



Safety, Immunogenicity, and Glycemic Control of Insulin Aspart Biosimilar SAR341402 Versus Originator Insulin Aspart in People with Diabetes Also Using Insulin Glargine: 12-Month Results from the GEMELLI 1 Trial

Satish K. Garg, MD,¹ Karin Wernicke-Panten, MD,² Marek Wardecki, MD,³ Daniel Kramer, PhD,² Francois Delalande, MSc,⁴ Edward Franek, MD,^{5,6} Karita Sadeharju, MD,⁷ Travis Monchamp, MD,⁸ Patrick Miossec, MD,⁹ Bhaswati Mukherjee, MD,⁹ and Viral N. Shah, MD¹

Abstract

Background: SAR341402 (SAR-Asp) is a biosimilar/follow-on of the originator insulin aspart-NovoLog[®]/NovoRapid[®] (NN-Asp). This study investigated whether the efficacy, safety, and immunogenicity findings for SAR-Asp versus NN-Asp, observed over 6 months in people with type 1 ($n=497$) or type 2 diabetes ($n=100$) treated with multiple daily injections in combination with insulin glargine (Lantus[®]), are maintained after 12 months.

Materials and Methods: GEMELLI 1 was a multicenter, randomized, open-label, phase 3 study. Participants completing the initial 6-month treatment period continued on SAR-Asp or NN-Asp, as randomized, for a 6-month safety extension.

Results: Of the 597 participants randomized, 264 out of 301 (87.7%) and 263 out of 296 (88.9%) assigned to SAR-Asp and NN-Asp, respectively, completed 12 months of treatment. Improved glycemic control was sustained at 12 months in both treatment groups, with similar least-squares mean reductions in glycated hemoglobin (HbA1c) from baseline (SAR-Asp: -0.25% ; NN-Asp: -0.26%). Fasting plasma glucose and seven-point self-monitored plasma glucose profile changes, including postprandial glucose excursions, and changes in mealtime and basal insulin dosages were similar between groups. Safety and tolerability, including anti-insulin aspart antibodies (AIAs; incidence, prevalence, titers, cross-reactivity to human insulin), neutralizing antibodies (incidence, prevalence), hypoglycemia, and treatment-emergent adverse events (including hypersensitivity events and injection site reactions), were similar between groups. No relationship was observed between maximum individual AIA titers and change in HbA1c or insulin dose, hypoglycemia, or hypersensitivity reactions or between efficacy/safety measures and subgroups by presence or absence of treatment-emergent AIA.

Conclusions: SAR-Asp and NN-Asp demonstrated similar efficacy and safety (including immunogenicity) in people with diabetes over 12 months of treatment.

¹Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus, Aurora, Colorado.

²Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany.

³Sanofi, Warszawa, Poland.

⁴Ivodata, Paris, France.

⁵Mossakowski Clinical Research Centre, Polish Academy of Sciences, Warszawa, Poland.

⁶CSK MSWiA, Warszawa, Poland.

⁷Terveystalo Seinäjoki, Seinäjoki, Finland.

⁸Endocrinology Services Northwest, Bend, Oregon.

⁹Sanofi, Paris, France.

Keywords: Biosimilar, Follow-on product, Insulin aspart, SAR341402.

Introduction

INTENSIVE INSULIN THERAPY with multiple daily injections (MDI) of basal and mealtime therapy is recommended for people with type 1 diabetes (T1D) and for those individuals with type 2 diabetes (T2D) requiring more intensive glycemic control.¹ Insulin aspart is one of the currently available rapid-acting mealtime insulin analogs. The originator insulin aspart, NovoLog[®]/NovoRapid[®] (NN-Asp; Novo Nordisk, Bagsvaerd, Denmark), has been approved and marketed for use in adults and children with T1D and T2D in many countries since 1999.² SAR341402 (SAR-Asp; Sanofi, Paris, France) is a proposed biosimilar/follow-on biologic product with the same amino acid sequence and structure as NN-Asp and formulated at a concentration of 100 U/mL. In accordance with relevant United States (US) and European Union (EU) guidelines,^{3–6} a stepwise approach has been utilized to show that SAR-Asp is similar to NN-Asp in physicochemical analyses, nonclinical and clinical studies.

A phase 1 euglycemic clamp study comparing SAR-Asp with US-approved (NovoLog) and EU-approved (NovoRapid) NN-Asp demonstrated similar pharmacokinetic exposure and pharmacodynamic activity between the three formulations in subjects with T1D.⁷

The phase 3 GEMELLI 1 study investigated the efficacy, safety, and immunogenicity of SAR-Asp and the reference product NN-Asp (100 U/mL) in adults with T1D or T2D treated with MDI in combination with basal insulin glargine (Lantus[®]; Gla-100). The 6-month GEMELLI 1 results demonstrated equivalent glycemic control with SAR-Asp and NN-Asp, associated with a similar safety and immunogenicity profile.⁸ We now report the 12-month safety, immunogenicity, and efficacy results from GEMELLI 1.

Materials and Methods

Study design, participants, and treatments

GEMELLI 1 (ClinicalTrials.gov identifier: NCT03211858) was a randomized, open-label, multicenter, two-arm, parallel-group, phase 3 study conducted in 2017–2019 at 82 active centers in the United States, Japan, and seven countries in Europe. Details of the study design have been previously described.⁸ Briefly, participants ≥ 18 years of age with T1D or with T2D (in the United States only) on insulin treatment for at least 1 year were randomized 1:1 to receive SAR-Asp or NN-Asp for a period of 12 months.

Inclusion criteria were glycated hemoglobin (HbA1c) in the range of 7.0%–10% (53–86 mmol/mol), treatment with either insulin glargine (100 U/mL) in the past 6 months or insulin detemir (100 U/mL, Levemir[®]) in the past 12 months before screening as basal insulin, and use of NN-Asp or insulin lispro (100 U/mL, Humalog[®]/Liprolog[®]) as rapid-acting mealtime insulin in an MDI regimen for at least 6 months before screening. The major exclusion criteria for participants with T1D and T2D have been previously described.⁸

Participants randomized to NN-Asp received US-approved NN-Asp (NovoLog) in the United States or EU-approved

NN-Asp (NovoRapid) in other countries, including Japan. Based on the similarity between NN-Asp-US and NN-Asp-EU shown in prior studies,⁷ data from both forms of insulin were pooled in the comparator group. SAR-Asp or NN-Asp was self-administered by a subcutaneous injection with an insulin pen within 5–10 min before the start of a meal.

Details of treatment regimens have been previously described.⁸ Mealtime insulin was titrated to a 2-h postprandial plasma glucose (PPG) level of <180 mg/dL (<10 mmol/L) while avoiding hypoglycemia or a preprandial target range of 80–130 mg/dL (4.4–7.2 mmol/L).⁹ Gla-100 was injected once daily and titrated to a fasting prebreakfast self-monitored plasma glucose (SMPG) level of 80–130 mg/dL (4.4–7.2 mmol/L), while avoiding hypoglycemia. Clinic visits were planned at screening, randomization (week 0), weeks 4, 12, 20, and 26 (6-month end point), and weeks 40 and 52 (12-month end point).

The protocol was approved by respective review boards/independent ethics committees and conducted in accordance with the Declaration of Helsinki.

Efficacy, safety, and immunogenicity outcomes

Efficacy, safety, and immunogenicity measured during the 12-month period were all secondary outcomes of the study. Details of the assessments have been previously described.⁸ The efficacy outcomes in this analysis included change in HbA1c from baseline to week 52, the percentage of study participants with HbA1c $<7.0\%$ (<53 mmol/mol) at week 52, change from baseline to week 52 in laboratory-measured fasting plasma glucose (FPG) and in mean 24-h plasma glucose concentration and PPG excursions (based on the seven-point SMPG profiles), and mean change from baseline to week 52 in seven-point SMPG profiles per time point (based on measurements taken before and 2 h after breakfast, lunch, and dinner, and at bedtime).

Safety/tolerability outcomes assessed during the 12-month treatment period included hypoglycemic events (classified according to the American Diabetes Association categories^{10–12}), as previously described,⁸ occurrence of treatment-emergent adverse events (TEAEs) including local (injection site) and systemic (hypersensitivity) allergic reactions, serious AEs (SAEs), change in body weight, and routine laboratory assessments.

Immunogenicity was a key secondary outcome of the study. Blood samples for immunogenicity assessments were collected at least 8 h after the last administration of mealtime insulin at baseline and weeks 4, 12, 26, 40, and 52, and at any early discontinuation visit. A three-tiered approach consisting of a screening-, confirmatory-, and neutralizing assay was employed to assess the immunogenicity of SAR-Asp and NN-Asp.^{13,14} Assessment for the presence of anti-insulin aspart antibodies (AIAs) was performed in a central laboratory by using a radio-immunoassay.⁸ Blinded assessments included AIA status (positive or negative), AIA titers, and cross-reactivity to human insulin at each sampling visit. AIA titers were defined as reciprocal of the highest dilution that yields a positive result; for example, dilution of 1/100 = titer of 100.¹⁵

AIA analyses focused on the change in AIA response with treatment and included assessment of the incidence (participants newly positive for AIA postbaseline [treatment-induced] or with a greater than or equal to fourfold increase in titer compared with baseline [treatment-boosted]), together called treatment-emergent, and the prevalence (participants with at least one positive sample at baseline or postbaseline) of AIA response over 12 months.¹⁵ For participants with treatment-emergent AIAs, the kinetics of the AIA response was further classified as whether it was transient, persistent, or indeterminate (see Supplementary Data for definitions). The peak AIA titer was defined as the maximal individual titers observed during the on-treatment period.

To assess the potential neutralizing capacity of confirmed positive AIAs, back-up AIA samples collected during the 12-month treatment period were used. Neutralizing antibodies (NABs) were analyzed in a central laboratory (Sanofi, Frankfurt, Germany) by using a validated competitive ligand binding assay. NAB analyses focused on the change in NAB response with treatment and included assessment of the incidence and prevalence of NAB response over 12 months.

As previously described,⁸ all potential hypersensitivity or hypersensitivity-like events were adjudicated by an independent Allergic Reaction Assessment Committee (ARAC), blinded to the treatment.

Data analysis and statistics

The efficacy analyses were performed by using the intent-to-treat (ITT) population, which included all randomized participants irrespective of compliance with the study protocol and procedures. Safety analyses used the safety population, comprising all randomized participants who received at least one dose of study insulin, analyzed according to the treatment actually received. The AIA population included all participants from the safety population with at least one AIA sample available for analysis (sample collected at least 8 h after the last administration of mealtime insulin) during the 12-month on-treatment period (time from the first dose of study medication up to 1 day after the last dose of study medication).

Statistical methods have been previously reported.⁸ Analyses of 12-month outcomes were descriptive, with no formal statistical testing. Change in HbA1c and FPG was analyzed by using all values regardless of adherence to treatment during the 12-month period with missing data imputed by a multiple imputation approach, separately for participants who prematurely discontinued or completed the 12-month treatment period, followed by an analysis of covariance (ANCOVA) model with fixed-effect term for treatment group and the randomization strata and baseline value as fixed covariate.⁸ The proportions of study participants meeting HbA1c <7.0% and other secondary end points based on seven-point SMPG profiles were analyzed by using models previously described.⁸

For exploratory purposes, the difference between SAR-Asp and NN-Asp in the percentage of participants with treatment-emergent AIAs was calculated with its associated 2-sided 90% confidence interval (CI) based on a binomial regression model with an identity-link function and fixed categorical effects for treatment and randomization strata. The risks within each treatment group and risk difference

were provided with their 90% CIs by using the adjusted least-squares (LS) mean estimates of the treatment effect.

To evaluate potential effects of AIAs on efficacy and safety parameters, participants with high AIA titers (AIA outliers) were reviewed. They were identified based on the boxplots of peak AIA titer in participants with treatment-emergent AIA, as values higher than the boxplot upper whisker (i.e., higher than 1.5 times the interquartile range [IQR] above the third quartile), corresponding to AIA titers ≥ 64 (1/dilution). The relationship between individual maximal AIA titers and selected efficacy and safety end points (e.g., change in HbA1c and total insulin dose from baseline to week 52, hypoglycemia rate, injection site reactions, and hypersensitivity reactions) were evaluated by using scatterplots of the peak AIA titer versus each parameter. These efficacy and safety end points, as well as TEAEs and SAEs, were further assessed in the subgroups of participants with or without treatment-emergent AIAs.

Subgroup analyses were performed for HbA1c and the proportion of participants with at least one hypoglycemia event (ANCOVA and logistic regression model, respectively, with fixed effects for the subgroup and subgroup-by-treatment interaction). A significant treatment-by-subgroup interaction ($P < 0.1$) indicated a potential differential treatment effect. Similar analyses were performed to assess potential effects of NABs on HbA1c or on the needs in insulin doses. AEs were analyzed descriptively and coded by using the Medical Dictionary for Regulatory Activities (MedDRA) system.

Results

Study population

As previously reported,⁸ 597 participants were randomized to receive SAR-Asp ($n = 301$) or NN-Asp ($n = 296$) (Supplementary Fig. S1); all randomized individuals were included in the safety and ITT populations. Baseline characteristics have been previously reported, and they were similar between treatment groups.⁸ The discontinuation rate was similar in the SAR-Asp ($n = 37$; 12.3%) and NN-Asp ($n = 33$; 11.1%) groups, with 264 and 263 participants, respectively, completing 12 months of treatment. The majority of discontinuations in the SAR-Asp ($n = 22$) and NN-Asp ($n = 21$) groups were due to other reasons (predominantly participant decision or consent withdrawal). Adverse events accounted for the discontinuation of eight participants (2.7%) in the SAR-Asp group and six participants (2.0%) in the NN-Asp group.

Changes in the daily mealtime and basal insulin doses over 12 months were small and similar in both treatment groups in participants with T1D (Fig. 1A) and T2D (Fig. 1B). Body weight increased by a similar degree between treatments from baseline through to week 52 (mean change: SAR-Asp: +1.6 kg; NN-Asp: +1.6 kg) (Table 1).

Glycemic control

The improvement in glycemic control observed during the first 6 months, as measured by HbA1c, was maintained through to week 52 and HbA1c was reduced by a similar extent in both treatment groups (Fig. 2A). At week 52, the LS mean change from baseline was -0.25% with SAR-Asp and -0.26% with NN-Asp (LS mean difference between

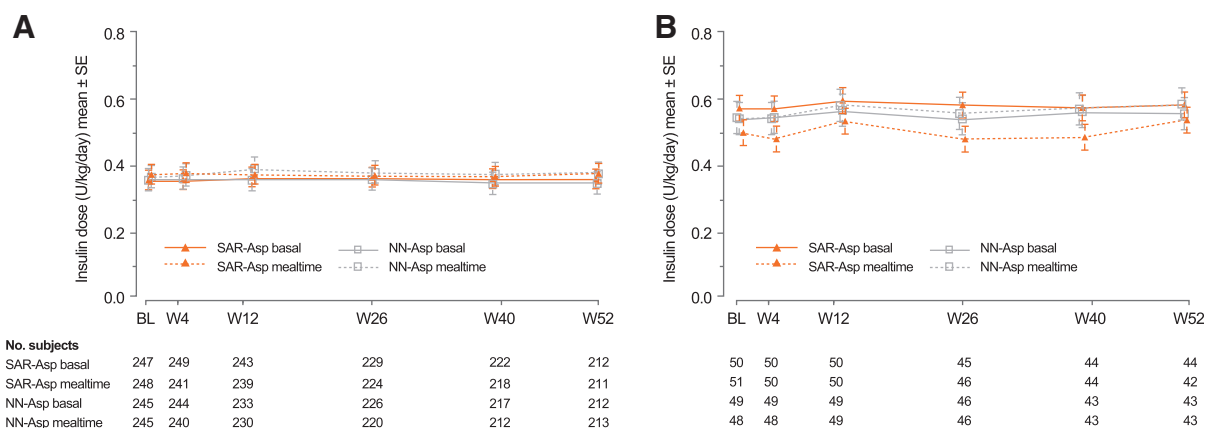


FIG. 1. Daily basal and mealtime insulin doses (U/kg/day) in participants with T1D (A) and T2D (B) (safety population). Data are mean ± SE. BL, baseline; SE, standard error; T1D, type 1 diabetes; T2D, type 2 diabetes; W, week.

SAR-Asp and NN-Asp was 0.01% [95% CI: -0.146 to 0.173]) (Table 1, Fig. 2B). No relevant differences between SAR-Asp and NN-Asp were seen in subgroup analyses defined by type of diabetes (T1D, T2D), type of comparator (NovoLog and NovoRapid) (Supplementary Table S1), prior

use of NN-Asp, geographical region (Europe, United States, Japan), race, ethnicity, age group (<65, 65–75, and ≥75 years), gender, baseline BMI (<30 and ≥30 kg/m²), baseline renal function (estimated glomerular filtration rate ≥60 and <60 mL/min/1.73 m²), randomization stratum of screening

TABLE 1. GLYCEMIC CONTROL, INSULIN DOSES, AND BODY WEIGHT ASSESSMENTS FROM BASELINE TO WEEK 52 (INTENT-TO-TREAT AND SAFETY POPULATION)

Parameter	SAR-Asp (N = 301)	NN-Asp (N = 296)
HbA1c, % (mmol/mol)		
Baseline [n]	8.00 ± 0.77 (63.89 ± 8.41) [301]	7.94 ± 0.70 (63.24 ± 7.67) [296]
Week 52 [n]	7.70 ± 0.97 (60.64 ± 10.58) [269]	7.63 ± 0.84 (59.86 ± 9.19) [265]
LS mean (±SE) change from baseline ^a [n]	-0.25 ± 0.06 (-2.70 ± 0.62) [301]	-0.26 ± 0.06 (-2.84 ± 0.64) [296]
LS mean (±SE) difference [95% CI] ^a	0.01 ± 0.082 [-0.146 to 0.173] (0.15 ± 0.89 [-1.60 to 1.90])	
FPG, mg/dL (mmol/L)		
Baseline [n]	177.92 ± 69.68 (9.87 ± 3.87) [290]	179.24 ± 79.25 (9.95 ± 4.40) [286]
Week 52 [n]	172.76 ± 68.52 (9.59 ± 3.80) [260]	171.12 ± 73.75 (9.50 ± 4.09) [264]
LS mean (±SE) change from baseline ^{a,b} [n]	-1.78 ± 6.60 (-0.10 ± 0.37) [301]	-6.10 ± 6.47 (-0.34 ± 0.36) [296]
LS mean (±SE) difference [95% CI] ^{a,b}	4.32 ± 9.23 [-13.77 to 22.40] (0.24 ± 0.51 [-0.76 to 1.24])	
Total insulin, U/kg/day		
Baseline [n]	0.79 ± 0.34 [295]	0.78 ± 0.40 [291]
Week 52 [n]	0.80 ± 0.37 [253]	0.80 ± 0.40 [254]
Change from baseline [n]	0.005 ± 0.18 [248]	0.013 ± 0.17 [251]
Basal insulin, U/kg/day		
Baseline [n]	0.39 ± 0.19 [297]	0.39 ± 0.23 [294]
Week 52 [n]	0.40 ± 0.19 [256]	0.38 ± 0.22 [255]
Change from baseline [n]	0.006 ± 0.09 [253]	0.005 ± 0.10 [253]
Mealtime insulin, U/kg/day		
Baseline [n]	0.40 ± 0.23 [299]	0.39 ± 0.25 [293]
Week 52 [n]	0.40 ± 0.25 [253]	0.42 ± 0.25 [256]
Change from baseline [n]	-0.001 ± 0.15 [251]	0.009 ± 0.12 [255]
Body weight, kg		
Baseline [n]	81.7 ± 17.6 [301]	81.6 ± 17.8 [296]
Week 52 [n]	83.5 ± 18.7 [265]	83.6 ± 18.7 [261]
Change from baseline [n]	+1.6 ± 3.6 [265] ^c	+1.6 ± 4.8 [261] ^c

All data are mean ± SD unless stated otherwise.

^aMissing data at week 52 were imputed by a multiple imputation approach (10,000 imputations using separate models for participants who prematurely discontinued or completed the 12-month treatment period) followed by ANCOVA with treatment group (SAR-Asp, NN-Asp), the randomization strata of geographical region and type of diabetes (Europe T1D, United States T1D, United States T2D, Japan T1D), and prior use of NN-Asp (Yes, No) as fixed categorical effects, as well as the baseline value (HbA1c or FPG) as the continuous fixed covariate. Results were combined by using Rubin's formulae.²¹

^bRandomization strata of screening HbA1c (<8.0, ≥8.0%) was also included as a fixed categorical effect.

^cChange in body weight only available for the overall study population and not by diabetes type.

ANCOVA, analysis of covariance; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; LS, least square; SD, standard deviation; SE, standard error; T1D, type 1 diabetes; T2D, type 2 diabetes.

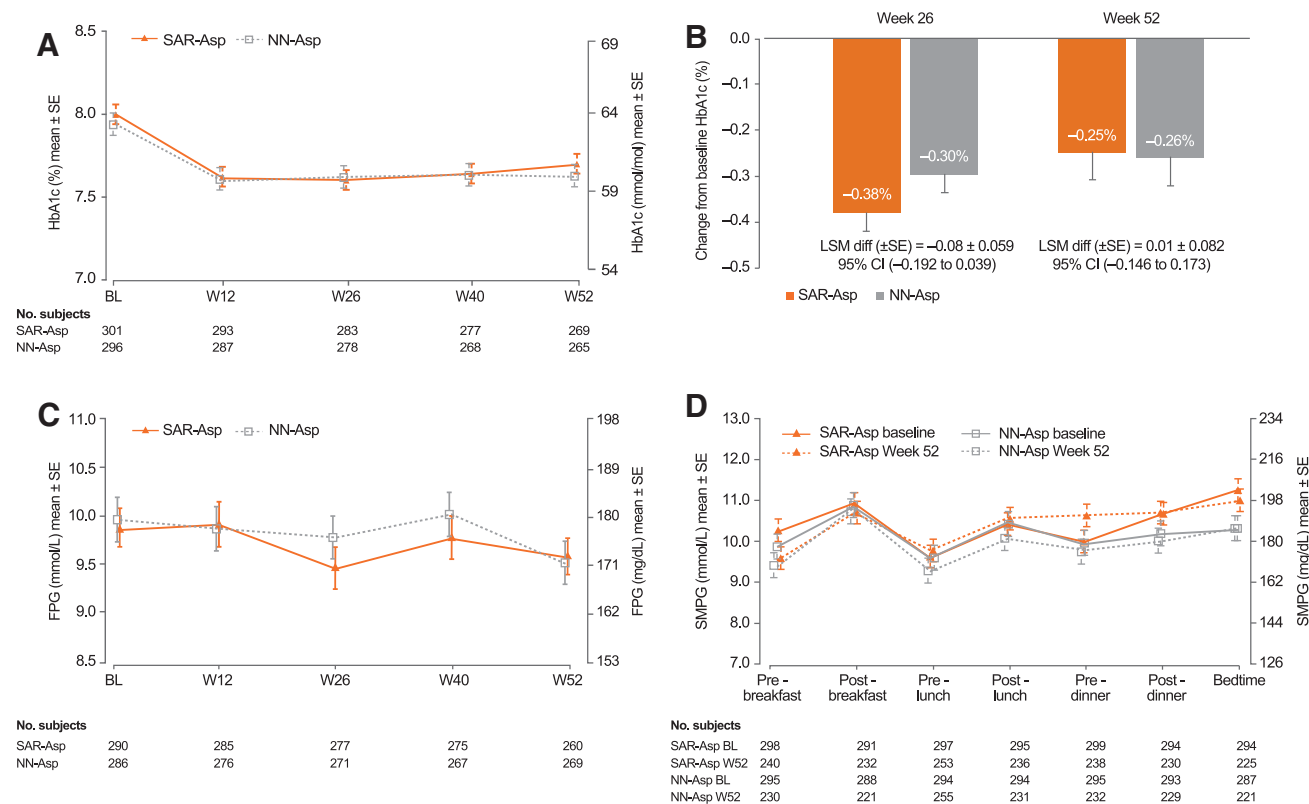


FIG. 2. HbA1c (% and mmol/mol) by study visit (A), least-squares mean change in HbA1c from baseline to week 26 and 52 (B), FPG (mmol/L and mg/dL) by study visit (C), and seven-point SMPG profiles (mmol/L and mg/dL) at baseline and week 52 (D). Data are mean ± SE. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SMPG, self-monitored plasma glucose.

HbA1c (<8%, ≥8%), and duration of diabetes (data not shown). There was no evidence of heterogeneity of treatment effect across any of the subgroups.

In both treatment groups, the LS mean change in HbA1c from baseline to week 52 was higher in participants with T2D (SAR-Asp: -0.61%, NN-Asp: -0.56%) than in participants with T1D (SAR-Asp: -0.17%, NN-Asp: -0.20%). Similar proportions of study participants achieved target HbA1c values of <7.0% (53 mmol/mol) at week 52 (SAR-Asp: 19.6%; NN-Asp: 18.2%).

The decrease in laboratory-measured FPG from baseline to week 52 was small and similar in the two treatment groups, with a LS mean difference of 4.32 mg/dL between SAR-Asp and NN-Asp (95% CI: -13.77 to 22.40 mg/dL) (Table 1, Fig. 2C). There were no relevant changes in the mean seven-point SMPG profiles between baseline and week 52 in the two treatment groups (Fig. 2D). The LS mean differences (95% CI) for SAR-Asp versus NN-Asp for PPG excursions at breakfast, lunch, and dinner were -3.28 (-15.99 to 9.43), 1.50 (-11.06 to 14.06), and -4.45 (-17.18 to 8.28) mg/dL, respectively (Supplementary Table S2). The change in mean 24-h plasma glucose values from baseline to week 52 was small in the two groups.

Hypoglycemia

During the 12-month study period, 98.0% of participants in each treatment group experienced at least one hypoglycemic event regardless of the category (Table 2). The corresponding number of events (any hypoglycemia) per patient-year at

week 52 was similar in the SAR-Asp group and NN-Asp group (66.00 vs. 64.46). Severe hypoglycemia was reported by a small and similar number of participants (SAR-Asp: 18/301 [6.0%]; NN-Asp: 14/296 [4.7%]). Of these, symptoms indicating severe neuroglycopenia, such as unconsciousness, coma, or seizure and/or a SMPG <50 mg/dL (2.8 mmol/L), were reported by 17 participants in the SAR-Asp group and by 12 participants in the NN-Asp group. Most participants with severe hypoglycemia had prompt recovery or significant improvement further to corrective treatment. Serious TEAEs involving hypoglycemia were reported in 15 participants (5.0%) in the SAR-Asp group and 9 participants (3.0%) in the NN-Asp group.

All categories of hypoglycemia were reported by a similar proportion and rate per patient-year of participants in each treatment group (Table 2, Supplementary Fig. S2). The hypoglycemia results observed in participants with T1D were consistent with those of the overall population. Similarly, hypoglycemia results were consistent irrespective of the comparator used (NovoLog or NovoRapid) (Supplementary Fig. S3). Most hypoglycemia was observed during daytime between 06:00 and 23:59 h, with small peaks around each meal (data not shown).

Adverse events

A similar proportion of participants in both groups reported TEAEs (61.1% [184/301] SAR-Asp; 56.8% [168/296] NN-Asp) (Table 3), most of which were of mild to moderate intensity. The most commonly reported of these were upper

TABLE 2. HYPOGLYCEMIA DURING THE 52-WEEK TREATMENT PERIOD IN THE OVERALL STUDY POPULATION AND PARTICIPANTS WITH TYPE 1 DIABETES (SAFETY POPULATION)

Category of hypoglycemia	Overall		T1D	
	SAR-Asp (N=301)	NN-Asp (N=296)	SAR-Asp (N=250)	NN-Asp (N=247)
Total patient-years	280.78	275.72	234.33	229.86
Any				
Participants with ≥1 event, <i>n</i> (%)	295 (98.0)	290 (98.0)	248 (99.2)	242 (98.0)
Events, <i>n</i> (events per patient-year)	18,530 (66.00)	17,773 (64.46)	17,017 (72.62)	16,293 (70.88)
Severe				
Participants with ≥1 event, <i>n</i> (%)	18 (6.0)	14 (4.7)	18 (7.2)	13 (5.3)
Events, <i>n</i> (events per patient-year)	33 (0.12)	22 (0.08)	33 (0.14)	18 (0.08)
Documented symptomatic ≤70 mg/dL (3.9 mmol/L)				
Participants with ≥1 event, <i>n</i> (%)	274 (91.0)	267 (90.2)	231 (92.4)	227 (91.9)
Events, <i>n</i> (events per patient-year)	10,017 (35.68)	9301 (33.73)	9201 (39.27)	8639 (37.58)
Documented symptomatic <54 mg/dL (3.0 mmol/L)				
Participants with ≥1 event, <i>n</i> (%)	223 (74.1)	220 (74.3)	196 (78.4)	199 (80.6)
Events, <i>n</i> (events per patient-year)	2631 (9.37)	2458 (8.91)	2501 (10.67)	2348 (10.21)
Asymptomatic ≤70 mg/dL (3.9 mmol/L)				
Participants with ≥1 event, <i>n</i> (%)	270 (89.7)	255 (86.1)	230 (92.0)	212 (85.8)
Events, <i>n</i> (events per patient-year)	6790 (24.18)	7116 (25.81)	6265 (26.74)	6554 (28.51)
Asymptomatic <54 mg/dL (3.0 mmol/L)				
Participants with ≥1 event, <i>n</i> (%)	152 (50.5)	139 (47.0)	134 (53.6)	125 (50.6)
Events, <i>n</i> (events per patient-year)	1102 (3.92)	1195 (4.33)	1043 (4.45)	1139 (4.96)

n (%), number and percentage of participants with at least one treatment-emergent hypoglycemia. Events per patient-year, number of episodes per patient-year of exposure.

respiratory tract infections (22.9% in the SAR-Asp group and 20.3% in the NN-Asp group, data not shown). The percentage of participants reporting treatment-emergent SAEs, and TEAEs leading to treatment discontinuation from the study was similar in the two treatment groups. Three participants died during the 12-month on-treatment period (SAR-Asp group, one attributed to diabetic ketoacidosis; NN-Asp group, one due to multiorgan failure and the other due to hypovolemic shock). Three post-treatment deaths were also reported, all in the NN-Asp group. None of the events leading to death were considered related to study medication.

Injection site reactions were reported by two participants (0.7%) after administration of SAR-Asp and four participants (1.4%) after NN-Asp. None of the events was considered as related to SAR-Asp whereas in three participants the events were considered as related to NN-Asp. The safety results observed in participants with T1D during the 12-month on-treatment period were consistent with those obtained in the overall population (Table 3). There were no clinically meaningful changes in any of the standard clinical laboratory and hematology parameters in either group (data not shown).

TABLE 3. ADVERSE EVENTS DURING THE 52-WEEK TREATMENT PERIOD IN THE OVERALL STUDY POPULATION AND PARTICIPANTS WITH TYPE 1 DIABETES (SAFETY POPULATION)

	Overall		T1D	
	SAR-Asp (N=301)	NN-Asp (N=296)	SAR-Asp (N=250)	NN-Asp (N=247)
TEAEs	184 (61.1)	168 (56.8)	147 (58.8)	131 (53.0)
Treatment-emergent SAEs	36 (12.0)	29 (9.8)	27 (10.8)	22 (8.9)
TEAEs leading to permanent treatment discontinuation	6 (2.0)	4 (1.4)	6 (2.4)	2 (0.8)
TEAEs leading to death	1 (0.3)	3 (1.0) ^a	1 (0.4)	1 (0.4)
Injection site reactions	2 (0.7)	4 (1.4)	2 (0.8)	1 (0.4)
Injection site bruising	1 (0.3)	3 (1.0)	1 (0.4)	1 (0.4)
Injection site nodule	1 (0.3)	0	1 (0.4)	0
Injection site mass	0	1 (0.3)	0	0
Hypersensitivity reactions	17 (5.6)	21 (7.1)	15 (6.0)	15 (6.1)
Adjudicated as allergic reaction	9 (3.0)	13 (4.4)	9 (3.6)	9 (3.6)

Data are shown as number of participants (%). TEAEs were defined as AEs that developed, worsened, or became serious during the 12-month on-treatment period.

^aIncludes two deaths during the 12-month treatment period and one death in the post-12-month treatment period.

AE, adverse event; SAE, serious AE; TEAEs, treatment-emergent AEs.

Hypersensitivity reactions were reported by similar and low percentages of participants (5.6% with SAR-Asp, 7.1% with NN-Asp) in the two treatment groups (Table 3). Most events were mild or moderate in intensity. Two events were considered serious and occurred in one participant in each treatment group (pneumonitis in the SAR-Asp group; acute respiratory failure in the NN-Asp group). Neither was considered related to the study treatment by the investigator. Three hypersensitivity reactions resulted in permanent discontinuation of study medication (two participants in the SAR-Asp group and one participant in the NN-Asp group).

A total of 46 potential hypersensitivity reactions reported by 42 participants in either treatment group were adjudicated by the ARAC. Of these, 10 events in 9 participants in the SAR-Asp group and 13 events in 13 participants in the NN-Asp group were adjudicated as allergic reactions; two events (urticaria, one in each treatment group) were considered as related to study medication and led to permanent treatment discontinuation.

Immunogenicity

AIA response, cross-reactivity, and titers. Similar percentages of participants in both treatment groups were positive for AIAs at baseline (SAR-Asp: 35.3%; NN-Asp: 36.7%) (Table 4). The proportion (incidence) of the study population found to have seroconverted (treatment-induced) or enhanced pre-existing AIA (treatment-boosted) during the 12-month treatment period (treatment-emergent AIAs) was similar in both groups (SAR-Asp: 76/298 [25.5%]; NN-Asp: 85/292 [29.1%]), with a risk difference of -2.9% between SAR-Asp and NN-Asp (90% CI: -8.58% to 2.84%).

The percentage of participants positive for AIA increased slightly and similarly in both treatment groups over the 12-month treatment period, with 39.2% of SAR-Asp participants (40.2% with T1D, 34.1% with T2D) and 38.9% of NN-Asp participants (40.7% with T1D, 29.3% with T2D) being AIA positive at 12 months (Supplementary Fig. S4). The maximum occurred at week 40 (41.9% of SAR-Asp participants and 46.2% of NN-Asp participants). The AIA prevalence, corresponding to the percentage of participants with detectable AIAs at least at one time point between baseline and week 52, was also similar with SAR-Asp and NN-Asp (54.7% and 58.2%, respectively). As expected by the sequence homology, in the majority of participants, AIAs cross-reacted with human insulin (range 87.5% to 96.9% in both groups). This was consistent between treatment groups. The AIA response in the T1D and T2D populations over the 12-month treatment period was generally similar between treatment groups (Table 4).

The kinetics of the AIA response in participants with treatment emergent AIAs, in terms of duration of the AIA response (transient or persistent), were generally comparable between both groups. Three participants with treatment-boosted AIAs had a persistent AIA response, 1 out of 9 in the SAR-Asp group and 2 out of 13 in the NN-Asp group. In participants with treatment-induced AIA, persistent response was found in similar percentages of participants in the two groups (SAR-Asp: 44.8%; NN-Asp: 48.6%).

Results of analyses of AIAs in subgroups defined by type of diabetes (Table 4), type of comparator (data not shown),

and prior use of NN-Asp (Supplementary Table S3) were generally consistent with the results from the overall study population. Differences were numerically small and can be explained by the small number of participants in the subgroups.

Over the 12-month treatment period, AIA titers were comparable between treatment groups and remained relatively low (Table 4). Median AIA titers (1/dilution) at baseline were the same (8.0) in the two treatment groups and remained relatively unchanged over time, with a maximum IQR of 4.00–16.00 in the SAR-Asp group and 4.00–32.00 in the NN-Asp group (Fig. 3). Maximum AIA titers of 256 (1/dilution) were seen in the SAR-Asp group at weeks 4 and 12, and they were 1024 (1/dilution) in the NN-Asp group at week 12 (seen in one participant with T1D with treatment-emergent AIA who had received NN-Asp before the study).

In participants with AIA titers at week 52 increased above the baseline titer and with potential effects on hypersensitivity events, the ARAC assessed whether any of these events were suspected to be AIA-mediated (and, if suspected to be AIA-mediated, whether follow-up of AIA titers after the end of study was recommended). No participants in either treatment group met these conditions, suggesting that none was resistant to insulin.

NAb response. The percentage of participants who had detectable NAb at baseline was low and similar in the two treatment groups (4.0% in the SAR-Asp group vs. 4.1% in the NN-Asp group) (Supplementary Table S4). The NAb incidence, corresponding to the proportion of participants with detectable NAb among those with treatment-emergent AIAs, was numerically lower with SAR-Asp than with NN-Asp (2.3% [7/298] vs. 5.8% [17/292]). The NAb prevalence (percentage of participants positive for NAb at least at one time point between baseline and week 52) was also numerically lower in the SAR-Asp group (8.7% [26/298 participants]) than in the NN-Asp group (12.0% [35/292 participants]). It must be noted that the numbers were low in the two groups.

The percentage of participants with detectable NAb slightly increased between baseline and week 4, similarly in the two groups. Thereafter, the percentage of participants with detectable NAb decreased below baseline values and at week 52, no participants had detectable NAb in either treatment group.

Influence of AIAs and NAb on efficacy and safety outcomes. The mean change in HbA1c and total insulin dose from baseline to week 52 as well as percentages of participants with at least one hypoglycemia (any, severe or documented symptomatic), with hypersensitivity reactions, injection site reactions, common TEAEs, and serious TEAEs were comparable between the SAR-Asp and NN-Asp groups, and similar in both participants with and without treatment-emergent AIA (Supplementary Table S5). The interaction between the treatment and treatment-emergent AIA effects in the statistical models showed no heterogeneity of treatment effect across the various subgroups of AIA status for HbA1c ($P=0.50$) and documented symptomatic hypoglycemia (measured plasma glucose ≤ 70 mg/dL, $P=0.27$; plasma glucose < 54 mg/dL, $P=0.54$) (data not shown).

TABLE 4. ANTI-INSULIN ASPART ANTIBODY RESPONSE FROM BASELINE TO WEEK 52 IN THE OVERALL STUDY POPULATION AND BY TYPE OF DIABETES (ANTI-INSULIN ASPART ANTIBODY POPULATION)

	Overall population			T1D			T2D		
	SAR-Asp (N = 298)	NN-Asp (N = 292)	SAR-Asp (N = 249)	NN-Asp (N = 243)	SAR-Asp (N = 49)	NN-Asp (N = 49)			
Participants AIA positive at baseline, <i>n/N</i> (%)	96/272 (35.3)	98/267 (36.7)	83/227 (36.6)	85/223 (38.1)	13/45 (28.9)	13/44 (29.5)			
Median titer (Q1–Q3), 1/dilution	8.0 (4.0–16.0)	8.0 (4.0–16.0)	8.0 (4.0–16.0)	8.0 (4.0–16.0)	8.0 (4.0–8.0)	8.0 (8.0–16.0)			
Participants with greater than or equal to fourfold increase in titer (treatment-boosted), <i>n/N</i> (%)	9/96 (9.4)	13/98 (13.3)	8/83 (9.6)	11/85 (12.9)	1/13 (7.7)	2/13 (15.4)			
Median peak titer (Q1–Q3), 1/dilution	32.0 (16.0–64.0)	64.0 (16.0–256.0)	24.0 (16.0–48.0)	64.0 (16.0–256.0)	256.0 (256.0–256.0)	48.0 (32.0–64.0)			
Transient AIA response, <i>n</i> (%)	7/9 (77.8)	4/13 (30.8)	7/8 (87.5)	4/11 (36.4)	0/1	0/2			
Persistent AIA response, <i>n</i> (%)	1/9 (11.1)	2/13 (15.4)	0/8	2/11 (18.2)	1/1 (100)	0/2			
Indeterminate AIA response, <i>n</i> (%)	1/9 (11.1)	7/13 (53.8)	1/8 (12.5)	5/11 (45.5)	0/1	2/2 (100)			
Participants AIA negative or missing at baseline, <i>n/N</i> (%)	202/298 (67.8)	194/292 (66.4)	166/249 (66.7)	158/243 (65.0)	36/49 (73.5)	36/49 (73.5)			
Participants newly positive at postbaseline (treatment-induced), <i>n/N</i> (%)	67/202 (33.2)	72/194 (37.1)	57/166 (34.3)	64/158 (40.5)	10/36 (27.8)	8/36 (22.2)			
Median peak titer (Q1–Q3), 1/dilution	8.0 (4.0–16.0)	8.0 (4.0–16.0)	8.0 (4.0–16.0)	8.0 (4.0–16.0)	6.0 (4.0–16.0)	4.0 (4.0–8.0)			
Transient AIA response, <i>n</i> (%)	15/67 (22.4)	24/72 (33.3)	12/57 (21.1)	22/64 (34.4)	3/10 (30.0)	2/8 (25.0)			
Persistent AIA response, <i>n</i> (%)	30/67 (44.8)	35/72 (48.6)	27/57 (47.4)	33/64 (51.6)	3/10 (30.0)	2/8 (25.0)			
Indeterminate AIA response, <i>n</i> (%)	22/67 (32.8)	13/72 (18.1)	18/57 (31.6)	9/64 (14.1)	4/10 (40.0)	4/8 (50.0)			
Participants with at least one positive AIA sample (prevalence), ^a <i>n/N</i> (%)	163/298 (54.7)	170/292 (58.2)	140/249 (56.2)	149/243 (61.3)	23/49 (46.9)	21/49 (42.9)			
Participants with treatment-emergent AIA (incidence), ^b <i>n/N</i> (%)	76/298 (25.5)	85/292 (29.1)	65/249 (26.1)	75/243 (30.9)	11/49 (22.4)	10/49 (20.4)			
Participants without treatment-emergent AIA	218/298 (73.2)	207/292 (70.9)	182/249 (73.1)	168/243 (69.1)	36/49 (73.5)	39/49 (79.6)			
Inconclusive participants	4/298 (1.3)	0/292	2/249 (0.8)	0/243	2/49 (4.1)	0/49			
Participants AIA positive at week 52, <i>n/N</i> (%)	102/260 (39.2)	100/257 (38.9)	88/219 (40.2)	88/216 (40.7)	14/41 (34.1)	12/41 (29.3)			

For definition of transient, persistent, and indeterminate responses, see Supplementary Data.

^aParticipants with at least one positive AIA sample at baseline or postbaseline.

^bParticipants with newly positive AIA postbaseline (treatment-induced) or with greater than or equal to fourfold increase in titer (treatment-boosted). AIA, anti-insulin aspart antibody; Q, quartile.

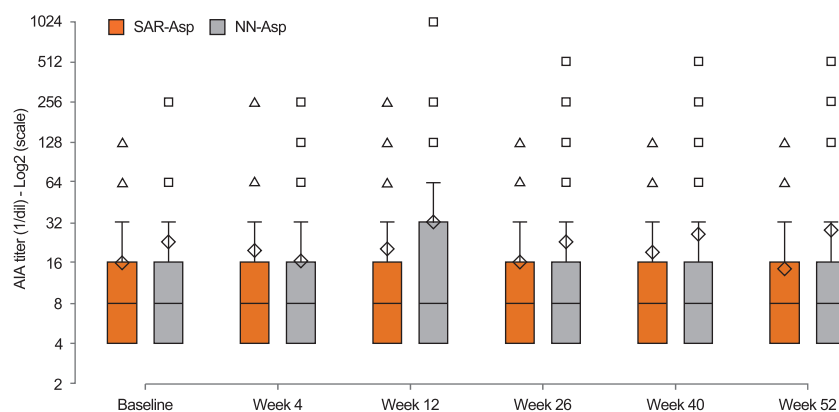


FIG. 3. Boxplots of AIA titer (1/dilution) at each study visit during the 12-month on-treatment period (AIA population). At each visit, AIA titers are described for participants with a positive-sample AIA status at the visit. The boxplot provides the 25% (Q1), 50% (median), and 75% (Q3) quartiles (lower, middle, and upper horizontal bars of the box, respectively). The diamond represents the mean, and triangles or squares represent values beyond the upper/lower whiskers (defined as 1.5 times the interquartile range). Each symbol for high/low values could represent more than one participant. AIA, anti-insulin aspart antibody; Q, quartile.

Similarly, no clinically meaningful difference was observed between the two groups in terms of NAb response. In participants with treatment-emergent NABs, no impact on HbA1c or on the needs in insulin doses was observed, neither in the overall population nor in any subgroup (data not shown).

The number of participants with high AIA titers (i.e., maximal titers ≥ 64 [1/dilution]) and treatment-emergent AIAs was small and similar in both treatment groups (nine participants in each group, seven with T1D and two with T2D). A review of change in HbA1c, insulin doses, and safety parameters (hypersensitivity events and hypoglycemia) in these participants did not suggest negative effects of high AIA titers on these parameters in either treatment group. Similarly, no relationship was observed between the individual maximal AIA titers and the change in HbA1c or total insulin dose, the rate of hypoglycemia events per year for each participant (shown for severe hypoglycemia and documented symptomatic hypoglycemia events with a measured plasma glucose < 54 mg/dL [3.0 mmol/L]), and the occurrence of hypersensitivity or injection site reactions (Supplementary Fig. S5).

Discussion

The use of biosimilar or follow-on insulin biologics for people with diabetes has the potential to reduce drug treatment costs, as they are priced lower than the originator products, while conferring comparable efficacy and safety, facilitating greater access to insulin treatment.¹⁶ Recently, the first rapid-acting insulin analog product SAR342434 was approved as biosimilar in Europe (Insulin Lispro Sanofi[®]) and as a follow-on product in the United States (Admelog[®]) and subsequently in other countries for the same indications as the originator product Humalog.^{17,18}

Regulatory guidelines for assessment of biosimilar/follow-on insulin therapies generally require evaluation of safety outcomes, including immunogenicity data, for between 6 months and up to a year.^{3,13} This 6-month extension of the main GEMELLI 1 study, therefore, provides valuable information on the safety, immunogenicity, and efficacy of treatment with

the biosimilar insulin analog SAR-Asp in people with diabetes over a long duration of follow-up, thereby increasing the ability to detect any differences in clinical outcomes.

Overall, results after 1 year of follow-up are largely consistent with those observed at the end of the main 6-month treatment period. Adherence to treatment was similar, with more than 87% of participants in each group completing the 12-month treatment period. At 12 months, HbA1c and FPG levels remained improved from baseline and were comparable between the SAR-Asp and NN-Asp treatment groups. The greatest improvement in glycemic control (decrease in HbA1c) for participants in both groups was observed during the first 6 months and was sustained until month 12. Both treatment groups showed a similar proportion of participants achieving an HbA1c target of $< 7\%$, along with similar changes in insulin dose and body weight. The SMPG profiles were similar in each treatment group.

The collection of safety data among participants with T1D and T2D for up to 12 months of treatment showed no difference in the overall percentage of individuals reporting any TEAE, serious TEAEs, TEAEs leading to study medication discontinuation, or any of the recorded categories of hypoglycemia. The observed AE profile was consistent with those reported in other studies assessing the efficacy and safety of NN-Asp in adults with T1D and T2D.^{19,20}

Subtle differences in the manufacturing process of biological proteins such as insulin have a potential to result in different immune responses. Hence, comparing the immunogenic profile of SAR-Asp and the reference drug NN-Asp was a key secondary end point of the study. Immunogenicity assessments, including the incidence and prevalence of AIA and NAb as well as median AIA titers and AIA cross-reactivity to human insulin, were similar with both treatments, implying that the immunogenicity of SAR-Asp did not differ from NN-Asp. The percentage of participants positive for AIA peaked at week 40, supporting the assessment of immunogenicity variables for longer than 6 months when the peak levels would not have been reached.

Treatment-emergent AIAs had no effect on glycemic control (change in HbA1c), insulin dose requirements, hypoglycemia events, local (injections site) and systemic hypersensitivity (allergic) reactions, TEAEs, or SAEs in either group. In addition, there was no relationship between the individual maximal AIA titers and these parameters, regardless of treatment-emergent AIA status.

Separate immunogenicity analyses for the two diabetic populations showed a similar AIA response to SAR-Asp and NN-Asp during 12-month treatment with respect to median titers, treatment-boosted, and treatment-induced AIAs. In addition, results of analyses of NABs showed a similar response in the two groups, with no evidence of an impact of NABs on HbA1c or on the needs in insulin doses. Other immunological phenomena related to insulin therapy, namely skin reactions and hypersensitivity reactions, were rare and showed no difference between the two treatments.

As previously highlighted,⁸ the main limitation of this study was the open-label design necessitated by the different injection devices used for SAR-Asp and NN-Asp (SAR-Asp and NN-Asp administered using different prefilled disposable pens). To partially overcome this limitation, assessments were based on objectively collected data that were analyzed by central laboratories and an adjudication committee, all blinded to the study treatment.

We conclude that SAR-Asp was well tolerated and demonstrated effective glycemic control with a similar safety and immunogenicity profile to commercially available insulin aspart in people with diabetes treated for 12 months.

Acknowledgments

Sanofi was the sponsor of the study and was responsible for the design and coordination of the trial, monitoring clinical sites, collecting and managing data, and performing all statistical analyses.

Author Disclosure Statement

S.K.G., advisory boards consulting fees: Medtronic, Roche, Lexicon, Novo Nordisk, Sanofi, Eli Lilly, Zealand Pharmaceuticals, AstraZeneca. Research grants: Eli Lilly, Novo Nordisk, Merck, Lexicon, Medtronic, Boehringer Ingelheim, NCI, T1D Exchange, NIDDK, JDRF, Sanofi. No stocks or equity in any device or pharmaceutical company. K.W.-P., M.W., D.K., P.M., and B.M. are all employees and stockholders of Sanofi. F.D., employee of Ividata. E.F., advisory boards consulting fees: Boehringer Ingelheim, Novartis, and Novo Nordisk. Speaker grants: AstraZeneca, Bioton, Boehringer Ingelheim, Novo Nordisk, Mundipharma. K.S., personal fees: Sanofi, AstraZeneca, Novo Nordisk, MSD, Bayer, ICON. T.M., research grants: Sanofi, Novo Nordisk, TrialNet, Amarin. V.N.S., V.N.S.' employer has received research funding from Type 1 Diabetes Exchange Registry (Jaeb Center for Health Research), National Institute of Health (NIDDK, NIAMS), Sanofi US, Dexcom, Inc., Novo Nordisk, Eyenuk, Mylan GmbH, and vTv Therapeutics. V.N.S. has served on an advisory board for Sanofi US and consulted Dexcom, Inc. in the past.

Funding Information

This study was funded by Sanofi.

Supplementary Material

Supplementary Data
 Supplementary Figure S1
 Supplementary Figure S2
 Supplementary Figure S3
 Supplementary Figure S4
 Supplementary Figure S5
 Supplementary Table S1
 Supplementary Table S2
 Supplementary Table S3
 Supplementary Table S4
 Supplementary Table S5

References

1. American Diabetes Association: Section 9. Pharmacologic approaches to glycemic treatment: standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43(Suppl. 1): S98–S110.
2. Hermansen K, Bohl M, Schioldan AG: Insulin aspart in the management of diabetes mellitus: 15 years of clinical experience. *Drugs* 2016;76:41–74.
3. European Medicines Agency: Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. 2015. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-0.pdf (accessed September 1, 2019).
4. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Guidance for industry. Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. 2008, pp. 1–30. <https://www.fda.gov/media/71289/download> (accessed September 1, 2019).
5. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Guidance for industry. Questions and answers on biosimilar development and the BPCI act (revision 1). 2018, pp. 1–19. <https://www.fda.gov/media/119258/download> (accessed September 1, 2019).
6. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Guidance for industry. New and revised draft Q&As on biosimilar development and the BPCI act (revision 2) (draft guidance). 2018, pp. 1–14. <https://www.fda.gov/media/119278/download> (accessed September 1, 2019).
7. Kapitza C, Nosek L, Schmider W, et al.: Single-dose euglycemic clamp study demonstrating pharmacokinetic and pharmacodynamic similarity between SAR341402 insulin aspart and US- and EU-approved versions of insulin aspart in subjects with type 1 diabetes. *Diabetes Technol Ther* 2019 [Epub ahead of print]; DOI: 10.1089/dia.2019.0351.
8. Garg SK, Wernicke-Panten K, Wardecki M, et al.: Efficacy and safety of insulin aspart biosimilar SAR341402 versus originator insulin aspart in people with diabetes treated for 26 weeks with multiple daily injections in combination with insulin glargine: a randomized, open-label trial (GEMELLI 1). *Diabetes Technol Ther* 2020;22:85–95.
9. American Diabetes Association: 8. Pharmacologic approaches to glycemic treatment. In *Standards of Medical Care in Diabetes-2017*. *Diabetes Care* 2017;40(Suppl. 1): S64–S74.

10. American Diabetes Association Workgroup on Hypoglycemia: Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 2005;28:1245–1249.
11. 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.
12. International Hypoglycaemia Study Group: Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017;40:155–157.
13. US Food and Drug Administration Center for Drug Evaluation and Research (CDER): Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. 2015, pp. 1–24. <https://www.fda.gov/media/82647/download> (accessed February 4, 2020).
14. European Medicines Agency: Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006 Rev.1. 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf (accessed February 4, 2020).
15. Shankar G, Arkin S, Cocea L, et al.: Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *AAPS J* 2014;16:658–673.
16. Fralick M, Kesselheim AS: The U.S. insulin crisis—rationing a lifesaving medication discovered in the 1920s. *New Engl J Med* 2019;381:1793–1795.
17. European Medicines Agency: Insulin lispro Sanofi: summary of product characteristics, version 17 June 2019. https://www.ema.europa.eu/en/documents/product-information/insulin-lispro-sanofi-epar-product-information_en.pdf (accessed February 4, 2020).
18. US Food and Drug Administration: FDA approves Admelog, the first short-acting “follow-on” insulin product to treat diabetes [news release]. 2017. <https://www.fda.gov/news-events/press-announcements/fda-approves-admelog-first-short-acting-follow-insulin-product-treat-diabetes> (accessed February 4, 2020).
19. European Medicines Agency: NovoRapid. Summary of product characteristics. 2019. https://www.ema.europa.eu/en/documents/product-information/novorapid-epar-product-information_en.pdf (accessed February 4, 2020).
20. NovoLog, insulin aspart injection 100 units/mL, Novo Nordisk. Prescribing information, revised: 11/2019. <https://www.novo-pi.com/novolog.pdf> (accessed February 4, 2020).
21. Little RJA, Rubin DB: *Statistical Analysis with Missing Data*, 1st ed. New York, NY: John Wiley & Sons, 1987.

Address correspondence to:

Satish K. Garg, MD

Barbara Davis Center for Diabetes

University of Colorado Anschutz Medical Campus

1775 Aurora Court, A140

Aurora, CO 80045

E-mail: satish.garg@cuanschutz.edu