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ORIGINAL ARTICLE

Safety and Tolerability of Insulin Aspart Biosimilar SAR341402 Versus Originator Insulin Aspart (NovoLog) When Used in Insulin Pumps in Adults with Type 1 Diabetes: A Randomized, Open-Label Clinical Trial

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Abstract

Background: The aim was to assess the safety and tolerability of the insulin aspart biosimilar/follow-on product SAR341402 (100 U/mL solution; SAR-Asp) and originator insulin aspart (100 U/mL; NN-Asp; NovoLog®) self-administered through an insulin pump.

Materials and Methods: This randomized, open-label, 2×4-week crossover study enrolled 45 adults with type 1 diabetes (T1D). Participants were randomized 1:1 to the treatment sequence SAR-Asp/NN-Asp or NN-Asp/SAR-Asp. The basal and prandial insulin doses were individually titrated. The primary outcome was the number of participants with at least one infusion set occlusion (infusion set change due to failure-to-correct hyperglycemia [plasma glucose ≥250 mg/dL] by insulin pump bolus) during the 4-week treatment. The main secondary outcome was the number of participants with at least one episode of unexplained hyperglycemia (regardless of correction by an insulin pump bolus without apparent material defect, medical, dietary, insulin dosing reason, or pump problem).

Results: The number of participants reporting ≥1 infusion set occlusion were similar between treatments: 14/43 on SAR-Asp (33 events) and 12/43 on NN-Asp (24 events). The estimated difference in infusion set occlusion risk for SAR-Asp versus NN-Asp was 4.1% (95% confidence interval: –9.3% to 17.4%). The number of participants with ≥1 episode of unexplained hyperglycemia was similar between treatments (31/43 on SAR-Asp [154 events]; 32/43 on NN-Asp [175 events]). Hypoglycemia, treatment-emergent adverse events, hypersensitivity, and injection site reactions were similar between treatments.

Conclusions: SAR-Asp and NN-Asp were well tolerated and had similar infusion set occlusions over a 4-week period in insulin pump users with T1D.

Keywords: Biosimilar, Continuous subcutaneous insulin infusion, Follow-on product, Infusion set occlusion, Insulin aspart, SAR341402.

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Introduction

Continuous subcutaneous insulin infusion (CSII) therapy (insulin pump) is a popular treatment option in people with type 1 diabetes (T1D). At least 60% of individuals participating in the T1D Exchange Network and Clinic Registry in the United States currently use CSII.[1] Rapid-acting insulin analogs (insulin aspart, insulin lispro, and insulin glulisine) are typically administered through CSII to manage glucose control.[2]

Insulin aspart (100 U/mL; NN-Asp; NovoLog®/NovoRapid®, Novo Nordisk, Bagsværd, Denmark) is a widely used rapid-acting insulin with a well-characterized pharmacological, efficacy, and safety profile.[3] SAR341402 (100 U/mL; SAR-Asp; Sanofi, Paris, France) has the same amino acid sequence and corresponding structure as the currently approved and marketed insulin aspart reference product, NN-Asp.[4,5] SAR-Asp is being developed as a biosimilar/follow-on product to NN-Asp in accordance with relevant United States and European Union (EU) guidelines.[6–9]

Similar pharmacokinetic exposure and pharmacodynamic activity were demonstrated for SAR-Asp versus both US-approved (NovoLog) and EU-approved (NovoRapid) NN-Asp, as well as between US-approved and EU-approved NN-Asp in a study in subjects with T1D using the euglycemic clamp technique.[10] In addition, similar efficacy and safety of SAR-Asp and NN-Asp have been reported in a multinational, open-label, randomized phase 3 study in participants with T1D and type 2 diabetes (T2D) using insulin glargine 100 U/mL as the basal insulin.[11]

An important aspect in the development of any rapid-acting insulin to be delivered through CSII is the physical stability and compatibility of the insulin within the infusion (pump) system (i.e., the infusion sets, tubing, and reservoirs) over the in-reservoir use period.[12] Infusion set occlusions are recognized as the most common causes of insulin infusion set problems with CSII therapy.[13]

This clinical trial (GEMELLI P) assessed the safety of SAR-Asp and the reference drug US-approved NN-Asp (NovoLog) when delivered by an insulin pump in US adults with T1D.

Materials and Methods

Study design

This was a randomized, open-label, two-sequence, two-treatment, two-period, active-controlled, crossover study (ClinicalTrials.gov identifier: NCT03436498) conducted in 2018 at three sites in the United States. Supplementary Figure S1 summarizes the study design. The trial included a 2-week screening period followed by two 4-week (28 ± 2 days) treatment periods, with no washout period in between, and a 1-day follow-up period. The study protocol was approved by relevant Institutional Review Boards and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before study entry. Clinic visits were scheduled at screening, randomization (day 1), and weeks 2, 4, 6, and 8 (Supplementary Fig. S1). Telephone contact was also made during screening, at weeks 1, 3, 5, 7, and 1 day after the last dose of study medication.

Study population

Enrolled participants included men and women ≥18 years of age, diagnosed with T1D (duration >12 months before screening), treated with insulin for >12 months and with CSII through an external insulin pump for >6 months before screening (either a Medtronic MiniMed® 530G-Model 751 pump or any other Medtronic pump with a 3-mL reservoir, including models 630G and 670G [Medtronic, Northridge, CA] or an Animas® pump [Vibe®, OneTouch Ping® or IR 1250 pump with a 2-mL reservoir; Animas Corp., West Chester, PA]) and who had demonstrated successful use of their insulin pump during a 2-week screening period (defined as ≥75% of the four self-monitored plasma glucose [SMPG] checks per day recorded in the participant diary). Use of the threshold suspend function and automatic insulin delivery in the hybrid closed-loop system were not allowed during the study period.

Key exclusion criteria were individuals with diabetes other than T1D, a glycated hemoglobin (HbA1c) ≥8.5% at screening, a history of infection at the infusion site within 3 months before the screening visit, hypoglycemia unawareness as judged by the investigator in the last 6 months before the screening visit, history of severe hypoglycemia requiring treatment by emergency room admission or hospitalization for recurrent diabetic ketoacidosis in the last 6 months before the screening visit, and use of oral or injectable glucose-lowering agents other than insulin during the 3 months before screening.

Treatments

Participants were randomized in a 1:1 ratio using a computer-generated list to receive SAR-Asp (3 mL cartridge, Sanofi) for 4 weeks in the first treatment period followed by NN-Asp (3 mL PenFill® cartridge, Novo Nordisk) for 4 weeks in the second treatment period, or vice versa.

Participants used their own insulin infusion pump, with the starting basal infusion rates and bolus doses of SAR-Asp or NN-Asp the same as participants had used before the trial. Doses were individually titrated and self-administered as required. Changes in the SAR-Asp or NN-Asp dose were based on SMPG measurements to achieve individualized plasma glucose targets of a preprandial blood glucose of 80–130 mg/dL (4.4–7.2 mmol/L) and a postprandial plasma glucose of <180 mg/dL (<10 mmol/L). When crossing over to the alternate treatment after the first 4-week treatment period, the starting dose was the same as the last dose used in the first treatment period.

Study procedures

Participants were instructed to change their infusion sets at least every 3 days, and just before the first administration on day 1 of each treatment period. Insulin in the reservoir was also changed at least once every 6 days, in accordance with the NovoLog prescribing information.[4]

Plasma glucose levels were monitored by SMPG measurements performed four times per day throughout the study and recorded in the participant's study diaries. Additional SMPG measurements were performed to document hypoglycemia or hyperglycemia. Participants were instructed to record any episode of hyperglycemia, defined as plasma glucose value ≥250 mg/dL (13.9 mmol/L), and the likely reason. For each episode, the participant had to check for ketones and administer an insulin bolus of SAR-Asp or NN-Asp through the insulin pump (dose based on insulin pump instructions). Plasma glucose was to be rechecked 60 min (interval 45–90 min) after the insulin bolus. Failure to lower

plasma glucose by ≥50 mg/dL (2.8 mmol/L) within 60 min (interval 45–90 min) after the insulin bolus was considered an infusion set occlusion. In this case, the participant was advised to administer a subcutaneous insulin bolus through syringe or pen and to change both the infusion set and infusion site. The date and time of the hyperglycemia event, the insulin bolus dose through CSII, and any administered subcutaneous insulin bolus through syringe or pen were recorded in the participant diary. Depending on the hyperglycemia reason reported by the participant, the site staff assessed whether the hyperglycemia was explained or not.

The date and time of each infusion set change, and the reason for changing (i.e., whether it was a scheduled change [maximum of 3 days from the last infusion set change, or change required to refill the pump reservoir], or due to another event such as unexplained plasma glucose ≥250 mg/dL (13.9 mmol/L) that was not reduced by an insulin bolus given through the insulin pump, pain or swelling at the infusion site, observed infusion set occlusion, insulin pump nondelivery alarm, or due to other reasons) were to be reported in the participant diary. No evaluation of the infusion sets was performed by the Investigator. Hypoglycemic events were documented by the participant in their study diaries.

Study endpoints

The primary endpoint of the study was the number of participants with at least one infusion set occlusion, defined as an infusion set change due to failure-to-correct hyperglycemia (plasma glucose ≥250 mg/dL [13.9 mmol/L]) within 60 min (interval 45–90 min) by an insulin bolus administered through the insulin pump (excluding any pump malfunction).

The main secondary endpoint was all cases of unexplained hyperglycemia, defined as plasma glucose ≥250 mg/dL (13.9 mmol/L) whether or not corrected by a bolus through the insulin pump with no apparent material defects, medical, dietary, insulin dosing, or pump failure.[13] This endpoint included any infusion set occlusions as defined in the primary endpoint.

Other secondary endpoints included the interval for infusion set changes (either on a routine basis or when occlusion occurred or was suspected or based on adverse events [AEs]), defined as the number of days in the treatment period divided by the number of infusion set changes in the treatment period, and the number of participant-observed infusion set occlusions and insulin pump alarms for nondelivery (both of these outcomes being independent of confirmation of occlusion by hyperglycemia and failure-to-correct hyperglycemia by insulin bolus through the insulin pump).

Other safety endpoints included the number of participants with hypoglycemic events during each 4-week treatment period, and the number of participants with treatment-emergent AEs (TEAEs) and/or treatment-emergent serious AEs (SAEs), including bruising at the infusion site, injection site, and hypersensitivity reactions during each 4-week treatment period. TEAEs were defined as AEs that developed, worsened, or became serious during the on-treatment periods (see statistical analyses section for further details). AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

Hypoglycemic episodes were categorized based on American Diabetes Association classifications.[14,15] Documented symptomatic and asymptomatic hypoglycemia episodes were defined separately using measured plasma glucose concentration thresholds of ≤70 mg/dL (3.9 mmol/L) and <54 mg/dL (3.0 mmol/L). Severe hypoglycemia was an event requiring assistance of another person to actively administer carbohydrates, glucagon, or other resuscitative actions. Any hypoglycemic event associated with seizure, unconsciousness, or coma was reported as an SAE.

An Allergic Reaction Assessment Committee of experts (all board certified in allergy and clinical immunology) independent from the Sponsor and the Investigators reviewed all hypersensitivity reactions reported on a specific allergic reaction AE form or identified by MedDRA search. They confirmed, based on the information reported by the Investigator, whether the event was allergic in nature. The committee was blinded to the study treatment. Vital signs and routine laboratory assessments were also performed.

Statistical analyses

No sample-size or power calculation or formal hypothesis testing was performed for this study. All analyses were qualitative and the sample size was based on empirical considerations. The study planned to recruit up to 46 participants to have a minimum of 30 participants completing the study. Statistical analyses were performed on the safety population defined as all randomized participants who received at least one dose of the investigational product or its comparator, analyzed according to the treatment actually received. The on-treatment period was defined separately for each treatment period as the time from the first infusion of study medication in the period up to 1 day (0 days for safety parameters related to the risk of infusion set occlusions) after the last dose of study medication in that same period or up to study medication change, whichever came earlier.

The number and percentage of participants with at least one infusion set occlusion was provided for each treatment. The risk of an infusion set occlusion (proportion of participants with at least one infusion set occlusion) under each treatment and the risk difference between treatments were estimated by fitting a repeated measures model using a binomial regression and an identity link function with fixed categorical effects for treatment, period, and sequence group, and an unstructured correlation matrix to model within-participant errors.

The risk of infusion set occlusion within each treatment and the risk difference were provided with their 95% confidence intervals (CIs) using the adjusted least square mean estimates of the treatment effect. The number of infusion set occlusion events and rate per participant month (defined as the total number of events × 30 divided by the total number of days exposed) was also determined for each treatment. The rate ratio (RR) between treatments was estimated by fitting an overdispersed Poisson regression model using a log link function and the logarithm of the treatment-emergent period as offset with fixed-effect terms for treatment, period, and sequence and an unstructured correlation matrix to model within-participant errors. The 95% CI of the RR was also provided. The same methodology was used to analyze the risk of unexplained hyperglycemia.

Descriptive statistics (frequency counts and percentage, mean, and standard deviation [SD]) were used to summarize other secondary endpoints. Statistical analyses were performed using SAS® Enterprise Guide, version 5.1 (SAS Institute, Inc., Cary, NC).

Results

Participant disposition and baseline characteristics

A total of 45 participants were randomized and treated (safety population): 24 in the SAR-Asp/NN-Asp sequence and 21 in the NN-Asp/SAR-Asp sequence. Of these, 40 completed the trial. Of the 5 participants who did not complete the two 4-week treatment periods, three discontinued treatment while on SAR-Asp: two during the first period (protocol compliance, problem using the infusion set) who were therefore not exposed to NN-Asp, and one during the second treatment period (problem using the infusion set). Two participants discontinued treatment while on NN-Asp during the first period (inconvenience of device use, problem using the infusion set) and therefore were not exposed to SAR-Asp. As a result 43 participants were exposed to each treatment. Participant disposition is presented in Supplementary Table S1.

Participants had a mean (±SD) age of 43.1 (±13.6) years, were mostly female (62.2%), predominantly white (91.1%), and had a median duration of diabetes of 22.7 years (Table 1). The enrolled population was representative of individuals receiving CSII. All had been on CSII for at least 6 months before the study with a median duration of CSII treatment of 8.2 years and a median duration of current pump use of 2.1 years. Most participants (41 [91.1%]) used Medtronic pumps.

Table 1. Demographics and Baseline Characteristics (Safety Population)

Characteristics	*All participants (n = 45)*
Age, years	43.1 ± 13.6
<65, *n* (%)	41 (91.1)
≥65, *n* (%)	4 (8.9)
Female, *n* (%)	28 (62.2)
Race, *n* (%)	
White	41 (91.1)
Black or African American	2 (4.4)
Native Hawaiian or other Pacific Islander	1 (2.2)
Multiple	1 (2.2)
Body weight, kg	88.7 ± 19.8
BMI, kg/m^2	30.5 ± 6.4
<25, *n* (%)	9 (20.0)
≥25 to <30, *n* (%)	13 (28.9)
≥30, *n* (%)	23 (51.1)
Duration of T1D, years	22.7 (3–50)
<10, *n* (%)	10 (22.2)
≥10, *n* (%)	35 (77.8)
Age at onset of T1D, years	18.0 (3–60)
Duration of CSII treatment, years	8.2 (1–28)
Type of external pump, *n* (%)	
Animas	4 (8.9)
Medtronic	41 (91.1)
Screening HbA1c	
<8.0%, *n* (%)	44 (97.8)
≥8.0%, *n* (%)	1 (2.2)
Duration of treatment with current pump, years	2.1 (0–12)

All data are mean ± SD or median (range) unless stated otherwise.
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin A1c; SD, standard deviation; T1D, type 1 diabetes.

Key safety endpoints

Infusion set occlusions (primary endpoint). The number of participants with at least one infusion set occlusion was similar while receiving SAR-Asp (14/43 [32.6%]) and while receiving NN-Asp (12/43 [27.9%]) (Table 2). The risk estimate was 32.4% and 28.3% for SAR-Asp and NN-Asp, respectively (risk difference was 4.1% [95% CI: −9.3% to 17.4%]).

Twenty-seven participants reported no infusion set occlusion on either treatment. Eighteen participants reported at least one infusion set occlusion, of which eight reported events on both treatments, six on SAR-Asp alone (including one participant not exposed to NN-Asp), and four on NN-Asp only (including one participant not exposed to SAR-Asp).

During period 1, 16 participants had at least 1 infusion set occlusion (9 while receiving SAR-Asp and 7 while receiving NN-Asp) versus 10 participants in period 2 (5 while receiving SAR-Asp and 5 while receiving NN-Asp) (Supplementary Table S2). All occlusions occurred in participants using Medtronic pumps.

The total number of infusion-set occlusions was 33 for SAR-Asp and 24 for NN-Asp. The corresponding rate per participant-month was 0.81 for SAR-Asp and 0.59 for NN-Asp (RR for SAR-Asp vs. NN-Asp of 1.34 [95% CI: 0.79–2.26]) (Table 2). Single infusion set occlusions were reported by seven participants while receiving SAR-Asp and by six participants receiving NN-Asp (Supplementary Table S2). More than three events were experienced by three participants on SAR-Asp and by two participants on NN-Asp.

Unexplained hyperglycemia (main secondary endpoint). The majority of participants experienced at least one unexplained hyperglycemic event. The number of participants with at least one event during the on-treatment period was similar while receiving SAR-Asp (31/43 [72.1%]) and NN-Asp (32/43 [74.4%]). The risk estimate was 71.9% and 74.4% for SAR-Asp and NN-Asp, respectively (risk difference for SAR-Asp vs. NN-Asp of −2.5% [95% CI: −19.17 to 14.22]) (Table 2).

Thirty-nine participants reported at least 1 unexplained hyperglycemic event, of which 24 reported events on both treatments, 7 on SAR-Asp alone (including 1 participant not exposed to NN-Asp), and 8 on NN-Asp only (including 1 participant not exposed to SAR-Asp). Only six participants reported no unexplained hyperglycemic event on either treatment.

During period 1, 34 participants had at least 1 unexplained hyperglycemic event (17 while receiving SAR-Asp and 17 while receiving NN-Asp) versus 29 participants in period 2 (14 participants while receiving SAR-Asp and 15 participants while receiving NN-Asp) (Supplementary Table S2).

The total number of unexplained hyperglycemic events was 154 while receiving SAR-Asp and 175 while receiving NN-Asp. The corresponding rate per participant-month was 3.78 for SAR-Asp and 4.33 for NN-Asp (RR for SAR-Asp vs. NN-Asp of 0.91 [95% CI: 0.67 to 1.23]) (Table 2). Single

Table 2. Infusion Set Occlusions and Unexplained Hyperglycemia During the On-Treatment Period (Safety Population)

	Infusion set occlusions[a]		*Unexplained hyperglycemia*[b]	
Parameter	*SAR-Asp* (n = *43*)	*NN-Asp* (n = *43*)	*SAR-Asp* (n = *43*)	*NN-Asp* (n = *43*)
Participants with ≥1 event				
No. of participants, *n* (%)	14 (32.6)	12 (27.9)	31 (72.1)	32 (74.4)
Risk estimate[c], % [95% CI]	32.4 [18.5 to 46.2]	28.3 [15.1 to 41.6]	71.9 [58.5 to 85.3]	74.4 [61.5 to 87.3]
Risk difference versus NN-Asp[c], % [95% CI]	4.1 [−9.3 to 17.4]		−2.5 [−19.2 to 14.2]	
Number and rate of events				
No. of events, *n*	33	24	154	175
Total participant-months	40.8	40.4	40.8	40.4
Rate per participant-month[d]	0.81	0.59	3.78	4.33
RR versus NN-Asp[e], RR [95% CI]	1.34 [0.79 to 2.26]		0.91 [0.67 to 1.23]	

[a]Infusion set occlusion defined as failure-to-correct hyperglycemia within 60 [45–90] min by insulin bolus through the insulin pump (excluding pump malfunction).

[b]Unexplained hyperglycemia defined as plasma glucose ≥250 mg/dL (13.9 mmol/L) whether or not corrected by a bolus through the insulin pump with no apparent materials defects, medical, dietary, insulin dosing, or pump failure. This includes all infusion set occlusions as defined above.

[c]Binomial regression with an identity link function, including fixed categorical effects for treatment, period, and sequence. Risks for each treatment, risk difference, and their 95% CI are provided using the adjusted least squares mean estimates of the treatment effect. For infusion set occlusions, *p*-value of sequence effect = 0.99 and for period effect = 0.14. For unexplained hyperglycemia, *p*-value of sequence effect = 0.46 and for period effect = 0.52.

[d]The rate per participant-month was calculated as: 30 × [number of events/total number of days exposed for each treatment].

[e]Overdispersed Poisson regression model with fixed-effect terms for treatment, period, and sequence with log link function and logarithm of treatment-emergent period as offset. For infusion set occlusions, *p*-value of sequence effect = 0.91 and for period effect = 0.18. For unexplained hyperglycemia, *p*-value of sequence effect = 0.62 and for period effect = 0.87.

CI, confidence interval; RR, rate ratio.

events of unexplained hyperglycemia were experienced by five participants while receiving SAR-Asp and by seven participants receiving NN-Asp (Supplementary Table S2). More than eight events were experienced by six participants on SAR-Asp and by eight participants on NN-Asp. One participant reported 32 unexplained hyperglycemic events during the treatment periods (16 on SAR-Asp, 16 on NN-Asp), having already reported 19 unexplained events during the screening period.

Other safety endpoints

Infusion set changes. Under each treatment, all 43 participants (100%) had at least 1 infusion set change and performed at least 1 scheduled change. Twenty participants (46.5%) on SAR-Asp and 15 participants (34.9%) on NN-Asp had an unscheduled infusion set change when an occlusion occurred or was suspected (defined as the combination of infusion set changes due to failure-to-correct hyperglycemia, pump alarm for nondelivery, or participant-observed infusion set occlusion) (Table 3). This was mostly due to failure-to-correct hyperglycemia (SAR-Asp: 14 participants; NN-Asp: 12 participants), and in a small number of cases participant-observed occlusions and insulin pump nondelivery alarm.

The mean interval for any infusion set change (independent of the reason of infusion set change), was similar while receiving SAR-Asp or NN-Asp: 3.33 (SD 1.95) days for SAR-Asp and 2.82 (0.51) days for NN-Asp (Table 4). Similar mean intervals for infusion set change were observed between SAR-Asp and NN-Asp whatever the reason (including occlusion due to failure-to-correct hyperglycemia and when occlusion occurred or was suspected).

Hypoglycemia

The number of hypoglycemic episodes reported was 297 while receiving SAR-Asp and 303 while receiving NN-Asp (Table 5). Forty (93%) participants on each treatment reported at least one episode of hypoglycemia. The number of events per participant-month for any hypoglycemia was comparable for the two treatments (7.16 for SAR-Asp vs.

Table 3. Reasons for Unscheduled Infusion Set Changes During the On-Treatment Period (Safety Population)

Participants with ≥1 unscheduled infusion set change, n *(%)*	*SAR-Asp* (n = *43*)	*NN-Asp* (n = *43*)
Occlusion occurred or was suspected[a]	20 (46.5)	15 (34.9)
Due to failure-to-correct hyperglycemia[b]	14 (32.6)	12 (27.9)
Due to visual infusion set occlusion	6 (14.0)	3 (7.0)
Due to pump alarm for nondelivery	2 (4.7)	3 (7.0)
Infusion set change based on pump malfunction	1 (2.3)	0
Pain or swelling at infusion site	1 (2.3)	4 (9.3)
Other	16 (37.2)	8 (18.6)

[a]Defined as a combination of infusion set changes due to failure-to-correct hyperglycemia (excluding pump malfunction), pump alarm for nondelivery, and visual infusion set occlusion. Participants with multiple reasons were only counted once.

[b]Infusion set occlusion defined as failure-to-correct hyperglycemia by insulin bolus through the insulin pump (excluding pump malfunction).

Table 4. Infusion Set Change Time Intervals (Days) During the On-Treatment Period (Safety Population)

Reason for infusion set change	*SAR-Asp* (n = *43*)	*NN-Asp* (n = *43*)
Any infusion set change	3.33 ± 1.95 [43]	2.82 ± 0.51 [43]
Scheduled infusion set change	3.97 ± 2.29 [43]	3.19 ± 0.61 [43]
Due to failure-to-correct hyperglycemia[a]	18.59 ± 10.16 [14]	19.06 ± 9.41 [12]
Occlusion occurred or was suspected[b]	19.58 ± 9.81 [20]	18.12 ± 9.45 [15]
Due to pump malfunction	29.00 ± NC [1]	[0]
Based on adverse events[c]	28.00 ± NC [4]	29.00 ± NC [4]

Data shown as mean ± SD intervals for infusion set change in days [no. of participants in analysis]. Individual intervals for infusion set changes were derived per treatment period as the number of days in the treatment period divided by the number of infusion set changes in the treatment period.

[a]Infusion set occlusion defined as failure-to-correct hyperglycemia by insulin bolus through the insulin pump (excluding pump malfunction).

[b]Infusion set changes due to failure-to-correct hyperglycemia (excluding pump malfunction), pump alarm for nondelivery or visual infusion set occlusion.

[c]Infusion set changes due to pain or swelling at infusion set site.

NC, not calculated.

7.35 for NN-Asp). Hypoglycemia event rates for all other categories of hypoglycemia were also similar for SAR-Asp and NN-Asp. Two (4.7%) participants experienced a single episode of severe hypoglycemia with each treatment. Neither was reported as an SAE.

Table 5. Hypoglycemic Events During the On-Treatment Period (Safety Population)

Category of hypoglycemia	*SAR-Asp* (n = *43*)	*NN-Asp* (n = *43*)
Total participant-months	41.5	41.2
Any hypoglycemia	297 (7.16)	303 (7.35)
Severe hypoglycemia	2 (0.05)	2 (0.05)
Documented symptomatic		
≤70 mg/dL (3.9 mmol/L)	201 (4.85)	189 (4.59)
<54 mg/dL (3.0 mmol/L)	45 (1.09)	37 (0.90)
Asymptomatic		
≤70 mg/dL (3.9 mmol/L)	89 (2.15)	110 (2.67)
<54 mg/dL (3.0 mmol/L)	6 (0.14)	15 (0.36)
Probable symptomatic hypoglycemia	2 (0.05)	2 (0.05)
Relative hypoglycemia[a]	0	0
Nonclassified hypoglycemia (not severe)	1 (0.02)	0
Nonclassified hypoglycemia (severity unknown)	2 (0.05)	0

Data shown as number of hypoglycemic events (rate per participant-month in parentheses).

[a]Events accompanied by typical symptoms of hypoglycemia but with a plasma glucose concentration of >70 mg/dL [>3.9 mmol/L].

Adverse events

Doses of the two insulin aspart preparations were well tolerated, with few AEs. TEAEs were reported in 9 of 43 participants following administration of SAR-Asp, and in 7 of 43 participants following administration of NN-Asp (Supplementary Table S3). The most common TEAE category was infections, reported in five participants following administration of SAR-Asp and in three participants following administration of NN-Asp. TEAEs were mainly of mild-to-moderate intensity in both treatments and no serious TEAEs were reported during the study. No TEAEs of ketoacidosis were reported during the study and there were no discontinuations during the study due to AEs.

One event (blister on right big toe) was identified by the Investigator as a hypersensitivity reaction in a participant receiving NN-Asp. The event was submitted to the ARAC and was adjudicated as not due to an allergic reaction. No injection site reaction TEAE was reported during the on-treatment period. Laboratory parameters, vital signs, and body weight did not reveal any specific changes or safety concerns.

Discussion

Due to rising prevalence and cost of diabetes treatment, the development of more affordable insulin products is needed.[16,17] Development of biosimilar or follow-on insulins, including rapid-acting insulins, has the potential to reduce diabetes treatment costs.[18] SAR-Asp, a rapid-acting insulin and biosimilar/follow-on product of NN-Asp, has previously been shown to have similar pharmacokinetic exposure and pharmacodynamic activity to both NN-Asp-EU and NN-Asp-US in subjects with T1D and similar efficacy and safety to NN-Asp in participants with T1D and T2D taking multiple daily injections while using insulin glargine.[10,11] The potential role of SAR-Asp when delivered by an insulin pump among participants with T1D was evaluated in this study.

The current study showed that CSII delivery of SAR-Asp and NN-Asp resulted in a similar number of participants reporting an infusion set occlusion, defined as an infusion set change due to failure-to-correct hyperglycemia by insulin pump bolus, during each 4-week treatment period. Similar proportions of participants treated with SAR-Asp and NN-Asp reported other secondary outcomes related to pump compatibility, including the key outcome of unexplained hyperglycemia. SAR-Asp was well tolerated, with a similar safety profile to that of NN-Asp.

Since clinically overt occlusive events with CSII are rare, the primary endpoint of the study included infusion set changes due to failure-to-correct hyperglycemia (plasma glucose ≥250 mg/dL [13.9 mmol/L]) within 60 min (interval 45–90 min) by an insulin bolus administered through the insulin pump. This definition is a specific and objective method to assess infusion set occlusions and enable early detection of infusion set failure during insulin pump therapy.[18,19] Patients with prolonged hyperglycemia due to infusion set occlusions are also recognized to be at subsequent risk of ketoacidosis and hospitalization.[20,21] The plasma glucose threshold of 250 mg/dL was chosen to enable detection of a higher number of events. This is in keeping with the results of a similarly designed study evaluating the insulin lispro biosimilar/follow-on product SAR342434 that

defined infusion set occlusions using a higher plasma glucose threshold (≥300 mg/dL).[18] In that study, the higher threshold resulted in a lower overall percentage of participants with at least one event (22.2%) compared with the current study (40.0%). Previous trials evaluating the incidence of infusion set occlusions of rapid-acting analog insulins administered by CSII in participants with T1D have varied in their definitions of infusion set occlusions precluding crosstrial comparisons.[20,22,23]

Supportive data for the primary endpoint of infusion set occlusions were provided by assessing the appearance of unexplained hyperglycemia, a recognized clinical surrogate for evaluation of possible infusion set occlusion.[2,24] This broader endpoint includes a larger number of participants and events compared with the subset of infusion set occlusions included within it, thereby providing greater ability to detect any differences in pump compatibility between the two insulin treatments. Consistent with the results of the primary endpoint, 31 participants receiving SAR–Asp reported 154 episodes of unexplained hyperglycemia compared with 32 participants who reported 175 events with NN-Asp. Additional secondary endpoints indicative of infusion set occlusions, including the number of participant-observed infusion set occlusions and insulin pump alarms for nondelivery, and the mean interval for infusion set changes, all showed no clinically relevant differences between the two treatments.

SAR-Asp was well tolerated during this study. There were no clinically meaningful differences in any of the safety measures (including the incidence and rate of severe and nonsevere hypoglycemia) between the two treatments. AEs reported for SAR-Asp were similar to those reported for NN-Asp and were consistent with the AE profile reported in previous studies assessing the safety of other insulin analogs administered by CSII in adults with T1D.[2,18,20,22,23,25] No confirmed allergic reactions or injection site reactions were observed with either treatment.

Differences in the size and shape of SAR-Asp and NN-Asp cartridges meant it was not possible to provide participants with identical insulin formulations to use in their insulin pumps at home. Blinding the study by asking participants to return to the site to have their insulin reservoirs refilled was also considered risky as the reservoirs could run dry during the evening or over the weekend. This could have compromised the study if participants were forced to use alternative sources of insulin. As such, an open-label study design was used.

Other limitations of the study include the small number of included participants and the short duration of treatment. A crossover design was used to maximize the data from a small sample size and to limit confounding effects. This was deemed suitable given the short half-life of insulin aspart and since the participants enrolled were already experienced in the use of short-acting insulin through CSII, a learning effect was unlikely. No wash-out period between treatments was used due to the participants requiring insulin treatment at all times. The number of participants included in the study was consistent with previous crossover trials evaluating the incidence of infusion set occlusions of rapid-acting analog insulins (insulin lispro biosimilar/follow-on product SAR342434) administered by CSII in adults with T1D.[18] The 4-week treatment period was based on the design of prior pump studies.[12]

Conclusion

We conclude that SAR-Asp demonstrated a similar safety and tolerability profile to NN-Asp, a commercially available insulin aspart formulation, supporting its use as an insulin aspart biosimilar/follow-on product in insulin pumps.

Author Disclosure Statement

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Supplementary Material

Supplementary Figure S1
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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