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ORIGINAL RESEARCH

Efficacy, Safety, and Immunogenicity of Insulin Aspart Biosimilar SAR341402 Compared with Originator Insulin Aspart in Adults with Diabetes (GEMELLI 1): A Subgroup Analysis by Prior Type of Mealtime Insulin

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ABSTRACT

Introduction: The biosimilar SAR341402 insulin aspart (SAR-Asp) was compared to its originator NovoLog®/NovoRapid® insulin aspart (NN-Asp) in terms of efficacy, safety, and immunogenicity, in adults with type 1 or type 2 diabetes switching from different rapid-acting insulin analogs.

Methods: This phase 3, randomized, open-label, multinational, 52-week study (GEMELLI 1) enrolled participants with type 1 or type 2 diabetes (n = 597). At randomization, participants transitioned from NovoLog/NovoRapid (n = 380) or Humalog®/Liprolog® (n = 217) to equivalent (1:1) doses (or a dose at the discretion of the investigator) of either SAR-Asp or NN-Asp (1:1 randomization). Participants were treated with multiple daily injections in combination with insulin glargine 100 U/mL (Lantus®). In this subgroup analysis, efficacy measures (change in hemoglobin A1c [HbA1c], insulin dose [total, basal and mealtime]), and safety outcomes (hypoglycemia incidence, adverse events, anti-insulin aspart antibodies) of SAR-Asp were compared with those of NN-Asp separately according to the participants' prestudy mealtime insulin.

Results: At week 26 (primary efficacy endpoint), change in HbA1c was similar between SAR-Asp and NN-Asp in those participants pre-treated with NovoLog/NovoRapid (least squares [LS] mean difference − 0.04%, 95% confidence interval [CI] − 0.182 to 0.106%) or Humalog/Liprolog (LS mean difference − 0.15%, 95% CI − 0.336 to 0.043%) (P value for treatment by subgroup interaction = 0.36). This HbA1c response persisted over the 52 weeks of the study similarly for both treatments within each subgroup. In both subgroups, changes in insulin doses were similar between treatments over 26 weeks and 52 weeks, as were the incidences of severe or any hypoglycemia, adverse events (including

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hypersensitivity and injection site reactions), and anti-insulin aspart antibodies.
Conclusions: Efficacy and safety (including immunogenicity) profiles of SAR-Asp are similar to those of NN-Asp over 52 weeks in adults with diabetes irrespective of prior type of mealtime insulin.
Trial Registration: ClinicalTrials.gov identifier: NCT03211858.

Keywords: Biosimilar insulin; GEMELLI 1; Insulin aspart; SAR341402; Subgroup by prior mealtime insulin

Key Summary Points

Why carry out this study?

In the GEMELLI 1 trial, enrolled participants with type 1 or type 2 diabetes were transitioned from NovoLog®/NovoRapid® (insulin aspart) or Humalog®/Liprolog® (insulin lispro) to equivalent (1:1) doses or a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization of the biosimilar insulin aspart product SAR341402 (SAR-Asp) or its reference insulin aspart product NovoLog/NovoRapid (NN-Asp).

The present study is a pre-planned subgroup analysis of GEMELLI 1 designed to confirm that SAR-Asp and NN-Asp had similar efficacy and safety profiles in participants who switched from either one of these commercial insulin analog preparations to study treatment at randomization.

What was learned from the study?

SAR-Asp and NN-Asp provide effective and comparable glycemic control and a similar incidence of hypoglycemia and anti-insulin aspart antibodies (AIAs) irrespective of the mealtime insulin treatment used prior to the study. No significant heterogeneity of treatment effect across the subgroups was observed for these outcomes, indicating that there was no differential treatment effect (SAR-Asp vs. NN-Asp) irrespective of prior type of mealtime insulin.

Most participants observed a unit-to-unit (1:1) conversion from their prestudy mealtime insulin. Within each prior mealtime insulin subgroup, similar results between SAR-Asp and NN-Asp were also observed for insulin dose, adverse events, and other AIA response outcomes.

Data from these subgroup analyses suggest that SAR-Asp is a well-tolerated and effective treatment option when prescribed for adults with diabetes who have had prior treatment with NovoLog/NovoRapid or Humalog/Liprolog.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13415591.

INTRODUCTION

Insulin aspart is the active ingredient of NovoLog®/NovoRapid® (Novo Nordisk, Bagsværd, Denmark; NN-Asp) [1, 2], a rapid-acting insulin analog, approved and marketed for use in adults and children with type 1 diabetes (T1D) and type 2 diabetes (T2D) in many countries [3]. SAR341402 (SAR-Asp; insulin aspart solution 100 U/mL; Sanofi, Paris, France), the first biosimilar insulin aspart product to receive marketing authorization in the European Union (Insulin aspart Sanofi®) [4], has the same amino acid sequence and structure as NN-Asp. With any biosimilar, subtle differences may exist among protein products manufactured in living cells via different processes that can result in different clinical effects. Physicochemical analyses and nonclinical and clinical phase I and phase III (GEMELLI 1) studies were therefore performed to demonstrate that SAR-Asp and NN-Asp are highly similar [5–8].

In GEMELLI 1, adults with T1D or T2D were pre-treated with commercial mealtime NN-Asp or insulin lispro (Humalog®/Liprolog® 100 U/mL; Eli-Lilly, Indianapolis, IN, USA) [9–11] therapy. Results for the overall study population following 6- and 12-months treatment have been previously reported [6, 7] and confirm that SAR-Asp and NN-Asp have similar efficacy, safety, and immunogenicity profiles.

To determine whether these profiles of SAR-Asp and NN-Asp remain consistent according to the type of mealtime insulin analog used prior to the trial, in the pre-planned subgroup analysis presented here, we compared the efficacy, safety, and immunogenicity of SAR-Asp to those of NN-Asp in GEMELLI 1 on the basis of mealtime insulin analog use (NovoLog/NovoRapid or Humalog/Liprolog) at study entry. The analyses evaluated whether the transition from the prior mealtime insulin therapy had an impact on the initial dose of randomized treatment (SAR-Asp or NN-Asp) and the subsequent efficacy and safety outcomes during the trial.

METHODS

GEMELLI 1 Design

GEMELLI 1 was a randomized, open-label, multinational, multicenter, two-arm, parallel-group, phase 3 clinical trial (ClinicalTrials.gov registration identifier: NCT03211858). 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 (for an overall 52-week period). The study design, participants, and methods of the trial, performed according to ethical principles described in the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki, have been previously reported [6, 7]. The protocol was approved by an independent ethics committee or institutional review board for each center; written informed consent was obtained from each patient before any trial-related activities.

Participants were randomized 1:1 to either SAR-Asp or NN-Asp, stratified by geographical region (Europe, USA, Japan), type of diabetes (T1D, T2D [T2D only for USA]), hemoglobin A1c (HbA1c) at the screening visit ($< 8.0\%$, $\geq 8.0\%$), and prior use of NN-Asp (Yes, No). Prefilled disposable pen devices were used to deliver study medication. All participants were treated with multiple daily injections in combination with insulin glargine (Lantus®; Sanofi SA, Paris, France; Gla-100). At randomization, participants received a SAR-Asp or NN-Asp starting dose that was a unit-to-unit (1:1) conversion from the NovoLog/NovoRapid or Humalog/Liprolog dose used prior to the trial or a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization. Mealtime insulin and Gla-100 doses were then titrated to achieve protocol-specified glycemic targets [6, 7].

Subgroup Definition and Outcomes

The separate analyses reported here compare SAR-Asp to NN-Asp according to prior use of NovoLog/NovoRapid or Humalog/Liprolog, as reported in the randomization stratum. As prespecified in the study protocol and/or statistical analysis plan, subgroup analyses were performed at week 26 and week 52 upon change from baseline in HbA1c (change at week 26 defined as primary efficacy endpoint), hypoglycemia incidence (participants with at least 1 episode of any, severe and documented symptomatic hypoglycemia with a measured plasma glucose concentration of ≤ 70 mg/dL or < 54 mg/dL, as defined previously [6]), treatment-emergent adverse events (including hypersensitivity and injection site reactions), and anti-insulin aspart antibody (AIA) response. Post hoc subgroup analyses were performed upon change in insulin dose (total, basal and mealtime) from baseline to day 1, week 26, and week 52. 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 other study visits, insulin dose values were reported as

the median of daily doses available in the week prior to the study visit. Details on efficacy, safety, and immunogenicity outcomes have been previously reported [6, 7].

Statistical Analysis

The HbA1c analyses were performed using the intent-to-treat population, which included all randomized participants irrespective of compliance with the study protocol and procedures [6, 7]. Insulin dose, hypoglycemia, and adverse event analyses used the safety population, comprising all randomized participants who received at least one dose of study insulin, analyzed according to the treatment actually received. The AIA population for AIA response analysis included all participants from the safety population with at least one AIA sample available for analysis (sample collected at least 8 h after the last administration of mealtime insulin) during the 6- and 12-month on-treatment periods, as defined previously [6, 7].

Statistical methods for the overall study populations have been previously reported [6, 7]. Subgroup analyses were descriptive, with no formal statistical testing. After multiple imputation of missing data (using separate models for participants who prematurely discontinued or completed the treatment period, as previous described [6, 7]), the change from baseline in HbA1c was analyzed using an analysis of covariance model with treatment group, subgroup, and subgroup-by-treatment interaction as fixed effects, and the baseline HbA1c value as a continuous fixed covariate. Treatment comparisons were made within the subgroup of participants who were pre-treated with NovoLog/NovoRapid and Humalog/Liprolog. For each subgroup, the least squares (LS) mean change in HbA1c was estimated for each treatment group as well as the between-group difference and the 95% confidence interval (CI). The P value of the subgroup-by-treatment interaction was also provided. A significant treatment-by-subgroup interaction ($P < 0.1$) was considered as indicating a potential differential treatment effect.

For each hypoglycemia category (any, severe, and documented symptomatic events), the incidence of participants with at least one event was compared between treatment groups using a logistic regression model. The model included fixed-effect terms for treatment group, the randomization strata of geographical region, and type of diabetes (Europe T1D, USA T1D, USA T2D, Japan T1D), screening HbA1c ($< 8\%$, $\geq 8\%$), subgroup, and subgroup-by-treatment interaction. If the model did not converge (e.g., due to sparse data), randomization strata were removed from the model. Odds ratios (OR) and 95% CI were evaluated within each subgroup and displayed using forest plots. The P value of the subgroup-by-treatment interaction was also provided.

For the percentage of participants with treatment-emergent AIAs (AIA incidence), a binomial regression model with an identity-link function was performed with fixed categorical effects for treatment group, the randomization strata, subgroup, and subgroup-by-treatment interaction. If the model did not converge, randomization strata were removed from the model. The risks within each treatment group and risk difference were provided with their 90% CI within each subgroup, as well as the P value of the subgroup-by-treatment interaction.

Analyses of other AIA response outcomes, treatment-emergent adverse events (TEAEs), and change in insulin dose were descriptive. The analyses were conducted as previously described for the overall population [6, 7].

RESULTS

Baseline Characteristics

Of the 597 participants randomized, 380 (63.7%) and 217 (36.3%) participants (as per the randomization strata) reported pre-treatment with commercial NovoLog/NovoRapid and Humalog/Liprolog, respectively. Within each subgroup, baseline characteristics were generally similar between both treatment groups and consistent with the overall study population

(Electronic Supplementary Material [ESM] Table S1).

HbA1c and Insulin Doses According to Prior Mealtime Insulin Treatment

In participants pre-treated with commercial NovoLog/NovoRapid, changes in HbA1c from baseline to week 26 were similar in those who had switched from NovoLog/NovoRapid to SAR-Asp at randomization (LS mean change − 0.37%) compared with participants who had continued NovoLog/NovoRapid (LS mean change − 0.33%). Similarly, in participants pre-treated with commercial Humalog/Liprolog, the decreases in HbA1c from baseline to week 26 were similar for participants switching from Humalog/Liprolog to SAR-Asp (− 0.39%) or to NN-Asp (− 0.24%) (Fig. 1a; ESM Table S2). The LS mean treatment difference between SAR-Asp and NN-Asp at week 26 was − 0.04% (95% CI − 0.182 to 0.106) for those pre-treated with NovoLog/NovoRapid and − 0.15% (95% CI − 0.336 to 0.043) for those pre-treated with Humalog/Liprolog. There was no evidence of heterogeneity of treatment effect on change in HbA1c according to the pre-study mealtime insulin, as illustrated by the nonsignificant interaction ($P = 0.36$). SAR-Asp and NN-Asp continued to have similar efficacy over the 12-month period based on the change in HbA1c from baseline to week 52, irrespective of whether participants were using commercial NovoLog/NovoRapid or Humalog/Liprolog prior to the study (Fig. 1b; Table S2). At week 52, the LS mean difference between SAR-Asp and NN-Asp was − 0.02% (95% CI − 0.204 to 0.170) for participants pre-treated with NovoLog/NovoRapid, and 0.06% (95% CI − 0.181 to 0.309) for participants pre-treated with Humalog/Liprolog (Fig. 1b, Table S2).

Changes in basal and mealtime insulin doses from baseline to day 1, week 26, and week 52 were similar between treatment groups, regardless of whether participants were using commercial NovoLog/NovoRapid or Humalog/Liprolog prior to the study (Fig. 2; ESM Table S3). Mean changes in mealtime insulin doses from baseline to week 52 were − 0.000 U/kg for SAR-Asp and 0.015 U/kg for NN-Asp in those pre-treated with NovoLog/NovoRapid, and − 0.001 U/kg for both treatment groups in those pre-treated with Humalog/Liprolog (ESM Table S3). For participants using commercial NovoLog/NovoRapid prior to the study, there was virtually no change in mealtime insulin doses from baseline to day 1 (i.e., from prestudy insulin to the first week of study medication), both in participants who had switched from NovoLog/NovoRapid to SAR-Asp at randomization (mean change − 0.000 U/kg) and in participants who continued on NovoLog/NovoRapid at randomization (mean change − 0.003 U/kg). For participants using commercial Humalog/Liprolog prior to the study, the change in mealtime insulin from baseline to day 1 was minimal, similarly for participants switching from insulin lispro to SAR-Asp (mean change 0.008 U/kg) or to the comparator NN-Asp (mean change 0.013 U/kg). Similar findings were observed for changes in basal and total insulin doses (ESM Table S3). Changes in insulin doses (basal, mealtime, and total) in this subgroup of participants using commercial NovoLog/NovoRapid or Humalog/Liprolog prior to the study were consistent with the results observed in the total study population.

Hypoglycemia, Adverse Events and AIAs According To Prior Mealtime Insulin Treatment

During the 6- and 12-month study periods, the percentages of participants reporting at least one episode of hypoglycemia were similar for SAR-Asp and NN-Asp regardless of pre-treatment with NovoLog/NovoRapid (at 6 months: 97.4 and 95.2% in the SAR-Asp and NN-Asp groups, respectively; at 12 months: 99.0 and 97.9% in the two groups, respectively) or Humalog/Liprolog (at 6 months: 95.4 and 98.1% in the SAR-Asp and NN-Asp groups, respectively; at 12 months: 96.3 and 98.1% in the two groups, respectively) (ESM Table S4). Severe hypoglycemia was reported by a small and similar number of participants in each treatment group for those pre-treated with NovoLog/NovoRapid (3.1 and 3.7% in the two

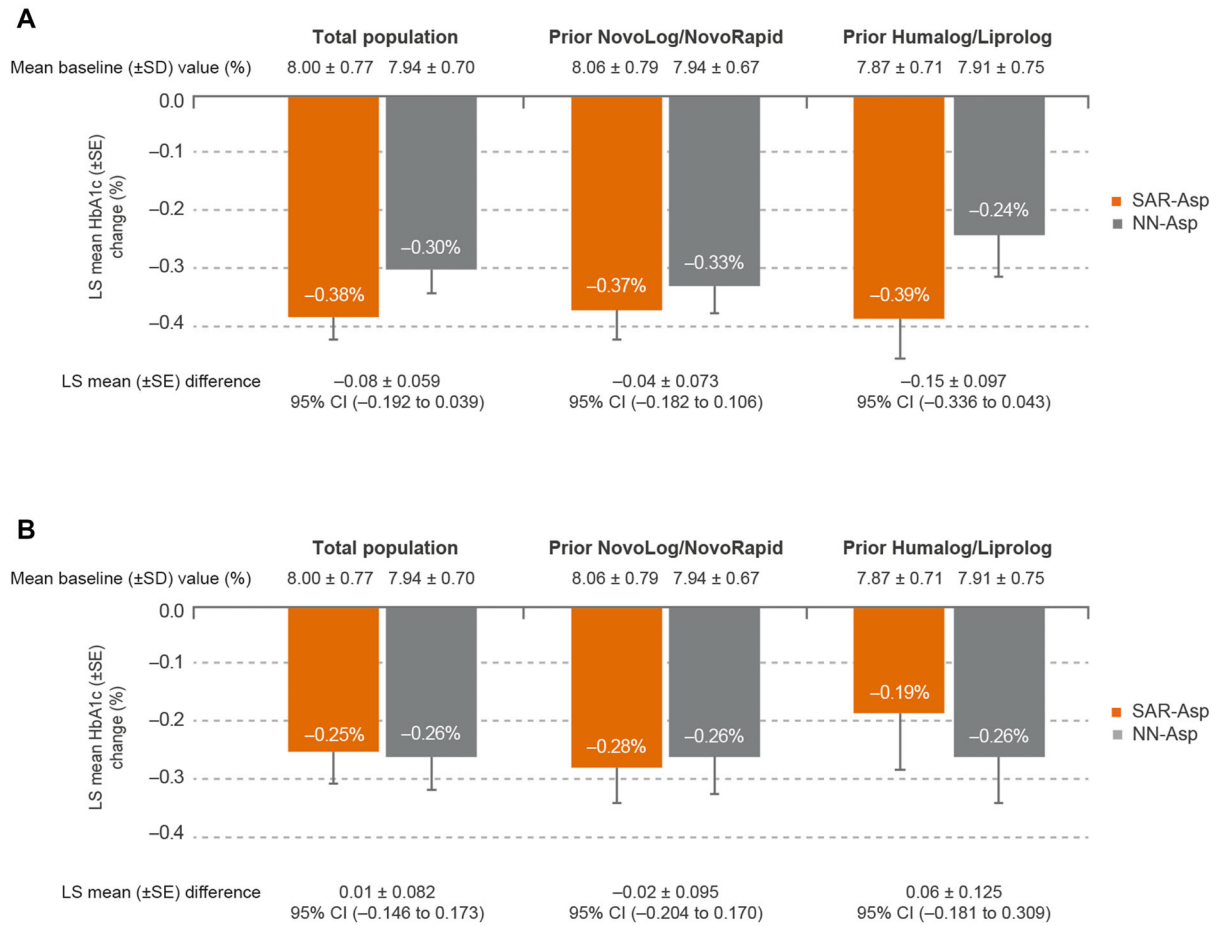

Fig. 1 Least squares (*LS*) mean change in hemoglobin A1c (*HbA1c*) (%-points) from baseline to week 26 (**a**) and week 52 (**b**) in the total study population and by subgroup of prior mealtime insulin (NovoLog/NovoRapid or Humalog/Liprolog) using the analysis of covariance model (with retrieved dropout multiple imputation) (intent-to-treat population). The statistical model used for the analysis is described in ESM Table S2. *P* value for treatment by subgroup interaction = 0.3566 at week 26 and 0.5677 at week 52. *CI* Confidence interval, *NN-Asp* NovoLog®/NovoRapid® insulin aspart, *SAR-Asp* biosimilar SAR341402 insulin aspart, *SD* standard deviation, *SE* standard error

groups at 6 months; 5.2 and 4.8% at 12 months) or Humalog/Liprolog (5.5 and 2.8% in the two groups at 6 months; 7.3 and 4.6% at 12 months). Documented symptomatic hypoglycemia events were also reported by a similar proportion of participants in each treatment group according to pre-treatment with either commercial insulin. Within each subgroup by prior mealtime insulin, no statistically significant treatment difference was observed for any category of hypoglycemia (all 95% CIs of the OR of SAR-Asp vs. NN-Asp including 1.0) (Fig. 3). Additionally, there was no evidence of heterogeneity of the treatment effect according to the pre-study mealtime insulin for any category of hypoglycemia (all $P > 0.1$) (Fig. 3). Hypoglycemia results observed in the subgroups were generally consistent with those in the overall study population.

Both insulin aspart products were well tolerated regardless of the type of prior mealtime insulin. In participants using commercial NovoLog/NovoRapid prior to the study, the incidence of treatment-emergent adverse events

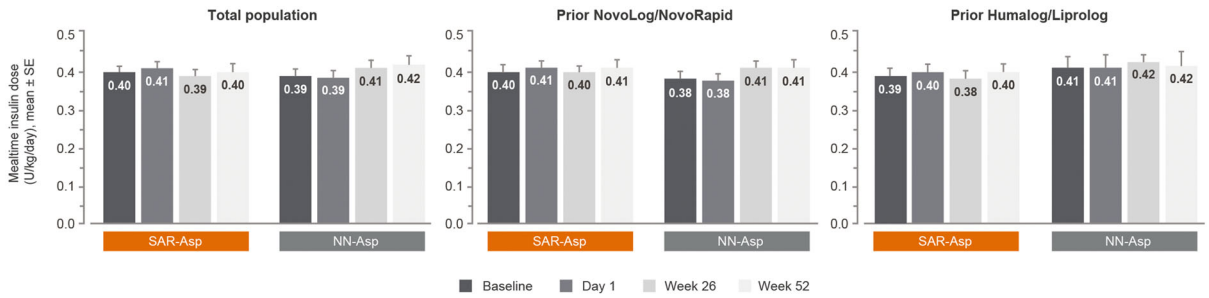

Fig. 2 Daily mealtime insulin doses (U/kg) in participants at baseline, day 1, week 26, and week 52 for the total study population and by subgroup of prior mealtime insulin (NovoLog/NovoRapid or Humalog/Liprolog) (safety population). Data are presented as the mean ± SE. Insulin doses are rounded to 2 decimal places. Baseline insulin dose is defined as the median of daily doses available in the week prior to the first injection of study medication (doses of prestudy insulin). The value at day 1 is defined as the median of daily doses available in the week after the first injection of study medication. For week 26 (week 52), the value presented is the median of daily doses available in the week prior to the visit

during the 6- and 12-month periods were similar in the two treatment groups (at 6 months: SAR-Asp 92 [47.9%], NN-Asp 94 [50.0%] participants; at 12 months: SAR-Asp 115 [59.9%], NN-Asp 109 [58.0%] participants) (ESM Table S5). In participants using Humalog/Liprolog prior to the study, the incidence of TEAEs during the 6- and 12-month periods were slightly higher in the SAR-Asp group (at 6 months: 64 [58.7%] vs. 52 [48.1%] in the NN-Asp group; at 12 months: 69 [63.3%] vs. 59 [54.6%] in the NN-Asp group). The incidence of serious TEAEs was similar between treatment groups in participants using prior NovoLog/NovoRapid, while small numerical differences were observed in the prior Humalog/Liprolog subgroup (ESM Table S5). Similar proportions of participants in both treatment groups reported injection site reactions and hypersensitivity reactions (including those events adjudicated as allergic), regardless of the prior mealtime insulin. The safety results observed in each subgroup during the 6- and 12-month treatment periods were generally consistent with those reported for the overall study population.

The percentage of participants who were positive for AIAs at baseline in each treatment group was similar irrespective of prior use of NovoLog/NovoRapid (SAR-Asp 38.2%, NN-Asp 38.7%) or prior Humalog/Liprolog (SAR-Asp 29.8%, NN-Asp 33.3%) (ESM Table S6; Fig. 4a). As expected, the percentage of participants positive for AIAs at baseline was slightly lower in those pre-treated with Humalog/Liprolog compared to those pre-treated with NovoLog/NovoRapid. Similarly, the AIA incidence, corresponding to the proportion of the study population found to have seroconverted or boosted preexisting AIA during the 6-month treatment period (treatment-emergent AIAs), was similar in both treatment groups according to prior use of NovoLog/NovoRapid (SAR-Asp 12.6%, NN-Asp 20.0%) or prior use of Humalog/Liprolog (SAR-Asp 24.8%, NN-Asp 21.5%) (ESM Table S6; Fig. 4b). Based on the binomial subgroup regression model, the risk difference in treatment-emergent AIAs between SAR-Asp and NN-Asp at 6 months was − 7.3% (90% CI − 13.6 to − 1.0) in the prior NovoLog/NovoRapid subgroup, and 3.7% (90% CI − 5.9 to 13.4) in the prior Humalog/Liprolog subgroup (interaction $P = 0.11$). The prevalence, corresponding to the percentage of participants with detectable AIAs at least at one time point during the study was also similar with SAR-Asp and NN-Asp irrespective of prior commercial mealtime insulin treatment. Following 12 months of treatment, the number of participants with at least one positive AIA sample (prevalence) or having developed treatment-emergent AIAs (incidence) remained similar according to the prior use of NovoLog/NovoRapid or Humalog/

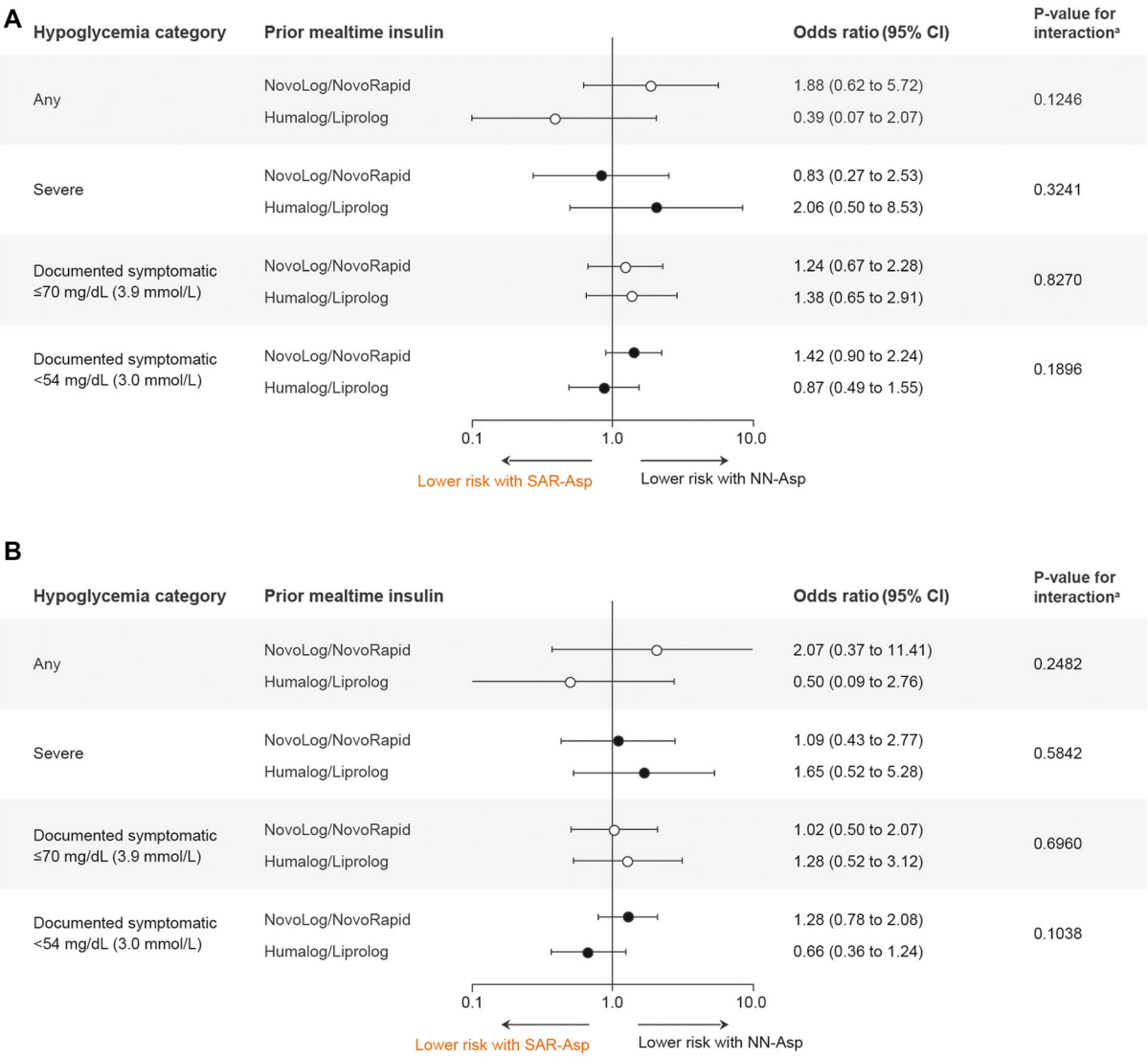

Fig. 3 Forest plot of the odds ratio of SAR-Asp vs. NN-Asp for participants with ≥ 1 hypoglycemic event during the 6-month (**a**) and 12-month (**b**) on-treatment period by subgroup of prior mealtime insulin (NovoLog/NovoRapid or Humalog/Liprolog) (safety population). Results are based on logistic regression model with fixed-effect terms for treatment, the randomization strata of geographical region, and type of diabetes (Europe type 1 diabetes [T1D], USA T1D, USA type 2 diabetes, Japan T1D), screening HbA1c (< 8.0, ≥ 8.0%), subgroup, and subgroup-by-treatment interaction. For the category of any hypoglycemia, randomization strata were removed from the model due to non-convergence. [a]*P* values of subgroup-by-treatment interaction are based on the model described above. The number of participants with ≥ 1 treatment-emergent event, number of participants included in the analysis population, and percentage of participants with ≥ 1 event are shown in ESM Table S4

Liprolog (ESM Table S6; Fig. 4c). At 12 months, the risk difference in treatment-emergent AIAs between SAR-Asp and NN-Asp was − 5.3% (90% CI − 12.1 to 1.5) in the prior NovoLog/NovoRapid subgroup, and 3.0% (90% CI − 7.5 to 13.4) in the prior Humalog/Liprolog subgroup (interaction $P = 0.27$). The risk differences observed at 6 and 12 months, including the statistically significant slightly lower AIA incidence in SAR-Asp versus NN-Asp at 6 months in

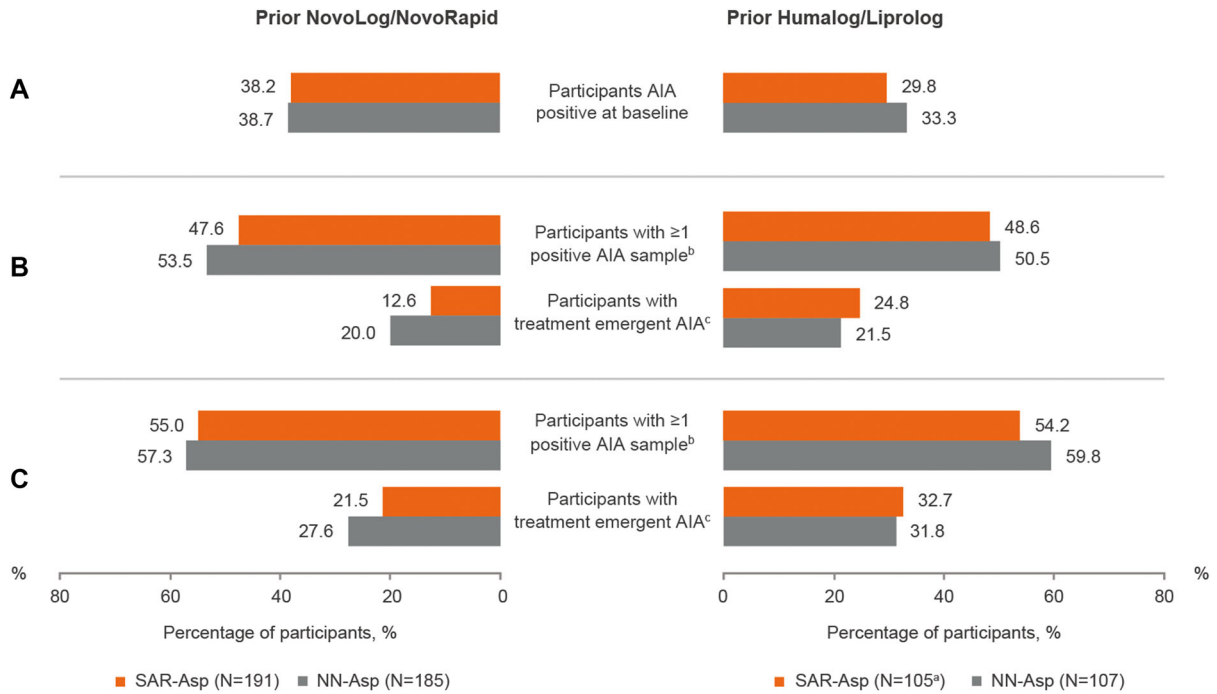

Fig. 4 Anti-insulin aspart antibody (*AIA*) response at baseline (**a**), week 26 (**b**), and week 52 (**c**) by subgroup of prior mealtime insulin (Novolog/NovoRapid or Humalog/Liprolog) (AIA population). Data are shown as the percentage of participants with each outcome (see ESM Table S6 for the denominators). [a]$N = 107$ in 52-week analysis. [b]Prevalence: participants with at least 1 positive AIA sample at baseline or post-baseline. [c]Incidence: participants with newly positive AIA post-baseline (treatment induced) or with ≥ fourfold increase in titer (treatment boosted) (i.e., participants with treatment-emergent AIAs).

the prior NovoLog/NovoRapid subgroup, were small and not considered to be clinically meaningful.

DISCUSSION

The aim of the present study was to provide further information about clinical outcomes when SAR-Asp is compared with NN-Asp in the subgroup of participants pre-treated with different commercial mealtime insulin analog preparations and switching insulin treatment at randomization. No relevant differences were observed for any of the clinical outcomes, with the findings in each subgroup also consistent and similar to the previously reported results for the overall study population [6, 7]. To maintain consistency with the previously reported data, separate analyses were performed for the 6- and 12-month outcomes, with the majority of these being prespecified.

Following randomization, participants switched from their previous commercial mealtime insulin (NovoLog/NovoRapid or Humalog/Liprolog) to an equivalent dose of the study medication (SAR-Asp or NN-Asp). When transitioning from the reference product (NovoLog/NovoRapid) to the biosimilar aspart product (SAR-Asp) at randomization, there was virtually no change in mealtime insulin doses, similarly as for participants who continued on NovoLog/NovoRapid. There was also only minimal change in mealtime insulin dose when participants were switched from previous commercial Humalog/Liprolog to study medication (SAR-Asp or NN-Asp). This indicates that most participants did indeed switch using a unit-to-unit (1:1) conversion from their prestudy mealtime insulin. Over the subsequent 6- and 12-month

periods, mealtime doses remained similar in both treatment groups within each subgroup. Similar findings were also observed for change in basal and total insulin doses over the first week of study treatment and the subsequent 6- and 12-months of treatment within each subgroup.

Regardless of the commercial mealtime insulin used before the study (NovoLog/NovoRapid or Humalog/Liprolog), both SAR-Asp and NN-Asp treatments were efficacious in improving glycemia, with participants showing a similar lowering of blood glucose levels from baseline to week 26 (primary study endpoint), which was thereafter maintained through to week 52.

The results showed a similar safety profile between the treatment groups, both for participants pre-treated with NovoLog/NovoRapid and those pre-treated with Humalog/Liprolog. The incidence of hypoglycemia was consistent between SAR-Asp and NN-Asp irrespective of the prestudy mealtime insulin. Hypoglycemia results observed in the subgroups were generally consistent with those in the overall study population. Treatment-related adverse events reported for SAR-Asp were similar to those reported for NN-Asp in each subgroup and were consistent with the adverse event profile reported in the overall study population [6]. Within each subgroup, similar proportions of participants in each treatment also had detectable AIAs at baseline and throughout the course of the 52-week study.

A limitation of the present analysis is that the study was not designed or powered to prospectively compare SAR-Asp and NN-Asp in participants with diabetes pre-treated with commercial NovoLog/NovoRapid or Humalog/Liprolog. In general, caution should be exercised in the interpretation of subgroup analysis results, and statistical limitations should be taken into account in order to avoid overinterpretation [12, 13]. In this analysis, the subgroups by prior mealtime insulin were used as stratification factor in the randomization process, and the majority of the subgroup analyses were pre-specified in the study statistical analysis plan. Statistical models were limited to the study primary efficacy outcome (HbA1c) and key safety outcomes (hypoglycemia incidence, treatment-emergent AIAs) as pre-specified in the study plans, in order to limit the risk of chance findings. Other outcomes were analyzed descriptively. In all statistical models, no significant subgroup-by-treatment interaction was observed (as defined by $P > 0.10$), thereby confirming that the treatment effect was not dependent on the participant's subgroup. Results in each subgroup were generally consistent with the analyses conducted for the overall study population [6, 7]. The limited number of participants in each subgroup is reflected by the wider confidence intervals generally obtained for the estimates of treatment effect compared with the overall study population, especially in those pre-treated with Humalog/Liprolog. Of note, the primary study objective was to demonstrate non-inferiority of SAR-Asp versus NN-Asp on the change in HbA1c from baseline to week 26 [6]. Although the subgroup analyses presented here were not powered to perform formal statistical testing between the two treatments, the criteria for non-inferiority of SAR-Asp versus NN-Asp was met in each subgroup, since the upper bound of the 95% CIs of the between-treatment difference on HbA1c change from baseline to week 26 was below the pre-defined non-inferiority margin of 0.3%. Regarding the safety analyses performed, we acknowledge that lack of a statistically significant effect is not evidence of lack of a real effect [13], but the results obtained were very similar between treatment groups and did not raise any clinical concern. The low number of participants in each subgroup precluded further evaluation of outcomes in the separate T1D and T2D populations. As previously reported [6, 7], another limitation of the study was the open-label design necessitated by the different injection devices used for SAR-Asp and NN-Asp, partially mitigated by performing assessment analyses in central laboratories blinded to treatment group.

In summary, the results of this subgroup analysis show that participants in GEMELLI 1 pre-treated with NovoLog/NovoRapid who were then randomized to SAR-Asp using the recommended 1:1 dose conversion have a similar efficacy and safety profile to those participants

who continued on their prestudy NovoLog/NovoRapid medication. Similar findings were observed in both treatment groups (SAR-Asp and NN-Asp) among participants who were switched 1:1 from Humalog/Liprolog to each study treatment. The findings of this study are clinically important and suggest that SAR-Asp is a well-tolerated, effective, and safe treatment option when prescribed for participants with diabetes who have had prior treatment with other commercial mealtime insulin analog therapies.

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Compliance with Ethics Guidelines. GEMELLI 1 is registered with ClinicalTrials.gov (NCT03211858) and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by an independent ethics committee or institutional review board for each center; 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 dataset 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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