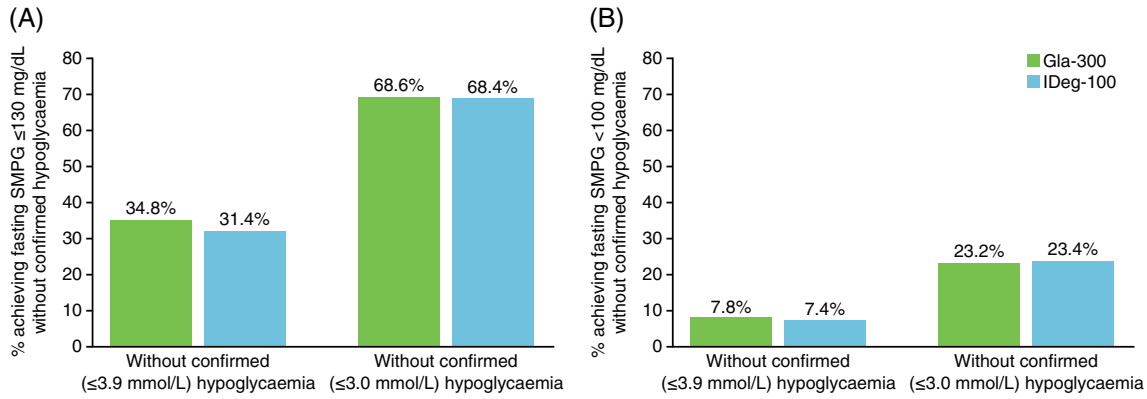

FIGURE 2 Achievement of (A) fasting self-monitored plasma glucose (FSMPG) target (≤130 mg/dL) without confirmed hypoglycaemia and (B) FSMPG target (≤100 mg/dL) without confirmed hypoglycaemia at the end of 12 weeks of treatment (titration period)

4 | DISCUSSION

The BRIGHT study was the first head-to-head randomized trial to investigate the clinical efficacy and safety of the two second-generation BI analogues Gla-300 and IDeg-100. Results from the analysis of the full 24-week study period showed similar reductions in HbA1c alongside comparable incidence and rates of hypoglycaemia.[13] As previously reported, during the initial 12-week titration period there were lower incidence and rates of confirmed (≤3.9 and <3.0 mmol/L [≤70 and <54 mg/dL]) hypoglycaemia at any time of day (24 hours), and lower rates of nocturnal (00:00–-06:00 hours) confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia with Gla-300 versus IDeg-100. Less hypoglycaemia soon after starting BI therapy, when most insulin titration occurs, may help patients to confidently optimize their dose and could translate into better glycaemic outcomes and less hypoglycaemia in the longer term.[6,8]

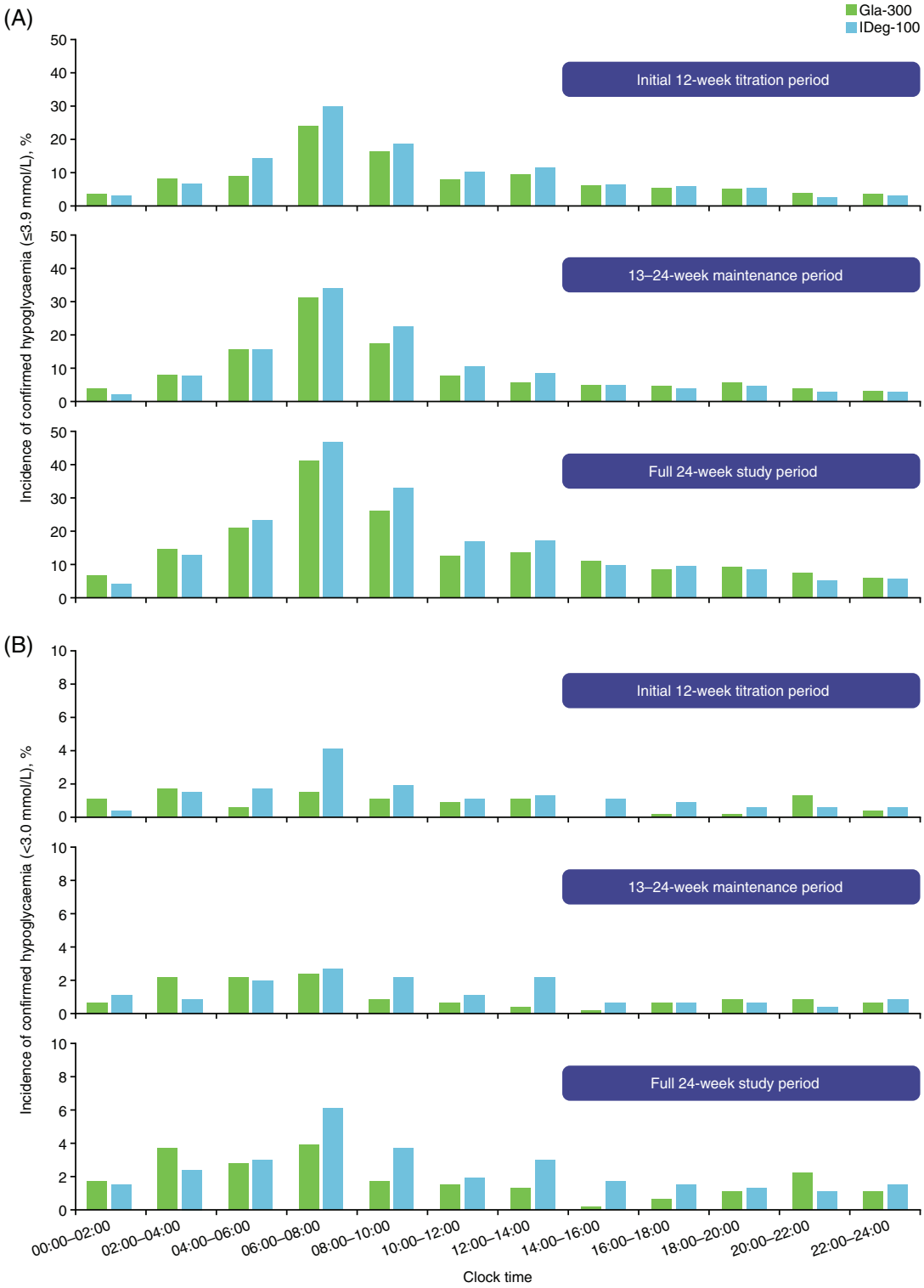

FIGURE 3 Incidence of confirmed (A) ≤3.9 and (B) <3.0 mmol/L hypoglycaemia by time of day

The lower incidence and rates of hypoglycaemia observed with Gla-300 versus IDeg-100 during the initial 12 weeks of BRIGHT cannot be explained by concomitant SU use or differences in glycaemic control. The results from the present analysis show that concomitant use of SUs was similar between treatment groups throughout the study and baseline SU use did not impact the incidence of hypoglycaemia during the 12-week period, while there were similar improvements in HbA1c and achievement of glycaemic targets with Gla-300 and IDeg-100 during the initial 12-week titration period. Baseline values of both HbA1c and FPG appeared slightly higher in

TABLE 2 Patient characteristics at baseline, glycaemic control and hypoglycaemia incidence in participants with and without confirmed (≤3.9 mmol/L) hypoglycaemia in the initial 12-week titration period

	Gla-300		IDeg-100		All	
	With (N = 219)	Without (N = 243)	With (N = 251)	Without (N = 211)	With (N = 470)	Without (n = 454)
Baseline characteristics						
Age, y	61.4 ± 9.5	59.7 ± 9.7	61.9 ± 9.3	58.9 ± 10.1	61.7 ± 9.4	59.4 ± 9.9
Age ≥ 65 y, n (%)	88 (40.2)	79 (32.5)	101 (40.2)	64 (30.3)	189 (40.2)	143 (31.5)
BMI, kg/m^2	30.8 ± 4.1	32.6 ± 4.4	30.3 ± 4.4	32.5 ± 4.1	30.5 ± 4.3	32.5 ± 4.2
BMI < 30 kg/m^2, n (%)	109 (49.8)	77 (31.7)	134 (53.4)	65 (30.8)	243 (51.7)	142 (31.3)
eGFR, mL/min/1.73 m^2	88.7 ± 26.5	95.5 ± 26.8	88.3 ± 24.3	93.5 ± 27.6	88.5 ± 25.3	94.6 ± 27.1
Duration of diabetes, y	11.7 ± 6.3	9.4 ± 5.7	11.9 ± 7.0	9.3 ± 5.6	11.8 ± 6.7	9.4 ± 5.7
SU use (yes), n (%)	174 (79.5)	136 (56.0)	200 (79.7)	114 (54.0)	374 (79.6)	250 (55.1)
HbA1c, %						
BL	8.74 ± 0.82	8.70 ± 0.84	8.54 ± 0.79	8.61 ± 0.81	8.63 ± 0.81	8.66 ± 0.83
Change from BL to week 12	−1.55 ± 0.85	−1.29 ± 0.92	−1.39 ± 0.86	−1.27 ± 0.90	−1.46 ± 0.86	−1.28 ± 0.91
Change from BL to week 24	−1.75 ± 0.96	−1.64 ± 0.94	−1.49 ± 0.98	−1.60 ± 1.04	−1.61 ± 0.98	−1.62 ± 0.98
Variability of fasting SMPG (%)[a]						
BL	15.15 ± 7.93	12.46 ± 5.61	15.88 ± 8.84	13.07 ± 5.67	15.54 ± 8.43	12.74 ± 5.64
Change from BL to week 12	3.75 ± 9.94	3.43 ± 7.67	3.44 ± 10.91	3.08 ± 8.22	3.58 ± 10.46	3.27 ± 7.92
Change from BL to week 24	2.78 ± 10.00	2.80 ± 7.56	2.90 ± 9.37	2.54 ± 8.08	2.85 ± 9.66	2.69 ± 7.79
Percentage of participants experiencing ≥ 1 confirmed (≤3.9 mmol/L) hypoglycaemic event between weeks 13–24, n (%)						
Any time of day (24 h)	155 (72.1)	88 (37.6)	182 (74.3)	68 (33.5)	337 (73.3)	156 (35.7)
Nocturnal (00:00 to 06:00 h)	65 (30.2)	31 (13.2)	73 (29.8)	21 (10.3)	138 (30.0)	52 (11.9)

Abbreviations: BL, baseline; BMI, body mass index; eGFR, estimated glomerular filtration rate; H, hours; SD, standard deviation; SMPG, self-monitored plasma glucose; Y, years.

Note: All data are mean ± SD unless otherwise stated.

[a]Determined using the coefficient of variation ([SD/mean] × 100) of ≥3 fasting SMPG measurements over 7 days prior to a visit.

the Gla-300 group than the IDeg-100 group, but this was adjusted for in the analysis of change from baseline. While the reduction in FPG from baseline to week 12 was slightly greater with IDeg-100 than Gla-300, fasting SMPG was reduced similarly in both groups and may be more clinically relevant given that it was the measurement used to guide BI dose titrations during the study. The greater FPG reduction with IDeg-100 versus Gla-300 may be related to specific patterns of glucose lowering with either BI throughout the day, based on their pharmacokinetic/pharmacodynamic profiles, especially as patients have to travel to the clinic in a fasted state (potentially lowering glucose levels further by around 8–12 hours postdosing, a time of peak activity with IDeg).[14,15] Furthermore, the percentage of patients achieving HbA1c of <7.0% without confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia at week 12 was similar, and even numerically greater, with Gla-300 than IDeg-100. The percentage of patients achieving HbA1c of <7.0% without confirmed (<3.0 mmol/L [<54 mg/dL]) hypoglycaemia at week 12 was similar with Gla-300 and IDeg-100, as was achievement of SMPG targets ≤7.2 and ≤5.6 mmol/L (≤130 and ≤100 mg/dL) without hypoglycaemia at either threshold. Therefore, from these analyses of the 12-week titration period in BRIGHT, the more favourable hypoglycaemia profile with Gla-300 does not appear to be related to differences in glycaemic control compared with IDeg-100.

The titration algorithm used in BRIGHT was the same as has been used in the EDITION treat-to-target randomized controlled trial programme for Gla-300, with titration occurring at least weekly and no more frequently than every 3 days. The algorithm was in line with the IDeg-100 label in the USA, the same recommendations for titration frequency were used in both groups and similar dose increases with Gla-300 and IDeg-100 were observed during the 12-week titration period. Furthermore, the SMPG titration target used in BRIGHT was the same as for the EDITION programme with Gla-300, but was less stringent than was used in the BEGIN programme with IDeg-100. However, SMPG profiles in both insulins were comparable, indicating that the titration algorithm was suitable for both Gla-300 and IDeg-100.

Management of diabetes, especially when using insulin, is always a balance between achieving appropriate glycaemic control and avoiding hypoglycaemia. Hypoglycaemia in the first weeks of BI treatment in insulin-naïve patients may be particularly impactful on patient adherence in clinical practice, with consequences for longer term glycaemic control.[6,8] Patients who experienced hypoglycaemia during

the initial 12-week titration period of BRIGHT tended to be older, with lower BMI, lower renal function and longer duration of diabetes. Furthermore, patients who experienced hypoglycaemia were more likely to be using SUs at baseline, but as previously mentioned, concomitant use of SUs remained similar throughout the study and did not impact the incidence of hypoglycaemia during the initial 12-week period. Although these patient characteristics did not generally impact upon the observed treatment effect in terms of hypoglycaemia incidence, special attention may need to be given to these patient groups when initiating BI treatment in clinical practice.

Patients who experienced early hypoglycaemia were more likely to experience hypoglycaemia during weeks 13–24 than patients who did not experience hypoglycaemia during the initial 12-week period. This result may initially seem at odds with the previously reported hypoglycaemia results from BRIGHT,[13] as the between-treatment difference in hypoglycaemia incidence and rates seen in the 12-week titration period was not replicated in the subsequent 13–24-week maintenance period. However, it is important to note that the original BRIGHT hypoglycaemia analyses directly compared incidence and rates between treatment groups, whereas the current analysis of the impact of early hypoglycaemia investigates maintenance period hypoglycaemia stratified by those who either experienced no hypoglycaemia at all or who experienced one or more events during the titration period. Such different approaches may not be expected to produce directly comparable results. It should also be highlighted that the current analysis provides descriptive results only, which cannot be used for predictive purposes. A dedicated study/analysis that investigates factors that predict hypoglycaemia when using Gla-300 or IDeg-100 may reveal more detailed information, and would be a useful future approach that could also take into account some differences in baseline characteristics (such as eGFR, which was lower in those with early hypoglycaemia than in those without) that were not adjusted for in the current descriptive analysis. Such an analysis may also help to further understand the reasons for the differences in titration-period hypoglycaemia between Gla-300 and IDeg-100.

For both BI analogues, experience of hypoglycaemia during the initial titration period was associated with a larger decrease in HbA1c and a greater increase in fasting SMPG variability from baseline to 12 weeks. Although these assessed glycaemic outcomes were similar by week 24 in those who did and did not experience early hypoglycaemia, this does not rule out a longer-term effect on glycaemic control; speculatively, as those with titration-period hypoglycaemia were more likely to experience hypoglycaemia in the maintenance period, these patients may then be less likely to continue up-titrating their BI dose and may have poorer glycaemic control in the future. Furthermore, the link between early and late hypoglycaemia alone makes these events important.

In conclusion, while the initial results from the BRIGHT trial showed less hypoglycaemia with Gla-300 versus IDeg-100 during the first 12 weeks, here we show that this does not reflect differences in glycaemic control or SU use during the same period. We also show that experiencing early hypoglycaemia during this 12-week titration period was associated with a larger initial HbA1c decrease during the same period, but was also associated with a higher incidence of hypoglycaemia during the subsequent weeks of treatment. Further understanding the mechanisms and risk factors for early hypoglycaemia may help with titrating BI more effectively and thus improve long-term outcomes.

ACKNOWLEDGMENTS

Editorial assistance was provided by Arthur Holland, PhD, of Fishawack Communications Ltd., and was funded by Sanofi. All authors take complete responsibility for the interpretation of the data in this review. This work was supported by Sanofi, Paris, France.

CONFLICT OF INTEREST

A. C. has served on advisory panels for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Medtronic, Novo Nordisk, Sanofi and HLS Therapeutics; and is a speaker for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi. S. H. has served as a consultant to Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi; and has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk and Sanofi. F. G. has served on advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diabetes Care and Sanofi; as a consultant for Boehringer Ingelheim, Lifescan, Merck Sharp & Dohme, Sanofi, AstraZeneca, Medimmune, Roche Diabetes Care and Sanofi; and received research support from Eli Lilly, Lifescan and Takeda. J. S. has acted as an advisory board member for Abbott, AstraZeneca, Boehringer Ingelheim, GI-Dynamics, Janssen, LifeScan, Mundipharma, Novartis, Novo Nordisk and Sanofi-Aventis; and as a speaker for Abbott, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Lilly, Merck Sharp & Dohme, MedScape, Novartis, Novo Nordisk, Omniamed and Sanofi-Aventis; he has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GI-Dynamics, Intarcia, Ipsen, Janssen, Novartis, Novo Nordisk, Sanofi Aventis and Ypsomed. R. R. has received honoraria or consulting fees from Sanofi, Novo Nordisk, MSD and Servier; and speakers' bureau fees from Sanofi, Novo Nordisk, Novartis, Eli Lilly, Berlin-Chemie, MSD and AstraZeneca. K. K. has served on advisory panels, is a board member of, and has received consulting and speakers' bureau fees from Novartis, Novo Nordisk, Sanofi, Eli Lilly, Servier and MSD; and has received research support from Novartis, Novo Nordisk, Sanofi, Eli Lilly, Pfizer, Boehringer Ingelheim and MSD. L. M.-M. is an employee of the IVIDATA Group, providing consultancy to Sanofi. F. L., J. W. and Z. B. are employees/shareholders of Sanofi. J. R. has served on scientific advisory boards and received honoraria or consulting fees from Eli Lilly, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim and Intarcia; and has received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, AstraZeneca, Janssen, Genentech, Boehringer Ingelheim, Intarcia and Lexicon.

AUTHOR CONTRIBUTIONS

A. C., R. R., J. W., Z. B. and J. R. all contributed to the concept or design of the study. J. W. contributed to data acquisition and L. M.-M. performed the statistical analysis of the data. All of the authors contributed to the interpretation of the data and the writing, reviewing and editing of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Cheng A, Harris S, Giorgino F, et al. Similar glycaemic control and less hypoglycaemia during active titration after insulin initiation with glargine 300 units/mL and degludec 100 units/mL: A subanalysis of the BRIGHT study. *Diabetes Obes Metab*. 2020;22:346–354. https://doi.org/10.1111/dom.13901