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Insulin glargine 300 U/mL versus first-generation basal insulin analogues in insulin-naïve adults with type 2 diabetes: 12-month outcomes of ACHIEVE Control, a prospective, randomized, pragmatic real-life clinical trial

Luigi Meneghini MD[1] | Lawrence Blonde MD[2] | Jasvinder Gill PhD[3] | Arnaud Dauchy MSc[4] | Andrius Bacevicius MD[4] | Jodi Strong DNP[5] | Timothy S. Bailey MD[6]

[1]Department of Internal Medicine, Division of Endocrinology, University of Texas Southwestern Medical Center and Parkland Health & Hospital System, Dallas, Texas, USA

[2]Frank Riddick Diabetes Institute, Endocrinology Department, Ochsner Medical Center, New Orleans, Louisiana, USA

[3]Sanofi, Bridgewater, New Jersey, USA

[4]Sanofi, Paris, France

[5]Ascension Health, Stevens Point, Wisconsin, USA

[6]AMCR Institute, Escondido, California, USA

Correspondence
Luigi Meneghini, University of Texas Southwestern Medical Center and Parkland Health and Hospital System, 5323 Harry Hines Blvd, Dallas, TX 75390, USA.
Email: luigi.meneghini@utsouthwestern.edu

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Abstract

Aim: To report the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) versus standard-of-care basal insulin analogues (SOC-BI) at 12 months in the ACHIEVE Control trial, which is a prospective pragmatic randomized real-life study in insulin-naïve adults with type 2 diabetes (T2D).

Methods: A total of 3304 insulin-naïve adults with T2D and glycated haemoglobin (HbA1c) concentration of 64 to 97 mmol/mol (8.0% to 11.0%) after ≥1 year of treatment with two or more antihyperglycaemic agents were randomized to Gla-300 or SOC-BI. Key secondary endpoints included HbA1c target attainment without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at 12 months.

Results: At 12 months, 26.1% (Gla-300) and 23.7% (SOC-BI) of adults achieved HbA1c targets without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia (odds ratio [OR] 1.14, 95% confidence interval [CI] 0.97–1.35); 33.0% and 29.5%, respectively, achieved HbA1c targets without documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia (OR 1.19, 95% CI 1.02–1.38). The OR for HbA1c target achievement was 1.15 (95% CI 0.99–1.34), and favoured Gla-300 versus SOC-BI for absence of documented symptomatic or severe hypoglycaemia at 12 months for both ≤3.9 mmol/L (≤70 mg/dL; OR 1.21, 95% CI 1.05–1.40) and < 3.0 mmol/L (<54 mg/dL; OR 1.26, 95% CI 1.07–1.48).

Conclusion: Gla-300 tended to be associated with lower hypoglycaemia risk than SOC-BI in real-world clinical practice during the 12-month follow-up.

KEYWORDS

basal insulin, glycaemic control, hypoglycaemia, insulin analogues, randomized trial, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic progressive disease that accounts for 90% to 95% of all adults with diabetes mellitus and affects an increasing proportion of the population of the United States.[1] The estimated prevalence of diabetes (type 1 or 2) among adults in the United States is 14.0%, including 9.7% with diagnosed and 4.3% with undiagnosed diabetes.[2] Despite the availability of various non-insulin treatments for T2D, many adults eventually require basal insulin (BI) therapy to achieve glycaemic control.[3]

Uncontrolled diabetes is associated with increased risk of complications, including cardiovascular and peripheral vascular disease, stroke, retinopathy, neuropathy and nephropathy,[4] which may severely impair health-related quality of life.[4] First-generation, long-acting BI analogues, such as glargine 100 U/mL (Gla-100) and insulin detemir (IDet), are widely used in combination with oral anti-hyperglycaemic drugs and/or glucagon-like peptide-1 receptor agonists (GLP-1RAs) to improve glycaemic control in adults with T2D.[5] However, hypoglycaemia and fear of hypoglycaemia remain major barriers to achieving glycaemic control in real-world clinical practice, as they impair adherence to and persistence with BI therapy.[6–8] The availability of BI analogues associated with reduced risk of hypoglycaemia may help adults with T2D requiring insulin therapy to improve blood glucose management and maintain adequate glycaemic control.

Insulin glargine 300 U/mL (Gla-300) and insulin degludec are second-generation, longer-acting BI analogues with improved pharmacokinetic and pharmacodynamic properties.[9,10] The longer and more stable action profile of second- versus first-generation BI analogues results in less within-24-hour variation in glycaemic excursions, thereby reducing the risk of hypoglycaemia.[9,11] In randomized controlled trials (RCTs), Gla-300 and Gla-100 demonstrated similar efficacy in reducing glycated haemoglobin (HbA1c), whereas Gla-300 was associated with a lower risk of hypoglycaemia in adults with T2D,[12,13] including insulin-naïve adults evaluated in the EDITION 3 RCT.[14,15] Similarly, real-world evidence from retrospective observational studies indicates that adults with T2D, including insulin-naïve adults, have a lower risk of hypoglycaemia with Gla-300 than with first-generation BIs.[16–18]

ACHIEVE Control (N = 3304) is the first prospective pragmatic randomized real-life trial that compared the efficacy and safety of a second-generation BI, Gla-300, with first-generation standard-of-care BIs (SOC-BIs) Gla-100 or IDet, in insulin-naïve adults with T2D and inadequate glycaemic control.[19,20] Pragmatic studies[21] preserve the internal validity of randomization,[22] while providing real-world evidence from usual clinical practice.[23] The results of ACHIEVE Control complement the findings of EDITION 3[14,15] and DELIVER Naive,[18] a real-world study based on electronic medical records of insulin-naïve adults with T2D. Compared with EDITION 3, ACHIEVE Control used more inclusive eligibility criteria and study procedures reflecting usual, real-world clinical practice.[19] To be more representative of the real-life T2D adult population, ACHIEVE Control allowed study participation of adults with diverse comorbidities and concomitant therapies, and defined inadequate control as HbA1c ≥64 mmol/mol (8.0%) after ≥1 year of treatment with two or more non-insulin anti-hyperglycaemic agents. To mimic real-life treatment procedures, many investigators had no or limited experience in clinical research, mandatory trial visits were limited to baseline, 6- and 12-month assessments, and the sponsor provided no formal guidance on BI dose titration beyond labelling information. Participants were offered patient support programmes (PSPs), where available, during the course of the study.

Individualized Healthcare Effectiveness Data and Information Set (HEDIS) HbA1c target attainment without documented symptomatic hypoglycaemia (blood glucose ≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at 6 months was chosen as the composite primary endpoint to reflect real-life treatment objectives. ACHIEVE Control met the primary endpoint of statistical superiority of Gla-300 over SOC-BI (odds ratio [OR], 95% confidence interval [CI] 1.19, 1.01–1.39; $P = 0.03$). Results for the individual components of the composite primary endpoint further suggested that avoidance of documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at 6 months was greater in the Gla-300 than in the SOC-BI treatment group (OR 1.19, 95% CI 1.01–1.41; $P = 0.03$).[20]

To explore whether the benefit of Gla-300 versus SOC-BI observed at 6 months was maintained with continued therapy, all outcomes were also evaluated at 12 months of treatment. In the present paper, we report the 12-month clinical outcomes of ACHIEVE Control, including results from prespecified analyses in all randomized adults and from a *post hoc* analysis in PSP participants. Healthcare Resource Utilization (HCRU) data provided by a small proportion of randomized adults are also reported.

2 | METHODS

2.1 | Study design and participants

ACHIEVE Control (ClinicalTrials.gov: NCT02451137) was a large 12-month pragmatic, randomized, multicentre, open-label, prospective real-life study, conducted in a real-world clinical setting in the United States and Canada. The full study design[19] has been reported previously.

Study participants were insulin-naïve adults (age ≥18 years) with T2D diagnosed ≥1 year before the screening visit and with HbA1c ≥64 mmol/mol (8.0%) and ≤97 mmol/mol (11.0%) after ≥1 year of treatment with two or more anti-hyperglycaemic agents, which could include oral anti-hyperglycaemic drugs and GLP-1RAs approved for concomitant use with insulin. Adults were randomized (1:1) to treatment with Gla-300 or SOC-BI (Gla-100 or IDet). Efficacy assessments were based on individualized HbA1c targets per 2015 HEDIS criteria, that is, <64 mmol/mol (8.0%) for participants aged ≥65 years or with defined comorbidities (coronary bypass surgery or percutaneous coronary intervention, ischaemic vascular disease, thoracic aortic aneurism, chronic heart failure, prior myocardial infarction, chronic renal failure/end-stage renal disease, dementia, blindness, or lower extremity amputation), and <53 mmol/mol (7.0%) for all other participants.[19,24] Randomization was stratified by HbA1c target (<53 mmol/mol [7.0%]/<64 mmol/mol

[8.0%]), sulphonylurea use (yes/no), GLP-1RA use (yes/no), and baseline HbA1c (</≥75 mmol/mol [9.0%]).

All participants were encouraged to participate in available PSP or diabetes management programmes. The COACH programme was available specifically for adults randomized to Gla-300.[19,25]

Study data were collected from case report forms, administrative claims, e-diaries (completed by study participants and used to document self-monitored plasma glucose levels [recommended ≥1 daily], adverse events, dose changes, and hypoglycaemia and its symptoms), and participant surveys/questionnaires.

2.2 | Endpoints and assessments

The composite primary endpoint was the proportion of adults with individualized HbA1c target attainment according to HEDIS criteria[24] at 6 months with no documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at any time of day from baseline to 6 months. Secondary composite endpoints evaluated for the present study included HbA1c target attainment without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) and/or severe hypoglycaemia at 12 months, and HbA1c target attainment without documented symptomatic (<3.0 mmol/L [<54 mg/dL]) and/or severe hypoglycaemia (at 6 and 12 months). Outcomes for the components of all composite endpoints will also be presented. Additional assessments included changes from baseline to 6 and 12 months in HbA1c, fasting plasma glucose (FPG), body weight and BI dose.

Safety assessments included incidence and rates of hypoglycaemic events and incidence of treatment-emergent adverse events (TEAEs). Hypoglycaemic events were categorized as severe hypoglycaemia (American Diabetes Association [ADA] level 3[26]), documented symptomatic hypoglycaemia (blood glucose ≤3.9 mmol/L [≤70 mg/dL; ADA levels 1 + 2 definition of <3.9 mmol/L][26]), and asymptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL] or < 3.0 mmol/L [<54 mg/dL]).

Healthcare Resource Utilization was evaluated in all randomized participants as part of prespecified endpoints, including frequency of hospitalization, emergency department visits, provider office visits, and specialty visits at 6 and 12 months. In addition, overall and diabetes-related medical costs were assessed in adults who provided separate written consent (voluntary choice to opt in) to share claims data other than those related to the use of BI.

2.3 | Statistical analyses

Efficacy was evaluated in all randomized adults and safety was evaluated in all randomized adults who received at least one dose of study BI. All secondary endpoints were exploratory, and statistical analyses for these endpoints are descriptive only, with no adjustments for multiple testing. ORs for efficacy endpoints were based on a logistic regression model, with adjustments as previously described.[20]

3 | RESULTS

3.1 | Participants

Of 3304 adults randomized to Gla-300 or SOC-BI (efficacy population), 3258 (98.6%) received at least one dose of study treatment. Of 1653 adults randomized to SOC-BI, 1069 received Gla-100 and 565 received IDet. Of 1651 adults randomized to Gla-300, 19 received no treatment. In the Gla-300 and SOC-BI arms, 90.7% and 89.1% of adults, respectively, completed 6 months of treatment, and 85.1% and 82.0% of adults, respectively, completed 12 months of treatment (Figure S1). Baseline demographic and clinical characteristics of the ACHIEVE Control population were similar in the two treatment groups (Table 1).

3.2 | Efficacy

At 12 months, 26.1% of adults randomized to Gla-300 versus 23.7% randomized to SOC-BI achieved the secondary composite endpoint of HbA1c target attainment without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia (OR 1.14, 95% CI 0.97–1.35; Figure 1A). Analysis of the two components of this composite endpoint yielded ORs of 1.15 (95% CI 0.99–1.34) for HbA1c target attainment (irrespective of hypoglycaemia) and 1.21 (95% CI 1.05–1.40) for absence of documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at 12 months (Figure 1B).

At 12 months, 33.0% of adults randomized to Gla-300 versus 29.5% randomized to SOC-BI achieved their HbA1c targets without documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia (OR 1.19, 95% CI 1.02–1.38; Figure 1A). The OR for absence of documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia was 1.26 (95% CI 1.07–1.48) in favour of Gla-300 versus SOC-BI (Figure 1B).

Overall, attainment of the composite endpoints and their components at 12 months was consistent with the corresponding findings at 6 months, showing favourable trends for Gla-300 versus SOC-BI across endpoints. Of note, some of these trends in favour of Gla-300 were increased at 12 versus 6 months, including those for the composite endpoint of HbA1c target attainment without documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia and for the endpoint of absence of documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia (Figure 2).

There were no clinically meaningful differences between treatment groups in changes from baseline in HbA1c, FPG or body weight (Figure 3A–C). Most of the reduction in mean HbA1c and mean FPG occurred during the first 6 months of treatment, followed by a slight increase between 6 and 12 months in the Gla-300 (HbA1c) and SOC-BI (HbA1c and FPG) groups. The mean daily doses of Gla-300 and SOC-BI increased similarly from 0.16 U/kg and 0.15 U/kg, respectively, at baseline to 0.34 U/kg for both treatment groups at 6 months and 0.38 U/kg for both treatment groups at 12 months (Figure 3D).

TABLE 1 Participants' demographic and clinical characteristics

	Gla-300 (n = 1651)	SOC-BI (n = 1653)	Total (N = 3304)
Age, years, mean (SD)	59.4 (10.8)	59.1 (11.0)	59.3 (10.9)
Men, n (%)	904 (54.8)	922 (55.8)	1826 (55.3)
Race, n (%)			
White	1283 (77.7)	1299 (78.6)	2582 (78.1)
Black	262 (15.9)	238 (14.4)	500 (15.1)
Asian	83 (5.0)	95 (5.7)	178 (5.4)
Other	33 (2.0)	30 (1.8)	63 (1.9)
BMI, kg/m^2, mean (SD)	33.9 (7.1) (n = 1650)	33.7 (7.3) (n = 1652)	33.8 (7.2) (n = 3302)
HbA1c, mmol/mol [%], mean (SD)	76 (8.7) [9.1 (0.8)]	77 (8.7) [9.2 (0.8)]	77 (8.7) [9.2 (0.8)]
Duration of diabetes, years, mean (SD)	11.4 (7.4)	11.2 (7.3)	11.3 (7.4)
Previous diabetic complications, n (%)			
Diabetic neuropathy	462 (28.0)	478 (28.9)	940 (28.5)
Diabetic nephropathy	172 (10.4)	183 (11.1)	355 (10.7)
Diabetic retinopathy	102 (6.2)	116 (7.0)	218 (6.6)
Number of previous non-insulin anti-hyperglycaemic agents, n (%)			
0	1 (0.1)	1 (0.1)	2 (0.1)
1	7 (0.4)	6 (0.4)	13 (0.4)
2	795 (48.2)	777 (47.0)	1572 (47.6)
>2	848 (51.4)	869 (52.6)	1717 (52.0)
Duration of previous non-insulin antihyperglycaemic treatment, years, mean (SD)	6.5 (5.3) (n = 1650)	6.4 (5.5) (n = 1651)	6.5 (5.4) (n = 3301)
Previous non-insulin anti-hyperglycaemic agents, n (%)	(n = 1650)	(n = 1652)	(n = 3302)
Biguanides	1519 (92.1)	1508 (91.3)	3027 (91.7)
Sulphonylureas	1264 (76.6)	1256 (76.0)	2520 (76.3)
DPP-4 inhibitors	702 (42.5)	740 (44.8)	1442 (43.7)
SGLT2 inhibitors	445 (27.0)	435 (26.3)	880 (26.7)
GLP-1RAs	285 (17.3)	259 (15.7)	544 (16.5)
Thiazolidinediones	201 (12.2)	204 (12.3)	405 (12.3)
Glinides	20 (1.2)	26 (1.6)	46 (1.4)
α-glucosidase inhibitors	13 (0.8)	8 (0.5)	21 (0.6)
Other	2 (0.1)	4 (0.2)	6 (0.2)
HEDIS HbA1c target, n (%)			
<53 mmol/mol (7.0%)	874 (52.9)	913 (55.2)	1787 (54.1)
<64 mmol/mol (8.0%)	777 (47.1)	740 (44.8)	1517 (45.9)
Medical history related to diabetes, n (%)			
Any	332 (20.1)	297 (18.0)	629 (19.0)
Coronary artery bypass graft	78 (4.7)	56 (3.4)	134 (4.1)
Percutaneous coronary intervention	92 (5.6)	91 (5.5)	183 (5.5)
Ischaemic vascular disease	165 (10.0)	138 (8.3)	303 (9.2)
Thoracic aortic aneurysm	5 (0.3)	4 (0.2)	9 (0.3)
Chronic heart failure	57 (3.5)	56 (3.4)	113 (3.4)
Myocardial infarction	85 (5.1)	79 (4.8)	164 (5.0)
Chronic renal failure or ESRD	74 (4.5)	59 (3.6)	133 (4.0)
Dementia	4 (0.2)	6 (0.4)	10 (0.3)
Blindness	7 (0.4)	6 (0.4)	13 (0.4)
Leg amputation	2 (0.1)	3 (0.2)	5 (0.2)

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase 4; ESRD, end-stage renal disease; Gla-300, insulin glargine 300 U/mL; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HEDIS, Healthcare Effectiveness Data and Information Set; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2; SOC-BI, standard-of-care basal insulin (insulin glargine 100 U/mL or insulin detemir).

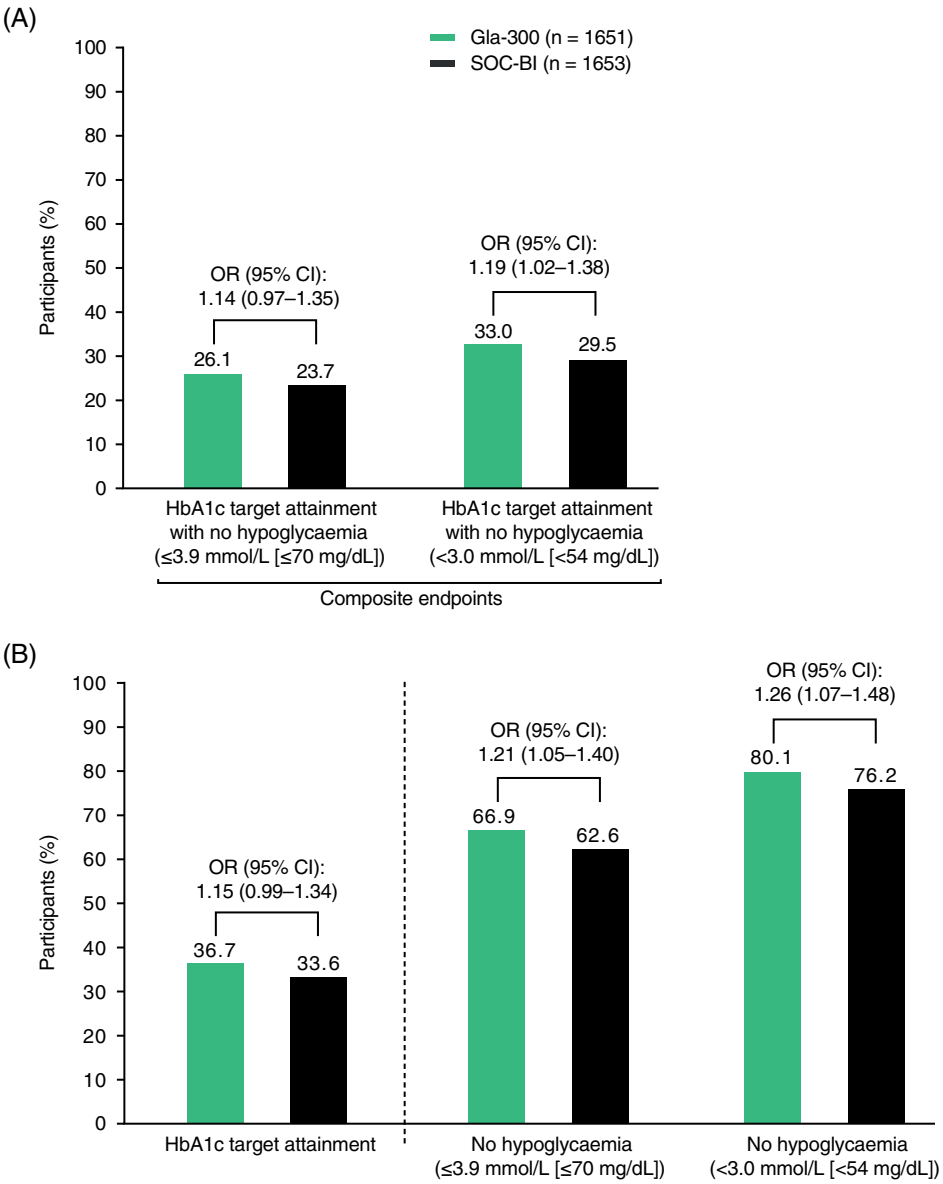

FIGURE 1 Attainment of composite endpoints **A**, and their components **B**, with insulin glargine 300 U/mL (Gla-300) versus standard-of-care basal insulin (SOC-BI) at 12 months in all randomized adults. Hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL]) and hypoglycaemia (<3.0 mmol/L [<54 mg/dL]) were defined as presence of severe hypoglycaemia and/or documented symptomatic hypoglycaemia with blood glucose ≤3.9 mmol/L (≤70 mg/dL) and <3.0 mmol/L [<54 mg/dL], respectively, at any time from baseline to month 12. CI, confidence interval; HbA1c, glycated haemoglobin; OR, odds ratio; SOC-BI, standard-of-care basal insulin (insulin glargine 100 U/mL or insulin detemir)

3.3 | Secondary analyses of efficacy by PSP participation

Overall, 23.1% of adults in the Gla-300 arm and 10.3% of adults in the SOC-BI arm participated in a PSP. In each treatment arm, baseline characteristics were similar between PSP participants and non-participants (Table S1).

In the Gla-300 arm, 24.9% of PSP participants versus 26.5% of non-participants achieved their HbA1c targets without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at 12 months; 34.6% versus 32.5%, respectively, achieved the corresponding composite endpoint without hypoglycaemia <3.0 mmol/L (<54 mg/dL). In the SOC-BI arm, 22.4% of PSP participants versus 23.8% of non-participants achieved their HbA1c targets without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia at 12 months, and 27.1% versus 29.7% achieved the corresponding composite endpoint without hypoglycaemia <3.0 mmol/L (<54 mg/dL). Attainment rates for the individual components of these composite endpoints by PSP participation and treatment arm are shown in Table S2, and changes in HbA1c, body weight and dose are shown in Table S3.

3.4 | Safety

During the 12-month treatment period, 39.1% of the participants treated with Gla-300 versus 41.8% treated with SOC-BI experienced at least one hypoglycaemic event of any kind regardless of symptomatic or symptomatic status (risk ratio 0.93, 95% CI 0.86–1.01). Most hypoglycaemia risk ratios showed minor to modest trends for reduced risk with Gla-300 versus SOC-BI; however, strong trends in favour of Gla-300 were observed for asymptomatic hypoglycaemia <3.0 mmol/L (<54 mg/dL) at any time of day (risk ratio 0.75, 95% CI 0.58–0.97) and for nocturnal documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia (risk ratio 0.78, 95% CI 0.62–0.99; Figure S2). The exposure-adjusted rate of hypoglycaemic events of any kind was

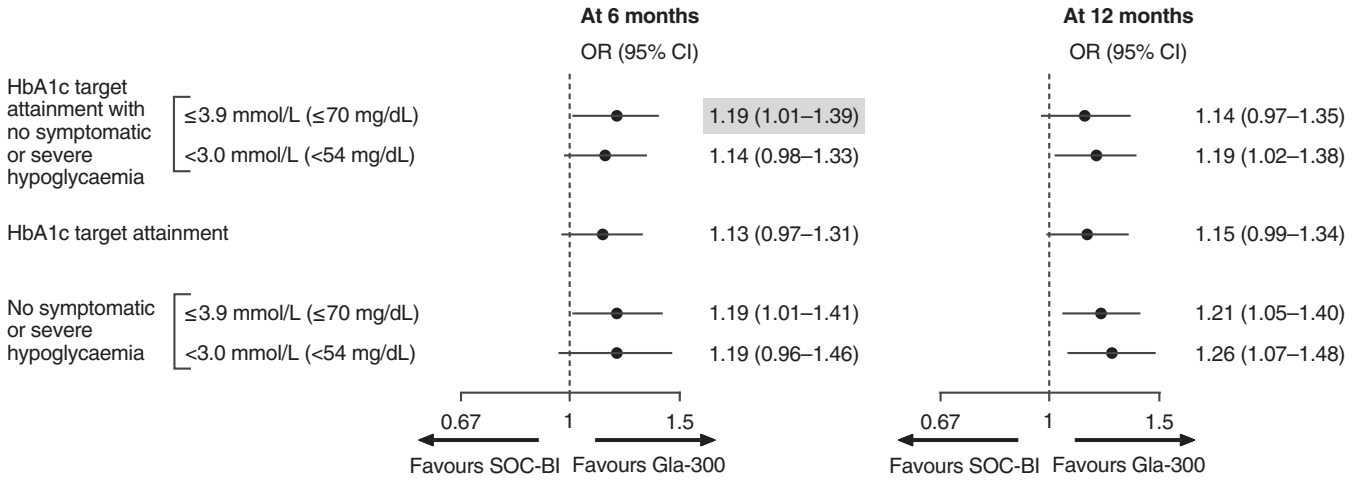

FIGURE 2 Comparison of odds ratios (ORs) for attainment of composite endpoints and their components at 6 and 12 months in all randomized adults. The OR for the composite primary endpoint is highlighted in grey. Hypoglycaemia was defined as presence of severe hypoglycaemia and/or documented symptomatic hypoglycaemia (with blood glucose ≤3.9 mmol/L [≤70 mg/dL] or < 3.0 mmol/L [<54 mg/dL]). CI, confidence interval; Gla-300, insulin glargine 300 U/mL; SOC-BI, standard-of-care basal insulin (insulin glargine 100 U/mL or insulin detemir)

2.29 events per participant-year with Gla-300 and 2.63 events per participant-year with SOC-BI (rate ratio 0.87, 95% CI 0.69–1.10).

Rates of TEAEs were similar in the Gla-300 and SOC-BI arms; the proportion of adults with at least one TEAE during the 12-month assessment was 50.0% and 47.1%, respectively (Table S4).

3.5 | Healthcare Resource Utilization

Healthcare Resource Utilization over 12 months in all randomized adults (N = 3304) was similar in the two treatment arms based on case report forms; 9.1% and 8.0% of adults in the Gla-300 and SOC-BI arms, respectively, required hospitalization, 12.7% and 11.1%, respectively, visited the emergency department, and 80.1% and 75.9%, respectively, visited a physician's office. However, only 147 adults (8.9%) in the Gla-300 arm and 126 adults (7.6%) in the SOC-BI arm consented to share their claims data for cost analyses (Table S5). Baseline characteristics for this self-selected subgroup showed potential imbalances in medical history between treatment group, such as numerically higher frequencies of cardiac disorders, respiratory, thoracic and mediastinal disorders, and renal and urinary disorders in adults randomized to Gla-300 versus SOC-BI (Table S6). HCRU in this subgroup did not accurately mirror HCRU in all randomized adults, showing a major imbalance in hospitalizations between the Gla-300 and SOC-BI arms (11.6% vs. 4.8% of adults; Table S5). Claims data were provided from two payers. Overall and diabetes-related HCRU and healthcare costs in participants who released claims data are summarized in Tables S7 and S8. Overall healthcare costs were higher with Gla-300 (n = 147) than SOC-BI (n = 126). Median diabetes-related healthcare costs over 12 months were similar for Gla-300 ($635.96) and SOC-BI ($693.17), although LS mean (SE) costs were higher with Gla-300 ($4888.04 [1059.02]) than with SOC-BI ($3323.48 [1143.88]; Table S8).

4 | DISCUSSION

The 6-month ACHIEVE Control results demonstrated significant superiority of Gla-300 over SOC-BI for the proportion of adults achieving individualized HEDIS HbA1c targets without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) and/or severe hypoglycaemia at any time of day from baseline to 6 months (composite primary endpoint: OR 1.19, 95% CI 1.01–1.39; $P = 0.03$).[20] The results of the present analyses continued to show a favourable, albeit non-significant, trend favouring Gla-300 versus SOC-BI for the secondary endpoint of individualized HbA1c target achievement without documented symptomatic (≤3.9 mmol/L [70 mg/dL]) or severe hypoglycaemia at 12 months. Trends favouring Gla-300 versus SOC-BI for other secondary endpoints at 6 months were maintained or strengthened at 12 months. Notably, ORs and their associated 95% CIs favoured Gla-300 versus SOC-BI at 12 months for the composite endpoint using the hypoglycaemia threshold of <3.0 mmol/L (<54 mg/dL), and for the absence of severe or documented symptomatic hypoglycaemia from baseline to 12 months using either threshold (≤3.9 mmol/L [≤70 mg/dL] or < 3.0 mmol/L [<54 mg/dL]). Overall, these findings suggest that adults receiving prolonged insulin treatment are more likely to avoid hypoglycaemia with Gla-300 than with first-generation BI analogues.

Changes from baseline to 12 months in HbA1c, FPG and body weight were similar in the two treatment arms, with most of the changes occurring in the first 6 months. Mean HbA1c and mean FPG were similar at 6 and 12 months. Similarly, mean BI doses for both treatments more than doubled during the first 6 months and then increased only by approximately 15% from month 6 to 12. The small increase in mean HbA1c observed between 6 and 12 months is consistent with findings of increasing or plateauing HbA1c during continued treatment with BI therapy of adults with T2D in RCTs[15,27,28] and real-world practice.[29]

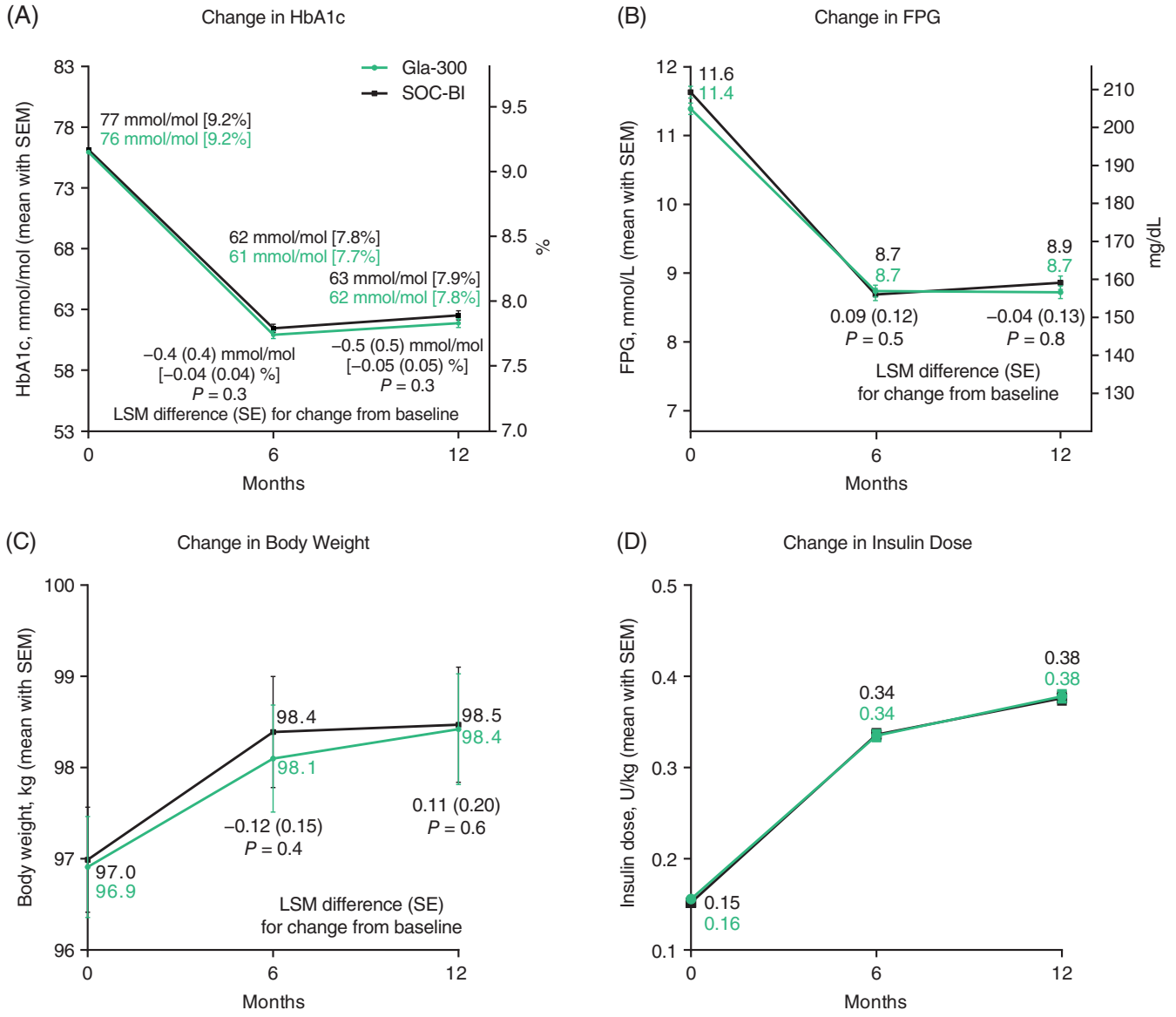

FIGURE 3 Changes in **A,** glycated haemoglobin (HbA1c), **B,** fasting plasma glucose (FPG) **C,** body weight and **D,** basal insulin (BI) dose during the 12-month study period. HbA1c, FPG and body weight were assessed in all randomized adults; BI dose was assessed in all treated adults. Gla-300, insulin glargine 300 U/mL; LSM, least squares mean; SE, standard error; SEM, standard error; SOC-BI, standard-of-care basal insulin (insulin glargine 100 U/mL or insulin detemir)

As previously noted,[20] PSP participation was low in both treatment arms and particularly low in the SOC-BI arm (10% vs. 23% in the Gla-300 arm). Participation in the COACH programme, which was available to adults receiving Gla-300, has been associated with significantly improved treatment adherence and persistence at 6 and 9 months.[25] It remains unclear whether or to what extent PSP participation may have affected 12-month outcomes for specific endpoints. Observed attainment rates (numerical values) at 12 months for the composite secondary endpoints and their components were consistently higher for Gla-300 than SOC-BI, regardless of PSP participation. However, PSP participation was associated with numerically greater HbA1c attainment in the Gla-300 arm, and with numerically greater proportions of adults with no documented symptomatic (≤3.9 mmol/L [≤70 mg/dL] or < 3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia in the SOC-BI arm. These differences may be attributable to differences in available support programmes between the two treatment arms. Of note, PSP participation had no clinically meaningful effects on weight gain or dosing.

Although HCRU assessments in ACHIEVE Control were based on prespecified endpoints, meaningful analyses (particularly of healthcare costs) were not possible because the vast majority of participants (92%) did not consent to release their claims data. Consequently, the statistical power of the cost analyses was compromised and randomization was not maintained. The baseline characteristics of the self-selected subgroup of adults who provided consent indicated potential imbalances in medical history between treatment groups, and HCRU data (particularly for hospitalization) were not representative of all randomized adults. Claims data came from only two payers and may not be representative of cost estimates by

the larger pool of payers for all randomized adults. Thus, the HCRU and associated costs data available for the current analyses may not reflect real-world data in a larger, insulin-naïve T2D population.

The current clinical findings complement the 12-month clinical outcomes observed in EDITION 3 as well as previous findings from the real-world DELIVER Naive study.

In EDITION 3, a tightly regimented RCT of Gla-300 versus Gla-100 in insulin-naïve adults with T2D and HbA1c of 53-97 mmol/mol (7.0%-11.0%), mean BI doses were higher and mean HbA1c and FPG levels were lower than in ACHIEVE Control, reflecting the difference between a protocol-driven and closely supervised insulin titration schedule in an RCT and the real-life practice adopted in ACHIEVE Control.[15] Safety data from EDITION 3 suggested a reduced risk of confirmed (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia with Gla-300 versus Gla-100 at any time of day (relative risk 0.66, 95% CI 0.50–0.88),[15] consistent with the results of ACHIEVE Control, suggesting a greater likelihood with Gla-300 versus SOC-BI of remaining without documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia after 12 months of treatment.

Besides ACHIEVE Control, DELIVER Naive is the only study that has provided real-world evidence regarding the effectiveness of Gla-300 versus first-generation BI analogues in insulin-naïve adults with T2D. DELIVER Naive was a retrospective, observational study that compared HbA1c target achievement and hypoglycaemia outcomes in propensity score-matched study cohorts treated with Gla-300 or Gla-100.[18] Follow-up was limited to 6 months. Overall, the findings suggested greater HbA1c reductions and similar or improved hypoglycaemia outcomes with Gla-300 versus Gla-100.[18]

The results of ACHIEVE Control add to the body of evidence suggesting a reduced risk of anytime hypoglycaemia and/or nocturnal hypoglycaemia with second- versus first-generation BI analogues in adults with T2D.[12–15,30,31] However, the study has some limitations. In this real-life study, no continuous glucose monitoring data were obtained. The unequal distribution of PSP participation between treatment arms and its unclear effect on overall outcomes have been noted. In addition, per study design, only the primary endpoint qualified for inferential statistical comparison of treatment arms. All other endpoints are exploratory and descriptive only. Some aspects of the real-world study design may have resulted in suboptimal treatment outcomes. As mentioned above, insulin dose titration was less aggressive in ACHIEVE Control than in EDITION 3, likely due to lack of protocol guidance and inexperience of many investigators in clinical trial conduct. For Gla-300, another factor contributing to a cautious titration approach may have been the relative novelty of this BI analogue and consequent inexperience with its use in clinical practice.

In conclusion, the 12-month results of ACHIEVE Control suggest that adults with insulin-naïve T2D treated with Gla-300 rather than Gla-100 or IDet in usual, real-world clinical practice may be more likely to achieve their individualized HbA1c targets without experiencing documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia. This benefit would apply to adults treated with Gla-300 versus Gla-100 or IDet at similar doses, which resulted in similar modest body weight changes. Furthermore, Gla-300 used for 12 months in usual clinical practice may be more likely than Gla-100 or IDet to help adults avoid ADA level 1 and 2 hypoglycaemia.

Overall, the results of ACHIEVE Control suggest that the hypoglycaemia-related benefits of Gla-300 versus first-generation SOC-BI persist with continued treatment. Comprehensive and complementary evidence from a clinical trial (EDITION 3) and real-world studies (ACHIEVE Control and DELIVER Naive) consistently suggests that Gla-300 is more effective than first-generation BI analogues in providing glycaemic control, with a low risk of hypoglycaemia for insulin-naïve adults with T2D who have not attained their glycaemic targets.

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CONFLICTS OF INTEREST

L.M. is an advisory board member for Novo Nordisk and Sanofi, and a consultant for Applied Therapeutics, Novo Nordisk and Sanofi. L.B. has received grant/research support for himself and/or his institution from Janssen Pharmaceuticals, Lexicon Pharmaceuticals, Merck & Co., Novo Nordisk and Sanofi, has received support as a speaker from Janssen Pharmaceuticals, Novo Nordisk and Sanofi, and is a consultant for AstraZeneca, Gilead Sciences, Janssen Pharmaceuticals, Merck & Co., Novo Nordisk and Sanofi. J.S. is an advisory board member for Merck, Novo Nordisk and Sanofi, and a speaker for Abbott, the ADA, AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, Salix and Sanofi. T.S.B. reports consultancy work for Lifescan, Novo and Sanofi, research support for Abbott, Capillary Biomedical, Dexcom, Diasome, Eli Lilly, Kowa, Lexicon, Medtronic, Medtrum, Novo Nordisk, REMD, Sanofi, Senseonics, Viacyte, vTv Therapeutics and Zealand Pharma, and participation in a speakers' bureau for Medtronic and Sanofi. J.G. and A.D. are employees and stockholders of Sanofi. A.B. is a stockholder and former employee of and clinical study supervisor for Sanofi.

AUTHOR CONTRIBUTIONS

L.M., J.G., A.D. and T.S.B. contributed to the conception and design of the study. A.B. and J.G. contributed to data acquisition, and all authors contributed to the analysis and interpretation of the data. All authors contributed to the drafting, critical review and revision of the manuscript and approved the final version.

ORCID

Luigi Meneghini https://orcid.org/0000-0003-4539-2725
Lawrence Blonde https://orcid.org/0000-0003-0492-6698

REFERENCES

1. Centers for Disease Control and Prevention (CDC). National diabetes statistics report, 2017. Estimates of diabetes and its burden in the United States 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed June 9, 2019.

2. Mendola ND, Chen TC, Gu Q, Eberhardt MS, Saydah S. Prevalence of total, diagnosed, and undiagnosed diabetes among adults: United States 2013-2016. *NCHS Data Brief*. 2018;319:1-8.
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41:2669-2701.
4. Cannon A, Handelsman Y, Heile M, Shannon M. Burden of illness in type 2 diabetes mellitus. *J Manag Care Spec Pharm*. 2018;24:S5-S13.
5. Wei W, Zhou S, Miao R, et al. Much ado about nothing? A real-world study of patients with type 2 diabetes switching basal insulin analogs. *Adv Ther*. 2014;31:539-560.
6. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
7. Dalal MR, Kazemi MR, Ye F. Hypoglycemia in patients with type 2 diabetes newly initiated on basal insulin in the US in a community setting: impact on treatment discontinuation and hospitalization. *Curr Med Res Opin*. 2017;33:209-214.
8. Peyrot M, Perez-Nieves M, Ivanova J, et al. Correlates of basal insulin persistence among insulin-naive people with type 2 diabetes: results from a multinational survey. *Curr Med Res Opin*. 2017;33:1843-1851.
9. Owens DR. Pharmacokinetics and pharmacodynamics of insulin glargine 300 U/mL in the treatment of diabetes and their clinical relevance. *Expert Opin Drug Metab Toxicol*. 2016;12:977-987.
10. Hompesch M, Patel DK, LaSalle JR, Bolli GB. Pharmacokinetic and pharmacodynamic differences of new generation, longer-acting basal insulins: potential implications for clinical practice in type 2 diabetes. *Postgrad Med*. 2019;131:117-128.
11. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 Units.mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units.mL-1. *Diabetes Care*. 2015;38:637-643.
12. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014;37:2755-2762.
13. Yki-Järvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014;37:3235-3243.
14. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17:386-394.
15. Bolli GB, Riddle MC, Bergenstal RM, et al. Glycaemic control and hypoglycaemia with insulin glargine 300U/mL versus insulin glargine 100U/mL in insulin-naive people with type 2 diabetes: 12-month results from the EDITION 3 trial. *Diabetes Metab*. 2017;43:351-358.
16. Zhou FL, Ye F, Berhanu P, et al. Real-world evidence concerning clinical and economic outcomes of switching to insulin glargine 300 units/mL vs other basal insulins in patients with type 2 diabetes using basal insulin. *Diabetes Obes Metab*. 2018;20:1293-1297.
17. Pettus J, Roussel R, Liz Zhou F, et al. Rates of hypoglycemia predicted in patients with type 2 diabetes on insulin glargine 300 U/ml versus first- and second-generation basal insulin analogs: the real-world LIGHTNING study. *Diabetes Ther*. 2019;10:617-633.
18. Bailey TS, Zhou FL, Gupta RA, et al. Glycaemic goal attainment and hypoglycaemia outcomes in type 2 diabetes patients initiating insulin glargine 300 units/mL or 100 units/mL: real-world results from the DELIVER Naive cohort study. *Diabetes Obes Metab*. 2019;21:1596-1605.
19. Oster G, Sullivan SD, Dalal MR, et al. Achieve Control: a pragmatic clinical trial of insulin glargine 300 U/mL versus other basal insulins in insulin-naive patients with type 2 diabetes. *Postgrad Med*. 2016;128:731-739.
20. Meneghini L, Sullivan SD, Oster G, et al. A pragmatic randomised clinical trial of insulin glargine 300 U/mL versus first-generation basal insulin analogues in insulin-näive patients with type 2 diabetes: ACHIEVE Control. *Diabetes Care*. 2020. In press.
21. Zuidgeest MGP, Goetz I, Groenwold RHH, et al. Series: pragmatic trials and real world evidence: paper 1 Introduction. *J Clin Epidemiol*. 2017;88:7-13.
22. Saunders C, Byrne CD, Guthrie B, et al. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? *Diabet Med*. 2013;30:300-308.
23. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016;375:2293-2297.
24. National Committee for Quality Assurance (NCQA). HEDIS measures and technical resources. 2015. http://www.ncqa.org/Portals/0/HEDISQM/Hedis2015/List_of_HEDIS_2015_Measures.pdf. Accessed September 5, 2019.
25. Goldman JD, Gill J, Horn T, Reid T, Strong J, Polonsky WH. Improved treatment engagement among patients with diabetes treated with insulin glargine 300 U/mL who participated in the COACH support program. *Diabetes Ther*. 2018;9:2143-2153.
26. American Diabetes Association (ADA). 6. Glycemic targets: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43(Suppl 1):S66-S76.
27. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012;35:2464-2471.
28. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017;377:723-732.
29. Blonde L, Meneghini L, Peng XV, et al. Probability of achieving glycemic control with basal insulin in patients with type 2 diabetes in real-world practice in the USA. *Diabetes Ther*. 2018;9:1347-1358.
30. Roussel R, Ritzel R, Boëlle-Le Corfec E, Balkau B, Rosenstock J. Clinical perspectives from the BEGIN and EDITION programmes: trial-level meta-analyses outcomes with either degludec or glargine 300U/mL vs glargine 100U/mL in T2DM. *Diabetes Metab*. 2018;44:402-409.
31. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379:1498-1507.

SUPPORTING INFORMATION

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

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