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Glycaemic control and hypoglycaemia risk with insulin glargine 300 U/mL and insulin degludec 100 U/mL in older participants in the BRIGHT trial

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Abstract

Aim: To evaluate the efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus insulin degludec 100 U/mL (IDeg-100) in predefined (</≥65 years) and post hoc (</≥70 years) age groups of people with type 2 diabetes (T2D) in the BRIGHT trial.

Materials and Methods: BRIGHT was the first head-to-head randomized trial comparing Gla-300 and Deg-100 in insulin-naïve adults with T2D. In this subanalysis, endpoints were studied by predefined (</≥65 years, N = 596/333) and post hoc (</≥70 years, N = 768/161) age groups.

Results: Heterogeneity of treatment effect was observed for HbA1c reductions across the </≥70 years subgroups, but not across the </≥ 65 years subgroups, with greater HbA1c reductions with Gla-300 versus IDeg-100 in those 70 years or older (least squares mean −0.34% [95% confidence interval: −0.589% to −0.100%]). There was no significant heterogeneity of treatment effect for incidence and rates of confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia across any age subgroups over 24 weeks, but numerically lower incidence and rates were consistently observed for Gla-300 versus IDeg-100 in the 65 years or older and 70 years or older age groups in the initial 12 weeks.

Conclusions: Gla-300 may be a suitable treatment option in the growing population of older people with T2D. Further investigation is required to determine Gla-300 glycaemic benefits in high-risk populations without increasing the risk of hypoglycaemia.

KEYWORDS
basal insulin, diabetes complications, insulin analogues, randomized trial, type 2 diabetes

1 | INTRODUCTION

Management of diabetes requires a balance between achieving glycaemic control and avoiding hypoglycaemia, especially in vulnerable populations at a higher risk of hypoglycaemia. The prevalence of diabetes worldwide has continuously increased, especially in people aged older than 65 years. In 2019, it was estimated that there were approximately 136 million people with diabetes aged older than 65 years and this population is expected to grow to 276 million people by 2045.[1] Worldwide, diabetes affects approximately 20% of

people aged 65–99 years and is associated with increased mortality rates.[1,2] Additionally, older adults with type 2 diabetes (T2D) often have more co-morbidities than younger adults and are at an increased risk of hypoglycaemia and its consequences, including a possible increased risk of cardiovascular events.[3]

The American Diabetes Association (ADA) recommends that for adults aged older than 65 years, glycaemic targets should be individualized depending on personal goals, life expectancy and overall health status, with an HbA1c level of less than 7.5% recommended in most older individuals with few co-morbidities.[4] Additionally, the Endocrine Society guidelines for older adults recommend minimization of hypoglycaemia in this age group.[5] ADA guidelines also suggest that basal insulin (BI) may be a suitable option for older individuals with T2D[4]; it is therefore important to establish the safety and efficacy of BI therapy in older adults with T2D, as both minimizing hypoglycaemia and achieving glycaemic control are equally important goals in this population at higher risk.

The SENIOR study was the first randomized controlled trial (RCT) dedicated to evaluating the efficacy and safety of the second-generation BI analogue glargine 300 U/mL (Gla-300) compared with the first-generation BI analogue glargine 100 U/mL (Gla-100) in older adults (aged ≥65 years) with T2D.[6] However, no head-to-head comparisons have been made between Gla-300 and the other second-generation BI analogue (insulin degludec [IDeg]) in older individuals with T2D.

BRIGHT (NCT02738151) was the first RCT to compare the efficacy and safety of Gla-300 and IDeg 100 U/mL (IDeg-100) in insulin-naïve people with T2D.[7] BRIGHT met its primary endpoint, showing non-inferior HbA1c reduction with Gla-300 versus IDeg-100 during the overall 24-week study period with a similar risk of hypoglycaemia over 24 weeks. However, hypoglycaemia incidence and rates were lower with Gla-300 versus IDeg-100 in the initial 12-week period, during which most insulin titration occurred.[7]

The aim of this BRIGHT subanalysis was to evaluate the efficacy and safety of Gla-300 versus IDeg-100 in predefined (</≥65 years) and post hoc (</≥70 years) age groups with T2D.

2 | MATERIALS AND METHODS

BRIGHT was a multicentre, multinational, open-label, randomized, parallel-group, 24-week study comparing the efficacy and safety of two second-generation BI analogues in insulin-naïve participants with T2D. The study methods have been previously described.[7]

Participants were aged 18 years or older (no upper limit) with T2D for 1 year or longer before screening, uncontrolled (HbA1c ≥7.5% to ≤10.5%) on oral antihyperglycaemic drugs with or without glucagon-like peptide-1 receptor agonists (stable dose ≥3 months). Participants were randomized 1:1 to once-daily self-administration of Gla-300 or IDeg-100 at starting daily doses of 0.2 U/kg and 10 U, respectively, as per labelling. Doses were titrated to a fasting self-monitored plasma glucose (SMPG) of 80–100 mg/dL (4.4–5.6 mmol/L) according to the same titration algorithm, with best efforts made to achieve the target within the first 12 weeks.

2.1 | Outcomes

A predefined subgroup analysis of BRIGHT investigated the effect of various participant characteristics (including age: </≥65 years) on HbA1c reduction with Gla-300 versus IDeg-100 (Table S1). All other analyses presented in this article are exploratory, such as the additional age subgroups of less than/70 years or older, which were analysed to investigate those who may be at an even higher risk of hypoglycaemia (participant numbers did not allow a higher cut-off of 75 years to be applied).

Efficacy outcomes include change in HbA1c over 24 weeks, and the percentage of participants reaching glycaemic targets (HbA1c <7.0% or <7.5%). Safety outcomes include the incidence and rates of confirmed (≤3.9 mmol/L [≤70 mg/dL] and <3.0 mmol/L [<54 mg/dL]) hypoglycaemia over 24 weeks and during the active titration period (the first 12 weeks). BI dose was also assessed.

2.2 | Data analysis and statistics

Efficacy assessments were performed in the intent-to-treat (ITT) population (all randomized subjects who received at least one dose of study BI, irrespective of the treatment being received). Safety assessments were performed in the safety population (all randomized participants who received at least one dose of study BI, regardless of the amount of treatment administered).

Change in HbA1c over 24 weeks was analysed 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, and the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction. Heterogeneity of treatment effect across age subgroups was assessed by adding an interaction term of treatment-by-age category.

The proportion of participants experiencing one or more hypoglycaemic event was analysed using logistic regression, including randomization strata as covariates. Hypoglycaemic event rates were analysed using an overdispersed Poisson regression model adjusted on randomization strata.

3 | RESULTS

Of 929 participants randomized, 333 were aged 65 years or older and 161 were aged 70 years or older. Of the 924 participants in the ITT population, 332 were aged 65 years or older and 160 were aged 70 years or older.

In the older versus younger populations, as expected, diabetes duration was longer and estimated glomerular filtration rate (eGFR) was lower, although on average most values were above 60 mL/min/1.73m^2 (Table S2). In the older populations, mean body mass index was slightly lower, although still in the obese range (>30 kg/m^2). Metformin use was lower in the older age groups and sulphonylurea use was comparable across all age groups.

3.1 | Efficacy

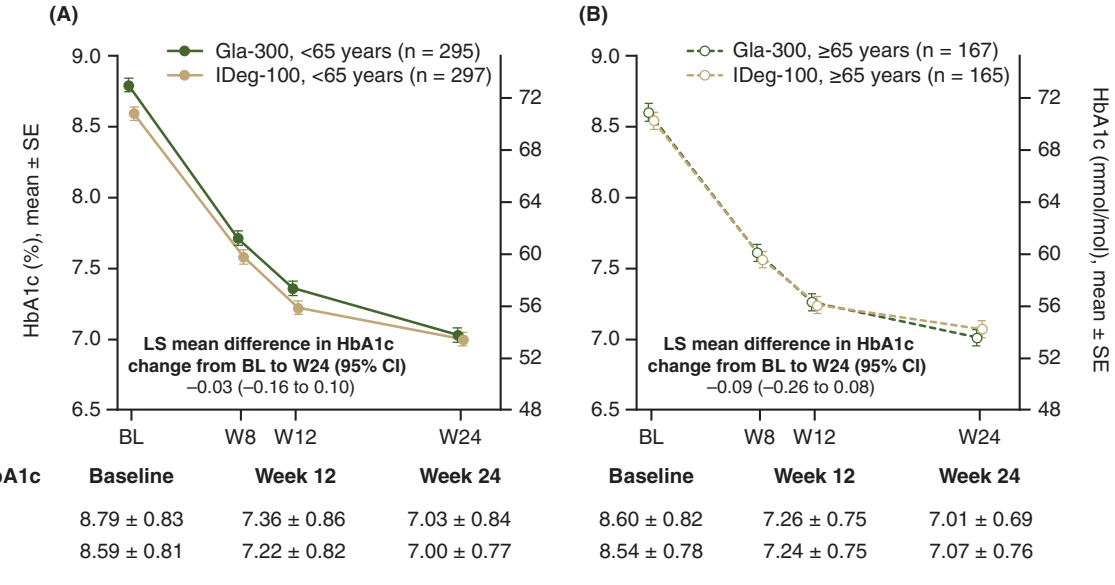
HbA1c reductions from baseline to week 24 were similar between treatment groups in the less than 65 and 65 years or older age subgroups (*p*-value, treatment-by-subgroup interaction = .596; Figure 1A,B).

Heterogeneity of treatment effect was observed across the </≥70 years age subgroups (*p* = .009). HbA1c reductions were similar between treatment groups in those aged less than 70 years (least squares [LS] mean difference 0.02% [95% confidence interval {CI}: −0.094% to 0.127%]), but HbA1c reductions with IDeg-100 were less in the 70 years or older versus the less than 70 years age subgroups, resulting in a greater HbA1c reduction with Gla-300 versus IDeg-100 in the 70 years or older age subgroup (LS mean difference −0.34% [95% CI: −0.589% to −0.100%]; Figure 1C,D).

Despite greater HbA1c reductions seen with Gla-300 versus IDeg-100 in the 70 years or older subgroup, glycaemic target achievement at week 24 was comparable between treatment arms, irrespective of age group or glycaemic target (HbA1c <7.0% or <7.5%; Figure S1).

3.2 | Safety

Hypoglycaemia was not reported as a serious treatment-emergent adverse event in any patient during the study period. Severe hypoglycaemia occurred in one patient (aged 49 years; one event) in



Mean ± SD HbA1c	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
Gla-300	8.79 ± 0.83	7.36 ± 0.86	7.03 ± 0.84	8.60 ± 0.82	7.26 ± 0.75	7.01 ± 0.69
IDeg-100	8.59 ± 0.81	7.22 ± 0.82	7.00 ± 0.77	8.54 ± 0.78	7.24 ± 0.75	7.07 ± 0.76

Mean ± SD HbA1c	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
Gla-300	8.75 ± 0.84	7.35 ± 0.85	7.04 ± 0.80	8.54 ± 0.76	7.19 ± 0.70	6.96 ± 0.73
IDeg-100	8.60 ± 0.82	7.20 ± 0.79	6.98 ± 0.75	8.44 ± 0.71	7.34 ± 0.83	7.24 ± 0.81

FIGURE 1 Mean HbA1c reductions from baseline to week 24 in participants aged, A, <65 years; B, ≥65 years; C, <70 years; and D, ≥70 years (ITT population). Data are shown as LS mean ± SE. Analysed using an MMRM approach. ITT, intent-to-treat; LS, least squares; MMRM, mixed models repeated measures; SE, standard error

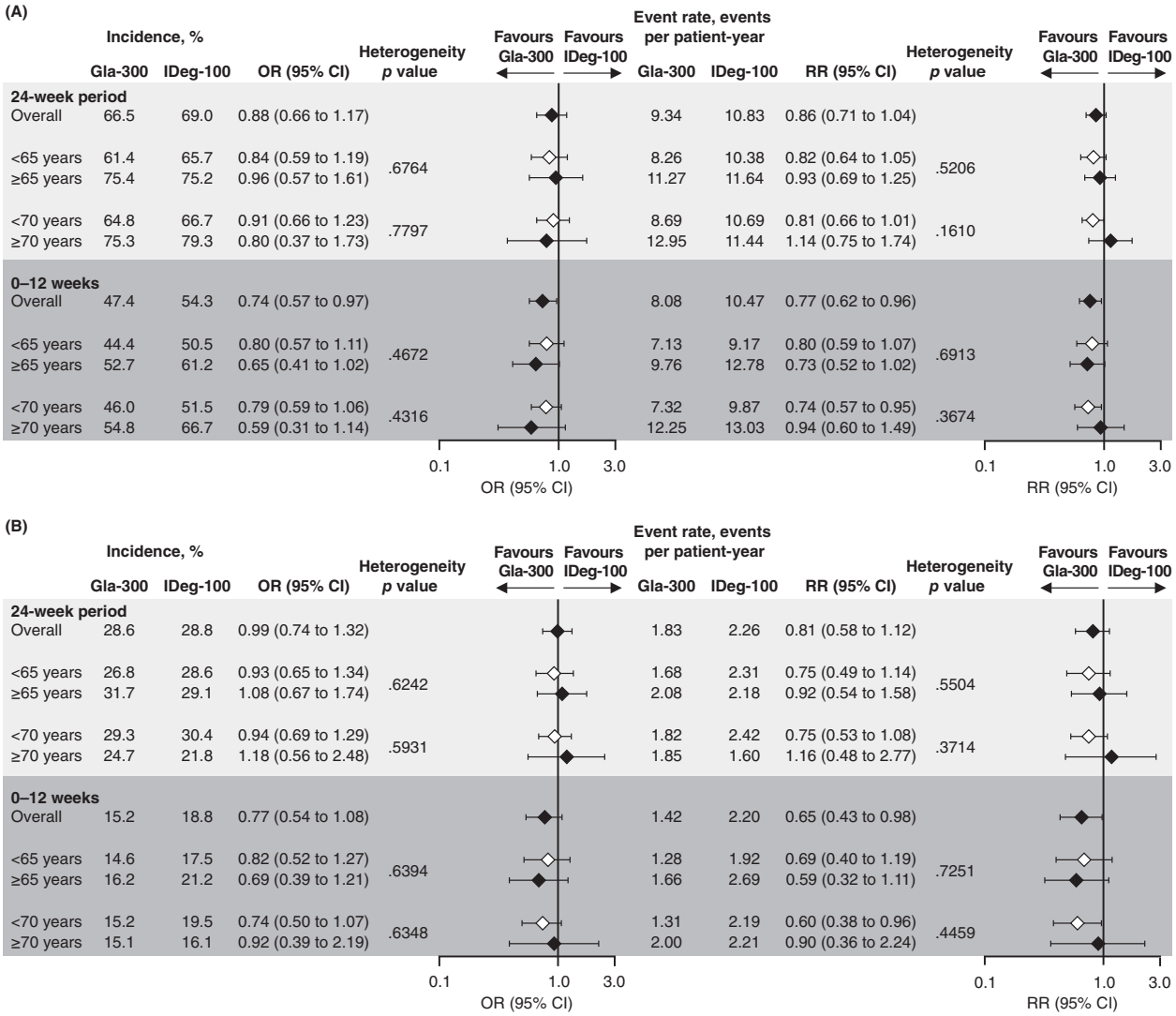


FIGURE 2 Incidence and rates of, A, anytime (24-h) and, B, nocturnal (0:00 AM–5:59 AM) severe or confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia in </≥65 years and </≥70 years subgroups over the 24-week study period and the 12-week titration period (safety population). Gla-300: overall, n = 462; <65 years, n = 295; ≥65, n = 167; <70 years, n = 389; ≥70 years, n = 73. IDeg-100: overall, n = 462; <65 years, n = 297; ≥65 years, n = 165; <70 years, n = 375; ≥70 years, n = 87. Incidence was analysed using a logistic regression model. Event rates were analysed using an over-dispersed Poisson regression model. CI, confidence interval; OR, odds ratio; RR, rate ratio

the Gla-300 group, which was a result of the patient skipping her evening meal and not reducing her insulin dose after a non-severe event 2 days prior. No significant heterogeneity of treatment effect was observed for incidence or rates of confirmed hypoglycaemia at either the 3.9 mmol/L or less (≤70 mg/dL; Figure 2) or less than 3.0 mmol/L (<54 mg/dL; Figure S2) blood glucose threshold, across any of the age subgroups over the 24-week study period or during the initial 12 weeks. There was a consistent numerical difference in the incidence and rates of anytime and nocturnal confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia, in favour of Gla-300, in the 0–12 week titration period for people aged 65 years or older and those aged 70 years or older (Figure 2).

In the main BRIGHT study, both treatments were well tolerated during the on-treatment period, and the rates of adverse events were comparable between treatments.[7]

3.3 | Insulin dose

Insulin dose was greater at study start (by study design) and remained greater with Gla-300 versus IDeg-100 in all subgroups at weeks 12 and 24. Smaller doses of both insulins were seen in the 70 years or older subgroup, who were leaner and had lower eGFR (Figure S3).

4 | DISCUSSION

This subanalysis investigated the efficacy and safety of initiating Gla-300 and IDeg-100 in older insulin-naïve people with T2D from the BRIGHT study by age. Similar HbA1c reduction has previously been observed with Gla-300 and IDeg-100 over 24 weeks in the full BRIGHT population. A preplanned analysis in participants aged

</≥65 years showed a similar HbA1c reduction between groups. In a post hoc analysis, HbA1c reductions over 24 weeks appeared greater with Gla-300 versus IDeg-100 in the 70 years or older subgroup. Glycaemic target achievement of either HbA1c less than 7.0% or less than 7.5% (recommended for most older individuals[4]) did not differ between treatment arms in any age group. Nevertheless, more than 50% of participants in each age group reached an HbA1c level of less than 7.5% by week 24.[4] Hypoglycaemia risk was similar between treatment groups for all age subgroups over the 24-week study period and the 12-week titration period, although a consistent numerical difference in the incidence of anytime hypoglycaemia in favour of Gla-300 in the 12-week titration period was observed, a finding which was consistent with the results of the BRIGHT study.[7]

These results suggest that Gla-300 may provide an effective therapy option in older people who are at a higher risk of hypoglycaemia and its consequences. A meta-analysis of the EDITION 1–3 studies (aged </≥65 years) and the SENIOR study (aged 65–75 and ≥75 years) both showed comparable glycaemic outcomes for Gla-300 versus Gla-100 irrespective of age, alongside a lower hypoglycaemia risk with Gla-300 in the older age group.[6,8] The efficacy and safety of BI analogues in the older population is confirmed by the present analysis, in which a direct comparison between Gla-300 and IDeg-100 shows comparable safety and efficacy in the 65 years or older population, with the potential for greater HbA1c reductions with Gla-300 versus IDeg-100 in the 70 years or older subgroup. Likewise, the real-world LIGHTNING study showed that predicted rates of severe hypoglycaemia were lower with Gla-300 versus first-generation BI analogues, including in older (aged ≥65 or ≥75 years) insulin-naïve populations, but rates were comparable between Gla-300 and IDeg-100.[9] Furthermore, the DELIVER D+ and DELIVER 3 real-world retrospective observational studies showed that, in individuals aged 65 years or older switching their BI, Gla-300 provided similar improvements in HbA1c and hypoglycaemia risk to IDeg-100 and greater or similar reductions in HbA1c in addition to lower rates of hypoglycaemia versus Gla-100/insulin detemir.[10,11] DEVOTE 7 showed a lower risk of severe hypoglycaemia with IDeg-100 versus Gla-100, regardless of age.[12] In addition to glycaemic outcomes with Gla-300, a subanalysis of the TAKE CONTROL study showed that, irrespective of age (</≥65 years), participants were able to self-titrate Gla-300 with similar glycaemic target achievement to physician-led titration without an increased risk of hypoglycaemia.[13] Overall, these results help to confirm the validity of those seen in the BRIGHT trial. The mechanism by which Gla-300 may provide improvements in glycaemic control versus IDeg-100 and in people aged 70 years or older is not clear. It may involve more favourable pharmacokinetics/pharmacodynamics,[14] although data in this older age group are not available. Similarly, in a separate BRIGHT subanalysis, participants with low eGFR were shown to experience similar benefits in glycaemic control favouring Gla-300 with no greater risk of hypoglycaemia.[15] As expected, there was a linear correlation between increase in age and lower eGFR in the BRIGHT population (Figure S4), suggesting a possible overlap between the finding of lower HbA1c with Gla-300 among those aged 70 years or older in the current study and the previous finding of lower HbA1c with Gla-300 among those with an eGFR of less than 60 mL/min/1.73m^2.[15] In fact, about 30% of BRIGHT participants aged 70 years or older had an eGFR of less than 60 mL/min/1.73m^2 (Table S2), and conversely, up to 49% of the participants in BRIGHT with an eGFR of less than 60 mL/min/1.73m^2 were aged 70 years or older. Therefore, it was uncertain to what extent age per se (in the current analysis) was independent of eGFR[15] in explaining the greater HbA1c reductions observed with Gla-300 versus IDeg-100. To assess this further, an additional analysis was conducted that adjusted the treatment effect for eGFR. After eGFR adjustment, the LS mean difference between treatments in HbA1c reduction was −0.00% (−0.115% to 0.109%) in the less than 70 years age group and −0.26% (−0.522% to −0.005%) in the 70 years or older age group (in favour of Gla-300). While the size of the difference in HbA1c reduction between Gla-300 and IDeg-100 in the 70 years or older age group was slightly attenuated by eGFR adjustment (from a previous value of −0.34%), and the heterogeneity of treatment effect across subgroups became nominally non-significant (p = .0730), this did not change the overall conclusion that a greater reduction in HbA1c is seen with Gla-300 versus IDeg-100 in the 70 years or older age subgroup. Our analyses suggest that, after adjusting for eGFR, a residual effect of age is seen on the efficacy of Gla-300 versus IDeg-100 on HbA1c reduction.

The strengths of this analysis include that BRIGHT was a head-to-head RCT that provides valuable information regarding Gla-300 and IDeg-100 in older patient subgroups. The multiple subgroup analyses and the univariate analyses of a single study were study limitations and the results of these post hoc analyses should be interpreted appropriately. The study was also limited by the small population size, in particular the number of participants aged 70 years or older. Furthermore, all participants in BRIGHT were selected partly for their willingness and ability to participate in the trial. While RCTs are the most reliable way to compare clinical outcomes with different insulins, they may not reflect real-life clinical circumstances in all cases. Hence, while the insulin-naïve older patients in BRIGHT were able to initiate, administer and be actively involved in insulin self-titration, some older people may find this more difficult, particularly if they are frail, cognitively impaired or lack a good support and/or care network. Despite this limitation, in BRIGHT the proportion of people aged 70 years or older was similar in both the screened population (17.2%) and those who failed screening (16.8%), indicating that the randomized population was representative of the screened population in terms of age.

In conclusion, Gla-300 provided similar HbA1c reductions to IDeg-100 in older (aged ≥65 years) adults with T2D; greater reductions were observed with Gla-300 versus IDeg-100 in those aged 70 years or older while the risk of hypoglycaemia remained similar with both insulins. However, as analyses in this 70 years or older age subgroup were post hoc and in a comparatively small population, further investigation is required to confirm these findings. Nevertheless, these results suggest that Gla-300 may be an efficacious and well-tolerated treatment option in the growing population of older people with T2D.

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CONFLICT OF INTEREST

GBB has served on advisory boards and received honoraria for Menarini and Sanofi; and has received research funding and speakers bureau fees from Sanofi. AC has received lecture fees or advisory board honorarium from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, Janssen, Medtronic, Merck, Novartis, Novo Nordisk and Sanofi. BC has worked on an advisory panel for AstraZeneca and has received consulting fees from AstraZeneca, Boehringer Ingelheim GmbH, Eli Lilly and Company, Merck Sharp & Dohme Corp., Novartis AG, Novo Nordisk A/S, Sanofi and Takeda Development Centre Europe Ltd. VRA has received consulting fees from Novo Nordisk Inc. and Sanofi, and has received research support from Applied Therapeutics, AstraZeneca, Calibra Medical, Eisai Inc., Novo Nordisk, Premier/Fractyl and Sanofi. Her spouse is an employee of Merck. JW is an employee of Sanofi. ZB was an employee of Sanofi when the work was conducted, but has since left the company. EB-LC is an employee of Sanofi. JR has received research funding from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GSK, AstraZeneca, Janssen, Asahi, Boehringer Ingelheim, Intarcia and Lexicon; and has received honoraria or consultation fees from Eli Lilly, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim, AstraZeneca and Intarcia.

AUTHOR CONTRIBUTIONS

All the named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. BC, JW, ZB, EB-LC and GB designed and conceptualized the study. JW contributed to the acquisition of data. JW and EB-LC contributed to the analysis of data. All the authors participated in the interpretation of the data, the writing, reviewing and editing of the manuscript, and had final responsibility for approving the published version.

DATA AVAILABILITY STATEMENT

Proposals relating to the data access should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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SUPPORTING INFORMATION

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

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