FEATURE ARTICLE

Post Hoc Analysis Evaluating the Impact of Antihyperglycemic Background Therapies on Attainment of A1C Targets Without Hypoglycemia in the ACHIEVE Control Pragmatic, Real-Life Study

Timothy S. Bailey,[1] Pierre Evenou,[2] Jasvinder Gill,[3] Paulos Berhanu,[3] Romain Raymond,[4] Jodi Strong,[5] and Eugene E. Wright Jr.[6]

[1]AMCR Institute, Escondido, CA; [2]Sanofi UK, Reading, UK; [3]Sanofi US, Inc., Bridgewater, NJ; [4]Ividata, Levallois-Perret, France; [5]Ascension Health, Stevens Point, WI; [6]Charlotte Area Health Education Center, Charlotte, NC

BACKGROUND | ACHIEVE Control, a prospective, open-label, randomized, pragmatic, real-life study in insulin-naive people with type 2 diabetes (A1C 8.0–11.0%), demonstrated superiority of insulin glargine 300 units/mL (Gla-300) versus first-generation standard-of-care basal insulin (SOC-BI; glargine 100 units/mL or insulin detemir) in achieving individualized A1C targets without documented symptomatic (glucose ≤3.9 mmol/L [≤70 mg/dL] or <3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia (American Diabetes Association level 3) at 6 months. Noninsulin antihyperglycemic background therapies are commonly used; however, sulfonylureas may increase hypoglycemia risk. This post hoc analysis assessed outcomes according to background therapy.

METHODS | Subgroup analyses were performed per concomitant use/nonuse of sulfonylureas, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase 4 inhibitors, or sodium–glucose cotransporter 2 (SGLT2) inhibitors. End points (6 and 12 months) included A1C target attainment without documented symptomatic or severe hypoglycemia, A1C target attainment, and absence of documented symptomatic or severe hypoglycemia.

RESULTS | Odds ratios (ORs) at 12 months mostly favored Gla-300 versus SOC-BI across subgroups except in analysis of SGLT2 inhibitors, in which ORs were similar. Among sulfonylurea users, ORs at 12 months strongly favored Gla-300 versus SOC-BI for all end points, particularly A1C target achievement without documented symptomatic hypoglycemia (glucose ≤3.9 mmol/L [≤70 mg/dL]; OR 1.25, 95% CI 1.02–1.53) or severe hypoglycemia and achievement of no documented symptomatic hypoglycemia (glucose <3.0 mmol/L [<54 mg/dL]; OR 1.25, 95% CI 1.02–1.52) or severe hypoglycemia.

CONCLUSION | The results suggest that, in insulin-naive people with type 2 diabetes, Gla-300 is effective with a risk of hypoglycemia that is lower than or similar to that of SOC-BI regardless of background medication. Individuals receiving concomitant sulfonylureas were more likely to remain without symptomatic or severe hypoglycemia with Gla-300.

Diabetes affects ~34 million people in the United States (1). The American Diabetes Association (ADA) recommends metformin as the preferred initial pharmacologic agent for the treatment of type 2 diabetes, with treatment intensification to occur via a stepwise approach (2). Choice of additional therapy depends on patient preference and clinical considerations such as effect on weight, risk of hypoglycemia, potential cardio- or renoprotective effects, and contraindications (3).

The U.S. Food and Drug Administration's approval of sulfonylureas was a pivotal moment in pharmacotherapy, as these agents were the first oral class of therapy approved for the treatment of type 2 diabetes. Sulfonylureas have an increased risk of hypoglycemia compared with other agents (4,5), although second-generation sulfonylureas have greater potency than first-generation agents within this class; thus, treatment can be given using lower doses (6). However, owing to their mechanism of action, sulfonylureas are effec-

Corresponding author: Timothy S. Bailey, tbailey@amcrinstitute.com
https://doi.org/10.2337/ds20-0079

tive only when there is residual pancreatic β-cell function. Thus, their effectiveness decreases progressively over time.

Because of the complex pathophysiology of type 2 diabetes, a broad range of therapies targeting the different pathophysiological derangements of type 2 diabetes are now available, including incretin-based therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, which stimulate insulin secretion in a glucose-dependent manner, and sodium–glucose cotransporter 2 (SGLT2) inhibitors, which facilitate urinary glucose excretion (6,7).

Despite the increased risk of hypoglycemia with the use of sulfonylureas compared with other agents (4,5), sulfonylureas remain widely used in the treatment of type 2 diabetes, likely because they are low in cost and readily available. Of individuals who require treatment with basal insulin (BI) to achieve glycemic control after failure of intensification of oral agents, a considerable proportion receive BI concomitantly with sulfonylurea therapy (3,8,9). Because both BI and sulfonylureas are associated with an increased risk of hypoglycemia, it is important that this risk is minimized as much as possible. With their more prolonged durations of action over 24 hours and reduced variability, second-generation, long-acting BI analogs such as insulin glargine 300 units/mL (Gla-300) and insulin degludec have improved pharmacokinetic (PK) and pharmacodynamic (PD) profiles compared with first-generation standard-of-care BI analogs (SOC-BI) such as insulin glargine 100 units/mL (Gla-100) (10,11) and insulin detemir. Therefore, second-generation BI analogs are associated with less variation in glycemic control (12) and have a lower risk of hypoglycemia (13,14). When BI is used in combination with sulfonylureas, the overall risk of hypoglycemia for the combination therapy could be lower with second- rather than first-generation BIs.

The effectiveness of Gla-300 versus first-generation BIs (Gla-100 or insulin detemir) was assessed in the ACHIEVE Control study. This was a 12-month, randomized, pragmatic, real-life study, conducted in the United States and Canada in 3,304 insulin-naive people with type 2 diabetes and inadequate glycemic control, that was designed to provide real-world evidence of treatment effectiveness while maintaining the internal validity of randomization (15–17). By minimizing restrictions on eligibility, the study permitted participation of a broad population of insulin-naive people with type 2 diabetes that was reflective of primary care. The primary composite end point—individualized Healthcare Effectiveness Data and Information Set (HEDIS) A1C target attainment at 6 months without occurrence of severe or documented symptomatic hypoglycemia (blood glucose ≤3.9 mmol/L [≤70 mg/dL])—was chosen to reflect real-life treatment objectives. Severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrates or glucagon or take other corrective actions (18) per ADA-defined level 3 hypoglycemia. Per HEDIS criteria (19), the A1C target was <8.0% for individuals ≥65 years of age or with defined comorbidities and <7.0% for all others (15).

The study met its composite primary end point, with 31.3 and 27.9% of participants randomized to Gla-300 and SOC-BI, respectively, achieving their HEDIS A1C target without documented symptomatic hypoglycemia (glucose ≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia at any time of the day at 6 months (odds ratio [OR] 1.19, 95% CI 1.01–1.39, P = 0.03 for superiority) (16). The study also included replicate end points with documented symptomatic hypoglycemia at blood glucose <3.0 mmol/L (<54 mg/dL), equivalent to the ADA's level 2 hypoglycemia definition (20).

The 12-month outcomes in the ACHIEVE Control study were consistent with those at 6 months (17) and similar to those of previous studies, including the EDITION 3 randomized study (21,22) and the real-world DELIVER Naive study (8).

Objectives

Primary care physicians have an increasingly important role in the treatment of type 2 diabetes (23), with >85% of recommendations to initiate BI therapy originating from them (24). It is important to understand how concomitant sulfonylurea use affects efficacy outcomes with BI, including A1C target achievement and risk of hypoglycemia. To simulate real-world clinical practice, treatment with other antihyperglycemic drugs in the ACHIEVE Control study was per clinician discretion and according to local labeling for concomitant use with BI. Thus, ACHIEVE Control provided the unique opportunity to evaluate potential effects of concomitant antihyperglycemic background therapies on BI treatment outcomes. We conducted post hoc analyses in subgroups of participants in ACHIEVE Control that were defined by the concomitant use or nonuse of common antihyperglycemic therapies, including sulfonylureas. Although GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors are not associated with increased risk of hypoglycemia, these agents were also included in the analysis.

Research Design and Methods

Study Design

The ACHIEVE Control study design (15) and primary outcomes (16) have been reported previously. Enrollment

occurred from June 2015 to July 2017. Insulin-naive individuals with type 2 diabetes and an A1C ≥8.0 and ≤11.0% were randomized (1:1) to Gla-300 or SOC-BI (Gla-100 or insulin detemir). Randomization was stratified by A1C target (<7/<8%), sulfonylurea use (yes/no), GLP-1 receptor agonist use (yes/no), and baseline A1C (<9/≥9%). Study participants had received their type 2 diabetes diagnosis ≥1 year before the screening visit and had not achieved glycemic control (A1C <8.0%) despite treatment with two or more oral antihyperglycemic drugs or GLP-1 receptor agonists approved for concomitant use with insulin.

Post Hoc Subgroup Analyses by Background Therapy

For the current analyses, participants in each subgroup were considered to be concomitant users of a background therapy if they were using it at the time of baseline assessment and continued use when starting BI therapy. Those who started background therapy at or after randomization were excluded from analysis. Analyses were conducted according to the intention-to-treat principle. The composite end points and components evaluated were A1C target attainment without documented symptomatic hypoglycemia (defined as glucose ≤3.9 mmol/L [≤70 mg/dL] or <3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia at 6 and 12 months, A1C target attainment (irrespective of hypoglycemia) at 6 and 12 months, and absence of documented symptomatic hypoglycemia (glucose ≤3.9 mmol/L [≤70 mg/dL] or <3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia at 6 and 12 months. ORs and associated 95% CIs were determined based on a logistic regression model.

Results

Change in Insulin Dose Over Study Period

The mean daily insulin doses were similar in the Gla-300 and SOC-BI treatment arms, both at the start of the study (0.156 ± 0.074 and 0.152 ± 0.079 units/kg, respectively) and at the 6- (0.335 ± 0.216 and 0.336 ± 0.220 units/kg, respectively) and 12-month time points (0.378 ± 0.235 and 0.376 ± 0.239 units/kg, respectively).

Sulfonylurea Background Therapy

Of 3,284 randomized participants who qualified for this subgroup analysis, 2,287 (69.6%) received a concomitant sulfonylurea; 20 individuals who started sulfonylurea therapy at or after randomization were excluded. Of those who did not use sulfonylurea therapy during the study, 23.4% had used it previously but stopped use before or at the time of BI initiation. Baseline characteristics were generally well balanced between the treatment arms of subgroups (Table 1).

In both the Gla-300 and SOC-BI treatment arms, the proportions of participants who achieved their A1C target without documented symptomatic hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia at 6 and 12 months were numerically greater among nonusers than users of concomitant sulfonylureas. Similarly, the proportions of participants with no documented symptomatic or severe hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) at 6 and 12 months were numerically greater among nonusers than users of concomitant sulfonylureas (Figure 1). ORs at 12 months (Figure 2*A*) strongly favored Gla-300 versus SOC-BI for all end points, including A1C target achievement without documented symptomatic hypoglycemia at either ≤3.9 mmol/L (≤70 mg/dL; OR 1.25, 95% CI 1.02–1.53) or <3.0 mmol/L (<54 mg/dL; OR 1.27, 95% CI 1.06–1.53) or severe hypoglycemia, A1C target achievement regardless of hypoglycemia (OR 1.21, 95% CI 1.01–1.44), and achievement of no documented symptomatic hypoglycemia at either ≤3.9 mmol/L (≤70 mg/dL; OR 1.23, 95% CI 1.04–1.46) or <3.0 mmol/L (<54 mg/dL; OR 1.25, 95% CI 1.02–1.52) or severe hypoglycemia.

Among those with no concomitant sulfonylurea use, the most favorable trends with Gla-300 versus SOC-BI were seen for achievement of no documented symptomatic hypoglycemia <3.0 mmol/L (<54 mg/dL) or severe hypoglycemia at 6 months (OR 1.20, 95% CI 0.83–1.73) and 12 months (OR 1.27, 95% CI 0.94–1.71) (Figure 2*A*). Because of the smaller sample size of this subgroup compared with users of a concomitant sulfonylurea, OR-associated 95% CIs were wider. ORs for treatment comparison in both subgroups were generally consistent with those in the overall study population, and no subgroup interactions were identified for any of the end points.

Other Background Therapies

Of the 3,224 randomized participants who qualified for the GLP-1 receptor agonist subgroup analysis, 428 (13.3%) received a concomitant GLP-1 receptor agonist, making this the smallest subgroup. Of the 3,273 randomized participants who qualified for the DPP-4 inhibitor subgroup analysis, 1,276 (39.0%) received a concomitant DPP-4 inhibitor. Of the 3,215 randomized participants who qualified for the SGLT2 inhibitor subgroup analysis, 756 (23.5%) received a concomitant SGLT2 inhibitor. Participants who started therapy at or after randomization were excluded (n = 80 for GLP-1 receptor agonist, n = 31 for DPP-4 inhibitor, and n = 89 for SGLT2 inhibitor therapy). Baseline

TABLE 1 Baseline Characteristics by Treatment Arm and Concomitant Use of Sulfonylurea or GLP-1 Receptor Agonist

	Concomitant Sulfonylurea Use		No Concomitant Sulfonylurea Use		Concomitant GLP-1 Receptor Agonist Use		No Concomitant GLP-1 Receptor Agonist Use	
	Gla-300 (*n* = 1,150)	SOC-BI (*n* = 1,137)	Gla-300 (*n* = 493)	SOC-BI (*n* = 504)	Gla-300 (*n* = 225)	SOC-BI (*n* = 203)	Gla-300 (*n* = 1,389)	SOC-BI (*n* = 1,407)
Age, years								
Median	60	60	59	58	58	59	60	59
Range	18–90	22–89	24–89	30–88	24–87	37–87	18–90	22–89
<65 years, %	64.4	65.4	71.0	70.8	73.8	70.4	64.9	66.7
Male, %	55.0	56.1	54.2	55.2	50.7	54.7	55.4	55.8
BMI, kg/m^2								
Mean	34.0	33.6	33.5	33.8	35.7	36.2	33.5	33.3
SD	7.3	7.6	6.8	6.7	7.2	7.5	7.1	7.2
Median	33.0	32.3	32.7	32.6	34.6	35.5	32.6	32.1
Range	19–75	18–85	20–60	20–65	20–60	20–65	19–75	18–85
A1C at screening, %								
Mean	9.2	9.2	9.1	9.1	9.1	9.1	9.1	9.2
SD	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Median	9.1	9.1	8.9	9.0	8.9	9.0	9.0	9.1
Range	8–11	8–11	8–11	8–11	8–11	8–11	8–11	8–11
HEDIS A1C target, %								
<8	48.7	47.1	43.4	39.7	42.7	44.3	48.4	44.8
<7	51.3	52.9	56.6	60.3	57.3	55.7	51.6	55.2
Duration of type 2 diabetes, years								
Mean	11.8	11.6	10.5	10.2	11.7	12.0	11.5	11.0
SD	7.6	7.3	7.0	7.1	7.2	7.8	7.5	7.3
Median	10.0	10.0	9.0	8.5	10.0	10.0	10.0	10.0
Range	1–56	1–50	1–50	1–58	1–47	1–40	1–56	1–58
Number of previous noninsulin antihyperglycemic agents [restore spaces between words], *n* (%)*								
1	1 (<0.1)	4 (0.4)	5 (1.0)	2 (0.4)	1 (0.4)	0	6 (0.4)	6 (0.4)
2	532 (46.3)	516 (45.4)	260 (52.8)	253 (50.3)	53 (23.6)	44 (21.7)	729 (52.5)	709 (50.4)
>2	617 (53.7)	617 (54.3)	227 (46.1)	248 (49.3)	171 (76.0)	159 (78.3)	653 (47.0)	691 (49.1)

*Two participants (one in the Gla-300 group and one in the SOC-BI group) were not receiving any noninsulin antidiabetic therapy before initiating insulin and were not included in the "no concomitant use" subgroups.

characteristics were well balanced between treatment groups in all three analyses (Tables 1 and 2).

Observed attainment rates for the composite end points were numerically higher for Gla-300 versus SOC-BI at both 6 and 12 months for both concomitant GLP-1 receptor agonist users versus nonusers (Figure 3) and concomitant DPP-4 inhibitor users versus nonusers (Figure 4). ORs were consistent with those in the overall study population, generally showing favorable trends for Gla-300 versus SOC-BI (Figures 2*B* and 5*A*).

Observed attainment rates of the end points for concomitant SGLT2 inhibitor users versus nonusers were similar for those who received Gla-300 or SOC-BI with the exception of absence of documented symptomatic hypoglycemia or severe hypoglycemia (Figure 6). OR estimates for concomitant SGLT2 inhibitor users did not suggest a greater benefit of Gla-300 versus SOC-BI for any of the efficacy end points tested (Figure 5*B*). There were no statistically significant subgroup interactions for any of the analyses except for absence of documented symptomatic hypoglycemia <3.0 mmol/L (<54 mg/dL) or severe hypoglycemia at 12 months for the SGLT2 inhibitor analysis (P = 0.0446). CIs were wide due to the relatively small sample sizes of participants who used concomitant GLP-1 receptor agonist, DDP-4 inhibitor, or SGLT2 inhibitor therapy.

Discussion and Conclusion

In these post hoc analyses of the prospective, randomized, pragmatic, real-life ACHIEVE Control study, we evaluated clinical outcomes for Gla-300 versus SOC-BI in adults

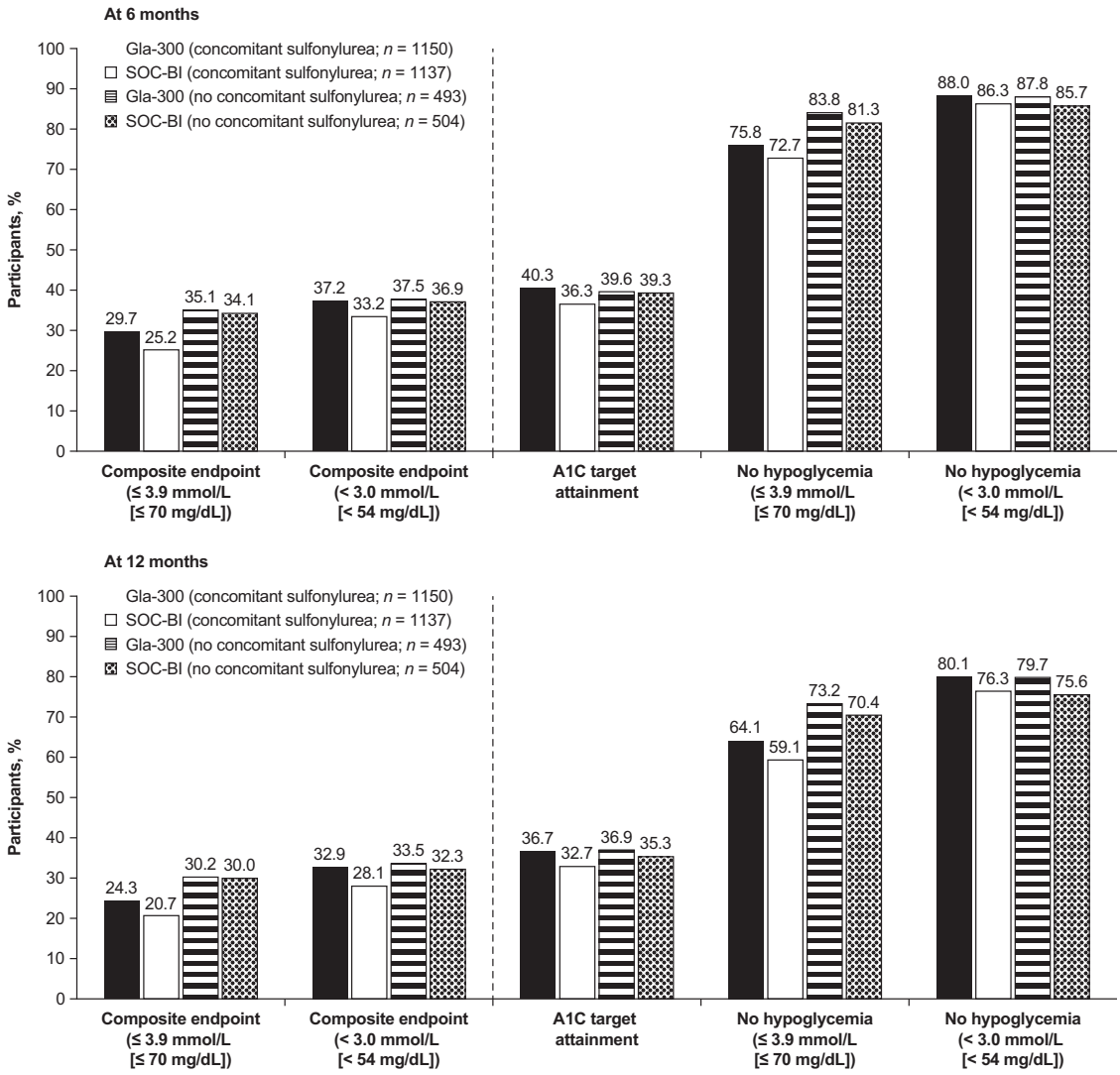

FIGURE 1 Observed proportions of participants who attained the composite end points and their components at 6 and 12 months in subgroups divided by use and nonuse of concomitant sulfonylurea.

using various background therapies, namely a sulfonylurea, GLP-1 receptor agonist, DPP-4 inhibitor, or SGLT2 inhibitor.

Sulfonylureas were used concomitantly by ∼70% of the study population, suggesting that, in real-world clinical practice, the concomitant use of sulfonylureas with insulin remains widespread despite sulfonylureas being associated with an increased risk of hypoglycemia (7). This analysis shows that, among participants treated with insulin and concomitant sulfonylureas, ORs consistently favored Gla-300 versus SOC-BI for all end points, suggesting that the use of Gla-300 may improve A1C target achievement without hypoglycemia and may be associated with lower risk of hypoglycemia versus first-generation BIs for this participant subgroup. This strategy may allow patients better control of their diabetes, which data suggest is associated with prevention of microvascular and macrovascular complications, while also limiting the risk of the serious impact of hypoglycemia on day-to-day life.

This potential benefit of Gla-300 compared with first-generation BI analogs is likely attributable to its prolonged and flatter PK and PD profiles (12). Although ORs for users of concomitant GLP-1 receptor agonist, DPP-4 inhibitor, or SGLT2 inhibitor therapy were associated with wide 95% CIs due to small sample sizes, our findings suggest that the hypoglycemia benefits of Gla-300 versus SOC-BI observed at 12 months in the overall study population were

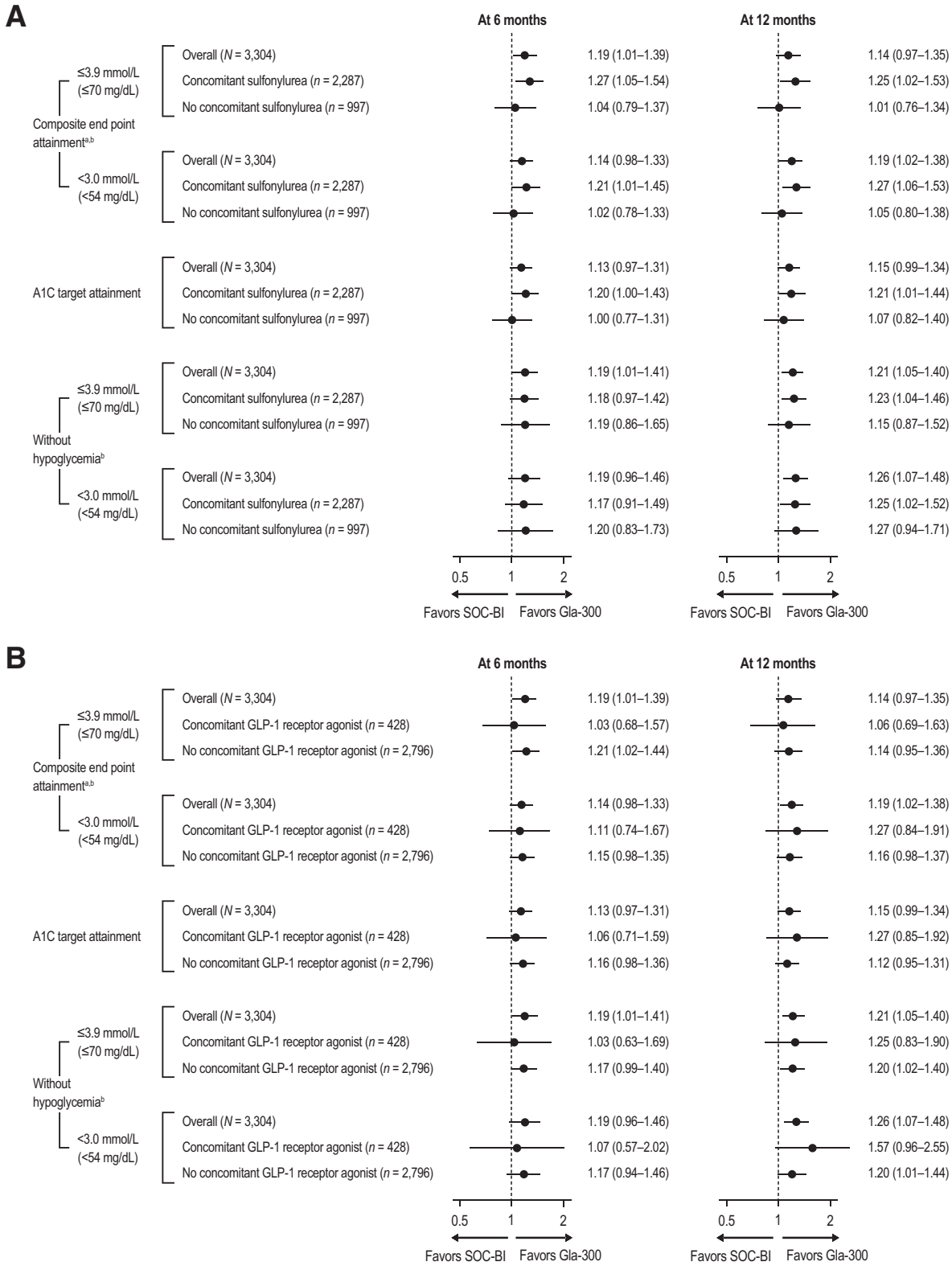

FIGURE 2 ORs with 95% CIs for attainment of composite end points and their components at 6 and 12 months by use/nonuse of concomitant sulfonylurea (*A*) and GLP-1 receptor agonist (*B*). Data are based on a logistic regression model with treatment arm as fixed effect and adjustment for randomization strata of A1C target, sulfonylurea use (except for sulfonylurea subgroup analyses), GLP-1 receptor agonist use (except for GLP-1 receptor agonist subgroup analyses), and baseline A1C (as continuous variable), with addition of the corresponding subgroup factor and the subgroup factor-by-treatment arm interaction. End points other than the composite primary were exploratory. [a]A1C target attainment without hypoglycemia. [b]Documented symptomatic (glucose ≤3.9 mmol/L [≤70 mg/dL] or <3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia.

TABLE 2 Baseline Characteristics by Treatment Arm and Concomitant Use of DPP-4 Inhibitor or SGLT2 Inhibitor

	Concomitant DPP-4 Inhibitor Use		No Concomitant DPP-4 Inhibitor Use		Concomitant SGLT2 Inhibitor Use		No Concomitant SGLT2 Inhibitor Use	
	Gla-300 (*n* = 627)	SOC-BI (*n* = 649)	Gla-300 (*n* = 1,012)	SOC-BI (*n* = 985)	Gla-300 (*n* = 372)	SOC-BI (*n* = 384)	Gla-300 (*n* = 1,237)	SOC-BI (*n* = 1,222)
Age								
Median, years	61	61	59	59	58	57	61	60
Range, years	26–88	30–89	18–90	22–88	31–80	22–89	18–90	24–88
<65 years, %	62.8	62.1	69.0	70.3	73.7	74.2	63.9	64.2
Male, %	53.7	57.3	55.4	55.1	62.1	60.2	52.1	53.9
BMI, kg/m^2								
Mean	33.5	33.2	34.1	34.0	33.6	33.5	33.9	33.7
SD	7.2	6.8	7.1	7.5	7.3	6.9	7.1	7.4
Median	32.7	32.0	33.2	32.8	33.0	32.2	32.9	32.5
Range	19–75	18–64	20–63	18–85	19–75	19–64	19–66	18–85
A1C at screening, %								
Mean	9.1	9.2	9.2	9.2	9.1	9.1	9.2	9.2
SD	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Median	9.0	9.0	9.0	9.1	8.9	8.9	9.1	9.1
Range	8–11	8–11	8–11	8–11	8–11	8–11	8–11	8–11
HEDIS A1C target, %								
<8	50.6	49.3	44.8	41.9	40.3	35.7	49.6	48.4
<7	49.4	50.7	55.2	58.1	59.7	64.3	50.4	51.6
Duration of type 2 diabetes, years								
Mean	11.3	11.2	11.4	11.1	11.1	10.6	11.6	11.4
SD	7.2	7.4	7.6	7.3	7.5	6.5	7.4	7.5
Median	10.0	10.0	10.0	10.0	9.6	10.0	10.0	10.0
Range	1–50	1–41	1–56	1–58	1–56	1–33	1–55	1–58
Number of previous noninsulin antihyperglycemic agents, *n* (%)*								
1	1 (0.2)	1 (0.2)	5 (0.5)	4 (0.4)	0	0	6 (0.5)	6 (0.5)
2	156 (24.9)	178 (27.4)	632 (62.5)	587 (59.7)	59 (15.9)	54 (14.1)	719 (58.2)	697 (57.1)
>2	470 (75.0)	470 (72.4)	374 (37.0)	393 (39.9)	313 (84.1)	330 (85.9)	511 (41.3)	518 (42.4)

*Two participants (one in the Gla-300 group and one in the SOC-BI group) were not receiving any noninsulin antidiabetic therapy before initiating insulin and were not included in the "no concomitant use" subgroups.

maintained in users of concomitant GLP-1 receptor agonist or concomitant DPP-4 inhibitor therapy and included a greater likelihood of remaining without serious or severe hypoglycemia at 12 months. Just under one-fourth of the ACHIEVE Control population used an SGLT2 inhibitor as background therapy, but the ORs in this subgroup did not support a greater benefit of Gla-300 versus SOC-BI for any end point, being similar for Gla-300 and SOC-BI.

The main limitation of these subgroup analyses is that all end points other than the composite primary end point for the overall study population were exploratory and did not qualify for statistical analysis of superiority due to the lack of prospective adjustments for multiple testing. Thus, interpretation of the results is limited by both multiple testing and variable statistical power, and the findings should be considered hypothesis-generating only.

Particularly in subgroups with small sample sizes such as users of concomitant GLP-1 receptor agonist or SGLT2 inhibitor therapy, ORs were associated with wide 95% CIs. The low percentage of patients on a GLP-1 receptor agonist could be explained by the time at which this study was initiated. At this time, use of GLP-1 receptor agonists in particular was not as widespread as it is today. Because of the statistical limitation of these post hoc analyses, OR estimates should not be used to infer efficacy differences between treatment groups.

It is also important to note that, with the exception of one exploratory end point in the SGLT2 inhibitor analysis, subgroup interactions were not statistically significant, consistent with large overlaps of the 95% CIs of ORs in binary subgroup analyses. Therefore, OR estimates suggesting potential differences in the comparative effectiveness of Gla-300 versus SOC-BI between binary subgroups (particularly in the SGLT2 inhibitor subgroup

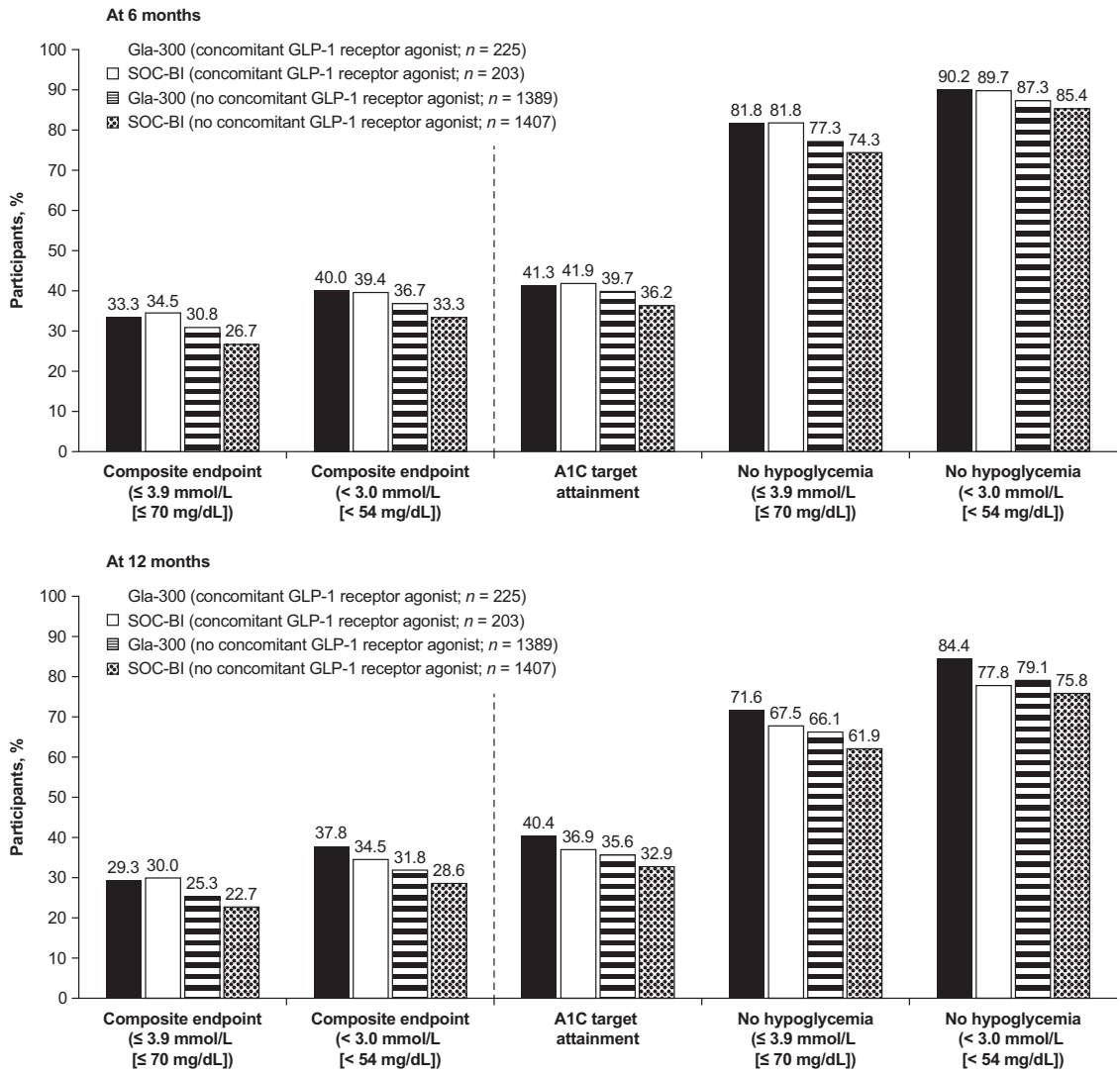

FIGURE 3 Observed proportions of participants who attained the composite end points and their components at 6 and 12 months in subgroups divided by use and nonuse of concomitant GLP-1 receptor agonist.

analyses) require confirmation in appropriately designed and powered prospective studies.

Another limitation is that information on the number of patients on maximal doses was not collected. Although treatment comparisons were adjusted for stratification factors and use-by-treatment interaction, outcomes in specific subgroups may have been influenced by use of additional background therapies. Thus, the results should be interpreted with caution when assessing the merit of using specific background therapies concomitantly with BIs.

Other limitations of these analyses were that, owing to the real-world design of the primary study, insulin titration was not mandated, and adjustment of background medication therapy after trial entry was at the discretion of the health care professional. Thus, it was not possible to assess treatment compliance. However, insulin doses were similar for both treatment arms throughout the study. The study had only three mandated visits, and as a result, participants were not assessed by their health care provider at regular mandated visits, but rather every 3–6 months.

To summarize, the results of these exploratory subgroup analyses were generally consistent with previously published findings from the primary analysis of the ACHIEVE Control study for the overall study population (16,17), suggesting similar benefits of Gla-300 versus SOC-BI (to varying degrees) for all subgroups except users of a concomitant SGLT2 inhibitor, for whom OR point estimates suggested similar effectiveness of Gla-300 and SOC-BI. Thus, the results suggest that the improved PK/PD profile of Gla-300 renders it a safe and effective

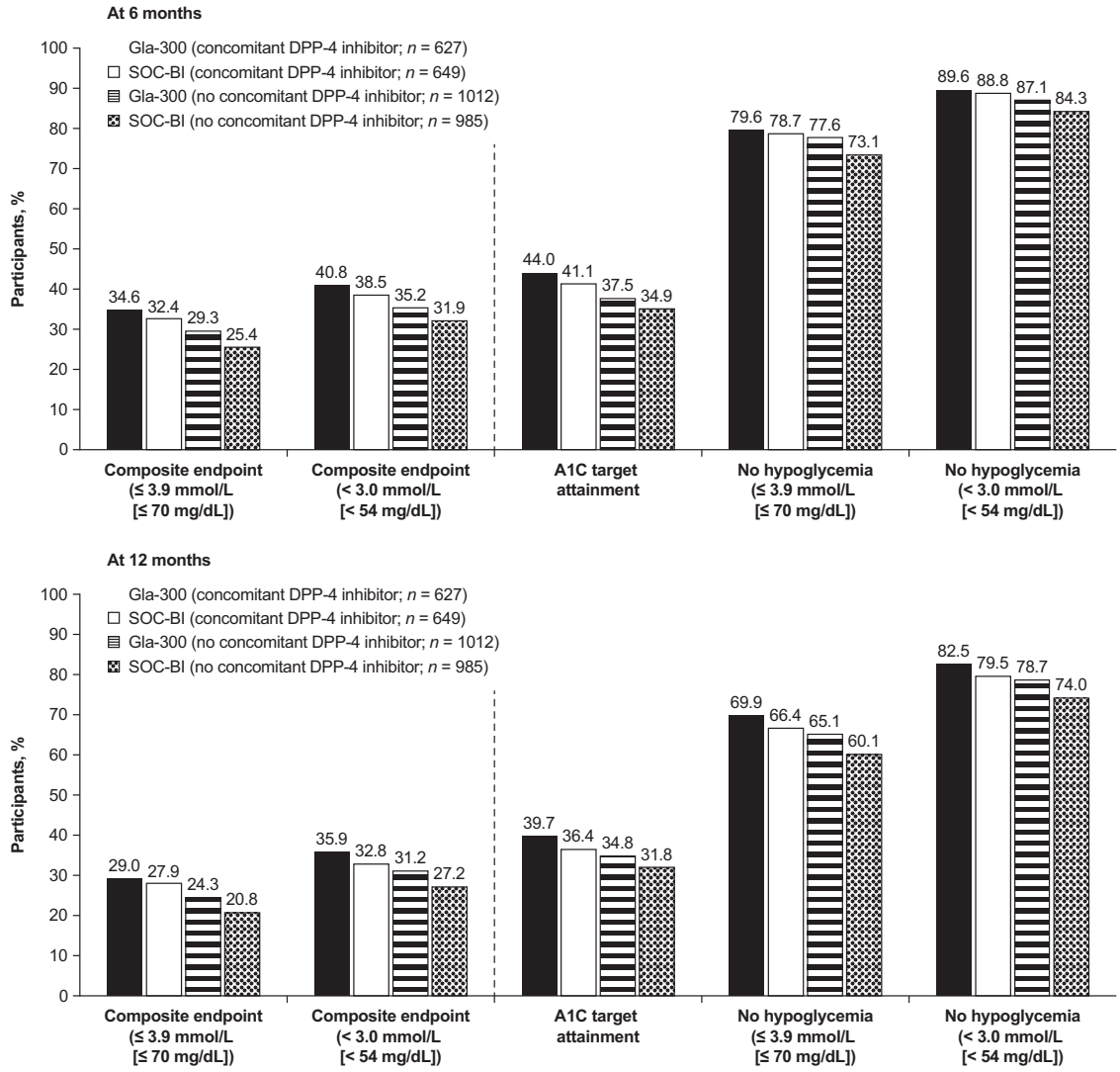

FIGURE 4 Observed proportions of participants who attained the composite end points and their components at 6 and 12 months in subgroups divided by use and nonuse of concomitant DPP-4 inhibitor.

BI for use in combination with insulin secretagogues, as well as with incretin-based and SGLT2 inhibitor therapies.

Our findings confirm that concomitant use of sulfonylureas with BIs remains common practice despite the increased risk of hypoglycemia and guidance that sulfonylurea therapy should be dose-reduced or discontinued when BI therapy is initiated (3). Importantly, we found that users of concomitant sulfonylureas achieved better outcomes with Gla-300 than with SOC-BI in the ACHIEVE Control study. These results suggest that, when individuals with type 2 diabetes use BI therapy in combination with sulfonylureas, Gla-300—a second-generation BI analog with a prolonged and more stable PK/PD profile (12)—is more likely than first-generation BI analogs to mitigate serious or severe hypoglycemia. This strategy may facilitate optimal dosing of BI and thereby support the goal of achieving better glycemic outcomes.

FUNDING

This study was funded by Sanofi. Medical writing support was provided by Roland Tacke, PhD, and Helen Jones, PhD, CMPP, of Evidence Scientific Solutions, Inc., and funded by Sanofi.

DUALITY OF INTEREST

T.S.B. received research support from Abbott Diabetes, Abbott Rapid Diagnostics, Bioliq, Capillary Biomedical, Dexcom, Eli Lilly, Kowa, Lexicon, Livongo, Medtronic, Medtrum, Novo Nordisk, REMD, Sanofi, Sanvita, Viacyte, vTv Therapeutics, and Zealand Pharma; is a consultant for Abbott, Lifescan, Novo Nordisk, and Sanofi; and is a speaker for BD, Medtronic, and Sanofi. P.E., J.G., and P.B. are employees and stockholders of Sanofi. R.R. is a biostatistician (as a contractor) for Sanofi. J.S. is on the advisory board of Merck, Novo Nordisk, and Sanofi and is a speaker for Abbott, the American Diabetes Association, AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, Salix, and Sanofi. E.E.W. is on the speakers' bureau of Abbott Diabetes, Boehringer Ingelheim, and Eli Lilly; on advisory boards for Abbott Diabetes, AstraZeneca,

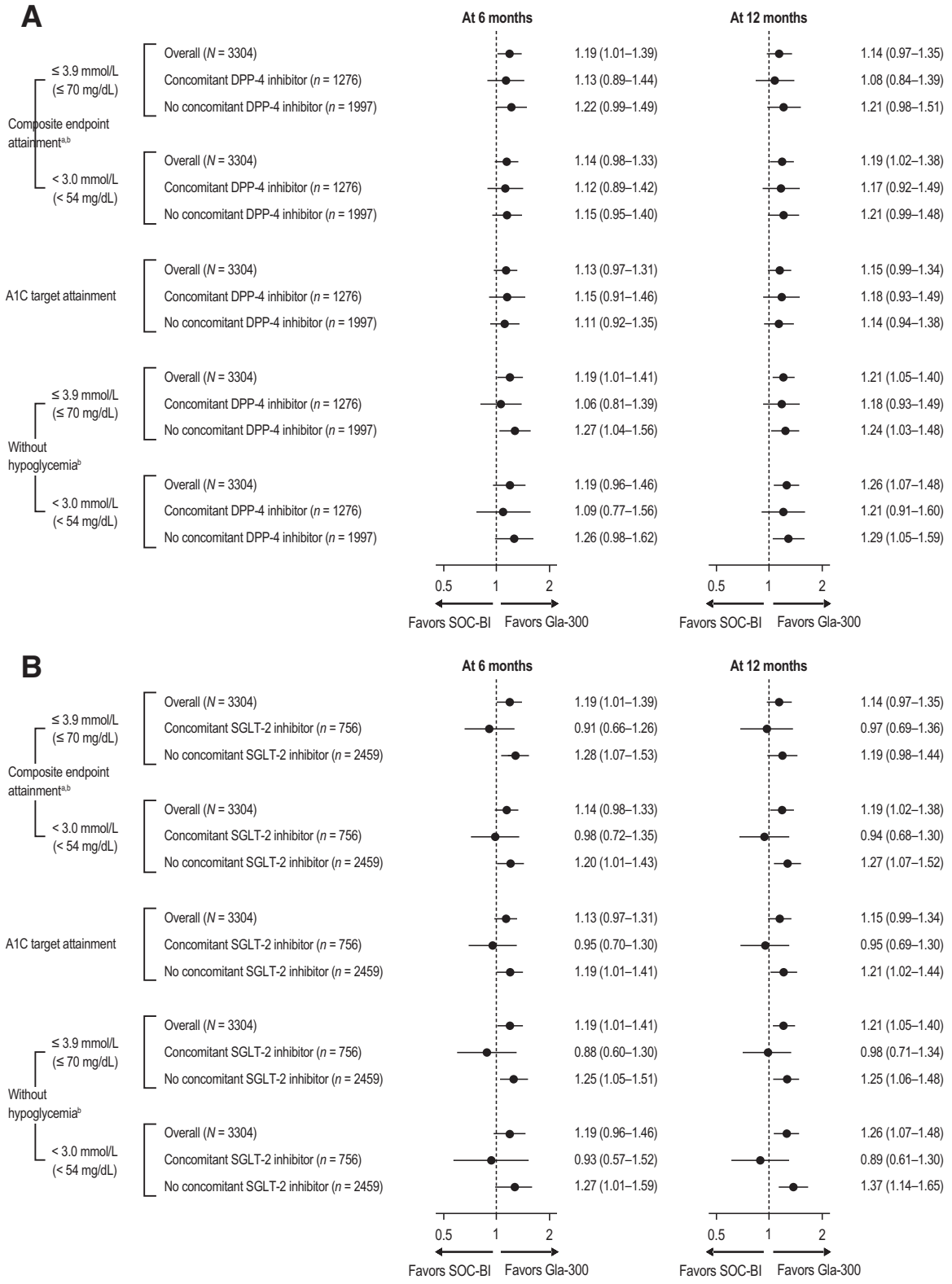

FIGURE 5 ORs with 95% CIs for attainment of composite end points and their components at 6 and 12 months by use/nonuse of concomitant DPP-4 inhibitor (*A*) and SGLT2 inhibitor (*B*). Data were based on a logistic regression model with the treatment arm as fixed effect and adjustment for randomization strata of A1C target, sulfonylurea use, GLP-1 receptor agonist use, and baseline A1C (as continuous variable), with addition of the corresponding subgroup factor and the subgroup factor-by-treatment arm interaction. End points other than the composite primary were exploratory. [a]A1C target attainment without hypoglycemia. [b]Documented symptomatic (glucose ≤3.9 mmol/L [≤70 mg/dL] or <3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia.

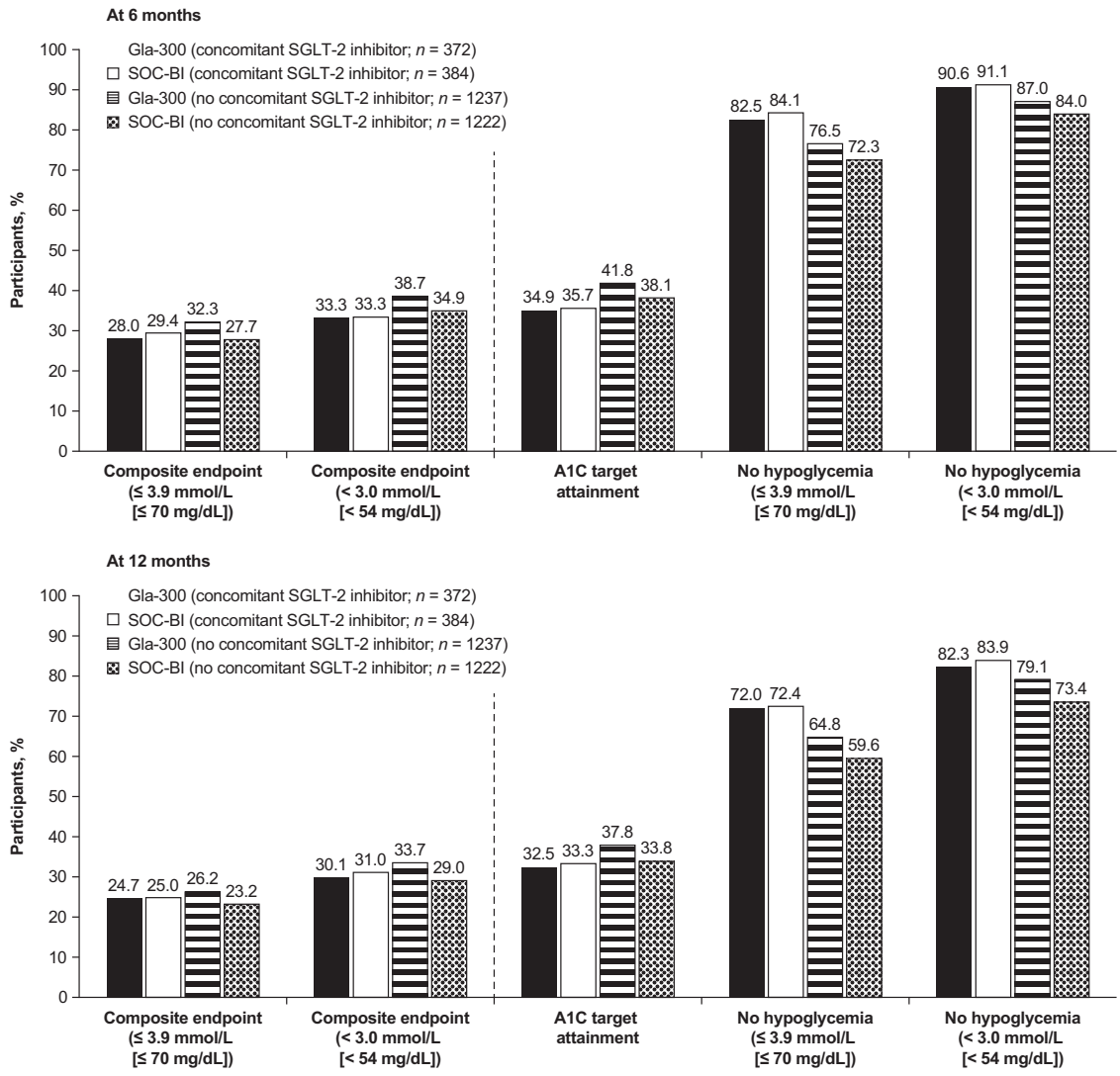

FIGURE 6 Observed proportions of participants who attained the composite end points and their components at 6 and 12 months in subgroups divided by use and nonuse of concomitant SGLT2 inhibitor.

Boehringer Ingelheim, Eli Lilly, Mannkind, Merck, PTS Diagnostics, Sanofi, and Voluntis; and serves as a consultant for Abbott Diabetes, Boehringer Ingelheim, Eli Lilly, and Voluntis. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

T.S.B., P.E., J.G., P.B., J.S., and E.E.W. contributed to research data, contributed to manuscript development and discussion, reviewed/edited the manuscript, and approved the final version of the manuscript. R.R. defined, provided, and interpreted the statistical analyses for these data; reviewed/edited the manuscript; and approved the final version of the manuscript. T.S.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PRIOR PUBLICATION AND PRESENTATION

Parts of this study were presented at the American Association of Clinical Endocrinologists' 28th Annual Meeting & Clinical Congress, 24–28 April 2019, and published in abstract form in Endocrine Practice 2019;25(Suppl. 1):138–139 (abstract 322).

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017: Estimates of Diabetes and Its Burden in the United States. Available from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed 9 June 2019
2. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S98–S110
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. Mishriky BM, Cummings DM, Tanenberg RJ. The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2015;109:378–388

5. Douros A, Dell'Aniello S, Yu OHY, Filion KB, Azoulay L, Suissa S. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. BMJ 2018;362:k2693
6. Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. Nat Rev Endocrinol 2016;12:566–592
7. Thrasher J. Pharmacologic management of type 2 diabetes mellitus: available therapies. Am J Med 2017;130(Suppl.):S4–S17
8. 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 Naïve cohort study. Diabetes Obes Metab 2019;21:1596–1605
9. 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
10. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab 2012;14:859–864
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. 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
13. 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
14. 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
15. 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-naïve patients with type 2 diabetes. Postgrad Med 2016;128:731–739
16. Meneghini LF, Sullivan SD, Oster G, et al. A pragmatic randomized clinical trial of insulin glargine 300 U/mL vs first-generation basal insulin analogues in insulin-naïve adults with type 2 diabetes: 6-month outcomes of the ACHIEVE Control study. Diabetes Obes Metab 2020;22:2004–2012
17. Meneghini L, Blonde L, Gill J, et al. Insulin glargine 300 U/mL versus first-generation basal insulin analogues in insulin-naive adults with type 2 diabetes: 12-month outcomes of ACHIEVE Control, a prospective, randomized, pragmatic real-life clinical trial. Diabetes Obes Metab 2020;22:1995–2003
18. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–1395
19. NCQA. HEDIS measures and technical resources. Available from https://www.ncqa.org/Portals/0/HEDISQM/Hedis2015/List_of_HEDIS_2015_Measures.pdf. Accessed 5 March 2018
20. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S73–S84
21. Bolli GB, Riddle MC, Bergenstal RM, et al.; on behalf of the EDITION 3 Study Investigators. New insulin glargine 300 U/mL compared with glargine 100 U/mL in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015;17:386–394
22. Bolli GB, Riddle MC, Bergenstal RM, Wardecki M, Goyeau H; EDITION 3 Study Investigators. Glycaemic control and hypoglycaemia with insulin glargine 300U/mL versus insulin glargine 100U/mL in insulin-naïve people with type 2 diabetes: 12-month results from the EDITION 3 trial. Diabetes Metab 2017;43:351–358
23. Perreault L, Vincent L, Neumiller JJ, Santos-Cavaiola T. Initiation and titration of basal insulin in primary care: barriers and practical solutions. J Am Board Fam Med 2019;32:431–447
24. Kalirai S, Stephenson J, Perez-Nieves M, et al. Primary care physician perspectives on basal insulin initiation and maintenance in patients with type 2 diabetes mellitus. Prim Care Diabetes 2018;12:155–162