

Pharmacokinetic Similarity between Biosimilar Insulin Aspart Premix SAR341402 Mix 70/30 and Originator Insulin Aspart Mix 70/30 (NovoMix 30) in Indian Adults with Type 2 Diabetes: GEMELLI M Substudy

Viswanathan Mohan, Wolfgang Schmider¹, Kiran P. Singh², Baerbel Rotthaeuser¹, Bhaswati Mukherjee³, S. R. Aravind^{4,5}

MV Diabetes Specialities Centre, Madras Diabetes Research Foundation, Chennai, India, ¹Sanofi, Frankfurt, Germany, ²Department of Endocrinology, Fortis Hospital Mohali, Chandigarh, India, ³Sanofi, Paris, France, ⁴Diabetes Care and Research Center, Diacon Hospital, Bengaluru, Karnataka, India, ⁵Columbia Asia Hospital, Bengaluru, Karnataka, India

Abstract

Background: We compared the pharmacokinetic exposure, efficacy, safety and immunogenicity of biosimilar insulin aspart premix SAR341402 Mix 70/30 (SAR_{Asp}-Mix) with its originator NovoMix[®] 30 insulin aspart mix (NN-Mix) in adults with type 2 diabetes. **Methods:** This was a randomized, open-label, parallel-group, substudy of the phase 3 GEMELLI M trial performed in three Indian centres. Totally 13 Indian participants previously treated with premix insulin received a single subcutaneous 0.3 U/kg dose of each treatment and underwent pharmacokinetic sampling for 16 h after dosing. Participants were then treated for 26 weeks as per the main GEMELLI M trial with efficacy, safety and immunogenicity compared between groups. **Results:** The extent of exposure (area under the plasma concentration-time curve and maximum insulin aspart concentration) to SAR341402 insulin aspart in SAR_{Asp}-Mix and to insulin aspart in NN-Mix was similar following single doses of the allocated treatment. After 26 weeks, the mean \pm SD [median] change in HbA_{1c} from baseline was similar in both treatment groups (SAR_{Asp}-Mix $-0.38\% \pm 1.54$ [-1.00%]; NN-Mix $-0.18\% \pm 1.97$ [-0.80%]). Other efficacy endpoints, insulin dosages, anti-insulin aspart antibody response, hypoglycemia and adverse events were similar between groups. **Conclusions:** Our results support the findings from previous studies, that SAR_{Asp}-Mix has a similar pharmacokinetic profile to NN-Mix and provides effective glycemic control with similar safety and immunogenicity profile in Indian adults with type 2 diabetes.

Keywords: Biosimilar, insulin aspart mix, pharmacokinetics, premix, SAR341402, type 2 diabetes

INTRODUCTION

SAR341402 Mix 70/30, suspension for injection 100 U/mL (SAR_{Asp}-Mix; Truvelog Mix 30[®], Sanofi, Paris, France), is a premixed suspension of insulin aspart, a human insulin analog.^[1] The active ingredient is SAR341402 insulin aspart (SAR-Asp, Insulin aspart Sanofi[®], Sanofi), a rapid-acting insulin analog produced by recombinant DNA technology, and the first approved biosimilar to NovoRapid[®] (NN-Asp; Novo Nordisk, Bagsvaerd, Denmark) in June 2020.^[2] The SAR_{Asp}-Mix suspension contains 70% intermediate-acting protamine SAR-Asp and 30% SAR-Asp solution,^[1] thereby providing basal and prandial insulin coverage in a single injection. This 70/30 intermediate-acting/rapid-acting insulin ratio remains the most common one used in clinical

practice.^[3] SAR_{Asp}-Mix was developed as a biosimilar to its reference insulin aspart premixed product NovoMix[®] 30 (Novo Nordisk; hereafter referred to as NN-Mix).

Phase 1^[4] and phase 3 (GEMELLI M)^[5] trials were performed to confirm that SAR_{Asp}-Mix and NN-Mix are highly

Address for correspondence: Dr. Bhaswati Mukherjee, MD, Sanofi, 54 Rue La Boétie, 75008 Paris, France. E-mail: Bhaswati.Mukherjee@sanofi.com

Submitted: 31-May-2022

Revised: 08-Jul-2022

Accepted: 21-Jul-2022

Published: 20-Sep-2022

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Mohan V, Schmider W, Singh KP, Rotthaeuser B, Mukherjee B, Aravind SR. Pharmacokinetic similarity between biosimilar insulin aspart premix SAR341402 Mix 70/30 and originator insulin aspart mix 70/30 (NovoMix 30) in Indian adults with type 2 diabetes: GEMELLI M substudy. Indian J Endocr Metab 2022;26:354-61.

Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/ijem.ijem_216_22

similar. A euglycemic clamp study in subjects with type 1 diabetes (T1D) confirmed similar pharmacokinetic exposure for SAR_{Asp}-Mix versus NN-Mix and versus US-approved NovoLog Mix 70/30, with a distinct exposure profile of SAR_{Asp}-Mix compared with SAR-Asp.^[4] Pharmacodynamic results were in support of the pharmacokinetic findings. A subsequent phase 3 clinical trial (GEMELLI M) compared the efficacy, safety, and immunogenicity of SAR_{Asp}-Mix and NN-Mix in people with T1D or type 2 diabetes (T2D).^[5] SAR_{Asp}-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.^[5]

At the request of the Indian Health Authority, a substudy of GEMELLI M was conducted to provide additional pharmacokinetic data following administration of single doses of SAR_{Asp}-Mix and NN-Mix in a subset of Indian participants with T2D.

MATERIALS AND METHODS

Study design

Three Indian sites from GEMELLI M participated in this randomized, single-blind, controlled, two-group, parallel-group, pharmacokinetic substudy. The study design is outlined in **Supplementary Figure 1**. The substudy was initiated in June 2020 and completed in March 2021. The substudy is registered on Clinical Trials Registry-India (CTRI/2019/05/019416) with the main GEMELLI M study registered on the European Union Drug Regulating Authorities Clinical Trials Database (2017-000092-84). The study comprised a 2-week screening period followed by an inpatient single-dose treatment on day 1 (week 0), a 16-h pharmacokinetic sampling period (with overnight stay), followed by a 26-week efficacy and safety treatment period as per the main GEMELLI M study.^[5]

The pharmacokinetic substudy protocol was approved by local review boards/independent ethics committees and conducted in accordance with the Declaration of Helsinki. Written informed consent for the procedures was obtained from all participants before study entry.

Study participants

Eligibility criteria for the main GEMELLI M study have been described previously.^[5] In this substudy, adults with T2D for at least 1 year prior to screening, a body-mass index (BMI) ≤ 40 kg/m², HbA1c levels of $\leq 10\%$ (86 mmol/mol), using premix insulin (NovoMix 30, Humalog Mix 25 or Liprolog Mix 25) at least two times daily for >3 months before the screening visit and willing to comply with the specific pharmacokinetic study procedures were eligible to participate. At the discretion of the investigator, participants with a measured HbA1c in the range of 9% (≥ 75 mmol/mol) to 10% (≤ 86 mmol/mol) could be included if they were not candidates for an MDI treatment regimen. Key exclusion criteria included the use of injectable glucose-lowering treatments other than premix insulin analogs

or the use of an insulin pump in the last 3 months before screening.

Pharmacokinetic study procedures and assessments

At the baseline visit, eligible participants for the substudy attended the study site and fasted without injecting their prestudy premixed insulin for at least 8 h. Confirmed eligible participants were randomized 1:1 to either SAR_{Asp}-Mix or NN-Mix, stratified by screening HbA1c ($<8.0\%$, $\geq 8.0\%$) and prior use of NN-Mix (Yes, No). Participants received a single subcutaneous 0.3 U/kg dose of their allocated treatment (SAR_{Asp}-Mix or NN-Mix) at approximately 08:00. SAR_{Asp}-Mix and NN-Mix 100 U/mL suspension were supplied in 3 mL prefilled disposable SoloSTAR and FlexPen pens, respectively. Participants then had breakfast with the meal content determined according to the investigator's judgement, with a focus on the prevention of hypoglycemia or significant hyperglycemia during the pharmacokinetic assessment period. The insulin dose of 0.3 U/kg was considered appropriate for pharmacokinetic assessment to cover carbohydrate intake during breakfast without significantly increasing the risk of hypoglycemia.

During the 16-h pharmacokinetic sampling period, the investigator managed any hypoglycemia or hyperglycemia according to his/her medical judgement and the protocol requirements. Seven-point self-monitored plasma glucose (SMPG) assessments during the 16-h sampling period were recommended. Countermeasures were administered if hypoglycemia was experienced, and human insulin was given if additional insulin was needed. Alternatively, administration of insulin lispro at low doses, according to the investigator's judgement, was also permitted. Participants had lunch and dinner at their usual times on the day of the pharmacokinetic visit. Participants remained in the study clinic overnight and were discharged home the next day after completing the mandated safety assessments. The total duration of the pharmacokinetic substudy was approximately 24 h.

Following discharge from the clinic, participants continued their allocated study medication (SAR_{Asp}-Mix or NN-Mix) according to their assigned treatment until the end-of-treatment (week 26). 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. Premixed doses were then titrated to achieve protocol-specified glycemic targets, as reported previously.^[5] The use of background oral anti-diabetic drug (OAD) treatment (except sulfonylureas or glinides) was permitted but was to be continued on a stable dose throughout the study.

Pharmacokinetic evaluation

During the 16-h pharmacokinetic sampling period, venous blood samples for pharmacokinetic analysis were collected before the single subcutaneous administration of the study drug, and then at frequent times (every 20 to 120 min) after dosing in each treatment group. The 16-h sampling period was

deemed appropriate based on the results of an earlier phase 1 study evaluating the pharmacokinetic profile of SAR_{Asp}-Mix.^[4] Samples were centrifuged within 20 min of collection. Plasma was collected and kept frozen (–60 to –80°C) until analysis. Plasma concentrations of insulin aspart following the administration of SAR_{Asp}-Mix and NN-Mix were analyzed by using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay at Syneos Health (Quebec, Canada). Plasma concentrations within the validated concentration range (50–4000 pg/mL) were used to calculate pharmacokinetic endpoints. Inter-assay precision (% coefficient of variation [CV]) and inter-assay accuracy (%bias) during validation were ≤15%.

Pharmacokinetic endpoints

Maximum observed plasma insulin aspart concentration (C_{max}), area under the plasma insulin aspart concentration-time curve from 0 to the time of the last concentration above the limit of quantification (AUC_{last}) and AUC versus time curve extrapolated to infinity (AUC_{inf}) were the exploratory pharmacokinetic endpoints of the substudy. Parameter estimates for insulin aspart after administration of SAR_{Asp}-Mix and NN-Mix were calculated using standard noncompartmental methods with Phoenix WinNonlin® version 8.1 (Certara USA, Inc., Princeton, NJ). AUC was calculated by the linear trapezoidal method.

Study procedures and assessments during the 26-week treatment period

Participants enrolled in the substudy continued their assigned treatment with efficacy, safety and immunogenicity assessments planned during the 26-week open-label treatment period as described previously for the main study.^[5]

The allocated treatment was administered at least two times daily during the 26-week treatment period via prefilled disposable pen devices (SoloSTAR® for SAR_{Asp}-Mix, FlexPen® for NN-Mix). Changes in the SAR_{Asp}-Mix or NN-Mix dose were based on SMPG measurements with insulin doses titrated to achieve protocol-specified glycemic targets. 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. Systems were put in place to ensure participant safety, retention and data capture, as reported previously.^[5]

Endpoints during the 26-week treatment period

The primary efficacy endpoint was the change in HbA1c from baseline to week 26. Other efficacy outcomes (tertiary/exploratory endpoints) included the percentage of participants with HbA1c <7.0% (<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 (2h PPG minus preprandial plasma glucose) at breakfast, lunch and dinner based on 7-point SMPG profiles, and in 7-point SMPG profiles.

The safety endpoints (secondary endpoints) included hypoglycemic events (classified according to American

Diabetes Association categories^[6-8]), 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 ≥4-fold 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,^[9,10] as reported previously.^[5]

Sample size and statistical analyses

In line with the exploratory objective, the sample size of this substudy was based on empirical considerations without a formal sample size calculation. Approximately 14 Indian participants with T2D (seven per treatment group) were planned to be enrolled to achieve a total of at least 12 evaluable participants. Pharmacokinetic endpoints were summarized by treatment group on the pharmacokinetic population (defined as subjects who had measurable insulin aspart concentrations and no major or critical protocol deviations related to study drug administration) using descriptive statistics.

To summarize pharmacokinetic data, primary analysis and a prespecified sensitivity analysis were conducted. The primary analysis included all pharmacokinetic profiles as measured, with no adjustments. As participants had administered a commercial premix insulin preparation (NovoMix 30 or Humalog Mix 25/Liprolog Mix 25) on the day before their pharmacokinetic assessment, a sensitivity analysis was conducted to explore whether incomplete washout of insulin aspart might have an impact on the pharmacokinetic comparisons. In the sensitivity analysis, profiles, where the predose (C_0) insulin aspart concentration exceeded 5% of C_{max} , were adjusted; concentrations were corrected as $C(t)_{adj} = C(t)_{obs} - C(0)e^{(-\lambda z)t}$, where 't' is the time postdose and λz is the elimination rate constant calculated from the unadjusted data.

Analyses of efficacy, safety and immunogenicity in this substudy during the 26-week treatment period were descriptive with no formal statistical testing. Hypoglycemia and adverse events were described in the safety population (all randomized participants who received at least one dose of study medication). The percentage of participants in which COVID-19 had a major impact on their participation in the study was determined.

Statistical analyses were performed using SAS[®], Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC).

RESULTS

Study population

Of the 21 participants screened, 13 individuals were randomized. All participants completed the pharmacokinetic assessment and subsequent 26-week treatment period. Demographics and baseline characteristics are shown in **Table 1**. Participants had a mean age of 54.7 years, were predominantly male (92%) and had a mean duration of diabetes of 12.9 years. The mean BMI at baseline was 26.3 kg/m².

Table 1: Baseline characteristics of participants with T2D included in the pharmacokinetic substudy (substudy safety population)

	SAR _{Asp} -Mix (n=6)	NN-Mix (n=7)
Male, n (%)	5 (83.3)	7 (100.0)
Age (years)	54.3±4.2 [49-59]	55.0±15.2 [39-77]
Asian race, n (%)	6 (100.0)	7 (100.0)
Body weight	74.8±13.3 [62-98]	69.2±8.3 [59-80]
Body mass index, kg/m ²	27.3±5.2 [21.3-36.7]	25.5±2.8 [21.9-29.7]
Duration of T2D, years	15.0±4.7 [8-20]	11.2±8.4 [3-24]
Duration of OAD treatment, years	13.2±4.4 [8-20]	11.0±8.5 [2-24]
Previous premix insulin*, n (%)		
NovoMix 30	5 (83.3)	5 (71.4)
Humalog Mix 25/Liprolog Mix 25	1 (16.7)	2 (28.6)
OAD treatment at screening, n (%)	6 (100.0)	7 (100.0)
HbA1c, %	8.35±0.47 [7.9-9.0]	8.10±1.19 [6.7-10.2]

All data are mean±standard deviation [range] unless stated otherwise.

*Previous premix insulin analog treatment within 3 months prior to screening HbA1c, glycated hemoglobin; OAD, oral anti-diabetic drug; T2D, type 2 diabetes

NN-Mix was used by 77% of participants before study entry and all participants were on concomitant OAD medications. Three participants had trial impact due to COVID-19 (2 in SAR_{Asp}-Mix and 1 in NN-Mix groups).

Single dose pharmacokinetics

Pharmacokinetic data were available for six participants receiving SAR_{Asp}-Mix and for seven participants receiving NN-Mix. The pharmacokinetic profiles of the two insulin aspart mix products following single doses (0.30 U/kg) are shown in **Figure 1**, with descriptive statistics per treatment for the pharmacokinetic parameters (AUC and C_{max}) shown in **Table 2**. Insulin exposure (C_{max} and AUC) in the primary analysis tended to be slightly higher for SAR_{Asp}-Mix relative to NN-Mix, but between-subject variability within a treatment group tended to be higher than differences between treatments. Between-subject variability was higher for NN-Mix (CVs between 56% and 59%) than for SAR_{Asp}-Mix (CVs between 11% and 34%).

The predose samples of five participants (three receiving SAR_{Asp}-Mix and two receiving NN-Mix) showed insulin aspart concentrations that exceeded 5% of C_{max} of the respective profiles. In a sensitivity analysis, where profiles for these participants were corrected to account for residual insulin aspart from the previous dose, exposure was slightly lower compared with the primary analysis [**Figure 2, Table 2**]. However, differences between treatments and between-subject variability were relatively unchanged between the primary and sensitivity analyses.

Insulin doses over the 26-week treatment period

Daily insulin doses increased over the course of the 26-week on-treatment period in both treatment groups (mean increases of 0.204 and 0.282 U/kg in the SAR_{Asp}-Mix and NN-Mix groups, respectively), with a relatively similar trajectory over time [**Figure 3a, Supplementary Table 1**]. No relevant changes in insulin doses from baseline to day 1 were

Table 2: Pharmacokinetic parameters following single doses (0.30 U/kg) of SAR_{Asp}-Mix and NN-Mix - Primary and sensitivity analyses (pharmacokinetic population)

Analysis	Parameter [unit]	SAR _{Asp} -Mix (n=6)	NN-Mix (n=7)
Primary*	C _{max} [pg/mL]	2080±625 (2000) [30]	1940±1110 (1670) [57]
	AUC _{last} [pg·h/mL]	13500±4520 (12900) [34]	11200±6570 (9860) [59]
	AUC _{inf} [pg·h/mL]	14300±1620 [†] (14200) [11]	13800±7640 [‡] (12100) [56]
Sensitivity§	C _{max} [pg/mL]	1850±682 (1750) [37]	1830±1040 (1590) [57]
	AUC _{last} [pg·h/mL]	11000±4010 (10100) [36]	10400±5770 (9310) [56]
	AUC _{inf} [pg·h/mL]	14400±1590 [†] (14400) [11]	12700±6910 [‡] (11200) [55]

Results are presented as mean±SD (geometric mean) [CV%]. *The primary analysis includes pharmacokinetic data for all participants in the substudy, with no adjustments made to any concentration data; predose concentrations exceeded 5% of C_{max} for three participants receiving SAR_{Asp}-Mix and for two participants receiving NN-Mix. [†]N=4; AUC_{inf} excluded where >30% extrapolated. [‡]N=6; AUC_{inf} excluded where >30% extrapolated. [§]In the sensitivity analysis, where a pharmacokinetic profile had a predose concentration >5% of C_{max}, concentrations were corrected as C(t)adj=C(t)obs - C(0)e^{-λz t}, where t=time postdose and λz=the elimination rate constant calculated from the unadjusted data. Profiles were corrected for three participants receiving SAR_{Asp}-Mix and for two participants receiving NovoMix 30. [†]N=5; AUC_{inf} excluded where >30% extrapolated. [‡]N=6; AUC_{inf} excluded where >30% extrapolated. AUC_{last}, area under the drug plasma concentration-time curve from time 0 to the time of the last quantifiable data point; AUC_{inf}, area under the drug plasma concentration-time curve from time 0 to infinity; C_{max}, maximum insulin aspart concentration in plasma; CV, coefficient of variation

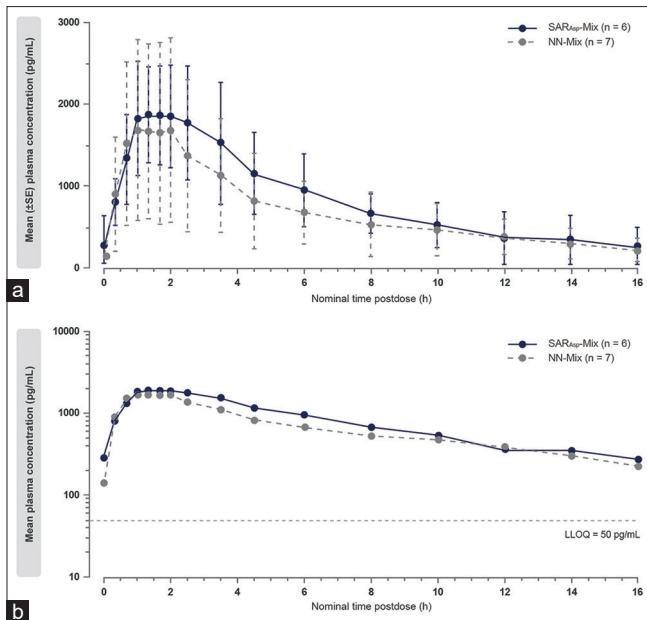


Figure 1: Mean plasma concentration profiles of SAR-Asp for SAR_{Asp}-Mix and insulin aspart for NN-Mix treatment (pharmacokinetic population, primary analysis). (a) Linear scale. (b) Semi-logarithmic scale. Values represent means \pm SD. LLOQ = lower level of quantification (50 pg/mL), shown as a dotted line in b

reported (i.e., from commercial prestudy insulin to the first week of study medication), in either treatment group. The change from baseline to day 1 was close to 0, confirming the 1:1 switch from pre-study insulin to study medication.

Glycemic control over the 26-week treatment period

In the substudy randomized population, HbA_{1c} decreased similarly in both groups from baseline to week 26, with a mean \pm SD (median) change of $-0.38 \pm 1.54\%$ (-1.00%) in the SAR_{Asp}-Mix group and $-0.18 \pm 1.97\%$ (-0.80%) in the NN-Mix group [Supplementary Table 2, Figure 3b].

Similar proportions of study participants achieved target HbA_{1c} values of $< 7.0\%$ at week 26 (SAR_{Asp}-Mix 33.3%; NN-Mix 28.6%). No clinically meaningful differences were observed between SAR_{Asp}-Mix and NN-Mix for any of the additional efficacy analyses, including the assessment of FPG and SMPG parameters (including PPG excursions) [Supplementary Table 2].

Hypoglycemia over the 26-week treatment period

The proportion of participants with at least one hypoglycemic was similar in the SAR_{Asp}-Mix group (66.7%) and the NN-Mix group (57.1%) [Supplementary Table 3]. There were no reported episodes of severe hypoglycemia, and no hypoglycemia event met the criteria for an SAE or led to permanent treatment discontinuation. Other categories of hypoglycemia showed a similar incidence of hypoglycemia in the two groups.

Rates of hypoglycemia showed the same pattern as incidence for all categories [Supplementary Table 3]. There was a similar

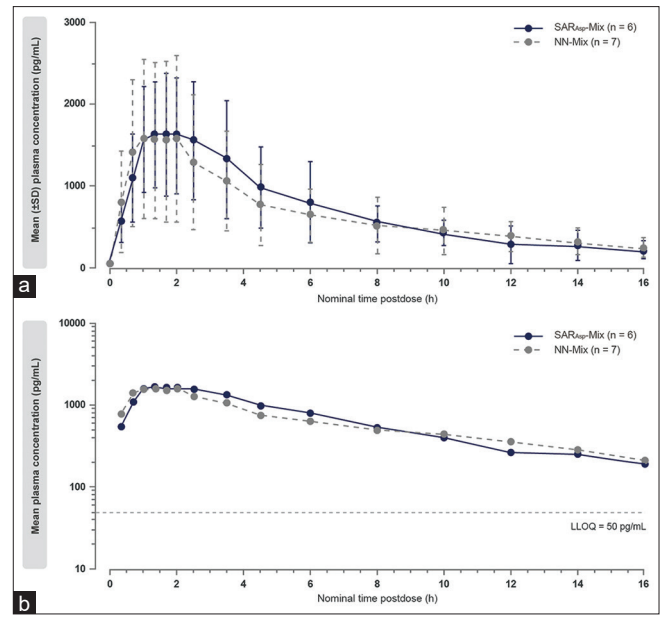


Figure 2: Mean plasma concentration profiles of SAR-Asp for SAR_{Asp}-Mix and insulin aspart for NN-Mix treatment (pharmacokinetic population, sensitivity analysis). (a) Linear scale. (b) Semi-logarithmic scale. Values represent means \pm SD. LLOQ = lower level of quantification (50 pg/mL), shown as a dotted line in b

overall rate of hypoglycemia in the two groups (SAR_{Asp}-Mix 5.28, NN-Mix 5.12).

In the three participants with trial impact due to COVID-19 (see below), the number of hypoglycemia events and event rates were similar between the two treatment groups for any hypoglycemia (SAR_{Asp}-Mix: 5 [4.92]; and NN-Mix: 3 [6.05]) and the other hypoglycemia categories (data not shown).

Adverse events during the 26-week treatment period

TEAEs were reported in five of the six participants (83.3%) in the SAR_{Asp}-Mix group and in two of the seven participants (28.6%) in the NN-Mix group (data not shown). Gastrointestinal disorders were the most frequently reported TEAEs (SAR_{Asp}-Mix three participants; NN-Mix no participants). There were no treatment-emergent SAEs, TEAEs leading to death, or TEAEs leading to permanent treatment discontinuation. No TEAEs in either treatment group were reported as related to COVID-19. One participant in the SAR_{Asp}-Mix group reported a hypersensitivity reaction. This event of asthma was mild in severity, non-serious, resolved without sequelae and did not result in permanent discontinuation of study treatment. The Investigator considered the event as not related to study medication and the event was adjudicated as not an allergic reaction by an independent adjudication committee. No injection site reactions were reported.

Immunogenicity over the 26-week treatment period

At baseline, detectable AIAs were found in five participants in the SAR_{Asp}-Mix group and two participants in the NN-Mix; no participants had a missing AIA sample at baseline [Supplementary Table 4]. The number of

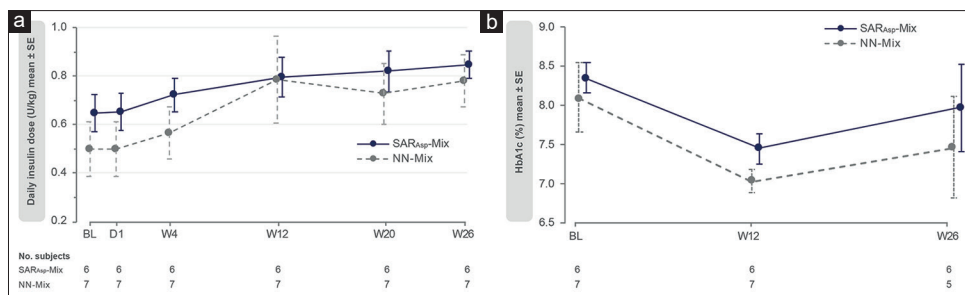


Figure 3: Daily insulin doses (U/kg) (a) and HbA1c (% and mmol/mol) by study visit during the 26-week on-treatment period (b) in the substudy safety and randomized populations. Data are mean \pm standard error. BL, baseline; HbA1c, glycosylated hemoglobin

participants with a treatment-emergent AIA response (i.e., treatment-boosted or treatment-induced AIAs) during the on-treatment period was similar between SAR_{Asp}-Mix (2/6 participants) and NN-Mix (4/7 participants)].

Similar percentages of participants in the SAR_{Asp}-Mix group (100% [6/6]) and in the NN-Mix group (85.7% [6/7]) were positive for AIA at least at one time-point between baseline and week 26 [Supplementary Table 4]. The kinetics of the AIA response, in terms of duration of the AIA response (transient or persistent), were comparable in the two treatment groups. Among participants with treatment-boosted AIA or treatment-induced AIA, no participant in either treatment group had a persistent response.

At baseline, no participants in either treatment group had detectable neutralizing anti-insulin aspart antibodies (NABs). During the 26-week on-treatment period, no participants in either treatment group had a treatment-emergent NAB response (i.e., treatment-induced or treatment-boosted NAB).

Impact of COVID-19 on the study

Three participants (SAR_{Asp}-Mix: 2; NN-Mix: 1) reported trial impact due to COVID-19. Each of these participants reported major protocol deviations related to COVID-19, such as planned hematology or clinical chemistry sample not performed. These deviations of assessments/procedures were within the recommended protocol adjustments advised to the sites to accommodate for the pandemic. Few hypoglycemia events were reported by the three participants with trial impact due to COVID-19. No participant had any TEAEs related to COVID-19 and there was no evidence in the safety data to suggest that trial disruption due to COVID-19 had an impact on TEAE reporting. Overall, the COVID-19 pandemic had minimal impact on this substudy.

DISCUSSION

This substudy of GEMELLI M was conducted to provide additional pharmacokinetic data following the administration of single doses of SAR_{Asp}-Mix and NN-Mix in Indian participants with T2D. The pharmacokinetic results confirmed that overall exposure (C_{max} and AUC) to SAR_{Asp}-Mix and insulin aspart in NN-Mix was similar with virtually no difference in the profile of the insulin aspart

plasma concentration curves. A sensitivity analysis performed to account for potential incomplete wash-out of the prior commercial premixed insulins (before the pharmacokinetic assessment) confirmed that while absolute exposure of the insulin aspart following administration of SAR_{Asp}-Mix and NN-Mix was influenced slightly, differences between treatments and variability were similar in the primary and sensitivity analyses.

Individuals with T2D were included in this substudy due to the high prevalence of T2D in India and wide use of premixed insulin in this population.^[11-14] The present study is the first to compare the pharmacokinetic characteristics of a biosimilar premix product and its reference treatment in people with T2D. Demographic and disease characteristics were reasonably balanced between treatment groups and reflected the target population of the study. The mean duration of diabetes in the substudy was ~13 years, with nine participants having a disease duration of ≥ 10 years.

In recent years, various biosimilar insulin products, both basal and prandial, have been developed and approved in India and other countries throughout the world.^[15] The regulatory approval process in India is designed to show that the proposed biosimilar (termed as 'similar biologic') is similar in terms of safety, efficacy and quality to a reference biologic, which has been granted marketing authorization in India or is approved in other international councils for harmonization countries (i.e., EU, Japan, US, Canada, etc.).^[16,17] The most recent Indian guidance for similar biologics (2016) requires an abridged preclinical and clinical (phase 1 and phase 3) data package.^[18] Comparable quality, preclinical and convincing pharmacokinetic/pharmacodynamic data are required.^[17] If a comparative phase 3 trial is waived, immunogenicity data should be gathered in a pharmacokinetic/pharmacodynamic study (provided there is a reliable pharmacodynamic marker) and a post-approval Phase 4 study.^[18] In contrast to the reduced data package employed when licensing a similar biologic product, originator biologics are licensed in India based on a full safety, efficacy and quality data package.^[18] Approval of innovator biologics follows the general pathway for new drug approval.^[19]

The rationale for the assessment of pharmacokinetic endpoints in this study, as distinguished from the clinical endpoints

over the 26-week treatment period, was based on the greater sensitivity of this outcome to detect any differences between SAR_{Asp}-Mix and its reference treatment NN-Mix in individuals with T2D. The 0.30 U/kg dose of SAR_{Asp}-Mix and NN-Mix formulations used in the pharmacokinetic assessment permitted effective pharmacokinetic characterization and comparison between groups; this dose was considered sufficient to cover for carbohydrate intake during breakfast on the pharmacokinetic assessment day without increasing the risk of hypoglycemia and provide interpretable insulin profiles over the pharmacokinetic assessment period of 16 h. Between-subject variability estimates for SAR_{Asp}-Mix were low to moderate for all pharmacokinetic parameters, and consistent with previously reported findings in subjects with T1D.^[4]

The 26-week efficacy, safety and immunogenicity results from this study, while supportive of the main GEMELLI M study that enrolled 402 people with T1D or T2D (including 153 participants from India with T2D),^[5] should be interpreted with caution due to the low number of participants included (13 in total). However, the 26-week treatment results raised no new concerns about the efficacy, safety or immunogenicity of SAR_{Asp}-Mix and are in line with the findings of the main GEMELLI M study. SAR_{Asp}-Mix and NN-Mix both effectively improved glycemic control during the 26-week treatment period with similar changes in other efficacy endpoints (HbA1c responders, FPG and SMPG parameters), and similar increases in daily insulin doses. The overall safety profiles of SAR_{Asp}-Mix and NN-Mix, including hypoglycemia, AEs, SAEs, hypersensitivity reactions and injection site reactions, were similar, and no new safety signals were identified. The higher number of TEAEs reported in the SAR_{Asp}-Mix group is not considered to be clinically relevant in view of the small number of included participants. Analysis of the AIAs showed overall a similar response to SAR_{Asp}-Mix and NN-Mix during the on-treatment period. No participants in either treatment group had detectable NABs. The COVID-19 pandemic had minimal impact on the pharmacokinetic substudy.

Similar to the present findings in Indian participants with T2D, similar insulin aspart exposure profiles and glucodynamic activity of SAR_{Asp}-Mix compared with NN-Mix were observed in an earlier randomized, double-blind, two-period, crossover euglycemic clamp study in 52 healthy Caucasian subjects with T1D.^[4] Consistent with our findings in Indian individuals with T2D, total insulin aspart exposure did not differ between SAR_{Asp}-Mix and NN-Mix. Taken together, observations from these two independent studies in differing study populations add to the totality of evidence that support that SAR_{Asp}-Mix has a similar pharmacological profile compared with NN-Mix.

The open-label design is a recognized potential limitation of this study. However, patient blinding was not possible as SAR_{Asp}-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,

pharmacokinetic, efficacy and immunogenicity assessments were based on objectively collected data that was analysed by central laboratories blinded to the study treatment.

In summary, the totality of data from this pharmacokinetic substudy indicates that exposure to SAR-Asp (insulin aspart) was similar between SAR_{Asp}-Mix and the reference product, NN-Mix, and no relevant differences with respect to immunogenicity, safety and efficacy parameters were identified. The findings of this substudy support the biosimilarity of SAR_{Asp}-Mix with NN-Mix.

Author contributions

W.S. and B.R. contributed to the conception and design of the study, V.M., K.P.S., and S.R.A., to the acquisition of data (as trial investigators), W.S. and B.R. to analysis of data, W.S., B.R., and B.M. to the interpretation of the data. W.S., B.R., and B.M. contributed to the drafting, and V.M., K.P.S., and S.R.A. 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. B.R. 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.

Author disclosure statement

Viswanathan Mohan, Kiran P Singh, and S.R Aravind report no disclosures. Wolfgang Schmider, Baerbel Rotthaeuser and Bhaswati Mukherjee are all employees and stockholders of Sanofi.

Acknowledgements

Sanofi was the sponsor of the study and was responsible for the design and coordination of the trial, monitoring clinical sites, collecting, and managing data, and performing all statistical analyses. Editorial support was provided by DJ Quinlan of Oberon Ltd (London, UK), funded by Sanofi.

Financial support and sponsorship

This study was funded by Sanofi.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. European Medicines Agency. Truvelog Mix 30: Summary of product characteristics, version 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/truvelog-mix-30-epar-product-information_en.pdf. [Last accessed on 2022 Aug 26].
2. European Medicines Agency. Insulin aspart Sanofi: Summary of product characteristics, version 27 January 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/insulin-aspart-sanofi-epar-product-information_en.pdf. [Last accessed on 2022 May 09].
3. Kumar A, Awata T, Bain SC, Ceriello A, Fulcher GR, Unnikrishnan AG, *et al.* Clinical use of the co-formulation of insulin degludec and insulin aspart. *Int J Clin Pract* 2016;70:657-67.
4. Kapitza C, Nosek L, Schmider W, Teichert L, Mukherjee B, Nowotny I. A single-dose euglycaemic clamp study in two cohorts to compare the exposure of SAR341402 (insulin aspart) Mix 70/30 with

- US- and European-approved versions of insulin aspart Mix 70/30 and SAR341402 rapid-acting solution in subjects with type 1 diabetes. *Diabetes Obes Metab* 2021;23:674-81.
5. Aravind SR, Singh KP, Aquitania G, Mogylnytska L, Zalevskaya AG, Matyjaszek-Matuszek B, *et al.* 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 (GEMELLI M). *Diabetes Ther* 2022;13:1053-71.
 6. American Diabetes Association Workgroup on Hypoglycemia: Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 2005;28:1245-9.
 7. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, *et al.* Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care* 2013;36:1384-95.
 8. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: A joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017;40:155-7.
 9. Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, *et al.* Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *AAPS J* 2014;16:658-673.
 10. European Medicines Agency: Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues, 26 February 2015. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-0.pdf. [Last accessed on 2022 May 09].
 11. Polinski JM, Kim SC, Jiang D, Hassoun A, Shrank WH, Cos X, *et al.* Geographic patterns in patient demographics and insulin use in 18 countries, a global perspective from the multinational observational study assessing insulin use: Understanding the challenges associated with progression of therapy (MOSAIC). *BMC Endocr Disord* 2015;15:46.
 12. Ji L, Min KW, Oliveira J, Lew T, Duan R. Comparison of efficacy and safety of two starting insulin regimens in non-Asian, Asian Indian, and East Asian patients with type 2 diabetes: A post hoc analysis of the PARADIGM study. *Diabetes Metab Syndr Obes* 2016;9:243-9.
 13. Mohan V, Kalra S, Kesavadev J, Singh AK, Kumar A, Unnikrishnan AG, *et al.* Consensus on initiation and intensification of premix insulin in type 2 diabetes management. *J Assoc Physicians India* 2017;65:59-73.
 14. Das AK, Mithal A, Joshi S, Kumar KMP, Kalra S, Unnikrishnan AF, *et al.* Baseline characteristics of participants in the LANDMARC trial: A 3-year, pan-india, prospective, longitudinal study to assess management and real-world outcomes of diabetes mellitus. *Endocrinol Diabetes Metab* 2021;4:e00231.
 15. White J, Wagner A, Patel H. The impact of biosimilar insulins on the diabetes landscape. *J Manag Care Spec Pharm* 2022;28:91-8.
 16. Ghosh S, Bose S, Gowda S, Mukhopadhyay P. Biosimilar insulins - What a clinician needs to know? *Indian J Endocrinol Metab* 2019;23:400-6.
 17. Meher BR, Balan S, Mohanty RR, Jena M, Das S. Biosimilars in India; Current status and future perspectives. *J Pharm Bioallied Sci* 2019;11:12-5.
 18. Central Drugs Standard Control Organization and Department of Biotechnology. Guideline on similar biologics: Regulatory requirements for marketing authorization in India, 2016. Available from: <https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadAlertsFiles/BiosimilarGuideline2016.pdf>. [Last accessed on 2022 Jul 06].
 19. Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, India. New drugs and clinical trial rules, 2019. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf. [Last accessed on 2022 Jul 07].