

# Similar Pharmacokinetics and Pharmacodynamics of Biosimilar SAR342434 Insulin Lispro and Japan-Approved Humalog Insulin Lispro in Healthy Japanese Subjects

Clinical Pharmacology  
in Drug Development  
2022, 11(6) 754–760  
© 2022 The Authors. *Clinical Pharmacology in Drug Development*  
published by Wiley Periodicals LLC  
on behalf of American College of  
Clinical Pharmacology.  
DOI: 10.1002/cpdd.1068

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## Abstract

This phase I study compared the pharmacokinetic (PK) and glucose pharmacodynamic (PD) characteristics of biosimilar SAR342434 insulin lispro and Japan-reference Humalog insulin lispro. This was a randomized, double-blind, 2-period, crossover study. Thirty-six healthy Japanese male subjects underwent a 10-hour euglycemic clamp following a single subcutaneous 0.3-U/kg dose of SAR342434 or Humalog. Insulin lispro concentration and blood glucose were measured, and the glucose infusion rate (GIR) was adjusted to maintain the target blood glucose level. Primary PK end points were maximum plasma insulin lispro concentration and area under the plasma insulin concentration–time curve (AUC) from time 0 to the last quantifiable concentration. Primary PD end points were area under the GIR–time curve from time 0 to 10 hours and maximum GIR. PK exposure (maximum plasma concentration and AUC from time 0 to the last quantifiable concentration) and PD activity (GIR–AUC from time 0 to 10 hours and maximum GIR) were similar between treatments. Geometric mean ratios were close to 1, and the corresponding 90% and 95% CIs (PK and PD activity, respectively) were within the 0.80 to 1.25 equivalence range. SAR342434 and Humalog were well tolerated. In healthy Japanese males, SAR342434 and Humalog showed similar PK exposure profiles and PD potency, in support of SAR342434 use as a biosimilar product.

## Keywords

biosimilar, healthy Japanese subjects, insulin analog, insulin lispro, SAR342434

Insulin lispro is the active ingredient of Humalog (Eli Lilly, Indianapolis, Indiana), a rapid-acting insulin analog product approved for improvement of glycemic control in adults and children with diabetes.<sup>1</sup> Humalog (Ly-Lis) has been available for use in people with type 1 (T1D) or type 2 diabetes (T2D) in many countries, including Japan, for about 25 years, with a well-recognized efficacy and safety profile.<sup>1</sup> SAR342434 (SAR-Lis; Sanofi, Paris, France), the first biosimilar insulin lispro product to receive marketing authorization in the European Union in 2017 and Japan in 2020, has the same amino acid sequence and structure as Ly-Lis.

With any biosimilar, subtle differences can exist among these protein products manufactured in living cells that can potentially result in differing clinical effects. Physicochemical analyses, nonclinical, clinical phase 1 and 3 studies were therefore conducted to confirm that SAR-Lis and Ly-Lis are highly sim-

ilar. In healthy subjects with T1D, similar pharmacokinetic (PK) exposure and pharmacodynamic (PD) activity was initially shown for SAR-Lis vs both US-reference and EU-reference Ly-Lis, as well as between

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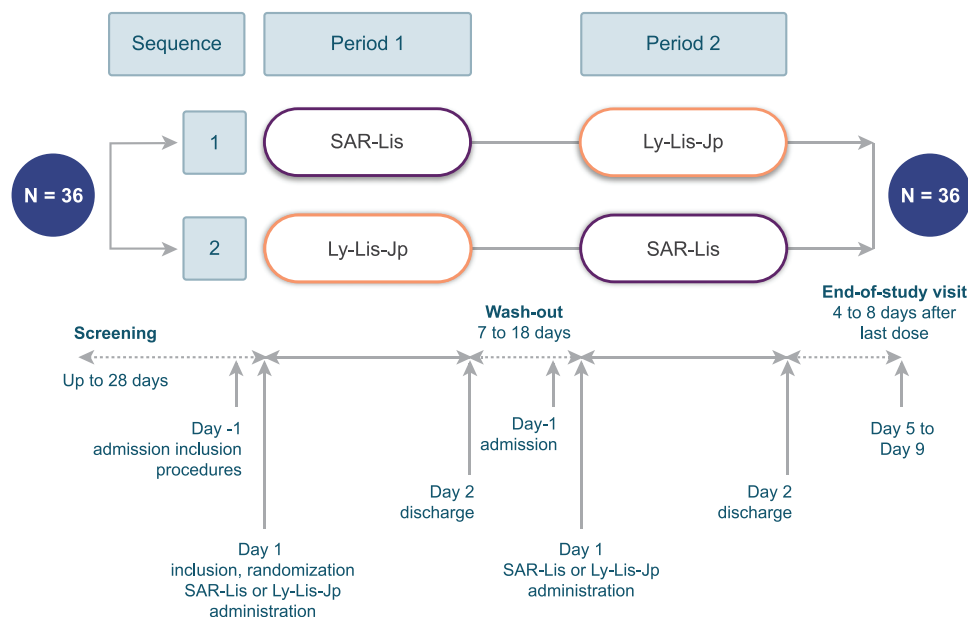
Submitted for publication 8 October 2021; accepted 12 December 2021.

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**Figure 1.** Study design. Subjects were randomized to 1 of 2 treatment sequences as shown. In both periods, subjects received a single 0.3-U/kg dose of each insulin followed by a 10-hour euglycemic clamp procedure. Subjects were discharged from the clinic 1 day following the clamp procedure.

US-reference and EU-reference Ly-Lis.<sup>2</sup> Subsequently, 2 multinational, randomized phase 3 trials in participants with T1D<sup>3</sup> or T2D<sup>4</sup> confirmed similar efficacy, safety, and immunogenicity of SAR-Lis and Ly-Lis. A small study of insulin pump users with T1D also showed that SAR-Lis and Ly-Lis were well tolerated during continuous treatment for 4 weeks.<sup>5</sup>

Regulatory guidelines for the approval of biosimilar insulins in Japan state that it is also necessary to demonstrate comparability in PK exposure and glucose PD activity vs the Japanese reference product. Here, we report data from a phase 1 trial of healthy Japanese volunteers that was conducted to assess the insulin lispro PK and PD characteristics of SAR-Lis and Japan-reference Humalog (Ly-Lis-Jp).

## Methods

### Subjects

The study protocol was reviewed and approved by the Hakata Clinic Institutional Review Board, Fukuoka, Japan, and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All subjects provided written informed consent before study entry.

Healthy Japanese men (based on a comprehensive clinical assessment that included normal vital signs, 12-lead electrocardiogram [ECG], and laboratory parameters) aged 20 to 45 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m<sup>2</sup> were eligible for inclusion in the study.

### Study Design

This was a randomized, single-site (Hakata Clinic, Fukuoka, Japan), investigator- and subject-blind, single-dose, 2-period, crossover study undertaken in 2017-2018 (trial registration: [www.clinicaltrials.jp](http://www.clinicaltrials.jp) identifier: JapicCTI-205379).

The study design is outlined in Figure 1. Following a screening visit 3 to 28 days before the first period, subjects were randomly assigned (computer generated by the sponsor considering 2-treatment, 2-period, 2-sequence crossover design) to 1 of the 2 treatment sequences. They received a single 0.3-U/kg dose of SAR-Lis or Ly-Lis-Jp in the first treatment period in randomized order followed by the other drug in the second treatment period. Subjects were closely observed in the clinic for at least 24 hours after dosing until discharge, and subsequently returned for the second treatment period. Each treatment day was separated by a washout period of 7 to 18 days, with an end-of-study visit performed 4 to 8 days after the last dose.

### Study Treatments

SAR-Lis (Sanofi, Frankfurt, Germany) and Ly-Lis-Jp (Humalog, Eli Lilly KK, Japan) were supplied as a 100-U/mL solution in a 3-mL cartridge. An independent pharmacist and assistant at the study site prepared syringes with the individual dose for each subject to maintain consistency of the dosing and blinding of the investigator and subject.

### Euglycemic Clamp Procedure

The PD effect of SAR-Lis and Ly-Lis-Jp was evaluated using the euglycemic clamp technique. Subjects underwent a 10-hour euglycemic clamp procedure at each dosing visit, as described previously.<sup>6,7</sup> Following an overnight fast of at least 10 hours in each treatment period, subjects were connected to the clamp device (Artificial Endocrine Pancreas, STG-22, Nikkiso Co, Ltd, Tokyo, Japan), and their baseline blood glucose (BG) was measured. This fasting baseline BG concentration was determined as the mean of 4 glucose measurements at -30, -20, -10, and -1 minutes before dosing with SAR-Lis or Ly-Lis-Jp. The clamp procedure was not performed in those subjects having a baseline BG of <70 mg/dL (3.92 mmol/L).

During the clamp procedure, the BG level and the amount of external glucose required to keep a subject's BG concentration at its target level (the glucose infusion rate [GIR]) were continuously measured and recorded by the STG-22 device. The target value for BG concentrations was 5 mg/dL (0.28 mmol/L) below the subject's fasting baseline BG concentration. The clamp device determined BG levels in 1-minute intervals and automatically adjusted the GIR, via variable infusion of 10% glucose, in response to changes in BG using a predefined algorithm to maintain the BG at its target level. To assess clamp quality, the coefficient of variation (CV) and mean of BG values between individual start and end of clamp and the absolute difference of individual mean BG measurements from the clamp target level were calculated, as described previously.<sup>2</sup>

### Bioanalytical Methods

Venous blood samples for PK analysis were collected in potassium-ethylenediaminetetraacetic acid-anticoagulant tubes before dosing and then every 15 to 60 minutes during the 10-hour clamp in each treatment period. Samples were centrifuged within 20 minutes of collection and plasma stored at -60 to -80°C until analysis. Plasma concentrations of SAR-Lis and Ly-Lis-Jp were analyzed using validated and specific liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods (Xevo TQS system; Waters Corp., Milford, Massachusetts) at Syneos Health, Québec, Canada. The assay was able to distinguish between exogenous insulin lispro and endogenous human insulin. Plasma samples were subjected to protein precipitation followed by solid-phase extraction before LC-MS/MS quantification of insulin lispro. The internal standard was bovine insulin. The assay volume was 0.25 mL per sample. Liquid chromatography was achieved on an analytical C18 reverse-phase column (50 × 2.1 mm, 1.7 μm; Acquity UPLC CSH, Waters Corp.) using gradient elution at 40°C. The mobile

phase A contained formic acid in Milli-Q type water, and phase B contained formic acid in acetonitrile and were delivered at 0.2 mL/min. The desired substance was detected and quantified by LC-MS/MS using electrospray ionization in the positive ion mode. For quantitation, the method monitored the precursor-to-product transitions of  $m/z$  1162.65 → 217.05 and  $m/z$  956.54 → 1121.62 for the analyte (insulin lispro) and the internal standard, respectively. The concentration of insulin lispro was extrapolated from a standard curve using a linear regression method, with a weighting factor of  $1/x^2$ . Plasma concentrations within the validated concentration range (100–8000 pg/mL) were used to calculate the PK parameters. Assay performance was assessed by back-calculation of calibration standards and measurement of quality control samples. Validation data showed the LC-MS/MS bioanalysis of SAR-Lis and Ly-Lis-Jp plasma concentrations was precise and accurate, with a lower limit of quantification of 100 pg/mL. The mean within-run and between-run precision (% CV) ranged from 2.6% to 6.1% and from 3.6% to 8.1%, respectively. The mean within-run accuracy showed a percent bias ranging between -4.9% and 6.4%, whereas the between-run bias was between -3.7% and 1.2%. Incurred sample reanalysis confirmed the initial value in 95.4%, thereby demonstrating good assay reproducibility.

### Safety Evaluation

The safety and tolerability of single doses of SAR-Lis and Ly-Lis-Jp were assessed by physical examination, vital signs (pulse, blood pressure), routine laboratory assessments, 12-lead ECG, and reporting of adverse events (AEs). AEs were classified according to the Medical Dictionary for Regulatory Activities version 20.1. The safety population included all randomized patients exposed to the study insulin (regardless of the amount of treatment administered), analyzed according to the treatment received. The treatment-emergent AE period was the time interval between (first) study drug administration and up to 72 hours later in each treatment period.

### Pharmacokinetic and PD Parameters

The PK analysis data set included subjects completing at least 1 treatment period and had measurable insulin lispro concentrations and no major or critical deviations. The primary PK end points were maximum plasma insulin lispro concentration ( $C_{max}$ ) and area under the insulin lispro concentration-time curve (AUC) from time 0 to the time of the last quantifiable data point ( $AUC_{last}$ ). The AUC from time 0 to infinity, time to  $C_{max}$  ( $t_{max}$ ), and terminal half-life were secondary PK end points.

PD parameters were measured throughout the glucose clamp, with the GIR used as a measure of insulin effect. Subjects who completed at least 1 clamp procedure with no major or critical deviations were included in the PD analysis data set. The individual time profiles of GIR and BG levels in each treatment group were standardized for body weight and a locally weighted scatterplot smoothing function (SAS, PROC LOESS, factor 0.06) was applied to all individual GIR- and BG-time profiles.<sup>8</sup> A smoothing factor of 6% was used based on the expected morphology of the GIR-profiles. The fitted GIR-time profiles were used to calculate the GIR-AUC from 0 to 10 hours (GIR-AUC<sub>0-10h</sub>) and maximum smoothed body weight standardized GIR (GIR<sub>max</sub>) (primary PD end points), and the time to reach GIR<sub>max</sub> (GIR-t<sub>max</sub>; secondary end point).

### Statistical Analyses

The study was designed to show bioequivalence in PK exposure and PD activity of a single dose (0.3 U/kg) of SAR-Lis or Ly-Lis-Jp under fasting conditions. To achieve this, 20 and 32 evaluable subjects, respectively, were required to ensure with at least 90% power that the 90% and 95% CIs for the estimated treatment ratios of the natural log-transformed PK and PD end points, respectively, were within the accepted bioequivalence range (0.8-1.25).<sup>9</sup> This assumed a true ratio between the 2 formulations of 0.93 for the PK end points and 1.07 for the PD end points, and a true within-subject standard deviation on natural log scale of 0.175 for PK parameters and 0.185 for the PD parameters. These calculations were based on within-subject variability estimates observed in a prior SAR-Lis study in subjects with T1D.<sup>2</sup> To allow for dropouts, the study planned to recruit at least 36 subjects (18 per sequence).

The log-transformed PK and PD parameter estimates for SAR-Lis and Ly-Lis-Jp were compared between groups using a linear mixed effects model, including period, sequence, and treatment as fixed effects, and subject as a random effect. For each parameter, the model-based difference in treatment means along with the confidence limits (90% for PK parameters, 95% for PD parameters) was back-transformed to provide estimates for the ratio of geometric means (gMeans) between treatments (SAR-Lis/Ly-Lis-Jp) and the corresponding confidence limits. For all other parameters, descriptive statistics were presented. Non-compartmental analysis of SAR-Lis and Ly-Lis-Jp plasma concentration-time data was performed using Phoenix WinNonlin version 6.4 (Certara, Princeton, New Jersey). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

**Table 1.** Baseline Characteristics of the Study Population (Safety Population)

	All subjects (n = 36)
Age, y	25.3 ± 5.2 (20-39)
Sex, male, n (%)	36 (100)
Race, Japanese, n (%)	36 (100)
Body weight, kg	64.88 ± 7.98 (53.9-85.5)
Body mass index, kg/m <sup>2</sup>	21.83 ± 2.52 (18.6-27.3)

All average data are mean ± standard deviation (min-max).

## Results

Thirty-six Japanese male subjects were randomized, treated, and completed both treatment periods. PK and PD parameters for SAR-Lis and Ly-Lis-Jp were available for all subjects. Baseline characteristics of the subjects are given in Table 1.

### Pharmacokinetics

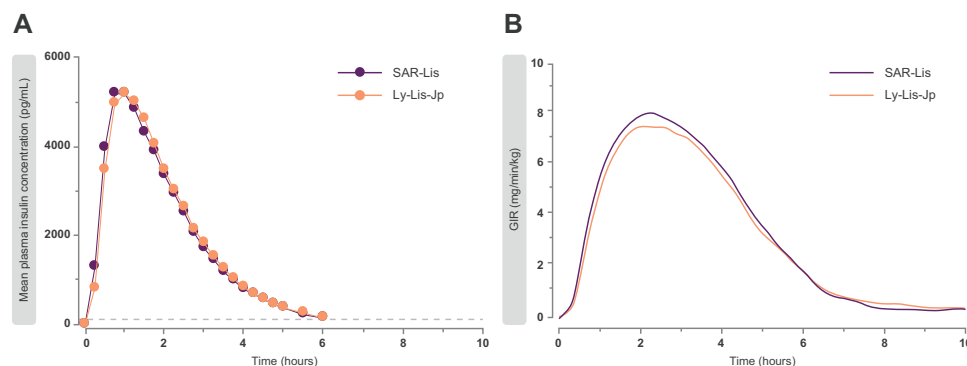
The mean insulin lispro concentration-time profiles following single 0.3 U/kg doses of SAR-Lis and Ly-Lis-Jp are shown in Figure 2A, and summarized PK parameters are given in Table 2.

Plasma concentration-time profiles of SAR-Lis and Ly-Lis-Jp were similar, and the point estimates for the gMean AUC<sub>last</sub> and C<sub>max</sub> ratios were close to 1. The corresponding 90% CIs for each parameter were completely within the bioequivalence limits of 0.80 to 1.25. This supports equivalent exposure of the 2 insulin lispro products. The secondary end point AUC from time 0 to infinity showed similar results to AUC<sub>last</sub>. Between-subject variability in the PK parameters was low to moderate (geometric CV values between 12% and 33%). The median t<sub>max</sub> for SAR-Lis (1 hour) was similar to that for Ly-Lis-Jp (1 hour) (data not shown).

### Pharmacodynamics

The mean smoothed body weight normalized GIR profiles during the euglycemic clamp procedure (from time 0 to 10 hours postdose) are shown in Figure 1B and summarized PD parameters are given in Table 2.

The mean GIR profiles of SAR-Lis and Ly-Lis-Jp were similar, displaying a short action-time profile. The point estimates for the gMean GIR-AUC<sub>0-10h</sub> and GIR<sub>max</sub> ratios were just above 1 for both outcomes, and the 95% CIs were within the equivalence interval (0.80-1.25), confirming equipotency of SAR-Lis and Ly-Lis-Jp. Between-subject variability for GIR-AUC<sub>0-10h</sub> and GIR<sub>max</sub> was low (geometric CV values between 17% and 27%). The median GIR-t<sub>max</sub> for SAR-Lis (2.32 hours) was similar to that for Ly-Lis-Jp (2.47 hours) (data not shown).



**Figure 2.** Mean insulin lispro plasma concentration–time profiles (A) and mean smoothed plots of body weight standardized glucose infusion rate (GIR)–time profiles (B). The horizontal dotted line in (A) is the lower level of quantification of 100 pg/mL.

**Table 2.** Primary and Secondary PK and PD End Points

End Point	SAR-Lis (n = 36)	Ly-Lis-Jp (n = 36)	Mean Ratio SAR-Lis/Ly-Lis-Jp
			Point estimates (90%CI PK and 95%CI PD) <sup>a</sup>
<b>PK end points</b>			
$C_{max}$ , pg/mL	5710 ± 1630 (5490) [29]	5830 ± 1930 (5560) [33]	0.99 (0.93-1.05)
$AUC_{last}$ , pg • h/mL	12300 ± 1450 (12 200) [12]	12400 ± 1800 (12 200) [15]	1.00 (0.97-1.02)
$AUC_{inf}$ , pg • h/mL	12400 ± 1460 (12 300) [12]	12500 ± 1790 (12 400) [14]	1.00 (0.97-1.02)
$t_{1/2z}$ , h	0.793 ± 0.189 (0.772) [24]	0.779 ± 0.237 (0.746) [30]	1.03 (0.96-1.11)
<b>PD end points</b>			
$GIR-AUC_{0-10h}$ , mg/kg <sup>b</sup>	1962.6 ± 378.8 (1927.96) [19.3]	1877.7 ± 503.3 (1807.94) [26.8]	1.07 (0.99-1.15)
$GIR_{max}$ , mg/kg • min	8.56 ± 1.47 (8.43) [17.2]	8.11 ± 1.91 (7.87) [23.5]	1.07 (1.00-1.15)

%CV, percent coefficient of variation;  $AUC_{last}$ , 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 lispro concentration in plasma; GIR, body weight standardized glucose infusion rate;  $GIR-AUC_{0-10h}$ , area under the body weight standardized GIR rate vs time curve from 0 to 10 hours;  $GIR_{max}$ , maximum smoothed body weight standardized GIR; gMean, geometric mean; PD, pharmacodynamic; PK, pharmacokinetic;  $t_{1/2z}$ , terminal half-life associated with the terminal slope ( $\lambda_z$ ).

Data shown as mean ± SD (geometric mean) [CV%].

<sup>a</sup> 90%CI and 95%CI for the pairwise treatment ratios.

<sup>b</sup>  $GIR_{max}$  determined from smoothed GIR data (locally weighted scatterplot smoothing method, tension 0.06).

### Clamp Performance

Table 3 shows the clamp quality assessments. The individual variability of BG measurements during euglycemia was low for both treatments (median CV values of 6.00% and 6.80% for SAR-Lis and Ly-Lis-Jp, respectively). Individual mean BG during euglycemia were also consistent for both treatments (mean values of 78.70 and 78.04 mg/dL for SAR-Lis and Ly-Lis-Jp, respectively). Similarly, absolute differences between individual mean BG measurements and the BG target level were low (mean of 1.90 mg/dL for SAR-Lis and 2.18 mg/dL for Ly-Lis-Jp).

### Safety and Tolerability

There were no serious AEs, AEs of special interest, or treatment-emergent AEs (TEAEs) leading to treatment discontinuation during the study. Three TEAEs were reported by 3 subjects during the study (2 and 1 following administration of SAR-Lis and Ly-Lis-Jp,

respectively). None were considered as related to the study medication. There were few potentially clinically significant abnormalities in laboratory tests and ECG parameters, with no notable difference between SAR-Lis and Ly-Lis-Jp.

### Discussion

In this crossover study, we compared PK exposure and glucose PD activity of SAR-Lis and Japan-approved Humalog (Ly-Lis-Jp) in healthy Japanese male subjects after administration of single subcutaneous doses using a euglycemia clamp device to measure insulin action.

We showed that SAR-Lis and Ly-Lis-Jp had similar overall PK exposure ( $C_{max}$  and AUC) with virtually no difference in the profile of the insulin lispro plasma concentration curves. Consistent with the PK findings, SAR-Lis showed similar insulin activity as assessed by glucose use in the euglycemic clamp. GIR-time profiles and estimates of PD parameters ( $GIR_{max}$  and

**Table 3.** Performance of Clamp During Euglycemia

Parameter and Unit	SAR-Lis (n = 36)	Ly-Lis-Jp (n = 36)
Individual mean of BG concentration (during euglycemia), mg/dL <sup>a</sup>		
Mean ± SD	78.70 ± 6.41	78.04 ± 5.34
Median (range)	78.30 (67.9-93.1)	77.25 (69.5-91.0)
Individual %CV of BG (during euglycemia), % <sup>a</sup>		
Mean ± SD	7.24 ± 3.61	7.69 ± 3.60
Median (range)	6.00 (3.8-19.7)	6.80 (3.0-14.8)
Absolute deviation of individual mean BG from clamp level (during euglycemia), mg/dL <sup>a</sup>		
Mean ± SD	1.90 ± 1.49	2.18 ± 2.19
Median (range)	1.80 (0.0-5.3)	1.45 (0.1-9.5)

BG, blood glucose; CV, coefficient of variation; SD, standard deviation.

<sup>a</sup>Euglycemia starts with dosing and ends with the last value of the smoothed BG concentration curve at or below the predetermined target blood glucose concentration for each individual subject, as described in the Methods. Clamp level (BG target) for each subject was 5 mg/dL (0.28 mmol/L) below the subject's baseline concentration.<sup>11</sup>

GIR-AUC) were similar for the 2 treatments. The between-subject variability estimates for both treatments were low to moderate for all PK and PD parameters. Single doses of SAR-Lis and Ly-Lis-Jp were well tolerated with the number of patients reporting a TEAE and the number of TEAEs reported being comparable between treatment groups. All TEAEs were mild or moderate in severity.

The euglycemic clamp procedure used in this study is the gold standard for assessment of insulin action and recommended by regulatory guidelines for use in these types of studies that aim to demonstrate biosimilarity between 2 insulin treatments.<sup>9</sup> The dose of insulin administered and the duration of the clamp are 2 important factors to consider when using these devices. The insulin dose of 0.3 U/kg used in this study under fasting conditions provided strong PD effects in the euglycemic clamp (ie, a sizable GIR response up to 10 hours) and has been used in other similarly designed clamp studies.<sup>2,10</sup> The short duration of action and rapid clearance of insulin lispro following subcutaneous administration meant that a 10-hour clamp was sufficient to account for individual variations in insulin elimination and the duration of PD activity. It also minimized the time during which subjects were required to remain fasted during the clamp procedure.<sup>11</sup> Clamp durations of 8 to 10 hours are generally sufficient for rapid-acting insulins. The washout period of 7 to 18 days between dosing periods ensured that insulin concentrations were below the lower limit of quantification before the second treatment period.

Like all devices, the quality of the clamp performance is critical for interpretation of the data. The clamp quality, assessed by the individual variability of BG over the clamp duration (from 0 to the end of euglycemia), was reliably maintained within reasonable variability (median CV values of 6.00% and 6.80% for

SAR-Lis and Ly-Lis-Jp, respectively). The mean difference between measured and target BG levels was also similarly low for both insulins. This indicates successful performance of the euglycemic clamp.

Normal-weight healthy subjects were included in this study, as this involves use of a homogenous population that is sensitive to insulin and enables detection of any potential treatment-related differences. Healthy subjects are also used in insulin bioequivalence studies as they usually exhibit lower within-subject variability compared with patients by avoiding potential confounding factors such as underlying and/or concomitant disease and concomitant medications.<sup>12</sup> The study was restricted to male subjects, as it was uncertain if the known insulin sensitivity in females during the menstrual cycle might affect the study results.<sup>10</sup>

Similar to the present findings in Japanese subjects, similar insulin lispro exposure profiles and glucodynamic activity of SAR-Lis compared with Ly-Lis were observed in an earlier randomized, double-blind, 2-period, crossover euglycemic clamp study in 30 White men with T1D.<sup>2</sup> Consistent with our findings in Japanese healthy men, total insulin lispro exposure and glucose infused during the clamp did not differ, and tolerability was similar between the 2 treatments. Taken together, observations from these 2 independent clamp studies in differing study populations add to the totality of evidence that support that SAR-Lis has a similar pharmacological profile compared with Ly-Lis.

## Conclusion

The results of this study demonstrated that SAR-Lis had similar PK exposure and glucodynamic activity compared with Japanese-approved insulin lispro formulation, supporting use of SAR-Lis as a biosimilar product.

## Acknowledgments

Sanofi K.K. (Tokyo, Japan) was the sponsor of the study and was responsible for the design and coordination of the trial, monitoring, collecting, and managing data, and performing all statistical analyses. The authors were responsible for the analysis and interpretation of the data and the preparation of the manuscript. D.J. Quinlan of Oberon Ltd (London, UK) provided editorial support, funded by Sanofi.

## Funding

This study was funded by Sanofi K.K., Tokyo, Japan.

## Conflicts of Interest

M.S. declares no conflict of interest. His current affiliation is Kashiwara Hospital, and this manuscript does not represent opinions of his current affiliation. T.Y. declares no conflict of interest. W.S., Y.T., and M.K. are employees and shareholders of Sanofi. I.N. is a former employee of Sanofi and is a current consultant to Sanofi. H.M. is a former employee of Sanofi and is a current employee of Novartis. H.M. declares no conflict of interest, as this manuscript does not represent opinions of his current affiliation.

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