

Safety of Insulin Lispro and a Biosimilar Insulin Lispro When Administered Through an Insulin Pump

James Thrasher, MD¹, Howard Surks, MD², Irene Nowotny, PhD³, Suzanne Pierre, MSc⁴, Baerbel Rotthaeuser, PhD³, Karin Wernicke-Panten, MD³, and Satish Garg, MD⁵

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Abstract

Background: SAR342434 (U100; SAR-Lis; insulin lispro) is a biosimilar/follow-on to insulin lispro (U100; Ly-Lis). Similar pharmacokinetics/pharmacodynamics between the two products has been demonstrated in a hyperinsulinemic euglycemic clamp study. The current study evaluated the safety of SAR-Lis and Ly-Lis when administered by continuous subcutaneous insulin infusion (CSII; insulin pumps).

Methods: This was a randomized, open-label, 2 × 4-week, two-arm crossover study in 27 patients with type 1 diabetes mellitus (NCT02603510). The main outcome was the incidence of infusion set occlusions (ISOs), defined as failure to correct hyperglycemia (plasma glucose ≥ 300 mg/dl) by 50 mg/dl within 60 minutes by insulin bolus via the pump. Secondary outcomes included intervals between infusion set changes, treatment-emergent adverse events (TEAEs) including infusion site, hypersensitivity reactions and hypoglycemic events, and safety.

Results: The number of patients reporting at least one ISO was small: 6/25 patients on SAR-Lis reported 14 ISOs and 4/27 on Ly-Lis reported nine ISOs. The estimated difference in ISO risk for SAR-Lis versus Ly-Lis was 7.9% (95% CI, -1.90 to 17.73). Mean interval between infusion set changes for any reason was similar with SAR-Lis (3.09 days) and Ly-Lis (2.95 days). The event rate (events/patient-month) of any hypoglycemia was similar with SAR-Lis (7.15) and Ly-Lis (7.98), as was the percentage of patients who experienced any TEAE (12.0% and 14.8%).

Conclusion: Both SAR-Lis and Ly-Lis were well tolerated by patients using insulin pumps. The results do not suggest a clinically significant difference in the risk of ISO between SAR-Lis and Ly-Lis when used in CSII.

Keywords

biosimilar, continuous subcutaneous insulin infusion, infusion set occlusion, insulin lispro, SAR342434, type 1 diabetes mellitus

Insulin lispro (U100; Ly-Lis; Humalog®; Lilly), a rapid-acting insulin, has a faster onset and shorter duration of action compared with regular human insulin.¹ SAR342434 (U100; SAR-Lis; insulin lispro, Sanofi) has been developed as a biosimilar to insulin lispro in the European Union and as a follow-on product in the United States in accordance with the relevant US and EU guidelines.²⁻⁶ Similar pharmacokinetic exposure and pharmacodynamics have been demonstrated for SAR-Lis to EU-approved and to US-approved Ly-Lis as well as between US-approved Ly-Lis and EU-approved Ly-Lis in a pharmacokinetic/pharmacodynamic study in patients with type 1 diabetes mellitus (T1DM) using the hyperinsulinemic euglycemic clamp technique.⁷ In addition, similar efficacy and safety of SAR-Lis and Ly-Lis have been

reported in multinational, open-label, randomized, controlled phase 3 studies in patients with T1DM (SORELLA 1; 12 months) and type 2 diabetes mellitus (SORELLA 2; 6 months) using insulin glargine (U100) as basal insulin.^{8,9}

¹Medical Investigations, Inc, Little Rock, AR, USA

²Sanofi, Bridgewater, NJ, USA

³Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

⁴Sanofi, Paris, France

⁵Barbara Davis Center for Diabetes, University of Colorado Denver, Aurora, CO, USA

Corresponding Author:

James Thrasher, MD, Medical Investigations, Inc, 500 S University Ave, Ste 615, Little Rock, AR 72205-5308, USA.
Email: jthrashermd@yahoo.com

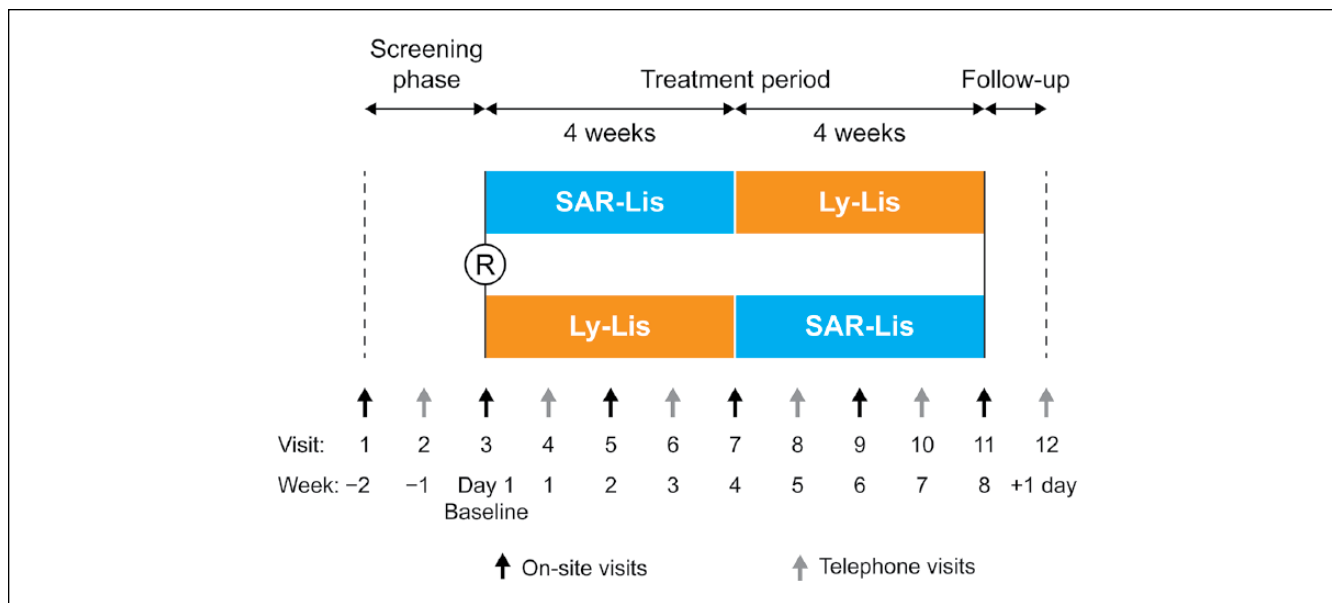


Figure 1. Study design. R, randomization if HbA1c <8.5%.

This study assessed the incidence of infusion set occlusions (ISOs) and safety of SAR-Lis and Ly-Lis when used in patients with T1DM using insulin pumps.

Methods

The study was conducted in two centers in the US in compliance with international and local laws and regulations, including approval by health authorities and ethics committees before initiation. All patients provided written informed consent prior to participation.

Patients

Adult patients aged ≥ 18 years and with T1DM for ≥ 1 year before screening visit were eligible if they had at least 1 year of insulin treatment with at least 6 months of continuous subcutaneous insulin infusion (CSII) treatment with either a Medtronic 530G Model 751 (or any other Medtronic pump with a 3-ml reservoir) or Animas (Vibe or OneTouch Ping) pump before the screening visit. Other inclusion criteria included demonstration of successful use of CSII and compliance with the four self-measured plasma glucose (SMPG) checks per day during the 2-week screening period ($\geq 75\%$ of the $4\times$ daily SMPGs recorded in the patient diary). Excluded were patients with glycated hemoglobin (HbA1c) $\geq 8.5\%$ at screening, history of abscess at the infusion site within 3 months before the screening visit, hypoglycemic 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 in the last 6 months before screening visit, and use of oral

glucose-lowering agents or any injectable glucose-lowering agents other than insulin during the 3 months before screening.

Study Design

This was an open-label, randomized, active-controlled, 2×4 -week, two-arm crossover study assessing the safety of SAR-Lis and Ly-Lis used in CSII in patients with T1DM (NCT02603510). Up to 28 patients were planned to enter the study to have 24 patients complete the study. Following a 2-week screening period, patients were randomized 1:1 to receive SAR-Lis or Ly-Lis for 4 weeks then crossed over to Ly-Lis or SAR-Lis for 4 weeks (Figure 1). Clinical visits were scheduled at screening, randomization (day 1), and weeks 2, 4, 6, and 8, with telephone visits during screening and at weeks 1, 3, 5, 7, and at follow-up 1 day after treatment ended.

When starting the study, patients continued using their own insulin pumps and continued the basal (rates) and bolus insulin regimens they were using before the study, with SAR-Lis or Ly-Lis as randomized. During the study, the dose was individually titrated as needed. Dose adjustments were made during the treatment period to achieve individualized plasma glucose (PG) targets between 70-130 mg/dl preprandial and <180 mg/dl postprandial. When crossing over to the alternate treatment after 4 weeks, the starting dose was the same as the last dose used in the first treatment period. Patients were instructed to change the infusion sets no later than every 3 days. Insulin in the reservoir was changed at least once every 7 days, in accordance with the Ly-Lis label.

Assessments

The main safety endpoint was the incidence of ISOs, defined as failure to correct hyperglycemia (PG ≥ 300 mg/dl) by 50 mg/dl within 60 minutes by insulin bolus via the insulin pump. PG levels were monitored by SMPG 4 \times daily throughout the course of the study and recorded in patient diaries. If the PG was ≥ 300 mg/dl by SMPG, the patient administered an insulin bolus via the insulin pump (dose based on insulin pump instructions), and PG was rechecked every 30 minutes until the value had fallen by ≥ 50 mg/dl and to < 300 mg/dl. Failure to lower PG by ≥ 50 mg/dl within 60 minutes of the insulin bolus was considered an ISO (if there was no pump failure), and a criterion for replacing the infusion set and moving the infusion site.

Patients recorded the date, time, and reason for the infusion set change in the diary. The primary reasons for each infusion set change were documented as either a scheduled change (3 days from the last infusion set change, or change required to refill the reservoir), unexplained PG ≥ 300 mg/dl, pain or swelling at infusion site, patient-observed ISO, insulin pump (no delivery) alarm for ISO, or other. Laboratory evaluation of the infusion sets was not conducted or planned.

Secondary safety endpoints were the incidence of patient-observed ISOs and of insulin pump (no delivery) alarm for ISOs (both, independent of confirmation of occlusion by hyperglycemia and failure to correct hyperglycemia by insulin bolus via the insulin pump) and the average interval for infusion set changes. The average interval was derived individually per treatment period as the number of days in the treatment period divided by the number of infusion set changes in the treatment period. The calculation was performed for any infusion set change (regardless of the reason) and separately for infusion set changes performed on a routine basis, when insulin set occlusion occurred or was suspected, for pump malfunction, or for an adverse event (AE).

Hypoglycemia events and insulin doses were to be documented by the patient in their diary. Hypoglycemic episodes were categorized based on American Diabetes Association classifications.¹⁰⁻¹² Documented hypoglycemia was defined as PG ≤ 70 mg/dl and separately as PG < 54 mg/dl. Nocturnal hypoglycemia was defined as any hypoglycemia that occurred between 00:00 and 05:59 hours. Severe hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Any hypoglycemic event leading to seizure, coma, or unconsciousness was reported as a serious AE (SAE). AEs including hypersensitivity events and infusion site reactions were documented throughout the study and coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0).

An allergic reaction assessment committee (ARAC), independent from the sponsor and the investigators, and comprising three allergy and clinical immunology experts, was convened. The ARAC members reviewed all

hypersensitivity reactions reported on a specific allergic reaction AE form or identified by MedDRA search, and confirmed, based on the information reported by the investigator, whether the event was allergic in nature. The ARAC was blinded regarding the study treatment. Additional safety monitoring included hematology, clinical chemistry, vital signs, and body weight.

Statistical Analyses

The analysis population was the safety population, defined as all patients randomized and exposed to any investigational medicinal product (IMP), regardless of the amount of IMP administered. All analyses were descriptive. Sample size was based on empirical considerations. No sample size or power calculation or formal hypothesis testing was performed.

Frequency distributions of ISOs during the on-treatment periods were provided as the number and percentage of patients with at least one ISO by treatment (incidence) and the number of events of ISO by treatment. The on-treatment period was defined separately for each treatment period as the time from the first infusion of IMP in the period up to 1 day (0 days for safety parameters related to risk of ISO) after the last infusion of IMP in the same period or up to the IMP change, whichever comes earlier.

The risk of ISO (proportion of patients with at least 1 ISO) within each treatment group and the risk difference between SAR-Lis and Ly-Lis were obtained by fitting a repeated measures model using a binomial regression and an identity-link function with fixed categorical effects for treatment, period, and sequence, and an unstructured correlation matrix to model within-patient errors. The risk of ISO within each treatment group and the risk difference were provided with their 95% confidence intervals (CIs) using the adjusted least squares mean estimates of the treatment effect.

Descriptive statistics were provided on hypoglycemia events and treatment-emergent AEs (TEAEs), defined as AEs that developed, worsened, or became serious during the on-treatment periods. Infusion site and hypersensitivity reactions were identified through MedDRA searches.

All summaries and statistical analyses were generated using SAS Enterprise Guide version 5.1 (SAS Institute, Cary, NC, USA).

Results

Patient Disposition and Demographic Characteristics

A total of 27 patients with T1DM were randomized and treated. Of the 27 patients, 13 were randomized to SAR-Lis for the first 4-week study period and to Ly-Lis for the second 4-week study period; 14 were randomized to Ly-Lis for the first 4-week study period and to SAR-Lis for the second 4-week study period. No patients discontinued the study while

Table 1. Demographic and Baseline Characteristics—Safety Population.

	All patients (n = 27)
Age, years, mean (SD)	42.2 (14.6)
<65, n (%)	25 (92.6)
≥65 to <75, n (%)	2 (7.4)
Sex, female, n (%)	19 (70.4)
Race, n (%)	
Caucasian/white	26 (96.3)
Black	1 (3.7)
Body weight, kg, mean (SD)	87.1 (19.8)
BMI, kg/m ² , mean (SD)	30.9 (6.1)
<25, n (%)	6 (24.0)
≥25 to <30, n (%)	5 (20.0)
≥30, n (%)	14 (56.0)
Duration of T1DM, years, mean (SD)	26.6 (12.2)
<10, n (%)	3 (11.1)
≥10, n (%)	24 (88.9)
Age at onset of T1DM, years, mean (SD)	16.2 (10.6)
Duration of CSII treatment, years, mean (SD)	9.4 (5.6)
Type of external pump, n (%)	
Animas	5 (18.5)
Medtronic	22 (81.5)
Duration of treatment with current pump, years, mean (SD)	1.9 (1.9)

on SAR-Lis, whereas three patients (11.1%) discontinued the study while on Ly-Lis, one for poor compliance, one withdrew voluntarily, and one experienced SAEs. All patients were exposed to Ly-Lis, whereas two patients were not exposed to SAR-Lis due to discontinuation during the first treatment period on Ly-Lis. The mean (SD) duration of exposure was 29.9 (2.1) days for SAR-Lis and 29.1 (2.0) for Ly-Lis.

The mean (SD) age was 42.2 (14.6) years, with two patients (7.4%) 65 years and older (Table 1). Most patients were female (19 [70.4%]) and Caucasian/white (26 [96.3%]). The mean (SD) body mass index (BMI) was 30.9 (6.1) kg/m², with 14 patients (56.0%) having a BMI ≥30 kg/m². The mean (SD) duration of T1DM was 26.6 (12.2) years; 24 patients (88.9%) had T1DM for ≥10 years. The mean (SD) age at onset of T1DM was 16.2 (10.6) years. All patients had been on CSII for at least 6 months prior to the study with a mean (SD) duration of CSII treatment of 9.4 (5.6) years. Most patients (22 [81.5%]) used Medtronic pumps. The “Threshold Suspend” function on the Medtronic pumps was not utilized during the study because Animas pumps do not have this functionality. The mean (SD) duration of current pump use was 1.9 (1.9) years.

Infusion Set Occlusions

Eighteen patients reported no ISOs during the study on either treatment. Four patients reported ISOs on both treatments,

while two patients reported ISOs only on SAR-Lis. During the first treatment period, the number of patients (three) and the number of occlusions (six) were identical between SAR-Lis and Ly-Lis. In the second treatment period, three patients (25.0%) reported occlusions while on SAR-Lis, whereas only one patient (7.7%) reported occlusions while on Ly-Lis (Table 2). The *P*-value for the period effect was 0.14; however, the study was not powered to detect a small period effect.

The number of patients who had at least one ISO was small: 6/25 (24.0%) on SAR-Lis and 4/27 (14.8%) on Ly-Lis. The risk estimate was 22.5% and 14.6% on SAR-Lis and Ly-Lis, respectively, with a risk difference for SAR-Lis versus Ly-Lis of 7.9% (95% CI, −1.90% to 17.73%) (Table 2). The total number of ISO events during the treatment period was 23; 14 on SAR-Lis and nine on Ly-Lis. The mean (SD) rate of ISOs per month was 0.59 (1.25) on SAR-Lis and 0.36 (1.01) on Ly-Lis. Two patients reported a single occlusion while on either SAR-Lis or Ly-Lis, and 4 patients experienced ≥1 event. One patient experienced 4 ISOs during each period. A small number of occlusions due to the insulin pump (no delivery) alarm (SAR-Lis, two [8.0%]; Ly-Lis, none) and patient observations (SAR-Lis, one [4.0%]; Ly-Lis, one [3.7%]) were also reported (no confirmed PG ≥300 mg/dl) (Table 2). Combining all ISOs, regardless of the reason, eight patients (32.0%) on SAR-Lis and five patients (18.5%) on Ly-Lis reported an occlusion.

The mean (SD) interval for any infusion set change (independent of the cause of infusion set change) was similar between the two treatment groups: 3.09 (0.97) days while on SAR-Lis and 2.95 (0.78) days while on Ly-Lis (Table 2), which is in line with the recommendation to change the infusion set no later than every 3 days. The mean interval between scheduled infusion set changes was 3.42 (0.95) days while on SAR-Lis and 3.16 (0.86) days while on Ly-Lis. The mean interval between infusion set changes due to ISO defined as failure to correct hyperglycemia was 16.44 (10.05) days on SAR-Lis and 18.73 (11.90) days on Ly-Lis. The mean interval between infusion set changes due to any occlusion (combined endpoint defined as failure to correct hyperglycemia, pump [no delivery] alarm for ISO, or patient observed ISO) was 18.46 (9.91) days while on SAR-Lis and 20.78 (11.28) days while on Ly-Lis. The mean interval between infusion set changes due to AEs (pain or swelling at infusion site) was 25.88 and 29.00 days on SAR-Lis and Ly-Lis, respectively.

Hypoglycemia

The number of patients with at least one hypoglycemia event was similar for the two treatments in all hypoglycemia categories; any hypoglycemia was reported by 21 patients (84.0%) while on SAR-Lis and 23 patients (85.2%) while on Ly-Lis. The event rate (events per patient-month) for any hypoglycemia was comparable on SAR-Lis (7.15) and Ly-Lis (7.98) as well as for documented symptomatic

Table 2. Summary of Infusion Set Occlusions During the On-Treatment Period—Safety Population.

	SAR-Lis (n = 25)	Ly-Lis (n = 27)
No. of patients with ≥ 1 ISO (%) ^a	6 (24.0)	4 (14.8)
Risk estimate ^b	22.5%	14.6%
95% CI	6.66 to 38.29	1.60 to 27.52
Risk difference versus Ly-Lis ^b	7.9%	
95% CI	-1.90 to 17.73	
No. of ISOs ^a	14	9
Rate of ISOs per month (SD)	0.59 (1.25)	0.36 (1.01)
Distribution of the no. of events by patient, n (%)		
1	2 (8.0)	2 (7.4)
2	1 (4.0)	0
3	2 (8.0)	1 (3.7)
>3	1 (4.0)	1 (3.7)
Average interval of infusion set changes, days; mean (SD) [n] ^c		
Any change	3.09 (0.97) [25]	2.95 (0.78) [26]
Scheduled infusion set change	3.42 (0.95) [25]	3.16 (0.86) [26]
Due to failure to correct hyperglycemia	16.44 (10.05) [6]	18.73 (11.90) [4]
Due to pump malfunction	0	29.00 (NC) [1]
Based on AE	25.88 (7.60) [4]	29.00 (NC) [1]
Due to any occlusion (combined endpoint)	18.46 (9.91) [8]	20.78 (11.28) [5]
No. of patients (%) with pump (no delivery) alarm for ISO	2 (8.0)	0
No. of patients (%) who identified ISOs	1 (4.0)	1 (3.7)
No. of patients (%) with any occlusion (combined endpoint ^d)	8 (32.0)	5 (18.5)
ISOs by period		
No. of patients with ≥ 1 ISO, (%) ^a		
Period 1	3/13 (23.1)	3/14 (21.4)
Period 2	3/12 (25.0)	1/13 (7.7)
Total	6/25 (24.0)	4/27 (14.8)
No. of ISOs ^a		
Period 1	6	6
Period 2	8	3
Total	14	9

^aISO defined as failure to correct hyperglycemia by insulin bolus via the insulin pump (excluding pump malfunction).

^bRepeated measures model using a binomial regression and an identity-link function, including fixed categorical effects for treatment, period, and sequence. Risks within each treatment group, risk difference, and their 95% CI provided using the adjusted least squares mean estimates of the treatment effect.

^cNo. of patients with ≥ 1 changes.

^dISO defined as failure to correct hyperglycemia by insulin bolus via the insulin pump (excluding pump malfunction), pump (no delivery) alarm for ISO, or patient-observed ISO.

hypoglycemia and severe and/or confirmed hypoglycemia (Table 3). No severe hypoglycemia was reported on the dedicated hypoglycemia form. One episode of hypoglycemia in the Ly-Lis group that met the criteria for “severe” was reported as SAE. There was no difference between treatments in nocturnal hypoglycemia.

Adverse Events

Three patients (12.0%) on SAR-Lis and four patients (14.8%) on Ly-Lis reported TEAEs. The most frequently reported TEAEs were upper respiratory tract infections (SAR-Lis, 1 [4.0%]; Ly-Lis, 2 [7.4%]) and potassium imbalance (SAR-Lis, 0; Ly-Lis, 2 [7.4%]). One 57-year-old white female patient on Ly-Lis experienced three

treatment-emergent SAEs (cardiorespiratory arrest, hypoglycemia, and accidental overdose); cardiorespiratory arrest led to permanent IMP discontinuation and death on day 25 of treatment. No TEAEs of diabetic ketoacidosis were reported. During the on-treatment period, one (4.0%) patient on SAR-Lis reported a mild infusion site reaction TEAE, characterized as infusion site pain and not considered to be related to SAR-Lis. No patients on Ly-Lis reported an infusion site reaction TEAE. In addition, four patients reported pain or swelling at the infusion site as the reason for unscheduled infusion set changes (three on SAR-Lis, one on both treatments).

No hypersensitivity reactions or allergic reactions were reported on either treatment. No significant changes in laboratory data, vital signs, or body weight were noted.

Table 3. Number of Anytime Hypoglycemic Events and Event Rate (Events/Patient-Month) by Type of Hypoglycemia During the On-Treatment Period—Safety Population.

	SAR-Lis (n = 25)	Ly-Lis (n = 27)
Total patient-months	25.30	25.70
Any hypoglycemia	181 (7.15)	205 (7.98)
Documented symptomatic hypoglycemia		
≤70 mg/dl	109 (4.31)	115 (4.47)
<54 mg/dl	34 (1.34)	41 (1.60)
Severe and/or confirmed hypoglycemia ^a		
≤70 mg/dl	181 (7.15)	203 (7.90)
<54 mg/dl	55 (2.17)	61 (2.37)

^aSevere and/or confirmed hypoglycemia = severe and/or confirmed by PG ≤70 mg/dl (resp. <54 mg/dl).

Discussion

Rising insulin costs have been a concern for providers and patients. Biosimilar or follow-on insulins, including rapid-acting insulins, have the potential to reduce diabetes treatment costs and increase the accessibility of insulin treatment for people with diabetes. SAR-Lis, a rapid-acting insulin and biosimilar/follow-on product of Ly-Lis, has previously been shown to have similar pharmacokinetics/pharmacodynamics to Ly-Lis in patients with T1DM and similar efficacy and safety to Ly-Lis in patients with T1DM and type 2 diabetes mellitus taking multiple daily injections while using insulin glargine.⁷⁻⁹ However, in patients with T1DM, administration of rapid-acting insulin using CSII may be favorable.¹⁰ Here, we report that SAR-Lis can also safely and effectively be used in insulin pumps. The number of patients who reported an ISO defined as failure to correct hyperglycemia by insulin bolus via the pump was small. Eighteen patients reported no ISO during either treatment, and four patients reported ISOs during both treatments (“concordant responses”). Two patients reported ISOs during SAR-Lis only (“discordant responses”), and caused the numerical difference between treatments with 6/25 (24.0%) patients with ISOs while receiving SAR-Lis and 4/27 (14.8%) patients while receiving Ly-Lis. One of the two patients with a discordant response reported an unexplained hyperglycemia with a blood glucose value of 445 mg/dl that resolved only after refilling the reservoir, which raises the question of whether the unexplained hyperglycemia was actually related to an ISO. However, the most conservative approach was taken and the event was counted as an ISO. The differences between treatment groups were not clinically meaningful as all of the patients with SAR-Lis completed the study as planned and no patient reported any AE linked to any occlusion event. We calculated the predictive probability of observing at least two more patients with ISOs in the SAR-Lis group than in the Ly-Lis group, assuming a same true rate of ISOs in both treatments varying from 15% to 24%. This predictive probability was at least 24%.

The two treatments were similar in terms of the secondary safety endpoints related to occlusions. In addition, hypoglycemia

occurred in similar numbers of patients and with similar rates of hypoglycemia on SAR-Lis or Ly-Lis. No severe hypoglycemia was reported on the dedicated hypoglycemia form for either treatment. One episode of hypoglycemia that met the criteria for “severe” was reported as SAE in the Ly-Lis group. The types of TEAEs and the frequency of their occurrence were also generally similar between the two treatments. One death was reported in the Ly-Lis group. Overall, the safety profile of SAR-Lis is similar to that of Ly-Lis, and SAR-Lis was well tolerated.

The incidence rates of ISO and hypoglycemic events reported here are generally similar to those reported in previous studies examining insulin analogs administered by continuous subcutaneous insulin infusion in patients with type 1 diabetes.¹³⁻¹⁶ The incidence rate of allergic reactions was very low in all these studies.

Limitations of this study include the small number of participants and the short duration of treatment. Laboratory evaluation of returned infusion sets to analyze for cannula plugging or kinking was not done.

We conclude that SAR-Lis and Ly-Lis were well tolerated, and that the results do not suggest clinically relevant differences in the risk of occlusions with SAR-Lis or Ly-Lis when used in CSII.

Abbreviations

AE, adverse event; ARAC, allergic reaction assessment committee; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin; IMP, investigational medicinal product; ISO, infusion set occlusion; MedDRA, Medical Dictionary for Regulatory Activities; NC, not calculated; PG, plasma glucose; SAE, serious adverse event; SD, standard deviation; SMPG, self-measured plasma glucose; TEAE, treatment-emergent adverse event; T1DM, type 1 diabetes mellitus.

Declaration of Conflicting Interests

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