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ORIGINAL ARTICLE

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)

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Abstract

Background: This study compared the efficacy, safety, and immunogenicity of insulin aspart biosimilar/follow-on biologic product SAR341402 (SAR-Asp) with originator insulin aspart-NovoLog®/NovoRapid® (NN-Asp) in people with type 1 diabetes (T1D) or type 2 diabetes (T2D) treated with multiple daily injections in combination with insulin glargine (Lantus®; Gla-100).

Materials and Methods: This 6-month, randomized, open-label, phase 3 study (NCT03211858) enrolled 597 people with T1D ($n = 497$) or T2D ($n = 100$). Participants were randomized 1:1 to mealtime SAR-Asp ($n = 301$) or NN-Asp ($n = 296$) in combination with Gla-100. The primary objective was to demonstrate noninferiority (by 0.3% margin in the intent-to-treat population) of SAR-Asp versus NN-Asp in HbA1c change from baseline to week 26. Immunogenicity was also assessed in terms of anti-insulin aspart antibody (AIA) status (positive/negative) and titers during the study.

Results: HbA1c was similarly improved in both treatment groups (SAR-Asp −0.38%; NN-Asp −0.30%); the least squares mean difference at week 26 for SAR-Asp minus NN-Asp was −0.08% (95% confidence interval: −0.192 to 0.039), thus meeting the criteria for noninferiority between SAR-Asp and NN-Asp and inverse noninferiority of NN-Asp versus SAR-Asp. Changes in fasting plasma glucose and seven-point self-monitored plasma glucose profile, including postprandial glucose excursions, and insulin dosages were similar in both groups at week 26. Safety and tolerability, including AIA responses (incidence, prevalence), hypoglycemia, and adverse events (including hypersensitivity events and injection site reactions), were similar between groups.

Conclusions: SAR-Asp demonstrated effective glycemic control with a similar safety and immunogenicity profile to NN-Asp in people with diabetes treated for 26 weeks.

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Introduction

INSULIN ASPART IS THE active ingredient of NovoLog®/NovoRapid® (NN-Asp) (Novo Nordisk, Bagsvaerd, Denmark), a rapid-acting insulin analog, with a faster onset and shorter duration of action than unmodified regular human insulin.[1,2] NovoLog/NovoRapid has been approved and marketed for use in adults and children with type 1 diabetes (T1D) and type 2 diabetes (T2D) in many countries since 1999.[3]

SAR341402 (SAR-Asp; insulin aspart solution 100 U/mL; Sanofi, Paris, France) has been developed as a biosimilar/follow-on biologic product to NN-Asp in accordance with relevant United States and European Union (EU) guidelines.[4–7] SAR-Asp has the same amino acid sequence and structure as NN-Asp. It is manufactured by recombinant DNA technology utilizing a nonpathogenic strain of *Escherichia coli*. Using a stepwise approach, similarity among the clinical pharmacology, safety, efficacy, and immunogenicity of SAR-Asp and NN-Asp has been demonstrated in physicochemical analyses, nonclinical studies, and clinical studies. A euglycemic clamp study demonstrated similar pharmacokinetic exposure and pharmacodynamic activity for SAR-Asp versus both US-approved (NovoLog) and EU-approved (NovoRapid) NN-Asp, as well as between US-approved and EU-approved NN-Asp, in subjects with T1D.[8]

We report the results of a phase 3 clinical trial (GEMELLI 1) comparing the efficacy, safety, and immunogenicity of SAR-Asp and the reference drug NN-Asp in people with T1D or T2D treated with multiple daily injections in combination with insulin glargine (Lantus®; Gla-100).

Methods

Study design and participants

The GEMELLI 1 study was an open-label, multicenter, two-arm, parallel-group phase 3 clinical trial (Clinical-Trials.gov identifier: NCT03211858). The study was initiated on August 2, 2017 and ended (last patient completed) on January 12, 2019. The study comprised a 2-week screening period, a 6-month (26-week) efficacy and safety period, and a 6-month (26-week) safety extension period (Supplementary Fig. S1). It was conducted in the United States, Japan, and seven countries in Europe.

Patients ≥18 years of age with T1D or with T2D (T2D patients were enrolled in the United States only) on insulin treatment for at least 1 year with a measured HbA1c in the range of 7% (≥53 mmol/mol) to 10% (≤86 mmol/mol) on a multiple daily insulin injection treatment regimen with insulin glargine (100 U/mL) for at least 6 months or insulin detemir (100 U/mL, Levemir®) for at least 12 months and that included either NN-Asp or insulin lispro (100 U/mL, Humalog/Liprolog®) as the rapid-acting insulin for at least 6 months before screening visit were eligible for the study. Major exclusion criteria for patients with T1D were non-insulin antidiabetic treatments, use of an insulin pump in last 3 months before screening, and a body mass index (BMI) ≥35 kg/m². Patients with T2D who used an insulin pump in last 3 months before screening, had a BMI ≥40 kg/m², or were using glucagon-like peptide-1 receptor agonists or oral antidiabetic drugs (other than sulfonylureas) and not on a stable dose in the last 3 months before screening were excluded. Additional exclusion criteria included a history of severe hypoglycemia requiring emergency room admission and recurrent diabetic ketoacidosis requiring hospitalization, all in the last 3 months before screening.

Participants were randomized 1:1 to either SAR-Asp or NN-Asp, stratified by geographical region (Europe, United States, Japan), type of diabetes (T1D, T2D [T2D only for United States]), HbA1c at the screening visit (<8.0%, ≥8.0%), and prior use of NN-Asp (Yes, No). An interactive voice/Web response system generated patient randomization. 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), depending on the location of their study site. Based on the similarity between NN-Asp (US) and NN-Asp (EU) shown in physicochemical analyses, nonclinical studies, and a pharmacokinetic/pharmacodynamic study,[8] data from both insulins were pooled in the comparator arm of this study. The study protocol was approved by local review boards/independent ethics committees and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before study entry. Clinic visits were planned at screening, randomization (week 0), and weeks 4, 12, 20, and 26 (Supplementary Fig. S1). Telephone contact was also made at weeks 2 and 8 and 1 day after the last dose of study medication.

Treatments

Study medications were dispensed on day 1 and weeks 4, 12, and 20. Study treatment compliance was checked by reviewing the patient's diary and counting/collecting used and unused pens. SAR-Asp was supplied in a 3 mL prefilled disposable SAR-Asp SoloSTAR® pen injector at a concentration of 100 U/mL for subcutaneous (SC) injection. NN-Asp was supplied as a 100 U/mL insulin solution for SC injection in 3 mL NN-Asp FlexPen disposable prefilled pens. The starting dose of SAR-Asp or NN-Asp was a unit-to-unit conversion from the insulin lispro or NN-Asp dose used before the trial. SAR-Asp or NN-Asp was to be injected subcutaneously immediately (within 5–10 min) before the start of a meal using the insulin pen. When necessary, SAR-Asp or NN-Asp could be given soon after a meal, if allowed by the national product label for NN-Asp. Changes in the SAR-Asp or NN-Asp dose were based on self-monitored plasma glucose (SMPG) measurements and the carbohydrate content of the meal (when available). Mealtime insulin dose was titrated to achieve a target 2-h postprandial plasma glucose of <180 mg/dL (<10 mmol/L) while avoiding hypoglycemia. If preprandial glucose tests were used, the recommended target range was 80–130 mg/dL (4.4–7.2 mmol/L).[9] Regular plasma glucose monitoring by SMPG was used to aid patients to achieve their plasma glucose target range for 2-h postprandial or preprandial plasma glucose during the first 12 weeks of the study.

Irrespective of their prior basal insulin treatment, patients were switched to basal insulin Gla-100 once daily. The starting dose of Gla-100 was the same as the last dose of insulin glargine (100 U/mL) or insulin detemir or was adjusted based on the investigator's clinical recommendation. Gla-100 was injected once daily at a consistent time (determined at baseline according to patient and provider preference) using the SoloSTAR pen; the dose was titrated to achieve a recommended fasting preprandial (prebreakfast) SMPG of 80–130 mg/dL (4.4–7.2 mmol/L) while avoiding hypoglycemia.

Study procedures and assessments

HbA1c and fasting plasma glucose (FPG) values were determined in a central laboratory (Central Laboratory Services LP, Geneva, Switzerland; Tokyo, Japan; and Indianapolis, IN), with samples collected at screening (HbA1c only), randomization (day 1), weeks 12 and 26, and at early discontinuation. Seven-point SMPG profiles were assessed at baseline (on at least 2 days in the week before randomization) and at weeks 12 and 26, based on measurements taken before and 2-h postmeal at breakfast, lunch and dinner, and at bedtime using a Bluetooth-enabled glucometer (BLE Smart Glucometer, Entra Health, El Cajon, CA) together with standardized test strips (BLE Smart Test, Osang Healthcare, Gyeonggi-do, South Korea) and transferred through Bluetooth to an electronic diary (e-diary; CRF Health, Plymouth Meeting, PA). SMPG data were analyzed when at least five of the seven SMPG measurements requested were available for at least one profile in the requested time frame before a visit. Basal and mealtime insulin doses were to be documented by the patients in their e-diary over prespecified period of time. SMPG data and patient-reported data in the e-diary were electronically transferred to the clinical database through a dedicated web-based portal.

Efficacy end points

The primary efficacy end point was the change in HbA1c from baseline to week 26. Secondary efficacy end points included the percentage of study participants with HbA1c <7.0% (<53 mmol/mol), change from baseline in laboratory-measured FPG to week 26, change in the mean glucose over 24 h, and postprandial plasma glucose excursions (difference between 2-h postprandial and preprandial plasma glucose values at breakfast, lunch, and dinner) from baseline to week 26 based on the seven-point SMPG profiles.

Safety end points

Safety end points included the percentage of participants reporting at least one hypoglycemic event, the number of hypoglycemia events per patient year of exposure, the number of patients with treatment-emergent adverse events (TEAEs), and/or treatment-emergent serious adverse events (SAEs), including injection site and hypersensitivity reactions, and change in body weight and routine laboratory assessments. TEAEs were defined as adverse events (AEs) that developed, worsened, or became serious during the main 6-month on-treatment period (see statistical analyses section for further details). AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

Hypoglycemic events were documented by the patients in their e-diary. Additional SMPG measurements were performed to document hypoglycemia in case a patient experienced symptoms that were suggestive for hypoglycemia. Hypoglycemia episodes were categorized based on American Diabetes Association classifications.[10–12] Documented symptomatic hypoglycemia (events associated with typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤70 mg/dL [≤3.9 mmol/L]) and asymptomatic hypoglycemia episodes (events not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration of ≤70 mg/dL [≤3.9 mmol/L]) were analyzed separately and using a lower more stringent plasma glucose concentration threshold of <54 mg/dL (3.0 mmol/L). Severe hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Symptoms indicating severe neuroglycopenia, such as loss of consciousness, coma, or seizure, were reported as an SAE.

Immunogenicity (the main secondary end point) was assessed in terms of anti-insulin aspart antibody (AIA) status (positive or negative), AIA titers, and cross-reactivity to human insulin at each sampling visit. AIAs were assessed at baseline and weeks 4, 12, and 26 and at any early discontinuation visit. Anti-SAR-Asp/NN-Asp antibodies were determined in a blinded manner at a central laboratory (Farmovs, Bloemfontein, South Africa) using a AIA binding assay developed and validated according to regulatory and industry standards.[5,13,14] AIA analyses focused on the change in AIA response with treatment and included assessment of the incidence (patients with newly positive postbaseline [treatment induced] or having a ≥4-fold increase in titers compared with baseline [treatment boosted]), together called treatment-emergent and the prevalence (patients with at least one positive sample at baseline or postbaseline) of AIA response during the main 6-month on-treatment period.[13] Additional data on AIA titers and the relationship between these and selected efficacy and safety parameters will be reported in a separate article following completion of the 6-month safety extension period.

An Allergic Reaction Assessment Committee (ARAC) of four experts (three who were board certified in allergy and clinical immunology) independent from the sponsor and the investigators reviewed all hypersensitivity reactions reported on a specific allergic reaction AE form or identified by MedDRA search. They confirmed, based on the information reported by the investigator, whether the event was allergic in nature. The committee was blinded to the study treatment. Two experts reviewed all cases of AIA titers increased at the end of study treatment and their effect on decreased efficacy and/or ongoing positively adjudicated hypersensitivity reactions.

Statistical analyses

A planned sample size of 580 patients (290 participants per treatment group; comprising ∼480 T1D patients [230 patients in the United States using NovoLog and 250 patients in countries using NovoRapid (185 patients in EU, 65 in Japan)] and 100 T2D patients [all in the United States using NovoLog]) would provide >95% power to show noninferiority of the SAR-Asp group to the NN-Asp group with respect to the

HbA1c change from baseline to week 26 on the basis of a true difference between the two groups of zero and a non-inferiority upper margin of 0.3% (common standard deviation 1.0%; 2.5% significance level; one-sided *t*-test). This sample size would also provide >90% power to show both noninferiority of SAR-Asp over NN-Asp (primary analysis) and inverse noninferiority of NN-Asp over SAR-Asp (secondary analysis). SAR-Asp was considered to have similar efficacy (equivalence) to NN-Asp (90% power) if both the lower and upper bounds of the two-sided 95% confidence interval (CI) of the between-treatment difference were between −0.30% and 0.30%. The HbA1c noninferiority margin of 0.3% is in line with recommendations by regulatory agencies.[15,16] An exploratory analysis of the percentage of patients with treatment-emergent AIAs was performed to compare the immunogenicity of SAR-Asp versus NN-Asp; a sample size of 580 patients was considered sufficient to ensure that the two-sided 90% CI for the adjusted risk difference between SAR-Asp and NN-Asp would be included within the [−10%; 10%] interval with at least 68% power.

Efficacy end points were analyzed in the intent-to-treat (ITT) population of all randomized participants, irrespective of compliance with the study protocol and procedures. The primary efficacy end point (change in HbA1c from baseline to week 26) was analyzed using all HbA1c values regardless of adherence to treatment during the 6-month randomized period (ITT estimand[17]) with missing data during this period imputed by a multiple imputation approach (10,000 imputations using separate models for patients who prematurely discontinued or completed the main 6-month treatment period). Least squares (LS) means for the primary efficacy end point were obtained from an analysis of covariance (ANCOVA) model that included the treatment group (SAR-Asp, NN-Asp) and randomization strata (geographic region, type of diabetes, prior use of NN-Asp) as fixed-effect factors and the baseline HbA1c value as the continuous fixed covariate. Results were combined using Rubin's formulae.[18] The LS mean change in HbA1c from baseline to week 26 for each treatment group was estimated, as well as the between-group difference and the 95% CI for the adjusted mean. If non-inferiority of SAR-Asp over NN-Asp was demonstrated, a secondary analysis using a hierarchical step-down testing procedure tested the inverse noninferiority of NN-Asp over SAR-Asp. Change in FPG was analyzed using a similar multiple imputation approach followed by a similar AN-COVA model. Other secondary end points based on seven-point SMPG profiles were analyzed using a return to baseline multiple imputation approach followed by a similar ANCOVA

TABLE 1. PARTICIPANT DEMOGRAPHICS AND BASELINE CHARACTERISTICS (RANDOMIZED POPULATION)

Characteristic	SAR-Asp (N = 301)	NN-Asp (N = 296)
Age, years	48.4 ± 14.8	47.8 ± 15.4
Male, *n* (%)	179 (59.5)	177 (59.8)
Race, *n* (%)		
White/Caucasian	248 (82.7)	242 (82.6)
Asian[a]	37 (12.3)	37 (12.6)
Black or African American	11 (3.7)	8 (2.7)
Other[b]	4 (1.3)	6 (2.0)
BMI, kg/m²	27.5 ± 4.6	27.5 ± 5.0
Diabetes type, *n* (%)		
T1D	250 (83.1)	247 (83.4)
T2D	51 (16.9)	49 (16.6)
Duration of diabetes, years	19.5 ± 11.9	19.4 ± 11.8
Previous basal insulin[c], *n* (%)		
Insulin glargine	238 (79.1)	237 (80.1)
Insulin detemir	62 (20.6)	59 (19.9)
Both[d]	1 (0.3)	0
Previous mealtime insulin[c], *n* (%)		
Insulin aspart	169 (56.5)	161 (54.4)
Insulin lispro	125 (41.8)	123 (41.6)
Both[d]	5 (1.7)	12 (4.1)
Type of comparator, *n* (%)		
NovoLog	170 (56.5)	165 (55.7)
NovoRapid	131 (43.5)	131 (44.3)
Baseline HbA1c, % [mmol/mol]	8.00 ± 0.77 [63.89 ± 8.41]	7.94 ± 0.70 [63.24 ± 7.67]
<8.0%, *n* (%)	143 (47.5)	138 (46.6)
≥8.0%, *n* (%)	158 (52.5)	158 (53.4)
Mean 24-h plasma glucose, mg/dL [mmol/L]	180.15 ± 39.96 [10.00 ± 2.22]	175.96 ± 36.62 [9.77 ± 2.03]

All data are mean ± SD unless stated otherwise.
[a]Most patients were from Japan (33 and 32, respectively).
[b]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple or unknown.
[c]Insulin use in the last 6 months before screening.
[d]Use of both insulins in last 6 months before screening but not at the same time.
BMI, body mass index; HbA1c, glycated hemoglobin; NN-Asp, Novo Nordisk-aspart (NovoLog®/NovoRapid®); SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

model. The proportions of study participants meeting HbA1c <7.0% were analyzed using a logistic regression model with fixed-effect term for treatment group and the randomization strata.

The safety population was defined as all randomized patients who received at least one dose of study insulin, analyzed according to the treatment actually received. The on-treatment period was defined as the time from the first dose of study medication up to week 26 or 1 day after the last dose of study medication, whichever came earlier. The AIA population was defined as all patients 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 6-month on treatment period. Statistical analyses were performed using SAS®, Enterprise Guide version 5.1 (SAS Institute, Inc., Cary, NC).

Results

Patient disposition and baseline characteristics

A total of 846 participants were screened, of whom 597 were randomized and received at least one dose of study insulin (Supplementary Fig. S2). The ITT and safety populations included 597 patients (497 with T1D and 100 with T2D). Of the treated participants, 279/301 (92.7%) in the SAR-Asp group and 274/296 (92.6%) in the NN-Asp group completed the 26-week treatment period. Reasons for discontinuation were similar between SAR-Asp and NN-Asp; the most common reasons were other reasons (predominantly patient decision or consent withdrawal) and AEs.

Demographics and baseline characteristics were similar in the two treatment groups for the overall population (Table 1) and patients with T1D and T2D (Supplementary Table S1). Patients had a mean age of 48.1 years (45.1 years in T1D, 63.0 years in T2D), were predominantly White/Caucasian (82.9%), and had a mean duration of diabetes of 19.5 years. The mean BMI at baseline was 27.5 kg/m^2 (26.4 kg/m^2 in T1D, 32.5 kg/m^2 in T2D). For mealtime insulin before study entry, insulin lispro and aspart were used by ~58% and 45% of participants, respectively. A small proportion of participants (2.8%) used both mealtime insulins in the 6 months before screening but not at the same time. For basal insulin, ~80% of patients were on Gla-100.

Efficacy

HbA1c decreased similarly in both groups from ~8.0% at baseline to ~7.6% at week 26 (Table 2 and Fig. 1A). The LS mean treatment difference at week 26 was −0.08% (95% CI

TABLE 2. GLYCEMIC CONTROL, INSULIN DOSES, AND BODY WEIGHT ASSESSMENTS
FROM BASELINE TO WEEK 26 (ITT 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 26 [n]	7.60 ± 0.80 (59.54 ± 8.75) [283]	7.62 ± 0.78 (59.82 ± 8.51) [278]
LS mean (±SE) change from baseline[a] [n]	−0.38 ± 0.04 (−4.11 ± 0.46) [301]	−0.30 ± 0.04 (−3.28 ± 0.45) [296]
LS mean (±SE) difference [95% CI][a]	−0.08 ± 0.059 [−0.192 to 0.039] (−0.84 ± 0.65 [−2.10 to 0.43])	
FPG, mg/dL (mmol/L)		
Baseline [n]	177.89 ± 69.67 (9.87 ± 3.87) [290]	179.57 ± 79.12 (9.97 ± 4.39) [285]
Week 26 [n]	170.39 ± 73.07 (9.46 ± 4.06) [277]	176.27 ± 70.83 (9.78 ± 3.93) [271]
LS mean (±SE) change from baseline[a,b] [n]	−8.78 ± 4.48 (−0.49 ± 0.25) [301]	−3.11 ± 4.42 (−0.17 ± 0.25) [296]
LS mean (±SE) difference [95% CI][a,b]	−5.66 ± 6.27 [−17.96 to 6.63] (−0.31 ± 0.35 [−1.00 to 0.37])	
Total insulin, U/kg/day		
Baseline [n]	0.79 ± 0.34 [295]	0.78 ± 0.40 [291]
Week 26 [n]	0.79 ± 0.34 [267]	0.80 ± 0.37 [265]
Change from baseline [n]	−0.007 ± 0.17 [263]	0.015 ± 0.17 [262]
Basal insulin, U/kg/day		
Baseline [n]	0.39 ± 0.19 [297]	0.39 ± 0.23 [294]
Week 26 [n]	0.40 ± 0.18 [273]	0.39 ± 0.21 [272]
Change from baseline [n]	0.005 ± 0.08 [271]	0.003 ± 0.09 [270]
Mealtime insulin, U/kg/day		
Baseline [n]	0.40 ± 0.23 [299]	0.39 ± 0.25 [293]
Week 26 [n]	0.39 ± 0.23 [270]	0.41 ± 0.23 [266]
Change from baseline [n]	−0.011 ± 0.13 [268]	0.011 ± 0.12 [265]
Body weight, kg		
Baseline [n]	81.7 ± 17.6 [301]	81.6 ± 17.8 [296]
Week 26 [n]	83.5 ± 18.7 [281]	82.9 ± 18.3 [274]
Change from baseline [n]	+1.5 ± 4.4 [281]	+1.1 ± 3.7 [274]

All data are mean ± SD unless stated otherwise.

[a]Retrieved dropout multiple imputations of missing changes at week 26 (10,000 imputations using separate models for patients who prematurely discontinued or completed the main 6-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 using Rubin's formulae.[18]

[b]Randomization strata of screening HbA1c (<8.0, ≥8.0%) also included as a fixed categorical effect.

CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; SE, standard error.
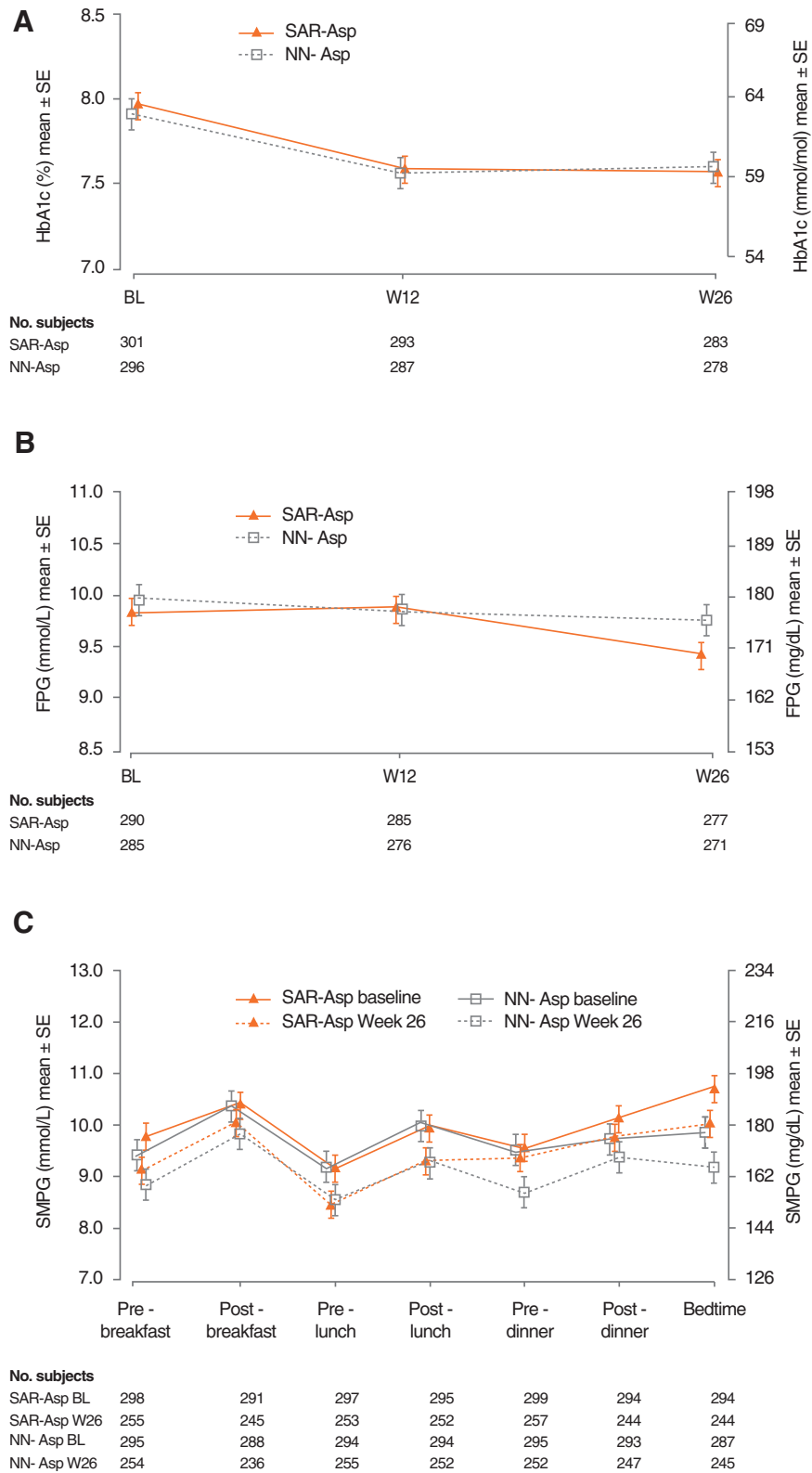
FIG. 1. HbA1c (% and mmol/mol) by study visit **(A)**, FPG (mmol/L and mg/dL) by study visit **(B)**, and seven-point SMPG profiles (mmol/L and mg/dL) at baseline and week 26 **(C)**. Data are mean ± standard error. BL, baseline; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SMPG, self-monitored plasma glucose; W, week.
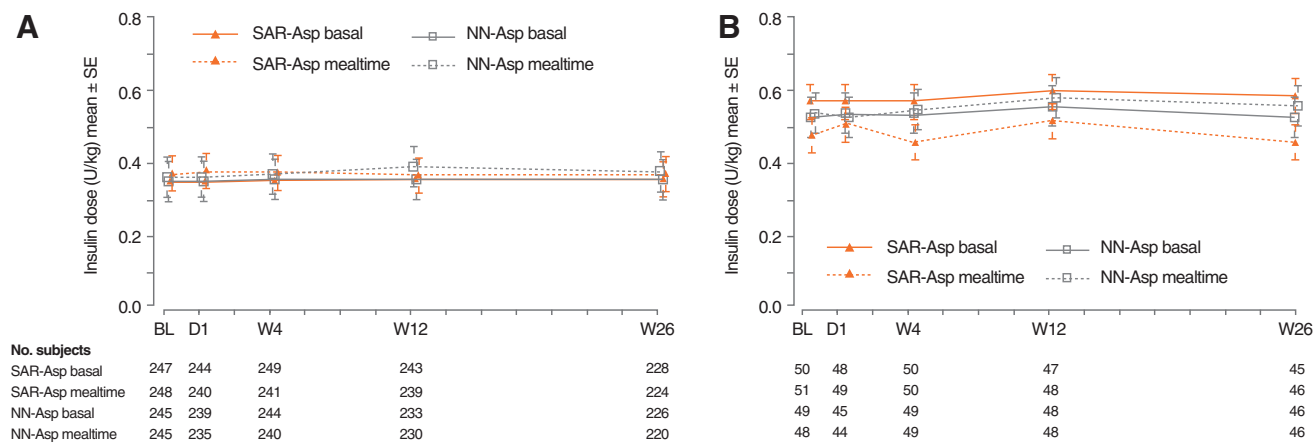
FIG. 2. Daily basal and mealtime insulin doses (U/kg) in patients with T1D **(A)** and T2D **(B)** (safety population). Data are mean ± standard error. BL, baseline; D, day; T1D, type 1 diabetes; T2D, type 2 diabetes; W, week.

−0.192 to 0.039), thus meeting the criteria for noninferiority between SAR-Asp and NN-Asp. The inverse noninferiority (of NN-Asp vs. SAR-Asp) was also demonstrated (lower bound of the 95% CI of the difference between SAR-Asp and NN-Asp was above −0.3%). Between treatment differences in week 26 HbA1c responses were generally consistent across subgroups of study participants defined by age (<65, 65–75, and ≥75 years of age), baseline BMI (<30 and ≥30 kg/m²), randomization strata (geographical region [Europe, United States, Japan]), type of diabetes [T1D, T2D], screening HbA1c categories [<8%, ≥8%], prior use of NN-Asp, and type of comparator (NovoLog and NovoRapid) (Supplementary Fig. S3). In both treatment groups, the LS mean change from baseline to week 26 was higher in patients with T2D (SAR-Asp: −0.69%, NN-Asp: −0.55%) than in patients with T1D (SAR-Asp: −0.31%, NN-Asp: −0.25%). Similar proportions of study participants achieved target HbA1c values of <7.0% at week 26 (SAR-Asp 16.6%; NN-Asp 14.5%).

Both treatment groups had similar reductions in laboratory measured FPG from baseline to week 26 (Table 2 and Fig. 1B). The seven-point SMPG profiles at baseline and week 26 were generally consistent between treatments over the 24-h period (Fig. 1C). The LS mean difference (95% CI) for SAR-Asp versus NN-Asp for postprandial glucose excursions at breakfast, lunch, and dinner was −2.72 (−14.32 to 8.88), 1.17 (−10.26 to 12.59), and −5.41 (−17.55 to 6.74)

mg/dL, respectively (Supplementary Table S2). Mean 24-h plasma glucose values at week 26 were also similar between the two groups, with a LS mean (SE; 95% CI) difference of 3.30 (3.08; −2.72 to 9.33) mg/dL.

No clinically relevant changes in insulin doses were observed over the main 6-month treatment period (Fig. 2). Basal insulin doses remained almost unchanged during the 6-month treatment period (Table 2). Changes in mealtime insulin doses were also small, with a mean decrease from baseline to week 26 of −0.011 U/kg in the SAR-Asp group and a mean increase of 0.011 U/kg in the NN-Asp. The ratio of daily basal insulin/total insulin dose was similar (∼0.5) in both treatment groups and remained stable over the study period. Changes in insulin dose (basal, mealtime, and total) were similar in participants with T1D and T2D (data not shown).

Body weight increased by a similar degree between treatments from baseline through to week 26 (mean change: SAR-Asp +1.5 kg; NN-Asp +1.1 kg) (Table 2).

Safety profile

During the 6-month study period, almost all the patients had at least one episode of hypoglycemia regardless of the category: 96.7% in the SAR-Asp group and 96.3% in the NN-Asp group (Table 3). The corresponding number of events (any hypoglycemia) per patient-year through to week 26 was

TABLE 3. HYPOGLYCEMIA (SAFETY POPULATION)

	No. of patients (%)		No. of events (rate per patient-year)	
Category of hypoglycemia	SAR-Asp (N = 301)	NN-Asp (N = 296)	SAR-Asp (N = 301)	NN-Asp (N = 296)
Total patient-years			145.92	143.09
Any	291 (96.7)	285 (96.3)	10646 (72.96)	9917 (69.31)
Severe	12 (4.0)	10 (3.4)	20 (0.14)	14 (0.10)
Documented symptomatic				
≤70 mg/dL (3.9 mmol/L)	264 (87.7)	251 (84.8)	5872 (40.24)	5190 (36.27)
<54 mg/dL (3.0 mmol/L)	206 (68.4)	193 (65.2)	1619 (11.10)	1400 (9.78)
Asymptomatic				
≤70 mg/dL (3.9 mmol/L)	251 (83.4)	227 (76.7)	3671 (25.16)	3834 (26.80)
<54 mg/dL (3.0 mmol/L)	125 (41.5)	117 (39.5)	592 (4.06)	655 (4.58)

No. of patients (%), number and percentage of patients with at least one treatment-emergent hypoglycemia.
Rate per patient-year, number of episodes per patient-years of exposure.

TABLE 4. ADVERSE EVENTS DURING THE 26-WEEK TREATMENT PERIOD IN THE OVERALL STUDY POPULATION AND PATIENTS 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	156 (51.8)	146 (49.3)	120 (48.0)	115 (46.6)
Treatment-emergent SAEs	25 (8.3)	18 (6.1)	17 (6.8)	12 (4.9)
TEAEs leading to permanent treatment discontinuation	5 (1.7)	3 (1.0)	5 (2.0)	1 (0.4)
TEAEs leading to death	0	2 (0.7)	0	0
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	11 (3.7)	11 (3.7)	10 (4.0)	7 (2.8)
Adjudicated as allergic reaction	5 (1.7)	8 (2.7)	5 (2.0)	5 (2.0)

Data shown as number of patients (%).
SAE, serious adverse event; TEAE, treatment-emergent adverse event; T1D, type 1 diabetes.

similar in the SAR-Asp group and NN-Asp group (72.96 vs. 69.31). Severe hypoglycemia was reported by a small and similar number of patients (SAR-Asp 4.0%; NN-Asp 3.4%). All categories of hypoglycemia events were reported by a similar proportion of patients in each treatment group (Table 3 and Supplementary Fig. S4).

Both insulin aspart products were well tolerated (Table 4). TEAEs were reported in 156 of 301 patients (51.8%) fol-

lowing administration of SAR-Asp and in 146 of 296 patients (49.3%) following administration of NN-Asp. They were mainly of mild-to-moderate intensity with the most commonly reported TEAE being upper respiratory tract infection in both treatment groups. There were two deaths during the 6-month study period in patients receiving NN-Asp, one due to multiorgan failure (73-year-old female with T2D who died at home while on study treatment) and the second due to

TABLE 5. ANTI-INSULIN ASPART ANTIBODY RESPONSE FROM BASELINE TO WEEK 26 IN THE OVERALL STUDY POPULATION AND BY TYPE OF DIABETES (ANTI-INSULIN ASPART ANTIBODY POPULATION)

	Overall population		T1D		T2D	
	SAR-Asp (N = 296)	NN-Asp (N = 292)	SAR-Asp (N = 247)	NN-Asp (N = 243)	SAR-Asp (N = 49)	NN-Asp (N = 49)
Patients with AIA positive at baseline, n/N (%)	96/272 (35.3)	98/267 (36.7)	83/227 (36.6)	85/223 (38.1)	13/45 (28.9)	13/44 (29.5)
Patients with ≥4-fold increase in titer, n/N (%)[a]	4/96 (4.2)	5/98 (5.1)	3/83 (3.6)	5/85 (5.9)	1/13 (7.7)	0/13
Patients with AIA negative or missing at baseline, n/N (%)	200/296 (67.6)	194/292 (66.4)	164/247 (66.4)	158/243 (65.0)	36/49 (73.5)	36/49 (73.5)
Patients newly positive postbaseline[b]	46/200 (23.0)	55/194 (28.4)	40/164 (24.4)	51/158 (32.3)	6/36 (16.7)	4/36 (11.1)
Patients with at least one positive AIA sample, n/N (%)[c]	142/296 (48.0)	153/292 (52.4)	123/247 (49.8)	136/243 (56.0)	19/49 (38.8)	17/49 (34.7)
Patients with treatment-emergent AIAs, n/N (%)[d]	50/296 (16.9)	60/292 (20.5)	43/247 (17.4)	56/243 (23.0)	7/49 (14.3)	4/49 (8.2)
Patients without treatment-emergent AIAs	242/296 (81.8)	232/292 (79.5)	202/247 (81.8)	187/243 (77.0)	40/49 (81.6)	45/49 (91.8)
Inconclusive patients	4/296 (1.4)	0/292	2/247 (0.8)	0/243	2/49 (4.1)	0/49
Patients AIA positive at week 26, n/N (%)	95/271 (35.1)	104/264 (39.4)	83/228 (36.4)	91/221 (41.2)	12/43 (27.9)	13/43 (30.2)

[a]Patients with treatment boosted AIA.
[b]Patients with treatment induced AIA.
[c]Prevalence: patients with at least one positive AIA sample at baseline or postbaseline.
[d]Incidence: patients with newly positive AIA postbaseline (treatment induced) or with ≥4-fold increase in titer (treatment boosted) (i.e., patients with treatment-emergent AIAs).
AIA, anti-insulin aspart antibody.

hypovolemic shock secondary to myocardial infarction and gastrointestinal bleeding (68-year-old male with T2D who died in hospital in the post-treatment period). Both were not considered to be related to study medication. Eight patients experienced a TEAE that led to study discontinuation, five patients in the SAR-Asp and three patients in the NN-Asp group. Injection site reactions were reported by two patients (0.7%) following administration of SAR-Asp and four patients (1.4%) following NN-Asp. Neither event was considered as related to SAR-Asp, while in three patients the events were considered as related to NN-Asp. The safety results observed in patients with T1D during the main 6-month on-treatment period were consistent with those obtained on the overall population (Table 4).

A low number of patients in both treatment groups reported hypersensitivity reactions (11 patients [3.7%] in each group) (Table 4). A total of 27 potential hypersensitivity reactions reported by 24 patients in either treatment group were adjudicated by the ARAC. Of these, five patients with six events in the SAR-Asp group and eight patients with eight events in the NN-Asp group were adjudicated as allergic reactions by the ARAC; two events (urticaria, one in each treatment group) were considered as related to study medication and led to permanent treatment discontinuation.

Immunogenicity

The percentage of patients who were positive for AIAs at baseline (SAR-Asp: 35.3%; NN-Asp: 36.7%) was similar between groups (Table 5). Similarly, the AIA incidence, corresponding to the proportion of the study population found to have seroconverted or boosted preexisting AIA during the main 6-month treatment period (treatment-emergent AIAs), was similar in both groups (SAR-Asp: 16.9%; NN-Asp: 20.5%), with a risk difference between SAR-Asp and NN-Asp of −3.5% (90% CI: −8.75 to 1.73). Over the 6-month on-treatment period, the percentage of patients positive for AIAs remained relatively stable in both treatment groups: 35.1% of SAR-Asp patients and 39.4% of NN-Asp patients were AIA positive at week 26 (Supplementary Fig. S5). The prevalence, corresponding to the percentage of patients with detectable AIAs of at least one time point during the study, was also similar with SAR-Asp and NN-Asp (48.0% and 52.4%, respectively). Cross-reactivity with human insulin was present in the majority of patients (range 83.9%–98.1%) and was consistent between treatment groups. Data observed in patients with T1D and T2D during the 6-month on-treatment period, regarding AIA response, were generally similar to those obtained for the overall population (Table 5) with numerical differences in the T2D population resulting from the small number of included patients.

Discussion

The use of biosimilar or follow-on insulin biologics for people with diabetes has the potential to reduce treatment costs as they are priced lower than the originator products thereby allowing greater access of insulin treatment for people with diabetes.[19] Recently, the first rapid-acting insulin biosimilar/follow-on product SAR342434 was approved in Europe (Insulin Lispro Sanofi®) and in the United States (Admelog®) and subsequently in other countries for the same indications as the originator product Humalog®.[20,21] SAR-Asp is the second rapid-acting insulin biosimilar/follow-on biologic to enter clinical development, having the same amino acid sequence as NN-Asp.

The current study in patients with T1D and T2D showed that SAR-Asp, when used in combination with basal Gla-100, was noninferior to the commercially available insulin aspart formulations NN-Asp, as measured by change in HbA1c from baseline to week 26. Both treatment groups improved glycemic control with similar lowering of glucose levels from baseline to 26 weeks, along with similar changes in insulin dose and body weight. Similar proportions of patients treated with SAR-Asp and NN-Asp achieved an HbA1c target of <7%, and SMBG profiles were similar in each treatment group. The incidence and rate of hypoglycemia were similar between treatment groups for all of the recorded categories.

SAR-Asp was well tolerated in both patients with T1D and T2D for up to 26 weeks treatment. There were no significant differences in safety measures between the treatment groups, including AEs and SAEs; the AE profile of SAR-Asp was also consistent with the AE profile reported in studies assessing the efficacy and safety of NN-Asp in adults with T1D and T2D.[1,2] Allergic reactions and injection site AEs were also similar between treatment groups.

The immunogenic potential of SAR-Asp, a key secondary end point of the study, was assessed by determination of antibody formation to SAR-Asp or NN-Asp. Antibody titers and cross-reactivity to human insulin were determined. The potential impact of AIA on safety, particularly as related to local (injection site reactions) and systemic (hypersensitivity) allergic reactions, was evaluated. Evaluation of immunogenicity was purely descriptive with no formal testing, in accordance with Health Authority recommendations.[4,5] In view of the underlying autoimmune disorder, patients with T1D were considered the more sensitive population to evaluate potential differences in the immune response of SAR-Asp compared with NN-Asp. As such, a larger number of patients with T1D were included in the study. However, as the T2D population represents the vast majority of patients with diabetes, the generation of data in both diabetes populations was considered appropriate to evaluate outcomes in a wide group of the diabetic population as possible. Separate immunogenicity analyses for the two diabetic populations showed a similar AIA response to SAR-Asp and NN-Asp during the main 6-month treatment period for treatment-boosted and treatment-induced AIAs.

During the study, a proportion of patients enrolled in the trial (226/335 in the United States, 197/197 in Europe, 0/65 in Japan) were inadvertently provided with defective test strips for SMPG measurements (duration 3–7 months) that did not meet the minimum blood glucose accuracy criteria required by the International Organization for Standardization (ISO) standards.[22,23] This resulted in falsely elevated blood glucose readings with the defective test strips compared with non-defective test strips (mean increase of 0.1%–14.8% depending on the lots used). The glucometer and control solutions were not affected. Exploratory analyses showed no impact of the transient use of these defective test strips on insulin doses and efficacy end points and provided reassurance that use of the defective test strips did not impact the between-group efficacy comparisons and conclusions. The rate of any hypoglycemia was higher with the use of defective test strips (79.12 and 74.58 events per patient-year for SAR-Asp and

NN-Asp, respectively) than with the use of nondefective test strips (68.30 and 65.33 events per patient-year for SAR-Asp and NN-Asp, respectively), with small numerical differences between the two treatment groups for some categories of hypoglycemia. However, no consistent trend in favor of one treatment group or the other was observed, and the rate of severe hypoglycemia remained low and similar with the defective and nondefective test strips. In addition, the use of defective test strips did not lead to an increased incidence of serious TEAEs related to hypoglycemia or medication errors, confirming the absence of an increased medical risk with use of the defective test strips.

The open-label design is a potential limitation of this study. However, patient blinding was not possible as SAR-Asp was administered using a prefilled disposable pen that was different from the approved prefilled disposable pen used for NN-Asp. To partially overcome this limitation, assessments were based on objectively collected data that were analyzed by central laboratories who were blinded to the study treatment. Second, most included patients were White/Caucasian and from Europe or the United States, and so caution should be adopted when extending the results to other ethnic populations. However, there was no evidence of differences in the study results by different baseline demographic characteristics.

Conclusion

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 formulations in people with diabetes treated for 26 weeks.

Author Disclosure Statement

Funding Information

Supplementary Material

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

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