



# Biosimilar Insulin Aspart Premix SAR341402 Mix 70/30 Versus Originator Insulin Aspart Mix 70/30 (NovoMix 30) in People with Diabetes: A 26-Week, Randomized, Open-Label Trial (GEMELLIM)

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Received: January 14, 2022 / Accepted: March 17, 2022 / Published online: April 14, 2022  
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## ABSTRACT

**Introduction:** This study compared the efficacy, safety, and immunogenicity of biosimilar insulin aspart premix SAR341402 Mix 70/30 (SAR<sub>ASP</sub>-Mix) with European-approved insulin aspart mix 70/30 – NovoMix® 30 (NN-Mix) in people with type 1 (T1D) or type 2 diabetes (T2D).

**Methods:** This 26-week, open-label, phase 3 trial enrolled 402 people with T1D ( $n = 105$ ) or

T2D ( $n = 297$ ) previously treated with premix insulin, who were randomized (1:1) to SAR<sub>ASP</sub>-Mix ( $n = 204$ ) or NN-Mix ( $n = 198$ ).

**Results:** After 26 weeks, the least squares (LS) mean [median] change in HbA1c from baseline was similar in both treatment groups (SAR<sub>ASP</sub>-Mix – 0.55% [– 0.60%]; NN-Mix – 0.64% [– 0.60%]). The LS mean difference for SAR<sub>ASP</sub>-Mix versus NN-Mix was 0.08%, with the upper bound of the two-sided 95% confidence interval (– 0.139 to 0.303) slightly above the prespecified noninferiority margin of 0.3%. Noninferiority of SAR<sub>ASP</sub>-Mix over NN-Mix was not demonstrated in the primary intent-to-treat

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s13300-022-01255-7>.

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analysis, primarily because of one extreme outlying value impacted by the COVID-19 pandemic in the SAR<sub>ASP</sub>-Mix group. Noninferiority was achieved in all secondary analyses, including prespecified per-protocol supportive and COVID-19 sensitivity analyses, as well as post hoc sensitivity analyses. Other efficacy endpoints, insulin dosages, anti-insulin aspart antibody response, hypoglycemia, and adverse events were similar between groups.

**Conclusions:** The totality of evidence indicates that SAR<sub>ASP</sub>-Mix provides effective glycemic control with a similar safety and immunogenicity profile to NN-Mix in people with diabetes treated for 26 weeks.

**Trial Registration:** EudraCT number 2017-000092-84.

**Keywords:** Biosimilar; GEMELLI M; Insulin aspart mix; Premix; SAR341402

## Key Summary Points

Why carry out this study?

Premixed insulins, delivering both rapid and longer-acting insulin in a single convenient injection, remain widely used in different regions of the world.

The use of biosimilar insulins for people with diabetes has the potential to reduce treatment costs as they are usually priced lower than the originator products, thereby allowing greater access of insulin treatment for people with diabetes.

SAR341402 Mix 70/30 (SAR<sub>ASP</sub>-Mix) is the first biosimilar premixed suspension of insulin aspart, containing 70% intermediate-acting protamine-crystallized SAR-Asp and 30% rapid-acting SAR-Asp solution.

This phase 3 clinical trial compared the efficacy, safety, and immunogenicity of SAR<sub>ASP</sub>-Mix and the reference product NovoMix® 30 (NN-Mix) in adults with diabetes.

What was learned from the study?

After 26 weeks of treatment, SAR<sub>ASP</sub>-Mix and NN-Mix provided effective and comparable glycemic control.

Noninferiority of SAR<sub>ASP</sub>-Mix over NN-Mix was not demonstrated in the primary intent-to-treat efficacy analysis, primarily because of one extreme outlying value impacted by the COVID-19 pandemic in the SAR<sub>ASP</sub>-Mix group, but was achieved in all prespecified and post hoc secondary analyses.

Other efficacy outcomes, insulin dosages, anti-insulin aspart antibody response, hypoglycemia, and adverse events were similar between groups.

Data from this study suggest SAR<sub>ASP</sub>-Mix is a well-tolerated and effective biosimilar to NN-Mix for the treatment of people with diabetes.

## INTRODUCTION

Premixed insulin aspart products, including US-approved NovoLog® Mix 70/30 [1] and EU-approved NovoMix® 30 [2] (Novo Nordisk), are approved for treatment of diabetes mellitus in adults, adolescents, and children aged 10 years or older in many countries, with a well-characterized pharmacological, efficacy, and safety profile [3, 4].

People with diabetes who are unable to cope with the demands of an intensive basal-bolus insulin regimen [5], consisting of multiple daily injection (MDI) therapy of prandial rapid-acting insulin in combination with a long-acting basal insulin, may instead choose a simpler biphasic premixed regimen, an attractive option of delivering both rapid- and longer-acting insulin in a single convenient injection. Two doses of premixed insulin daily, theoretically, address fasting, nocturnal, and prandial aspects of glucose management [6]. Premixed insulins remain widely used in different regions of the world [7, 8]. Although premixed insulins are available in various basal/bolus ratios, the 70/30 intermediate-acting/rapid-acting insulin ratio remains the most common one used in clinical practice [9].

The introduction of biosimilar insulin formulations has the potential to reduce drug treatment costs as they are priced lower than the originator products, making them affordable while conferring comparable efficacy and safety, thereby facilitating greater access to insulin treatment [10–12]. One-quarter of patients with diabetes cite the high cost of insulin as a reason for underuse [13]. In 2021, the World Health Organization prioritized access to insulin analogues and their biosimilars in their list of essential medicines, thereby increasing access to diabetes treatments by expanding the choice of treatment [14].

SAR341402 Mix 70/30, suspension for injection 100 U/mL (Sanofi, Paris, France) is a biosimilar insulin aspart premixed suspension (hereafter referred to as SAR<sub>ASP</sub>-Mix) [15]. The active ingredient is SAR341402 insulin aspart (SAR-Asp), a rapid-acting insulin analogue produced by recombinant DNA technology

[15, 16]. The SAR<sub>ASP</sub>-Mix suspension contains 70% intermediate-acting protamine-crystallized SAR-Asp and 30% rapid-acting SAR-Asp solution, thereby providing basal and prandial insulin coverage in a single injection [1, 2, 15].

SAR<sub>ASP</sub>-Mix is being developed as a biosimilar to NovoMix 30 (hereafter referred to as NN-Mix). A euglycemic clamp study in subjects with type 1 diabetes (T1D) demonstrated similar pharmacokinetic exposure for SAR<sub>ASP</sub>-Mix versus the reference therapy (NN-Mix and NovoLog Mix 70/30), and a distinct exposure profile of SAR<sub>ASP</sub>-Mix compared with the rapid-acting solution SAR-Asp [17]. Pharmacodynamic results were in support of the pharmacokinetic findings. Here we report the results of a phase 3 registration clinical trial (GEMELLI M) comparing the efficacy, safety, and immunogenicity of SAR<sub>ASP</sub>-Mix and the reference product NN-Mix in people with T1D or type 2 diabetes (T2D).

## METHODS

### Trial Design

Fifty-four active sites in five countries (India, the Philippines, Poland, Russia, and Ukraine) participated in this 26-week, open-label, randomized, active-controlled, parallel-group, phase 3 trial (EudraCT number 2017-000092-84) in approximately 400 participants. The trial was initiated in July 2019. It comprised a 2-week screening period, a 26-week efficacy and safety treatment period, and a 2-day post-treatment follow-up period (Electronic Supplementary Material [ESM] Fig. S1). GEMELLI M is registered with European Union Clinical Trials Register (EudraCT number 2017-000092-84) and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki of 1964 and its later amendments. The protocol was approved by an independent ethics committee or institutional review board for each center except in Poland where approval was by a national ethics committee (Komisja Bioetyczna przy Okregowej, Lublin); written informed consent was obtained from each patient before any trial-related activities.

During the trial, the protocol was amended to include an exploratory pharmacokinetic substudy in a subset of approximately 14 additional participants from India with T2D. Results of this substudy will be reported in a separate article.

The trial was ongoing when the coronavirus disease 2019 (COVID-19) pandemic occurred in early 2020. In March 2020, the sponsor implemented contingency measures, as per US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance [18, 19], to prioritize participants' safety and to ensure adequate trial conduct and oversight during this period. The impact of COVID-19 on the overall trial design, duration, and planned assessments are detailed in the ESM Appendix. The trial was completed in August 2020.

## Participants

Inclusion criteria were a diagnosis of T1D or T2D at least 12 months before screening, age at least 18 years, a body mass index (BMI) at most 35 kg/m<sup>2</sup> in participants with T1D and at most 40 kg/m<sup>2</sup> in participants with T2D, a glycated hemoglobin (HbA1c) level of 10% (86 mmol/mol) or lower at screening, and previous treatment with premix insulin (NovoMix 30, Humalog Mix 25®, or Liprolog Mix 25®) at least twice daily for at least 3 months before the screening visit. At the discretion of the investigator, participants with a measured HbA1c in the range of 9% (at least 75 mmol/mol) to 10% (at most 86 mmol/mol) could be included if they were not candidates for an MDI treatment regimen. Key exclusion criteria included use of injectable glucose-lowering treatments other than premix insulin analogues or use of an insulin pump in last 3 months before screening. Participants with T2D not on a stable dose of oral antidiabetic drugs in the last 3 months before screening were excluded. Oral antidiabetic drugs were to be continued at a stable dose during the trial, except sulfonylureas or glinides that were to be discontinued at randomization.

## Trial Procedures and Assessments

Eligible participants were randomized 1:1 to either SAR<sub>ASP</sub>-Mix or NN-Mix, stratified by geographical region (India, non-India), type of diabetes (T1D, T2D), screening HbA1c (less than 8.0%, 8.0% or higher), and prior use of NN-Mix (Yes, No). Randomization was performed centrally using an interactive response technology system. The recommended starting dose of SAR<sub>ASP</sub>-Mix or NN-Mix was a unit-to-unit (1:1) conversion from the prestudy insulin dose used at the end of the screening period, with the same frequency of administration. The allocated treatment was administered at least twice daily during the 26-week treatment period via prefilled disposable pen devices (SoloSTAR® for SAR<sub>ASP</sub>-Mix, FlexPen® for NN-Mix). Adjustments in the SAR<sub>ASP</sub>-Mix or NN-Mix dose were based on self-monitored plasma glucose (SMPG) measurements with insulin doses titrated to achieve protocol-specified glycemic targets. Further details on study procedures, glycemic targets and assessments are provided in the ESM Appendix.

## Objectives and Endpoints

The primary objective of this study was to demonstrate non-inferiority of SAR<sub>ASP</sub>-Mix in comparison to NN-Mix on HbA1c change from baseline to week 26 in participants with T1D or T2D. The secondary objectives were the comparison of the immunogenicity and safety of SAR<sub>ASP</sub>-Mix and NN-Mix during the 26-week treatment period. Tertiary exploratory objectives included the effect of SAR<sub>ASP</sub>-Mix and NN-Mix on glycemic control and insulin dose, additional immunogenicity parameters, and the clinical effects of immunogenicity parameters on glycemic control, insulin dose, and safety outcomes.

ESM Table S1 provides details of the trial endpoints. The primary efficacy endpoint was the change from baseline to week 26 in HbA1c. Tertiary exploratory efficacy endpoints included the percentage of participants with HbA1c less than 7.0% (less than 53 mmol/mol) at week 26 and change from baseline to week 26 in fasting

plasma glucose (FPG), in mean 24-h plasma concentration and postprandial plasma glucose (PPG) excursions (2-h PPG minus preprandial plasma glucose) at breakfast, lunch, and dinner based on 7-point SMPG profiles, and in 7-point SMPG profiles (See ESM Appendix for further details).

The safety endpoints (secondary endpoints) included hypoglycemic events (classified according to American Diabetes Association categories [20–22]), adverse events (AEs) recorded throughout the study, serious AEs (SAEs), and AEs requiring special monitoring (injection site reactions, hypersensitivity reactions). Vital signs, body weight, and laboratory parameters were also assessed. Treatment-emergent AEs (TEAEs) were defined as AEs that developed, worsened, or became serious during the 26-week on-treatment period, defined from the first dose of study medication up to 2 days after the last dose of study medication.

Immunogenicity was assessed in terms of anti-insulin aspart antibody (AIA) status (positive/negative), titers, cross reactivity to human insulin and neutralizing capacity of confirmed positive AIAs during the study. The number of participants with treatment-emergent AIAs (defined as those with newly positive post-baseline [treatment-induced] or developing a fourfold or larger increase in titer compared with baseline [treatment-boosted] during the 26-week treatment period) was a secondary endpoint of the study. All other immunogenicity outcomes were tertiary exploratory endpoints, defined according to recommendations for reporting of clinical immunogenicity (See ESM Appendix for definitions) [23, 24].

## Data Analysis and Statistics

The primary efficacy endpoint was analyzed in the intent-to-treat (ITT) population (all randomized participants) using all HbA1c values regardless of adherence to treatment during the 26-week period (ITT estimand with treatment policy strategy [25]). Missing data were imputed by a return-to-baseline multiple imputation approach (missing values at week 26 imputed as equal to participants baseline HbA1c value plus

an error). This was followed by an analysis of covariance (ANCOVA) model with fixed-effect term for treatment group (SAR<sub>Asp</sub>-Mix, NN-Mix) and the randomization strata (geographic region [Indian, non-Indian], type of diabetes, prior use of NN-Mix) and baseline HbA1c value as fixed covariate. Results were combined using Rubin's formula [26]. The adjusted least square (LS) mean change from baseline to week 26 in HbA1c for each treatment group was estimated as well as the between-group difference and the corresponding 95% confidence interval (CI). Noninferiority was demonstrated if the upper bound of the two-sided 95% CI of the difference between SAR<sub>Asp</sub>-Mix and NN-Mix in the ITT population was less than 0.3%. If noninferiority was demonstrated, a secondary analysis using a hierarchical step-down testing procedure, tested the inverse noninferiority of NN-Mix over SAR<sub>Asp</sub>-Mix.

Secondary analyses for the primary efficacy endpoint were conducted to assess the robustness of the results, including one sensitivity analysis that assessed the impact of the COVID-19 pandemic and was prespecified before database lock. In this analysis, HbA1c values potentially impacted by COVID-19 were treated as missing values with all missing data due to COVID-19 imputed using a missing at random [MAR] approach (see ESM Appendix for further details). A second prespecified supportive analysis using the per-protocol (PP) population excluded those participants that could significantly impact the analysis, including those with major or critical protocol deviations related to COVID-19 (see ESM Appendix). In addition, a further post hoc sensitivity analysis was performed to evaluate the impact of a single participant with extreme outlying value on the primary ITT efficacy analysis (see details below).

Analyses of safety and immunogenicity data were descriptive with no formal statistical testing. Hypoglycemia and adverse events were described on the safety population (all randomized participants who received at least one dose of study medication). Statistical analyses were performed using SAS®, Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC). The sample-size calculation and further details on statistical methods for the primary, secondary,



and tertiary/exploratory endpoints are provided in the ESM Appendix. Data is reported for the overall study population and in most analyses by the randomization stratum of diabetes type (T1D, T2D).

## RESULTS

### Study Population

A total of 509 participants were screened, of whom 402 were randomized and 400 received at least one dose of study medication (ESM Fig. S2). The ITT population ( $n = 402$ ) included 105 participants with T1D and 297 with T2D. Of the treated participants, 200/203 (98.0%) in the SAR<sub>ASP</sub>-Mix group and 191/197 (96.5%) in the NN-Mix group completed the 26-week treatment period. Reasons for discontinuation were similar between SAR<sub>ASP</sub>-Mix and NN-Mix (predominantly patient decision or consent withdrawal).

Demographics and baseline characteristics were similar in the two treatment groups for the overall population (Table 1) and by type of diabetes (ESM Table S2). Participants had a mean age of 53.1 years (34.7 years in T1D, 59.6 years in T2D), were predominantly Asian (60.9%), and had a mean duration of diabetes of 13.2 years. The mean BMI at baseline was 26.8 kg/m<sup>2</sup> (23.2 kg/m<sup>2</sup> in T1D, 28.0 kg/m<sup>2</sup> in T2D). NN-Mix was used by approximately 79% of participants before trial entry.

### Glycemic Control

In the ITT population, HbA1c decreased similarly in both groups from baseline to week 26, with a LS mean (median) change of  $-0.55\%$  ( $-0.60\%$ ) in the SAR<sub>ASP</sub>-Mix group and  $-0.64\%$  ( $-0.60\%$ ) in the NN-Mix group (Table 2, Fig. 1a). The LS mean difference of the change from baseline to week 26 in HbA1c for SAR<sub>ASP</sub>-Mix minus NN-Mix was 0.08% (95% CI  $-0.139$  to 0.303). As the upper bound of the two-sided 95% CI was slightly above the prespecified margin of 0.3%, noninferiority of SAR<sub>ASP</sub>-Mix over NN-Mix was not demonstrated

in the ITT population. This result was primarily driven by one extreme outlying value in a single participant in the SAR<sub>ASP</sub>-Mix group who had an increase in HbA1c from baseline to week 26 of 5.9% (increase from 7.1% to 13.0%), due to a major impact of COVID-19 on this individual in the latter part of the trial (week 26 visit delayed by more than 8 weeks and missed insulin doses). See participant narrative in ESM Appendix for further details. Since noninferiority of SAR<sub>ASP</sub>-Mix over NN-Mix was not demonstrated, the inverse noninferiority (of NN-Mix over SAR<sub>ASP</sub>-Mix) was not formally tested in the ITT population.

In the supportive analysis using the PP population (which excluded the participant with an extreme outlying HbA1c increase) and a prespecified sensitivity analysis assessing the impact of COVID-19 in the ITT population (in which the aforementioned participant was included but the extreme outlying value was considered as missing), noninferiority of SAR<sub>ASP</sub>-Mix over NN-Mix on change from baseline to week 26 in HbA1c was demonstrated (Table 2). In a further post hoc sensitivity analysis that excluded this participant with an extreme outlying HbA1c increase from the ITT population, noninferiority of SAR<sub>ASP</sub>-Mix over NN-Mix on change from baseline to week 26 in HbA1c was also demonstrated (Table 2). Inverse noninferiority of NN-Mix over SAR<sub>ASP</sub>-Mix was demonstrated in all secondary analyses.

Between treatment differences in the week 26 HbA1c responses were generally consistent across subgroups of study participants, including randomization strata of type of diabetes (T1D, T2D), screening HbA1c categories (less than 8%, 8% or higher), prior use of NN-Mix (Yes, No), and geographical region (Indian, non-Indian) (ESM Fig. S3). There was no evidence of heterogeneity of treatment effect across any of the subgroups (all  $p$  values of treatment-by-subgroup interaction above 0.10). Similar proportions of study participants achieved target HbA1c values of less than 7.0% at week 26 (SAR<sub>ASP</sub>-Mix 28.4%; NN-Mix 31.3%).

In the T1D subgroup, the LS mean decrease from baseline to week 26 in HbA1c was numerically higher in the NN-Mix group ( $-0.65$ ) compared to the SAR<sub>ASP</sub>-Mix group

**Table 1** Participant demographics and baseline characteristics (randomized population)

Characteristic	SAR <sub>ASP</sub> -Mix (N = 204)	NN-Mix (N = 198)
Age, years	53.2 ± 14.9	53.0 ± 15.5
Male, n (%)	113 (55.4)	89 (44.9)
Race, n (%)		
White/Caucasian	76 (37.3)	81 (40.9)
Asian	128 (62.7)	117 (59.1)
Countries, n (%)		
India	107 (52.5)	103 (52.0)
Philippines	21 (10.3)	14 (7.1)
Poland	22 (10.8)	28 (14.1)
Russian Federation	14 (6.9)	18 (9.1)
Ukraine	40 (19.6)	35 (17.7)
Body weight, kg	71.0 ± 13.1	71.5 ± 14.6
Body mass index, kg/m <sup>2</sup>	26.6 ± 4.7	26.9 ± 4.7
Diabetes type, n (%)		
T1D	54 (26.5)	51 (25.8)
T2D	150 (73.5)	147 (74.2)
Duration of diabetes, years	13.5 ± 8.4	12.9 ± 8.4
Previous premix insulin <sup>a</sup> , n (%)		
NovoMix 30	158 (77.5)	158 (79.8)
Humalog Mix 25/Liprolog Mix 25	46 (22.5)	38 (19.2)
Other	0	2 (1.0) <sup>b</sup>
Baseline HbA1c, %	8.16 ± 1.05	8.28 ± 1.09
Screening HbA1c < 8.0%, n (%)	80 (39.2)	73 (36.9)
Screening HbA1c ≥ 8.0%, n (%)	124 (60.8)	125 (63.1)
Mean 24-h plasma glucose, mg/dL [mmol/L]	182.2 ± 44.4 [10.1 ± 2.5]	180.6 ± 47.5 [10.0 ± 2.6]

Data are n (%), means ± standard deviation (SD)

HbA1c glycated hemoglobin, T1D type 1 diabetes, T2D type 2 diabetes

<sup>a</sup>Previous premix insulin analogue treatment within 3 months before screening

<sup>b</sup>Eglucent Mix 25 and Mixtard 30/70

(− 0.38) (Fig. 1b). Interpretation of the results should consider the small sample size for the T1D population (SAR<sub>ASP</sub>-Mix: 54 participants; and NN-Mix: 51 participants). Of note, among the seven participants with the highest and

lowest changes in HbA1c observed at week 26, four participants had T1D: two participants in the SAR<sub>ASP</sub>-Mix group with high increases from baseline and two participants in the NN-Mix group with high decreases from baseline (ESM

**Table 2** Change from baseline to week 26 in HbA1c (%) in primary, sensitivity, and supportive analyses

	Primary analysis		Prespecified supportive analysis		Prespecified COVID-19 sensitivity analysis <sup>b</sup>		Post hoc sensitivity analysis	
	ITT population		PP population <sup>a</sup>		ITT population		ITT population excluding single outlier	
	SAR <sub>Asp</sub> -Mix (N = 204)	NN-Mix (N = 198)	SAR <sub>Asp</sub> -Mix (N = 162)	NN-Mix (N = 156)	SAR <sub>Asp</sub> -Mix (N = 204)	NN-Mix (N = 198)	SAR <sub>Asp</sub> -Mix (N = 203)	NN-Mix (N = 198)
Baseline [n]	8.16 ± 1.05 [204]	8.28 ± 1.09 [198]	8.17 ± 1.05 [162]	8.29 ± 1.11 [156]	8.16 ± 1.05 [204]	8.28 ± 1.09 [198]	8.16 ± 1.05 [203]	8.28 ± 1.09 [198]
Week 26 [n]	7.56 ± 1.20 [179]	7.55 ± 1.11 [178]						
LS mean (± SE) change from baseline [n]	-0.55 ± 0.08 [204] <sup>c</sup>	-0.64 ± 0.08 [198] <sup>c</sup>	-0.65 ± 0.07 [162] <sup>d</sup>	-0.72 ± 0.07 [156] <sup>d</sup>	-0.63 ± 0.07 [204] <sup>e</sup>	-0.68 ± 0.07 [198] <sup>e</sup>	-0.58 ± 0.08 [203] <sup>e</sup>	-0.64 ± 0.08 [198] <sup>e</sup>
LS mean (± SE) difference [95% CI]	0.08 ± 0.113 [-0.139 to 0.303] <sup>c</sup>		0.07 ± 0.102 [-0.131 to 0.269] <sup>d</sup>		0.05 ± 0.102 [-0.149 to 0.253] <sup>e</sup>		0.05 ± 0.108 [-0.158 to 0.266] <sup>e</sup>	
Noninferiority of SAR <sub>Asp</sub> -Mix vs. NN-Mix on change in HbA1c	Not demonstrated		Demonstrated		Demonstrated		Demonstrated	
Inverse noninferiority of NN-Mix vs. SAR <sub>Asp</sub> -Mix on change in HbA1c	Observed <sup>f</sup>		Demonstrated		Demonstrated		Demonstrated	

All data are mean ± SD unless stated otherwise

ITT intent-to-treat, LS least square, PP per protocol, SD standard deviation, SE standard error, T1D type 1 diabetes, T2D type 2 diabetes

<sup>a</sup>Excluding participants that could significantly impact the analysis, including those with major or critical protocol deviations related to COVID-19. The participant with an extreme outlying change in HbA1c was excluded since the week 26 visit was delayed by more than 8 weeks because of COVID-19

<sup>b</sup>HbA1c values potentially impacted by COVID-19 were treated as missing values. The participant with an extreme outlying change in HbA1c was included but the HbA1c value at week 26 was treated as missing (week 26 visit delayed by more than 8 weeks)

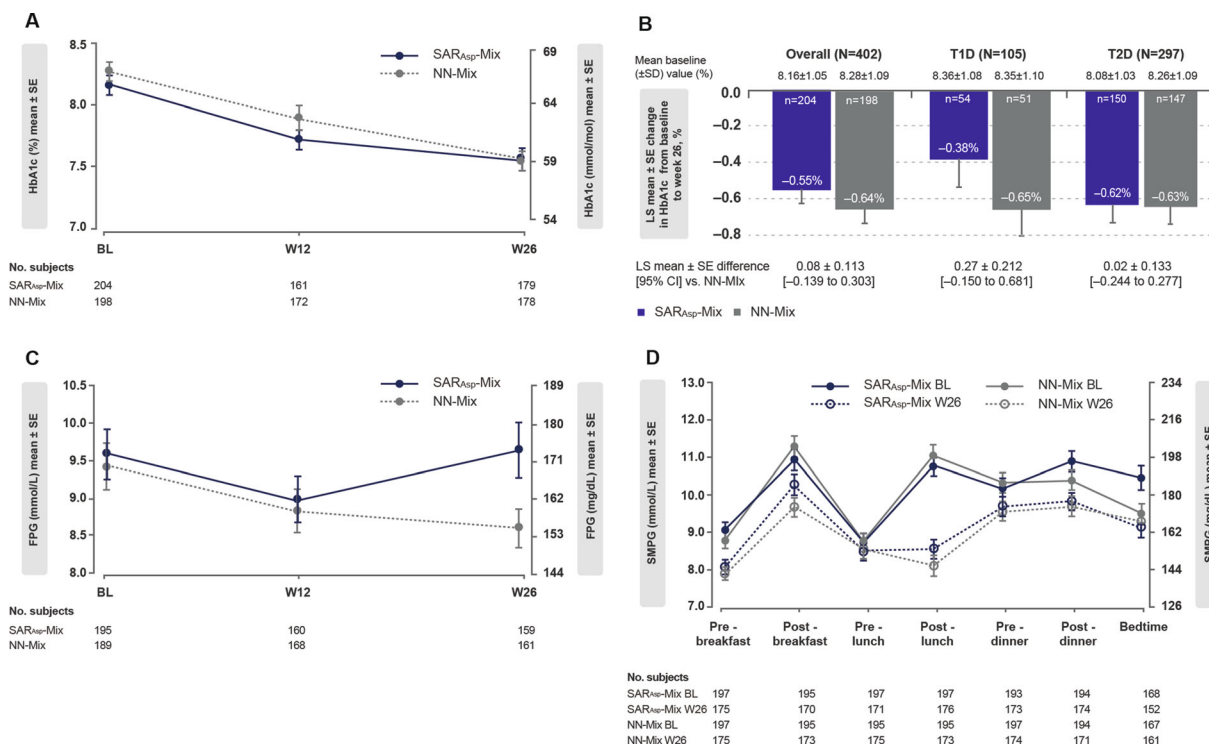
<sup>c</sup>Return-to-baseline multiple imputations of missing values at week 26 (10,000 imputations as participant's baseline plus an error) followed by ANCOVA with treatment group (SAR<sub>Asp</sub>-Mix, NN-Mix), the randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1D, T2D), and prior use of NN-Mix (Yes, No) as fixed categorical effects, as well as the continuous fixed covariate of baseline HbA1c value. Results were combined using Rubin's formula [26]

<sup>d</sup>ANCOVA with treatment group (SAR<sub>Asp</sub>-Mix, NN-Mix), the randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1D, T2D), and prior use of NN-Mix (Yes, No) as fixed categorical effects, as well as the continuous fixed covariate of baseline HbA1c value

<sup>e</sup>Return-to-baseline multiple imputations of missing values not due to COVID-19 and missing at random (MAR) imputations of missing values due to COVID-19 at week 26 (10,000 imputations with combined completed data sets) followed by ANCOVA described above in <sup>c</sup>. Results were combined using Rubin's formula [26]

<sup>f</sup>Not formally tested as the primary analysis failed





**Fig. 1** HbA1c (% and mmol/mol) by study visit (a), least squares mean change in HbA1c (%) from baseline to week 26 in overall study population and by subgroup of diabetes type (T1D or T2D) using ANCOVA analysis (with return to baseline multiple imputation). The statistical model used for the analysis is described in Table 2 for the overall study population and in ESM Fig. S3 by subgroup of diabetes type. *P* value for treatment-

by-subgroup interaction = 0.3199 (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 26 (d) in the ITT population. Data are mean ± standard error. ANCOVA analysis of covariance, BL baseline, FPG fasting plasma glucose, HbA1c glycosylated hemoglobin, ITT intent-to-treat, SMPG self-monitored plasma glucose, T1D type 1 diabetes, T2D type 2 diabetes, W week

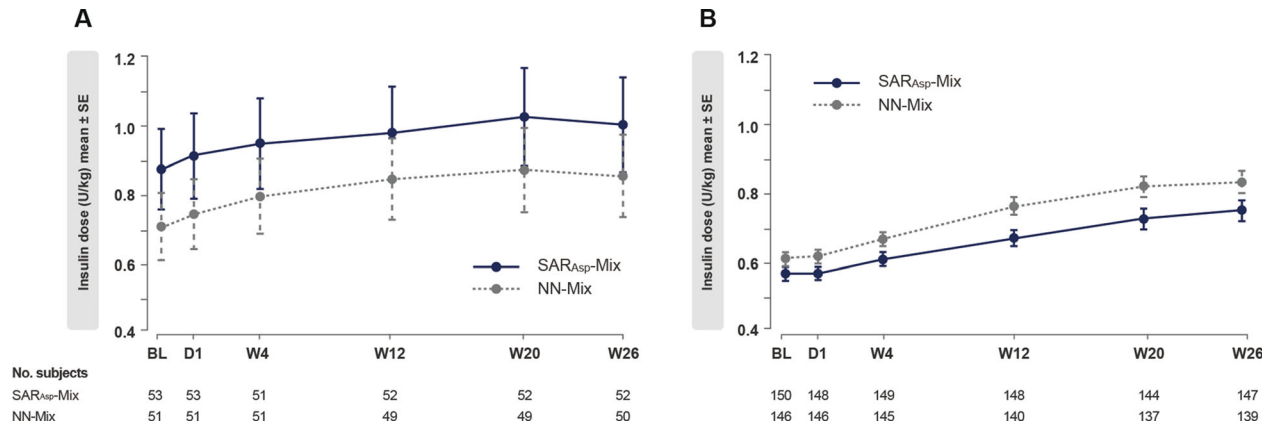
Fig. S4a). These four participants drive the numerical difference in this small subgroup. This is supported by the median changes from baseline to week 26 that are similar between groups (− 0.50 for SAR<sub>ASP</sub>-Mix, − 0.45 for NN-Mix) (ESM Fig. S4b). In the T2D subgroup with a large sample size (SAR<sub>ASP</sub>-Mix: 150 participants; and NN-Mix: 147 participants), the LS mean change from baseline to week 26 in HbA1c was similar with SAR<sub>ASP</sub>-Mix (− 0.62) and NN-Mix (− 0.63) (Fig. 1b). In the T2D subgroup, the median changes from baseline to week 26 were also similar between groups (− 0.70 for SAR<sub>ASP</sub>-Mix, − 0.65 for NN-Mix) (ESM Fig. S4b).

FPG decreased from baseline to week 26, with no clinically relevant difference between the two treatment groups (ESM Table S4, Fig. 1c). The increase in FPG between week 12

and week 26 in the SAR<sub>ASP</sub>-Mix group was due to a small number of participants with T1D and was not seen in individuals with T2D. The mean 7-point SMPG profiles in the two treatment groups improved at all time points from baseline to week 26 (Fig. 1d). On the basis of these profiles, there was no clinically meaningful difference between SAR<sub>ASP</sub>-Mix and NN-Mix in the change from baseline in mean 24-h SMPG or PPG excursions at breakfast, lunch, and dinner (ESM Table S4).

### Insulin Doses

Daily insulin doses increased similarly in both treatment groups over the 26-week on-treatment period in the overall population and by



**Fig. 2** Daily insulin doses (U/kg) by study visit during the on-treatment period in participants with T1D (**a**) and T2D (**b**) (safety population). Data are mean ± SE. Baseline insulin doses were defined as the median of daily doses available in the week prior to the first injection of study medication (corresponding to doses of the prestudy insulin). Insulin doses at day 1 were defined as the median

of daily doses available in the week after the first injection of study medication. For weeks 4, 12, 20, and 26, insulin dose values were reported as the median of daily doses available in the week prior to the study visit. *BL* baseline, *D* day, *SE* standard error, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *W* week

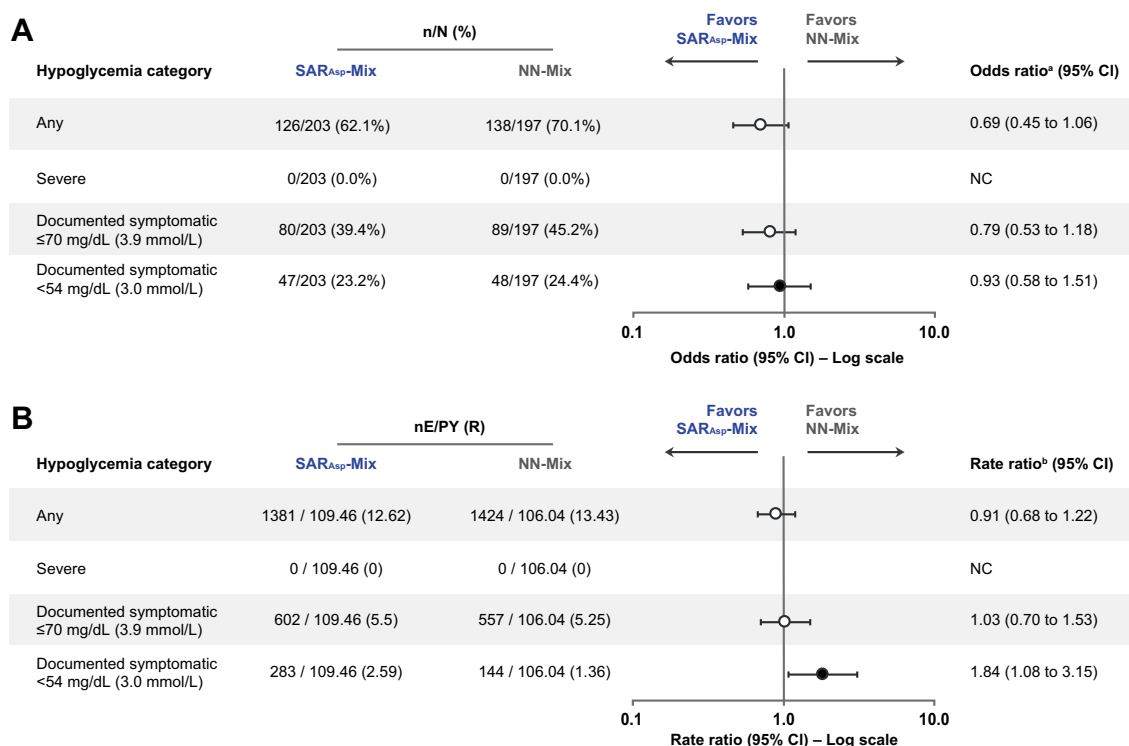
subgroup of diabetes type (T1D, T2D) (Fig. 2, ESM Table S3). Overall mean (SD) change from baseline to week 26 was 0.166 U/kg (0.298 U/kg) in the SAR<sub>ASP</sub>-Mix group and 0.213 U/kg (0.278 U/kg) in the NN-Mix group.

### Hypoglycemia

During the 26-week on-treatment period, 62.1% of participants in the SAR<sub>ASP</sub>-Mix group and 70.1% in the NN-Mix group reported at least one episode of hypoglycemia regardless of the category (Fig. 3, ESM Table S5). There were no reported episodes of severe hypoglycemia. No hypoglycemia event met the criteria for an SAE or led to permanent treatment discontinuation. As expected, more T1D participants reported hypoglycemic events compared to T2D participants (ESM Fig. S5a). Small numerical differences were seen for the categories of documented symptomatic and asymptomatic hypoglycemia with a glucose level of less than 54 mg/dL in people with T1D (higher incidence in the SAR<sub>ASP</sub>-Mix group), but a limited number of participants ( $N = 104$ ) was included in this subgroup and no consistent trend was observed by type of diabetes. The incidence of hypoglycemia by other predefined subgroups,

including race, age group, gender, baseline BMI, baseline renal function, screening HbA1c, prior use of NN-Mix, geographical region (Indian or non-Indian), and duration of diabetes, was generally consistent with the overall population, with no relevant difference between treatment groups (data not shown).

The number of hypoglycemia events and event rates per patient-year of exposure were similar between the two treatment groups for all categories, except for documented symptomatic hypoglycemia (glucose level less than 54 mg/dL), where the values were higher in the SAR<sub>ASP</sub>-Mix group (283 [2.59]) compared with the NN-Mix group (144 [1.36]) (Fig. 3, ESM Table S5, ESM Fig. S5b). This numerical difference between treatment groups was driven by six participants in the SAR<sub>ASP</sub>-Mix group (five with T1D and one with T2D) who reported at least 20 events each and accounted for 155/283 events in this group. Most of these events were induced by missed, delayed, or smaller meal and/or physical activity. Only one of these participants adjusted the insulin dose as requested following repeated episodes of hypoglycemia. Post hoc sensitivity analyses excluding these six participants show similar results between treatment groups (data not shown).



**Fig. 3** Forest plot of the odds ratio of participants experiencing at least one episode of hypoglycemia (a) and rate ratio (events per patient-year) (b) by category of hypoglycemia during the 26-week on-treatment period for the overall population (safety population). Odds ratio results (a) based on a logistic regression model with fixed-effect terms for treatment group and randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1D, T2D), screening HbA1c (less than 8%, 8% or higher), and prior use of NN-Mix (Yes, No). Rate ratio results (b) based on an overdispersed Poisson

regression model with fixed-effect terms as described above for odds ratio results. If the model did not converge (e.g., because of sparse data), randomization strata were removed from the model. <sup>a</sup>Odds ratio SAR<sub>Asp</sub>-Mix versus NN-Mix for participants with at least one hypoglycemic event. <sup>b</sup>Rate ratio SAR<sub>Asp</sub>-Mix versus NN-Mix for hypoglycemic events per patient-year. *HbA1c* glycated hemoglobin, *n* number of patients with at least one treatment-emergent event, % percentage of participants with at least one event, *nE* number of events, *PY* total patient-years, *R* rate per patient-year, *NC* model did not converge

**Adverse Events**

Both insulin aspart products were well tolerated (ESM Table S6). TEAEs were reported in 36 of 203 participants (17.7%) in the SAR<sub>Asp</sub>-Mix group and in 41 of 197 participants (20.8%) in the NN-Mix group. Most were mild to moderate in severity with nasopharyngitis and upper respiratory tract infection being the most reported TEAEs in each treatment group. The percentage of participants reporting serious TEAEs was similar in the two treatment groups. There were no TEAEs leading to permanent treatment discontinuation in either treatment group. One

death occurred during the 26-week on-treatment period in a participant in the NN-Mix group as a result of sudden cardiac death (50-year-old man with T2D who had a history of hypertension). A further post-treatment death was reported, also in the NN-Mix group. None of the events leading to death were considered related to study medication. One potential hypersensitivity reaction reported by a participant in the SAR<sub>Asp</sub>-Mix treatment group (pruritis) was adjudicated by an independent committee as not an allergic reaction. No injection site reactions were reported. The safety results in the subgroup by type of diabetes

(ESM Table S6) were consistent with those reported in the overall study population.

## Immunogenicity

### *AIA Response, Cross-Reactivity, and Titers*

Similar percentages of participants in both treatment groups were positive for AIAs at baseline (SAR<sub>ASP</sub>-Mix: 49.2%; NN-Mix: 54.0%) (Table 3). The percentage of participants with a treatment-emergent AIA response during the on-treatment period (incidence) was similar in both groups (SAR<sub>ASP</sub>-Mix: 33.2%; NN-Mix: 31.8%), with an absolute risk difference between SAR<sub>ASP</sub>-Mix and NN-Mix of 1.7% (90% CI – 5.90% to 9.22%). The percentage of participants positive for AIAs increased slightly and similarly in both treatment groups during the treatment period, with 62.9% of SAR<sub>ASP</sub>-Mix participants (70.0% with T1D, 60.3% with T2D) and 66.5% of NN-Mix participants (79.6% with T1D, 61.3% with T2D) being AIA positive at week 26 (ESM Fig. S6).

The AIA prevalence, corresponding to the percentage of participants with detectable AIAs at least at one timepoint during the study, was also similar with SAR<sub>ASP</sub>-Mix and NN-Mix (70.4% and 71.8%, respectively) (Table 3). Cross-reactivity with human insulin was present in most participants during the on-treatment period and was consistent between treatment groups (range 86.7–94.0% for SAR<sub>ASP</sub>-Mix, 90.4–94.1% for NN-Mix).

Results of AIA analyses in subgroups defined by baseline and screening factors were generally consistent with the results in the overall study population. Subgroup analysis by type of diabetes (Table 3) revealed similar AIA response between the two treatment groups following study drug administration.

Over the 26-week treatment period, AIA titers were comparable between treatment groups and remained relatively low and unchanged over time (Table 3). The median AIA titer was similar in both groups (16.0 [1/dil]) throughout the on-treatment period with a maximum interquartile range of 8.0–64.0 in the SAR<sub>ASP</sub>-Mix group and 8.0–32.0 in the NN-Mix

group (ESM Fig. S7). Additional details are shown in the ESM Appendix.

### *Influence of AIA on Efficacy and Safety Parameters and Insulin Doses*

The mean change from baseline to week 26 in HbA1c and insulin dose, as well as safety outcomes, including hypoglycemia, hypersensitivity reactions, injection site reactions, TEAEs, and serious TEAEs were comparable between treatment groups in both subgroups of participants with and without treatment-emergent AIA (ESM Table S7).

Among participants with treatment-emergent AIAs, 11 participants (9 in the SAR<sub>ASP</sub>-Mix group, 2 in the NN-Mix group) had relatively high AIA titers (i.e., maximal titers of at least 128 [1/dilution]). Scatterplots showed no relationship between the individual maximal AIA titers and the change in HbA1c, insulin dose, and rate per year of documented symptomatic hypoglycemia in the overall population (ESM Fig. S8).

### *Neutralizing Antibody (NAb) Response*

During the 26-week on-treatment period, the percentage of participants with treatment-emergent NABs was low and similar between the SAR<sub>ASP</sub>-Mix and the NN-Mix groups (8.0% [16/199] and 8.2% [16/195], respectively) (ESM Table S8). Additional details about the NAb response are shown in the ESM Appendix.

### **Impact of COVID-19 on the Study**

At the time of the COVID-19 pandemic disruption in early 2020, most participants were still under treatment, and all had reached week 4. The percentage of participants in which COVID-19 had a major impact on their participation in the study was 42.6% (87/204) in the SAR<sub>ASP</sub>-Mix group and 36.9% (73/198) in the NN-Mix group. Major protocol deviations related to assessments/procedures not performed were the main type of COVID-19 impact reported in both groups. However, they were within the recommended adjustments advised to the sites to accommodate for the pandemic. Thirty-five participants (16 in the SAR<sub>ASP</sub>-Mix

**Table 3** Anti-insulin aspart antibody (AIA) response from baseline to week 26 in the overall study population and by type of diabetes (AIA population)

	Overall population			T1D			T2D		
	SAR <sub>Asp</sub> -Mix (N = 199)	NN-Mix (N = 195)	SAR <sub>Asp</sub> -Mix (N = 51)	NN-Mix (N = 51)	SAR <sub>Asp</sub> -Mix (N = 148)	NN-Mix (N = 144)			
Participants with AIA positive at baseline, n/N (%)	91/185* (49.2)	95/176* (54.0)	26/51* (51.0)	31/46* (67.4)	65/134* (48.5)	64/130* (49.2)			
Median titer (Q1–Q3), 1/dilution	16.0 (8.0–32.0)	16.0 (8.0–32.0)	16.0 (8.0–32.0)	8.0 (8.0–32.0)	32.0 (8.0–48.0)	16.0 (8.0–32.0)			
Participants with ≥ fourfold increase in titer (treatment-boosted), n/N (%)	17/91 (18.7)	17/95 (17.9)	6/26 (23.1)	6/31 (19.4)	11/65 (16.9)	11/64 (17.2)			
Median peak titer (Q1–Q3), 1/dilution	64.0 (32.0–128.0)	32.0 (32.0–64.0)	32.0 (32.0–64.0)	32.0 (32.0–128.0)	128.0 (32.0–256.0)	32.0 (32.0–64.0)			
Transient AIA response, n (%)	1/17 (5.9)	5/17 (29.4)	1/6 (16.7)	2/6 (33.3)	0/11	3/11 (27.3)			
Persistent AIA response, n (%)	3/17 (17.6)	5/17 (29.4)	1/6 (16.7)	2/6 (33.3)	2/11 (18.2)	3/11 (27.3)			
Indeterminate AIA response, n (%)	13/17 (76.5)	7/17 (41.2)	4/6 (66.7)	2/6 (33.3)	9/11 (81.8)	5/11 (45.5)			
Participants with AIA negative or missing at baseline, n/N (%)	108/199 (54.3)	100/195 (51.3)	25/51 (49.0)	20/51 (39.2)	83/148 (56.1)	80/144 (55.6)			
Participants newly positive postbaseline (treatment-induced), n/N (%)	49/108 (45.4)	45/100 (45.0)	14/25 (56.0)	14/20 (70.0)	35/83 (42.2)	31/80 (38.8)			
Median peak titer (Q1–Q3), 1/dilution	8.0 (8.0–32.0)	8.0 (4.0–16.0)	8.0 (4.0–16.0)	8.0 (4.0–16.0)	16.0 (8.0–32.0)	8.0 (8.0–16.0)			
Transient AIA response, n (%)	8/49 (16.3)	2/45 (4.4)	2/14 (14.3)	0/14	6/35 (17.1)	2/31 (6.5)			
Persistent AIA response, n (%)	10/49 (20.4)	12/45 (26.7)	2/14 (14.3)	4/14 (28.6)	8/35 (22.9)	8/31 (25.8)			
Indeterminate AIA response, n (%)	31/49 (63.3)	31/45 (68.9)	10/14 (71.4)	10/14 (71.4)	21/35 (60.0)	21/31 (67.7)			
Participants with at least one positive AIA sample (prevalence) <sup>a</sup> , n/N (%)	140/199 (70.4)	140/195 (71.8)	40/51 (78.4)	45/51 (88.2)	100/148 (67.6)	95/144 (66.0)			
Participants with treatment-emergent AIAs (incidence) <sup>b</sup> , n/N (%)	66/199 (33.2)	62/195 (31.8)	20/51 (39.2)	20/51 (39.2)	46/148 (31.1)	42/144 (29.2)			



Table 3 continued

	Overall population		T1D		T2D	
	SAR <sub>Asp</sub> -Mix (N = 199)	NN-Mix (N = 195)	SAR <sub>Asp</sub> -Mix (N = 51)	NN-Mix (N = 51)	SAR <sub>Asp</sub> -Mix (N = 148)	NN-Mix (N = 144)
Participants without treatment-emergent AIAs, n/N (%)	131/199 (65.8)	132/195 (67.7)	30/51 (58.8)	30/51 (58.8)	101/148 (68.2)	102/144 (70.8)
Inconclusive participants, n/N (%)	2/199 (1.0)	1/195 (0.5)	1/51 (2.0)	1/51 (2.0)	1/148 (0.7)	0/144
Participants AIA positive at week 26, n/N (%)	117/186 (62.9)	115/173 (66.5)	35/50 (70.0)	39/49 (79.6)	82/136 (60.3)	76/124 (61.3)

Percentages are calculated using as denominator the number of participants: with positive or negative AIA sample at baseline (for participants with AIA positive at baseline), with AIA positive (resp. negative or missing) at baseline (for treatment-boostered [resp. treatment-induced] AIA), with treatment-boostered (or treatment-induced) AIA for transient/persistent/intermediate AIA response, in the AIA population for all other categories. For definition of transient, persistent, and intermediate responses, see Supplementary Appendix

AIA anti-insulin aspart antibody, T1D type 1 diabetes, T2D type 2 diabetes

<sup>a</sup>Participants with at least one positive AIA sample at baseline or postbaseline

<sup>b</sup>Participants with newly positive AIA postbaseline (treatment-induced) or with at least a fourfold increase in titer (treatment-boostered)

<sup>c</sup>Participants with missing AIA sample at baseline (14 in the SAR<sub>Asp</sub>-Mix group and 19 in the NN-Mix group for the overall population) are not included in the calculations

group and 19 in the NN-Mix group) had their week 26 visit delayed by more than 8 weeks. Overall, study treatment exposure was prolonged in COVID-19-impacted participants, with a maximum treatment duration of 319 days for SAR<sub>ASP</sub>-Mix and 274 days for NN-Mix, versus 239 days and 241 days, respectively, for non-impacted participants.

Only one participant in the NN-Mix group prematurely discontinued study medication as a result of COVID-19. Insulin doses in participants with or without trial impact due to COVID-19 were comparable throughout the 26-week on-treatment period and similar in both treatment groups (data not shown). For efficacy, the inability to reach noninferiority in the primary analysis on the ITT population was primarily driven by one participant in the SAR<sub>ASP</sub>-Mix group impacted by COVID-19 (described above). For safety, there was no evidence to suggest that trial disruption due to COVID-19 had an impact on TEAE reporting, including SAEs and deaths. No participant had any TEAEs related to COVID-19. AIA data indicates that COVID-19 had a limited impact on AIA response compared to the overall study population. For hypoglycemia, subgroups analyses suggest that trial impact due to COVID-19 resulted in an underreporting of hypoglycemia events. This occurred similarly in both treatment groups with no impact on the between-group comparisons and overall conclusions.

## DISCUSSION

The current trial showed that SAR<sub>ASP</sub>-Mix and NN-Mix both effectively improved glycemic control in participants with T1D and T2D with similar lowering of glucose levels from baseline to 26 weeks, along with similar changes in insulin dose. The noninferiority of SAR<sub>ASP</sub>-Mix compared with NN-Mix based on the primary analysis in the ITT population was not confirmed at week 26 at the 0.3% noninferiority margin (upper bound of 95% CI was 0.303%), primarily because of a single participant in the SAR<sub>ASP</sub>-Mix group who had an extreme outlying increase in HbA1c from baseline to week 26 of 5.9%, related to the COVID-19 impact in the

later part of the trial. The median change from baseline to week 26 was the same in both groups (− 0.60), supporting the conclusion that the negative result was related to few values and does not indicate a shift of the distribution between groups.

Noninferiority of SAR<sub>ASP</sub>-Mix compared with NN-Mix on the change from baseline to week 26 in HbA1c was achieved in the supportive PP population, and in all other secondary analyses in the ITT population, including the prespecified COVID-19 sensitivity analysis and a post hoc analysis excluding the participant with the extreme outlying value. Inverse noninferiority of NN-Mix over SAR<sub>ASP</sub>-Mix was also demonstrated for all sensitivity and supportive analyses. Taken together, the totality of evidence for glycemic control supports the noninferiority of SAR<sub>ASP</sub>-Mix to NN-Mix.

The mean change from baseline to week 26 in HbA1c, in the SAR<sub>ASP</sub>-Mix versus the NN-Mix group, was generally consistent across subgroups defined by screening and baseline covariates, with no relevant differences identified for type of diabetes (T1D, T2D), prior use of NN-Mix (Yes, No), and geographical region (Indian, non-Indian). No clinically relevant differences were observed between treatment groups for other efficacy endpoints (HbA1c responders less than 7%, FPG, and SMPG parameters) or change in daily insulin dose.

SAR<sub>ASP</sub>-Mix was well tolerated in both participants with T1D and T2D for up to 26 weeks treatment. Hypoglycemia incidence and event rates per patient-year of exposure were similar for SAR<sub>ASP</sub>-Mix and NN-Mix groups. The numerical difference observed in the event rate of documented symptomatic hypoglycemia (glucose level less than 54 mg/dL) was driven by a few participants (mainly with T1D), with events mainly induced by precipitating factors (missed, delayed, or smaller meal and/or physical activity) and not requiring a change in insulin dose, and therefore was not considered clinically relevant. The overall incidence of hypoglycemia in the T1D population is comparable to results previously observed in people treated with premixed insulins [27]. The overall safety profiles of SAR<sub>ASP</sub>-Mix and NN-Mix, including TEAEs, SAEs, hypersensitivity

reactions, and injection site reactions, were similar, and no new safety signals were identified.

Immunogenicity assessments, including the number of participants with treatment-emergent AIAs and median titers, showed a similar response to SAR<sub>ASP</sub>-Mix and NN-Mix during the 26-week treatment period. The AIA response 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, NAB results showed a low and similar response in the two treatment groups, with no impact detected on efficacy and insulin doses.

The overall impact of COVID-19 on the study was evaluated. Around 40% of participants in both treatment groups were impacted by COVID-19 during the on-treatment period, mostly related to assessments/procedures not performed and prolonged study treatment exposure. The impact of COVID-19 on the overall study results was kept to a minimum but the inability to reach noninferiority in the primary efficacy analysis was due to one participant in the SAR<sub>ASP</sub>-Mix group who was impacted by COVID-19 and reported an extreme outlying HbA1c increase. The impact of COVID-19 on safety data was limited to under-reporting of hypoglycemia events, with no overall impact on the evaluation of the similarity between treatments groups in relation to hypoglycemia, TEAEs, SAEs, deaths, or immunogenicity.

In recent years, some biosimilar insulin treatments, both basal and prandial insulin products, have been developed and approved in various countries throughout the world [11, 28]. The regulatory approval process, while differing slightly between countries [24, 29–31], is designed to show that the proposed biosimilar product is similar to the reference product in physicochemical analyses, nonclinical and clinical studies. Clinical evaluation includes human pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness [30]. The totality-of-evidence is used in the regulatory review of new biosimilar insulin products. Regulatory

guidance for the conduct of trials evaluating new insulin biosimilar products has also changed in recent years. For example, the most recent FDA guidance for insulin biosimilars (Nov 2019) [32] indicates that a comparative phase 3 clinical immunogenicity trial may no longer be necessary for approval of a biosimilar or interchangeable insulin product. In their 2015 guidance [24], the EMA may also waive the requirement for a safety study with immunogenicity assessment to support a biosimilar marketing application. In addition, the EMA regards efficacy endpoints in phase 3 trials (usually HbA1c) as supportive (to an immunogenicity assessment) as they are not considered sensitive enough to detect potentially clinically relevant differences between two insulin products.

The open-label design is a potential limitation of this study. However, patient blinding was not possible as SAR<sub>ASP</sub>-Mix was administered via a prefilled disposable pen that was different from the approved prefilled disposable pen used for NN-Mix. To partially overcome this limitation, efficacy and immunogenicity assessments were based on objectively collected data that was analyzed by central laboratories blinded to the study treatment. In addition, the sponsor study team remained blinded to the treatment group until database lock. Another limitation is that the COVID-19 pandemic occurred during the last few weeks of the study in some countries. Systems were put in place to ensure participant safety, retention, and data capture. The impact of COVID-19 on the study results was largely restricted to the primary efficacy endpoint.

## CONCLUSIONS

In summary, the premixed insulin aspart analogue SAR<sub>ASP</sub>-Mix was well tolerated and demonstrated effective glycemic control with a similar safety and immunogenicity profile to the commercially available premixed insulin aspart product (NN-Mix) in people with diabetes treated for 26 weeks.

## ACKNOWLEDGEMENTS

**Funding.** The trial and the Rapid Service Fee were funded by Sanofi. Sanofi participated in trial design, data collection, and performed all the statistical analyses, the results of which were reviewed by the authors and the sponsor.

**Editorial Assistance.** Editorial support was provided by DJ Quinlan of Oberon Ltd (London, UK), funded by Sanofi.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

**Author Contributions.** Karin Wernicke-Panten, Suzanne Pierre, Baerbel Rotthaeuser, and Daniel Kramer contributed to the conception and design of the study; S. Aravind, Kiran Singh, Grace Aquitania, Liliia Mogylnytska, Alsu Zalevskaya, and Beata Matyjaszek-Matuszek to the acquisition of data (as trial investigators); Karin Wernicke-Panten, Suzanne Pierre, Baerbel Rotthaeuser, Daniel Kramer, and Bhaswati Mukherjee to analysis of data; Karin Wernicke-Panten, Suzanne Pierre, Baerbel Rotthaeuser, Daniel Kramer, and Bhaswati Mukherjee to the interpretation of the data. Karin Wernicke-Panten, My-Liên Nguyễn-Pascal, Suzanne Pierre, Baerbel Rotthaeuser, Daniel Kramer, and Bhaswati Mukherjee contributed to the drafting, and S. Aravind, Kiran Singh, Grace Aquitania, Liliia Mogylnytska, Alsu Zalevskaya, Beata Matyjaszek-Matuszek, Karin Wernicke-Panten, My-Liên Nguyễn-Pascal, Suzanne Pierre, Baerbel Rotthaeuser, Daniel Kramer, and Bhaswati Mukherjee to critical revision of the work for important intellectual content. All authors approved the final manuscript for submission and are accountable for the accuracy and integrity of the manuscript. Baerbel Rotthaeuser is the guarantor of this work and confirms access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Disclosures.** S.R Aravind, Kiran P Singh, Grace Aquitania, Liliia Mogylnytska, Alsu G Zalevskaya, and Beata Matyjaszek-Matuszek report no disclosures. Karin Wernicke-Panten, My-Liên Nguyễn-Pascal, Suzanne Pierre, Baerbel Rotthaeuser, Daniel Kramer, and Bhaswati Mukherjee are all employees and stockholders of Sanofi.

**Compliance with Ethics Guidelines.** GEMELLI M is registered with European Union Clinical Trials Register (EudraCT number 2017-000092-84) and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki of 1964 and its later amendments. The protocol was approved by an independent ethics committee or institutional review board for each center except in Poland where approval was by a national ethics committee (Komisja Bioetyczna przy Okregowej, Lublin); written informed consent was obtained from each patient before any trial-related activities.

**Data Availability.** Qualified researchers may request access to participant level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Participant level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at <https://www.clinicalstudydatarequest.com/>.

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