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ORIGINAL RESEARCH

Efficacy, Safety, and Immunogenicity of Biosimilar Insulin Aspart Premix SAR341402 Mix 70/30 Compared with Originator Insulin Aspart Mix 70/30 in Adults with Diabetes (GEMELLI M): A Subgroup Analysis by Prior Type of Premix Insulin

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ABSTRACT

Introduction: We compared the efficacy, safety, and immunogenicity of biosimilar insulin aspart premix SAR341402 Mix 70/30 (70% intermediate SAR341402 protamine and 30% rapid SAR341402 solution) (SAR_{Asp}-Mix) with its originator NovoMix 30 insulin aspart mix (NN-Mix) in adults with type 1 or type 2 diabetes switching from different premix insulin analogs.

Methods: This phase 3, randomized, open-label, multinational, 26-week trial (GEMELLI M) enrolled 402 participants with type 1 or type 2 diabetes. At randomization, participants switched from their prestudy premix insulin NovoMix 30 ($n = 341$) or Humalog Mix 25/Liprolog Mix 25 ($n = 61$) to equivalent (1:1) doses of either SAR_{Asp}-Mix or NN-Mix at least twice daily (1:1 randomization). In this subgroup analysis, efficacy measures [change in hemoglobin A1c (HbA1c), daily insulin dose], and safety outcomes [hypoglycemia incidence, adverse events (including hypersensitivity and injection site reactions), anti-insulin aspart antibodies] of SAR_{Asp}-Mix were compared with those of NN-Mix separately according to the participants' prestudy premix insulin.

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Results: At week 26, change from baseline in HbA1c (primary efficacy endpoint) was similar between SAR_{Asp}-Mix and NN-Mix in those participants pretreated with NovoMix 30 [least squares (LS) mean difference 0.05%, 95% confidence interval (CI) −0.195% to 0.289%] or Humalog Mix 25/Liprolog Mix 25 (LS mean difference 0.28%, 95% CI −0.279% to 0.830%) (*P* value for treatment-by-subgroup interaction = 0.46). In both subgroups, safety outcomes, including immunogenicity, and changes in daily insulin doses were similar between treatments over 26 weeks.
Conclusions: Efficacy, safety, and immunogenicity profiles of SAR_{Asp}-Mix are similar to NN-Mix over 26 weeks in adults with diabetes irrespective of prior type of premix insulin.
Trial Registration: EudraCT number 2017-000092-84.

Keywords: Biosimilar insulin; GEMELLI M; Insulin aspart mix; Premix; SAR341402; Subgroup by prior premix insulin

Key Summary Points

Why carry out this study?

The GEMELLI M trial enrolled participants with diabetes who switched from NovoMix 30 or Humalog Mix 25/Liprolog Mix 25 to equivalent (1:1) doses of either the biosimilar insulin aspart premix product SAR341402 Mix 70/30 (SAR_{Asp}-Mix) or its reference insulin aspart premix product NovoMix 30 (NN-Mix).

This preplanned subgroup analysis of GEMELLI M was performed to confirm that SAR_{Asp}-Mix and NN-Mix show similar efficacy, safety and immunogenicity in participants who switched from either one of these commercial premix insulin preparations to study treatment at randomization.

What was learned from the study?

SAR_{Asp}-Mix or NN-Mix provide effective and comparable glycemic control and a similar incidence of hypoglycemia and anti-insulin aspart antibodies (AIAs) irrespective of the prior premix insulin treatment. No significant heterogeneity across the subgroups was observed, indicating that there was no differential treatment effect of SAR_{Asp}-Mix or NN-Mix irrespective of prior type of premix insulin.

Most participants showed a unit-to-unit (1:1) conversion from their prestudy premix insulin. Within each prior premix insulin subgroup, insulin dose, adverse events, and other AIA response outcomes were similar for SAR_{Asp}-Mix and NN-Mix over 26-week treatment.

These subgroup analyses suggest that SAR_{Asp}-Mix is a well-tolerated and effective treatment option when administered to adults with diabetes who received prior treatment with NovoMix 30 or Humalog Mix 25/Liprolog Mix 25.

INTRODUCTION

SAR341402 Mix 70/30, suspension for injection 100 U/mL (SAR_{Asp}-Mix), is a biosimilar premix formulation [1] of the European-approved biosimilar product SAR341402 insulin aspart (SAR-Asp, insulin aspart Sanofi, Sanofi, Paris, France) [2], a rapid-acting insulin analog that has the same amino acid sequence as its reference product NovoRapid (NN-Asp; Novo Nordisk A/S, Bagsværd, Denmark) [3]. SAR_{Asp}-Mix contains 70% intermediate SAR-Asp protamine and 30% rapid SAR-Asp solution [1], thereby providing basal and prandial insulin coverage in a single injection. SAR_{Asp}-Mix is being developed as a biosimilar to its reference insulin aspart premix product NovoMix 30 (Novo Nordisk; hereafter referred to as NN-Mix).

Similarity of SAR-Asp and NN-Asp was initially demonstrated in physicochemical analyses and nonclinical studies. Phase 1 [4] and phase 3 (GEMELLI M) [5] trials were performed to confirm that SAR_{Asp}-Mix and NN-Mix are highly similar. In GEMELLI M, adults with type 1 diabetes (T1D) or type 2 diabetes (T2D) were pretreated with commercial premix NN-Mix or insulin lispro mix (Humalog Mix 25/Liprolog Mix 25, Eli Lilly) therapy. Results for the total study population following treatment for 26 weeks have been previously reported and confirm that SAR_{Asp}-Mix and NN-Mix have similar efficacy, safety, and immunogenicity profiles [5].

To confirm whether these profiles of SAR_{Asp}-Mix and NN-Mix remain consistent according to the type of premix insulin used prior to the trial, this preplanned subgroup analysis of GEMELLI M compared the efficacy, safety, and immunogenicity of SAR_{Asp}-Mix and NN-Mix based on the prior premix insulin analog use (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) reported at study randomization. The analyses evaluated whether the switch from the prior premix insulin therapy had an impact on the initial dose of randomized treatment (SAR_{Asp}-Mix and NN-Mix) and the subsequent efficacy, safety, and immunogenicity outcomes during the trial.

METHODS

GEMELLI M Design and Participants

Detailed methods of the trial have been previously reported [5]. In brief, GEMELLI M was a randomized, open-label, multinational, multicenter, active-controlled, parallel-group, phase 3 trial initiated in July 2019 and completed in August 2020. The study comprised a 2-week screening period, a 26-week efficacy and safety treatment period, and a 2-day post-treatment follow-up period. This study is registered on the European Union Drug Regulating Authorities Clinical Trials Database (2017-000092-84) and was conducted in accordance with the ethics principles of the Declaration of Helsinki of 1964 and its later amendments, the International Conference on Harmonization Guidelines for Good Clinical Practice, and all applicable laws, rules, and regulations. 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). The committee names and reference numbers of all research ethics boards/institutional review boards are provided in the Electronic Supplementary Material (ESM) Appendix. Written informed consent was obtained from each participant before any trial-related activities.

Participants were randomized (1:1) to receive either SAR_{Asp}-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. Prefilled disposable pen devices were used to administer the study treatment at least twice daily. Participants were switched from their prior premix insulin (NovoMix 30, Humalog Mix 25, or Liprolog Mix 25) at randomization. The starting dose of SAR_{Asp}-Mix or NN-Mix was a unit-to-unit (1:1) conversion from participants' prestudy insulin dose at the end of the screening period, using the same frequency of administration. Premix doses were

then titrated to achieve protocol-specified glycemic targets, as reported previously [5].

Subgroup Definition and Outcomes

Separate analyses reported here compare SAR$_{Asp}$-Mix with NN-Mix according to prior use of NovoMix 30 or Humalog Mix 25/Liprolog Mix 25, as reported in the randomization stratum. Prespecified subgroup analyses were performed at week 26 on change from baseline in glycated hemoglobin (HbA1c) (primary efficacy endpoint), hypoglycemia incidence (participants with at least one episode of any, severe, and documented symptomatic hypoglycemia with a measured plasma glucose concentration of 70 mg/dL or less, or less than 54 mg/dL, classified according to American Diabetes Association (ADA) categories [6–8]), treatment-emergent adverse events (TEAEs) (including hypersensitivity and injection site reactions), and immunogenicity outcomes including anti-insulin aspart antibody (AIA) and neutralizing antibody (NAb) response. Post hoc subgroup analyses were performed on change in daily insulin dose from baseline to day 1 and week 26. 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. At week 26, 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 [5].

Statistical Analysis

The HbA1c analyses were performed on data from the intent-to-treat (ITT) population, defined as all randomized participants [5]. Insulin dose and safety analyses were based on data from the safety population, defined as all randomized participants who received at least one dose of study medication. The AIA population for AIA and NAb 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 last administration of premix insulin) during the 26-week on-treatment period, as defined previously [5].

Statistical methods for the total study population have been previously reported [5]. Subgroup analyses reported here were descriptive, with no formal statistical testing. As reported previously [5], the HbA1c change from baseline to week 26 was analyzed using a return to baseline multiple imputation approach for missing data, followed by an analysis of covariance (ANCOVA) model including treatment group, the randomization strata of geographical region (Indian, non-Indian) and type of diabetes (T1D, T2D), subgroup [prior use of NN-Mix (yes, no)] 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 pretreated with NovoMix 30 or Humalog Mix 25/Liprolog Mix 25, as per the randomization strata of prior use of NovoMix 30 (yes, no). For each subgroup, the adjusted least squares (LS) mean change in HbA1c was estimated for each treatment group as well as the between-group difference and the corresponding 95% confidence interval (CI). The *P* value of the subgroup-by-treatment interaction was also reported with values less than 0.1 considered as indicating a potential differential treatment effect.

For each hypoglycemia category (any, severe, and documented symptomatic events), the proportion 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 (India, non-India), type of diabetes (T1D, T2D), and screening HbA1c (less than 8%, 8% or higher), subgroup [prior use of NN-Mix (yes, no)] and subgroup-by-treatment interaction. If the model did not converge (e.g., because of sparse data), randomization strata were removed from the model. Odds ratios and 95% CIs were evaluated within each subgroup and displayed using forest plots. The *P* value of the

subgroup-by-treatment interaction was also provided.

Analyses of AIA and NAb response, TEAEs recorded throughout the study, serious TEAEs, AEs requiring special monitoring (injection site reactions, hypersensitivity reactions), and change in insulin dose were descriptive. The analyses were conducted as previously described for the total population [5]. The coronavirus disease 2019 (COVID-19) pandemic occurred during the last few months of the study, resulting in difficulty for some participants to comply with the protocol, as reported previously [5]. No further analyses of the COVID-19 impact were performed by prior use of premix insulin.

RESULTS

Baseline Characteristics

Of the 402 participants randomized, 341 (84.8%) and 61 (15.2%) participants [as per the randomization strata of prior use of NovoMix 30 (yes, no)] reported pretreatment with commercial NovoMix 30 and Humalog Mix 25/Liprolog Mix 25, respectively. Within each subgroup, demographic and baseline characteristics did not reveal any notable differences between the two treatment groups and were consistent with the total study population (ESM Table S1).

The subgroup of 341 participants with prior use of NovoMix 30 as per randomization stratum (172 and 169 participants in the SAR_{Asp}-Mix and NN-Mix groups, respectively) corresponded mostly to participants who switched from commercial NovoMix 30 to study medication at randomization. This subgroup also included some randomization stratification errors (reported as protocol deviations) in 29 participants. These participants were using commercial insulin other than NovoMix 30 (27 had used Humalog Mix 25/Liprolog Mix 25 and 2 had used Eglucent Mix 25 or Mixtard 30/70) in the last 3 months prior to the study [SAR_{Asp}-Mix: 15/172 (8.7%) participants; NN-Mix: 14/169 (8.3%) participants]. As the number of participants was relatively limited and evenly distributed between the two groups, the impact on the subgroup analysis is considered negligible.

HbA1c and Insulin Doses According to Prior Premix Insulin Treatment

In participants pretreated with commercial NovoMix 30, the LS mean decrease from baseline to week 26 in HbA1c was similar in the two treatment groups, i.e., between participants switching to SAR_{Asp}-Mix at randomization (−0.49%) compared with those continuing with NovoMix 30 (−0.54%) (Fig. 1, ESM Table S2). In participants pretreated with commercial Humalog Mix 25/Liprolog Mix 25, the LS mean decrease from baseline to week 26 in HbA1c was numerically greater in the NN-Mix group (−1.18%) compared with the SAR_{Asp}-Mix group (−0.90%), but this difference is not clinically relevant and can most probably be attributed to the small sample size in this subgroup (SAR_{Asp}-Mix: 32 participants; NN-Mix: 29 participants) (ESM Table S1).

The LS mean treatment difference between SAR_{Asp}-Mix and NN-Mix at week 26 was 0.05% (95% CI −0.195% to 0.289%) for those pretreated with NovoMix 30 and 0.28% (95% CI −0.279% to 0.830%) for those pretreated with Humalog Mix 25/Liprolog Mix 25. There was no evidence of heterogeneity of treatment effect on change in HbA1c according to the prestudy premix insulin, as illustrated by the nonsignificant interaction ($P = 0.46$).

Daily insulin doses throughout the study were similar in the two treatment groups, regardless of whether participants were using commercial NovoMix 30 or Humalog Mix 25/Liprolog Mix 25 prior to the study (Fig. 2, ESM Table S3). For participants using prior commercial NovoMix 30, there was no relevant change in daily insulin doses from baseline to day 1 (i.e., from prestudy insulin to the first week of study medication), both in participants who switched from NovoMix 30 to SAR_{Asp}-Mix at randomization (mean change 0.008 U/kg) and in participants who remained on NovoMix 30 at randomization (mean change 0.019 U/kg). Similarly, for participants using prior

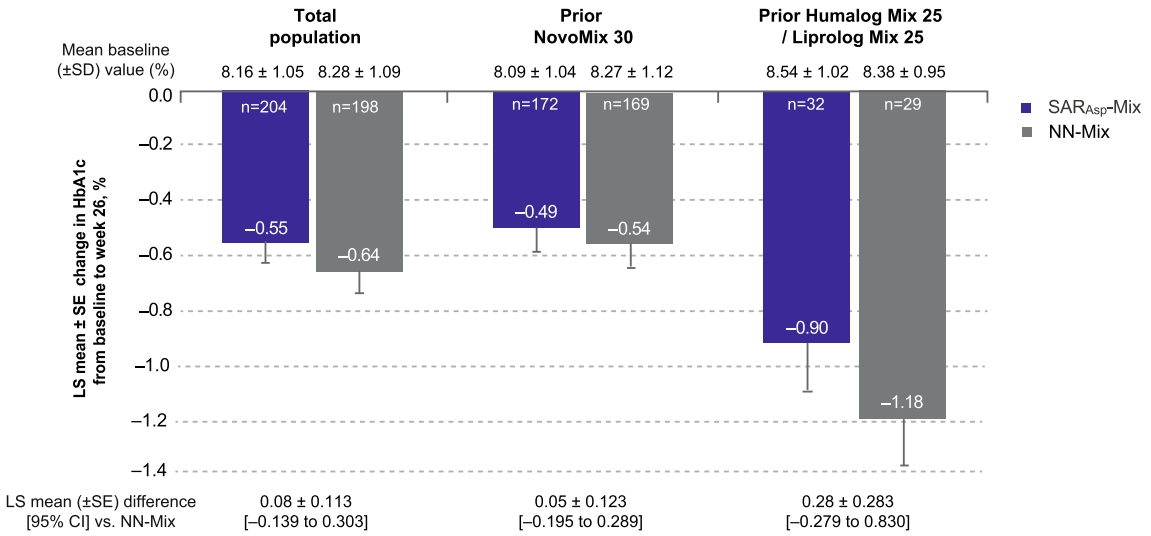

Fig. 1 Least squares mean change in HbA1c (%) from baseline to week 26 in total study population and by subgroup of prior of prior premix insulin (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) using ANCOVA analysis (with return to baseline multiple imputation) (ITT population). The statistical model used for the analysis is described in Table S2. *P* value for treatment-by-subgroup interaction = 0.4594 at week 26. *ANCOVA* analysis of covariance

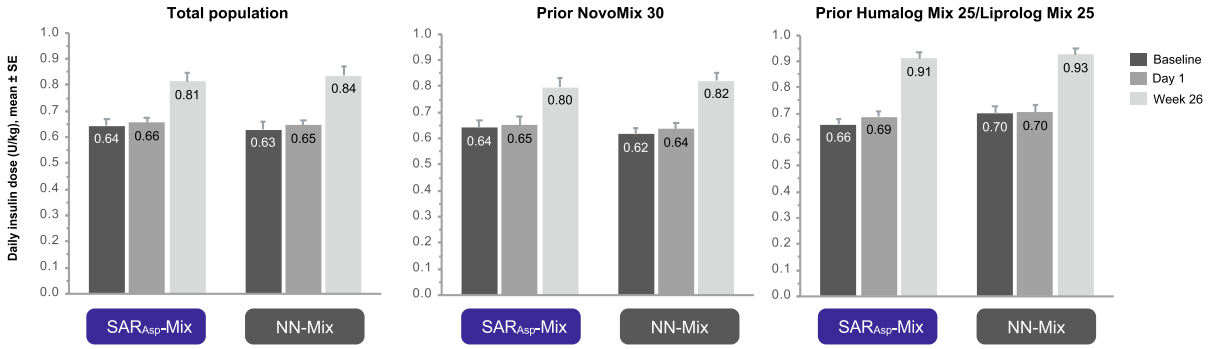

Fig. 2 Daily premix insulin doses (U/kg) in participants at baseline, day 1, and week 26 for total study population and by subgroup of prior premix insulin (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) (safety population). Data are mean ± standard error. Insulin doses are rounded to two decimal places. 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, the value presented is the median of daily doses available in the week prior to the visit

commercial Humalog Mix 25/Liprolog Mix 25, the change in daily insulin doses from baseline to day 1 was minimal, both for participants switching from Humalog Mix 25/Liprolog Mix 25 to SAR_{Asp}-Mix (mean change 0.031 U/kg) or to the comparator NN-Mix (mean change 0.004 U/kg). The change in daily insulin doses over the 26-week treatment period was comparable between the two treatment groups irrespective of the premix insulin used prior to the study. Mean increase in daily insulin doses from baseline to week 26 were 0.150 U/kg for SAR_{Asp}-

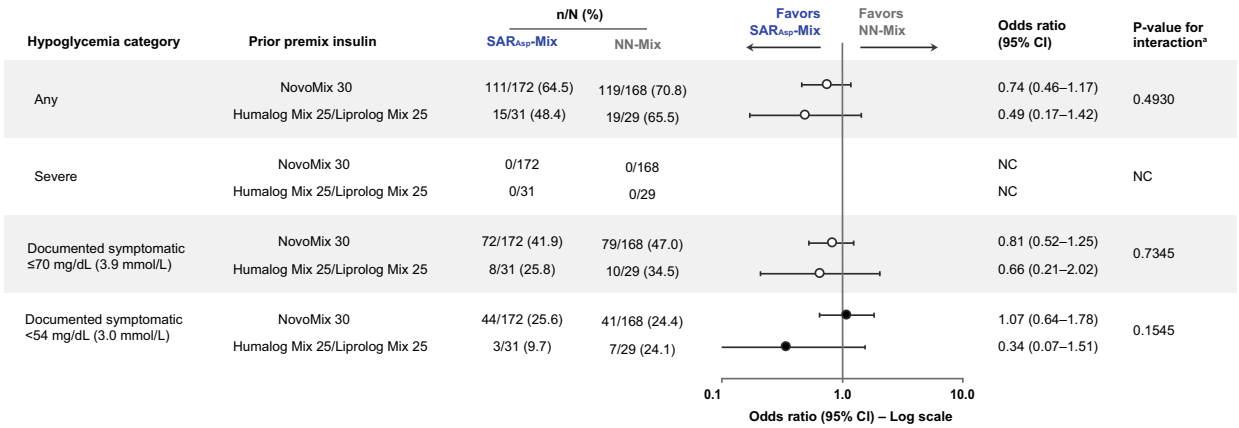

Fig. 3 Forest plot of the odds ratio of SAR_{Asp}-Mix versus NN-Mix for participants with one or more hypoglycemic events during the 26-week on-treatment period by subgroup of prior premix insulin (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) (safety population). Results are based on logistic regression model with fixed-effect terms for treatment group, randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1D, T2D), and screening HbA1c (less than 8%, 8% or higher), subgroup, and subgroup-by-treatment interaction. For the category of severe hypoglycemia, randomization strata were removed from the model because of nonconvergence. [a]*P* values of subgroup-by-treatment interaction based on the model described above. *n* number of participants with one or more treatment-emergent events, *%* percentage of participants with one or more event, *NC* model did not converge

Mix and 0.209 U/kg for NN-Mix in those pretreated with NovoMix 30. In those pretreated with Humalog Mix 25/Liprolog Mix 25, mean daily doses increased by 0.254 and 0.236 U/kg, respectively, in the two treatment groups. Changes in daily insulin doses observed in the subgroups were consistent with results observed in the total study population.

Hypoglycemia, TEAEs, AIAs, and NAbs According to Prior Premix Insulin Treatment

During the 26-week study period, the percentage of participants reporting at least one episode of hypoglycemia were similar for SAR_{Asp}-Mix and NN-Mix regardless of pretreatment with NovoMix 30 (64.5% and 70.8% in the SAR_{Asp}-Mix and NN-Mix groups, respectively) or Humalog Mix 25/Liprolog Mix 25 (48.4% and 65.5% in the SAR_{Asp}-Mix and NN-Mix groups, respectively) (Fig. 3). The small sample size in the prior use of Humalog Mix 25/Liprolog Mix 25 subgroup ($n = 60$) should be considered when interpreting these results. There were no reported episodes of severe hypoglycemia in either subgroup. Documented symptomatic hypoglycemia events were also reported by a similar proportion of participants in each treatment group regardless of pretreatment with either commercial premix insulin. Within each subgroup by prior premix insulin, the absence of a relevant treatment difference on the percentage of participants reporting at least one hypoglycemia event was supported by the 95% CIs of the odds ratio of SAR_{Asp}-Mix versus NN-Mix (including 1.0 for each category of hypoglycemia) (Fig. 3). Additionally, there was no evidence of heterogeneity of the treatment effect according to the prestudy premix insulin for any category of hypoglycemia (all *P* greater than 0.1) (Fig. 3). Hypoglycemia results observed in the subgroups were generally consistent with those in the total study population [5].

A summary of TEAEs reported during the 26-week treatment period is outlined in ESM Table S4. Both SAR_{Asp}-Mix and NN-Mix were

well tolerated regardless of the type of prior premix mealtime insulin. In participants using commercial NovoMix 30 prior to the study, TEAEs were reported in similar proportions in the two treatment groups (SAR_{Asp}-Mix: 18.6%; NN-Mix: 22.0% participants). In participants using Humalog Mix 25/Liprolog Mix 25 prior to the study, the proportion of TEAEs during the 26-week period was also similar in the two treatment groups (SAR_{Asp}-Mix: 12.9%; NN-Mix: 13.8% participants). Consistent with the total population, the most frequently reported TEAEs in both treatment groups were infections and infestations, regardless of the type of prior premix insulin (data not shown). The incidence of serious TEAEs was similar between treatment groups in participants using prior NovoMix 30 or prior Humalog Mix 25/Liprolog Mix 25 (ESM Table S4). There were no TEAEs leading to permanent treatment discontinuation and no injection site reactions. One potential hypersensitivity reaction (pruritis) was reported by a participant in the SAR_{Asp}-Mix group with prior use of NovoMix 30; the event was adjudicated by an independent committee as not an allergic reaction. A single death occurred during the on-treatment period in a participant in the NN-Mix group with prior use of NovoMix 30 and was not considered to be related to study medication. The safety results observed in each subgroup during the 26-week treatment period were generally consistent with those reported for the total study population.

The percentage of participants who were positive for AIAs at baseline in each treatment group was similar irrespective of prior use of NovoMix 30 (SAR_{Asp}-Mix: 46.5%; NN-Mix: 52.3%) or prior Humalog Mix 25/Liprolog Mix 25 (SAR_{Asp}-Mix: 64.3%; NN-Mix: 64.0%) (ESM Table S5, Fig. 4). The percentage of participants positive for AIA at baseline was slightly higher in those pretreated with Humalog Mix 25/Liprolog Mix 25 compared with those pretreated with NovoMix 30. The percentage of participants with a treatment-emergent AIA response (participants who either de novo developed positive AIAs postbaseline or exhibited a $\geq$ 4-fold increase in titer compared with baseline) during the 26-week treatment period was similar in both treatment groups according to prior use of NovoMix 30 (SAR_{Asp}-Mix: 32.7%; NN-Mix: 31.3%) or prior Humalog Mix 25/Liprolog Mix 25 (SAR_{Asp}-Mix: 35.5%; NN-Mix: 34.5%) (ESM Table S5, Fig. 4). The percentage of participants with detectable AIAs at least at one timepoint during the study was also similar with SAR_{Asp}-Mix and NN-Mix irrespective of prior commercial premix insulin treatment (ESM Table S5, Fig. 4).

The percentages of participants with AIA cross-reacting with human insulin during the 26-week on-treatment period were similar between SAR_{Asp}-Mix and NN-Mix, ranging between 86.7% and 95.1% for participants pretreated with NovoMix 30, and between 86.7 and 100% for participants pretreated with Humalog Mix 25/Liprolog Mix 25. Over the 26-week treatment period, AIA titers were comparable between treatment groups and remained relatively low and unchanged over time (data not shown).

The percentage of participants who were positive for NAbs at baseline in each treatment group was similar in participants using prior NovoMix 30 [SAR_{Asp}-Mix: 5/157 (3.2%) participants; NN-Mix: 6/151 (4.0%) participants], while small numerical differences were observed in the prior Humalog Mix 25/Liprolog Mix 25 subgroup [SAR_{Asp}-Mix: 2/28 (7.1%) participants; NN-Mix: 4/25 (16.0%) participants] (ESM Table S6, Fig. 4). The percentage of participants positive for NAb at baseline was slightly higher in those pretreated with Humalog Mix 25/Liprolog Mix 25 compared with those pretreated with NovoMix 30. The percentage of participants with a treatment-emergent NAb response during the 26-week treatment period was similar between treatment groups in participants using prior NovoMix 30 [SAR_{Asp}-Mix: 14/168 (8.3%) participants; NN-Mix: 16/166 (9.6%) participants], while small numerical differences were seen in the prior Humalog Mix 25/Liprolog Mix 25 subgroup [SAR_{Asp}-Mix: 2/31 (6.5%) participants; NN-Mix: 0/29 participants] (ESM Table S6, Fig. 4). The percentage of participants with detectable NAbs at least at one timepoint during the study was similar with SAR_{Asp}-Mix and NN-Mix irrespective of prior commercial premix insulin treatment.

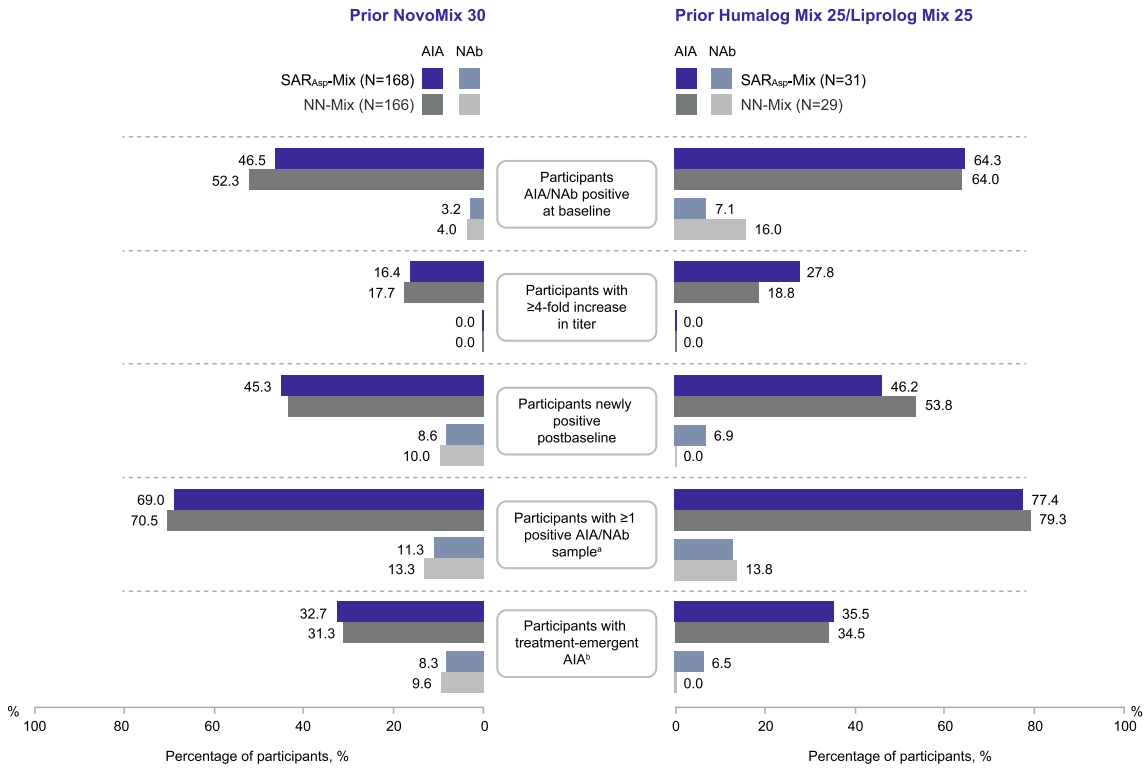

Fig. 4 Anti-insulin aspart antibody (AIA) and neutralizing antibody (NAb) response at baseline and week 26 by subgroup of prior premix insulin (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) (AIA population). Data shown as percentage of participants with each outcome [see ESM Table S5 (AIA) and ESM Table S6 (NAb) for the denominators]. [a]Prevalence: participants with at least one positive AIA/NAb sample at baseline or postbaseline. [b]Incidence: participants with newly positive AIA/NAb postbaseline (treatment-induced) or with ≥ 4-fold increase in titer (treatment-boosted) (i.e., participants with treatment-emergent AIAs/NAbs). *AIA* anti-insulin aspart antibody, *NAb* neutralizing antibody

DISCUSSION

The GEMELLI M study showed that SAR_{Asp}-Mix provides effective glycemic control with a safety and immunogenicity profile similar to NN-Mix in people with diabetes treated for 26 weeks [5]. This subgroup analysis compares clinical outcomes of SAR_{Asp}-Mix versus NN-Mix in the subgroup of participants pretreated with different commercial premix insulin analog preparations who then switched insulin treatment at randomization. There were no relevant differences observed for any of the clinical outcomes, with findings generally consistent between subgroups and similar to the previously reported results for the total study population [5].

Following randomization, participants were to switch from their previous commercial premix insulin (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) to an equivalent dose of SAR_{Asp}-Mix or NN-Mix. When switching from the reference product [prestudy NovoMix 30 (NN-Mix)] to the biosimilar premix aspart product (SAR_{Asp}-Mix) at randomization, there was minimal change in insulin doses during the first week of study treatment, as for participants who continued on NovoMix 30 (as NN-Mix). There was also only minimal change in daily insulin dose when participants switched from previous Humalog Mix 25/Liprolog Mix 25 to study medication (SAR_{Asp}-Mix or NN-Mix). This indicates that most participants actually switched from their prestudy premix insulin to study medication using a unit-to-unit (1:1) conversion.

The mean change from baseline to week 26 in HbA1c levels, in the SAR_{Asp}-Mix versus the NN-Mix group by prior use of commercial premix insulin, was generally consistent with the results for the total population. The limited number of participants pretreated with Humalog Mix 25/Liprolog Mix 25 ($\sim$ 15%) is reflected by the wider confidence intervals and greater uncertainty for the estimates of differences in HbA1c between treatments compared with the analysis by prior use of NovoMix 30. The safety profile of both treatments was similar for participants pretreated with NovoMix 30 and with Humalog Mix 25/Liprolog Mix 25. Hypoglycemia outcomes were consistent between SAR_{Asp}-Mix and NN-Mix irrespective of the prestudy premix insulin, with the results observed in the subgroups generally consistent with those in the total study population. Similarly, TEAEs reported for the two treatment groups were similar in each subgroup and were consistent with the AE profile reported in total study population [5]. Within each subgroup, no relevant treatment difference was observed in the number of participants who had detectable AIAs and NAbs at baseline and during the subsequent 26 weeks of treatment.

A limitation of this subgroup analysis is that the study was not designed or powered to prospectively compare SAR_{Asp}-Mix and NN-Mix in participants with diabetes pretreated with commercial NovoMix 30 and with Humalog Mix 25/Liprolog Mix 25. Therefore, caution should be exercised in the interpretation of the results, and statistical limitations should be acknowledged to avoid overinterpretation [9]. Statistical models for these subgroup analyses were limited to the change in HbA1c and hypoglycemia incidence as prespecified in the statistical plan, to limit the risk of chance findings. Other outcomes were analyzed descriptively. No significant subgroup-by-treatment interaction was observed in both statistical models (as defined by P greater than 0.10), thereby confirming that the treatment effect for HbA1c and hypoglycemia was not dependent on the participant's subgroup. The subgroups by prior premix insulin were used as stratification factor in the randomization process. Although some randomization errors were noted, the number was relatively low and they were evenly distributed between groups, so that the impact on the analysis findings were negligible. Although the AIA and NAb response is generally greater in patients with T1D compared with T2D, the small number of enrolled participants with T1D meant that it was not possible to evaluate potential differences in the immune response of SAR_{Asp}-Mix versus NN-Mix by prior premix insulin treatment.

The open-label design necessitated by the different injection devices used for SAR_{Asp}-Mix and NN-Mix was another potential limitation of the study. This was partially mitigated by performing assessments of objectively collected data in central laboratories that were blinded to the study treatment. In addition, the sponsor study team remained blinded to the treatment group until database lock. As reported previously [5], the COVID-19 pandemic also occurred during the last few weeks of the study in some countries. Systems were put in place to ensure participants' safety, retention, and data capture. The impact of COVID-19 on the study results was kept to a minimum and restricted to the primary efficacy endpoint with limited impact on safety data (mainly underreporting of hypoglycemia events, similarly in both treatment groups) but with no overall impact on difference between treatments groups in relation to safety or immunogenicity. No analyses of the COVID-19 impact were performed by prior use of premix insulin.

CONCLUSIONS

In summary, this subgroup analysis show that participants in GEMELLI M pretreated with NovoMix 30 who were then randomized to SAR_{Asp}-Mix using the recommended 1:1 dose conversion have an efficacy, safety, and immunogenicity profile similar to those participants who continued their prestudy NovoMix 30 medication. Similar findings were observed among participants who were switched 1:1 from Humalog Mix 25/Liprolog Mix 25 to SAR_{Asp}-Mix and NN-Mix study treatment. The findings of this study suggest that SAR_{Asp}-Mix is a well-

tolerated, effective, and safe treatment option when prescribed for participants with diabetes who have had prior treatment with other commercial premix insulin analog therapies and that patients can conveniently be switched to SAR_{Asp}-Mix on a unit-to-unit (1:1) conversion.

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List of Investigators. The participating investigators are listed in the Appendix of the Electronic Supplementary Material.

Disclosures. S.R Aravind, Kiran P Singh, Liliia Mogylnytska, Alsu G Zalevskaya, and Beata Matyjaszek-Matuszek report no disclosures. Karin Wernicke-Panten, My-Liên Nguyên-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 on the European Union Drug Regulatory Clinical Trials Database (2017-000092-84) and was conducted in accordance with the ethical principles of the Declaration of Helsinki of 1964 and its later amendments, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and all applicable laws, rules, and regulations. 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 participant 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 anal-

ysis 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.vivli.org/.

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