CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209196Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	209-196 Serials 0000, 0013
Submission Dates	November 1, 2016; April 20, 2017
Brand Name	To be determined
Generic Name	Insulin lispro (SAR342434)
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	sanofi-aventis U.S. LLC
Formulation; Strength	Solution for injection; 100 units/mL
Relevant IND	(b) (4)
Indication	Improve glycemic control in adults with diabetes mellitus

Table of Contents **Page**

1 Executive Summary

The sponsor submitted NDA 209-196 via the 505(b)(2) regulatory pathway to seek approval of subcutaneous (SC) administration of SAR342434 (insulin lispro) for the indication to improve glycemic control in adults and children with diabetes mellitus. SAR342434 has 100 units of insulin lispro/mL as compared to the comparator, Humalog (insulin lispro 100 units/mL; NDA 20-563 approved on June 14, 1996 for Eli Lilly). This document reviews the Clinical Pharmacology data of NDA 209-196. For simplicity, this review refers the following:

- SAR342434 for the sponsor's insulin lispro
- US-Humalog for the Humalog approved and marketed in the United States
- EU-sourced insulin lispro for the insulin lispro approved and marketed in the European Union

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 209-196 Serials 0000 and 0013 and finds them acceptable. See this review's section on "Preliminary Labeling Recommendations" for label recommendations.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor submitted the following 4 clinical studies to support NDA 209-196:

- Study PDY12704 to characterize and compare the pharmacokinetics (PK) and pharmacodynamics (PD, namely glucose infusion rate [GIR]) of SAR342434, US-Humalog, and EU-sourced insulin lispro upon single subcutaneous doses of 0.3 unit/kg in a euglycemic clamp study in patients with type 1 diabetes mellitus (T1DM)
- Study EFC12619 to demonstrate non-inferiority of SAR342434 versus US-Humalog and EU-sourced insulin lispro for change in hemoglobin A1c (HbA1c) from baseline to Week 26 in patients with T1DM also receiving Lantus
- Study EFC13403 to demonstrate non-inferiority of SAR342434 versus US-Humalog and EU-sourced insulin lispro for change in HbA1c from baseline to Week 26 in patients with type 2 diabetes mellitus (T2DM) also receiving Lantus
- Study PDY13502 to assess the safety of SAR342434 and US-Humalog when used in external pumps for the incidence of infusion set occlusions.

Highlights of PK/PD comparisons:

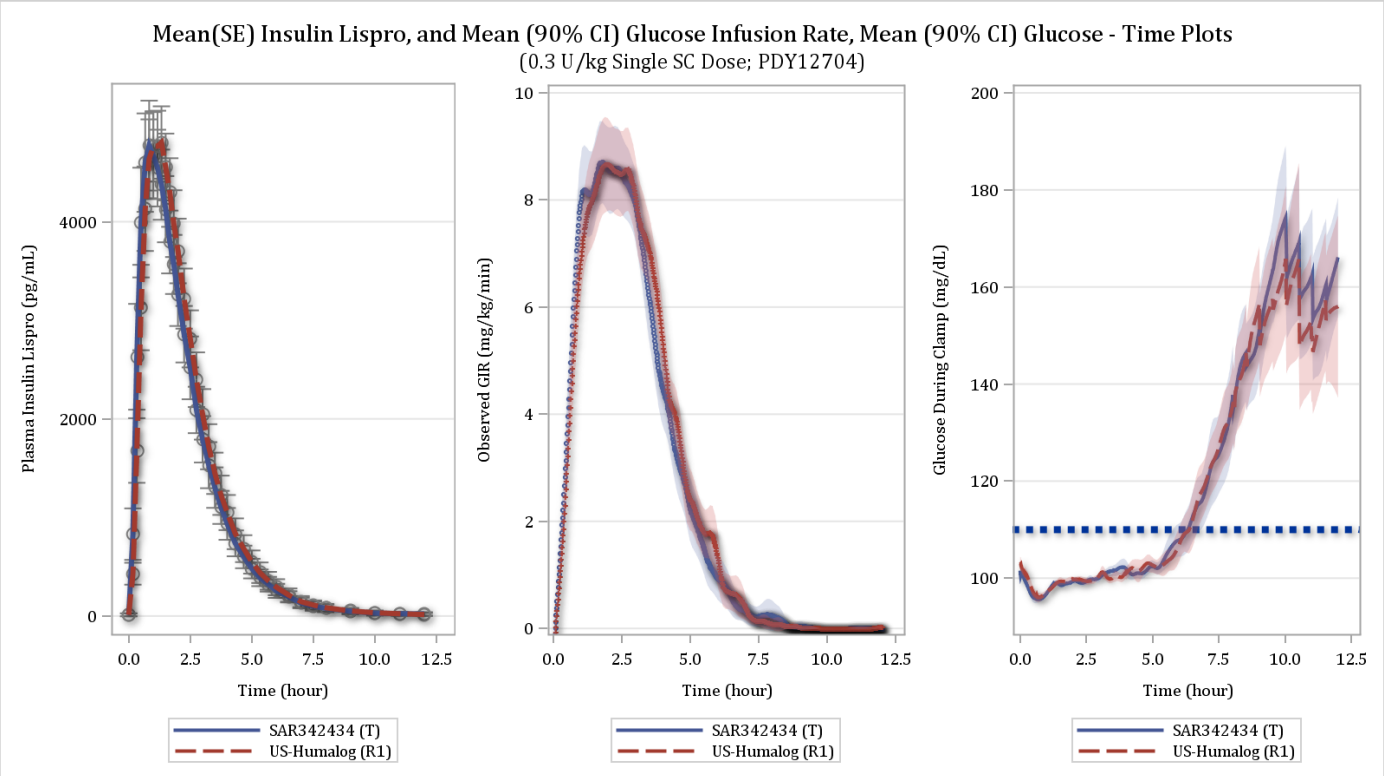
- For the comparison of SAR342434 to US-Humalog, Study PDY12704 showed that the geometric mean ratios and 90% confidence interval (CI) for both primary PK (C_{max} , $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) and PD (GIR_{max} and $GIRAUC_{0\text{-}12}$) parameters were within the prespecified goalpost of 0.80 – 1.25.
- Figure 1 shows the mean (SE) PK, mean (90% CI bands) smoothed GIR (PD), mean (90% CI bands) glucose profiles of SAR342434 and US-Humalog. Figures 2 and 3 show the statistical comparisons of PK and PD parameters for Study PDY12704.
- For the secondary PK (time to maximum plasma insulin lispro concentration [INS-t_{max}]) and PD (time to maximum smoothed body weight standardized GIR [GIR-t_{max})]) parameters, the median difference and (90% CI) showed significant difference as the following via the Hodges-Lehmann analysis:
    - INS-t_{max} of -0.17 hour (-0.25 – -0.08) when compared SAR342434 with US-Humalog
    - GIR-t_{max} of -0.30 hour (-0.56 – -0.03) when compared SAR342434 with US-Humalog

- Of note, the mean PD profile did not point to a clear maximum for SAR342434 and US-Humalog on average. However, the ranges of time to GIR_{max} were almost identical between the 3 treatments (see Table 2 of this review).
- The statistical comparison of composite PD effect measure as $GIRAUC_{0-2}$ (the time to GIR_{max} was about 2 hours), which reflects the clinical relevance of any changes in PK did not reveal any deviation from the 0.8 – 1.25% CI goalpost. Further, the safety and efficacy measures of hypoglycemia rate and hemoglobin A1c (HbA1c) do not differ between SAR342434 and Humalog in the 2 clinical studies (see Dr. Sonia Doi's clinical review in DARRTS).
- The duration of action was on average around 6 hours for SAR342434 and US-Humalog after 0.3 unit/kg dose as indicated by the GIR-time and glucose-time profile in Figure 1 (time when glucose exceeded 110 mg/dL - upper threshold of 10% of the euglycemic clamp target of 100 mg/dL).

In sum, Study PDY12704 showed the PK and PD data:

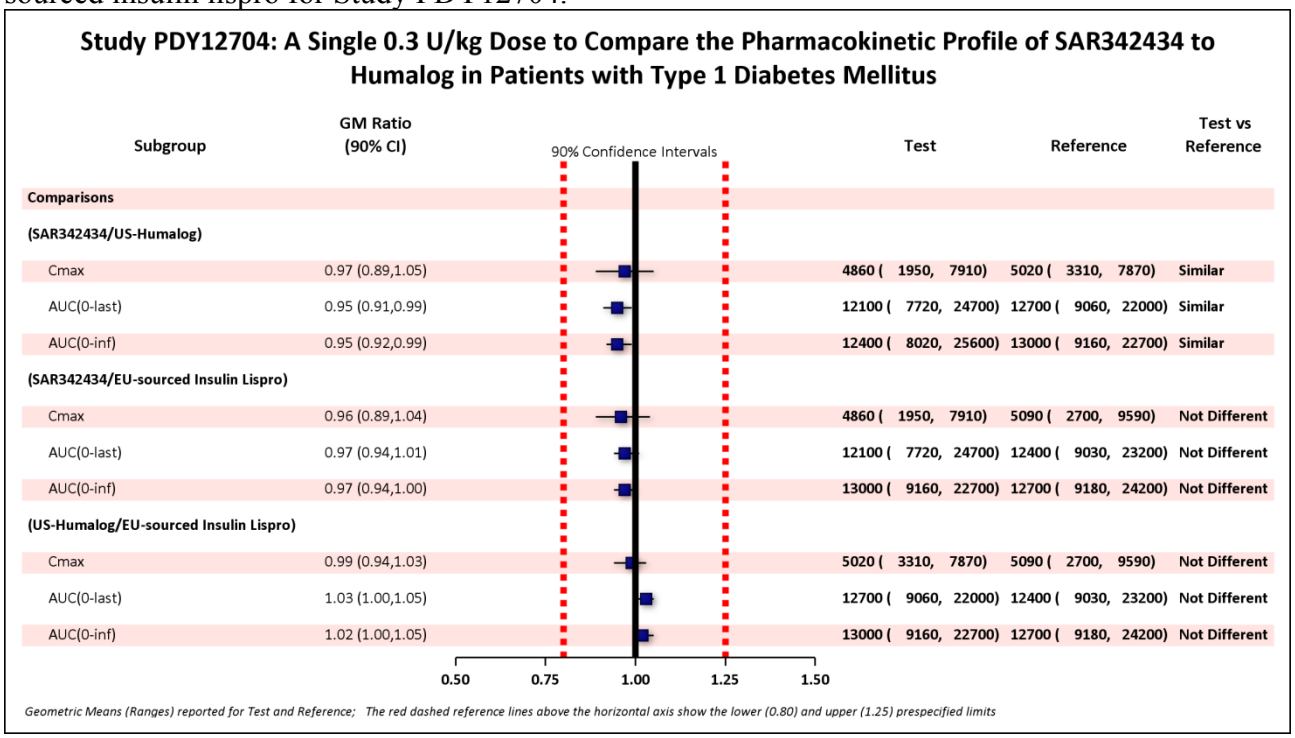
- are similar between SAR342434 and US-Humalog
- are not different between SAR342434 and EU-sourced insulin lispro
- are not different between US-Humalog and EU-sourced insulin lispro

Figure 1. Mean plasma insulin lispro concentration – time, smoothed glucose infusion rate (GIR) – time, and blood glucose concentration – time profiles upon single SC dose administration of SAR342434 and US-Humalog.



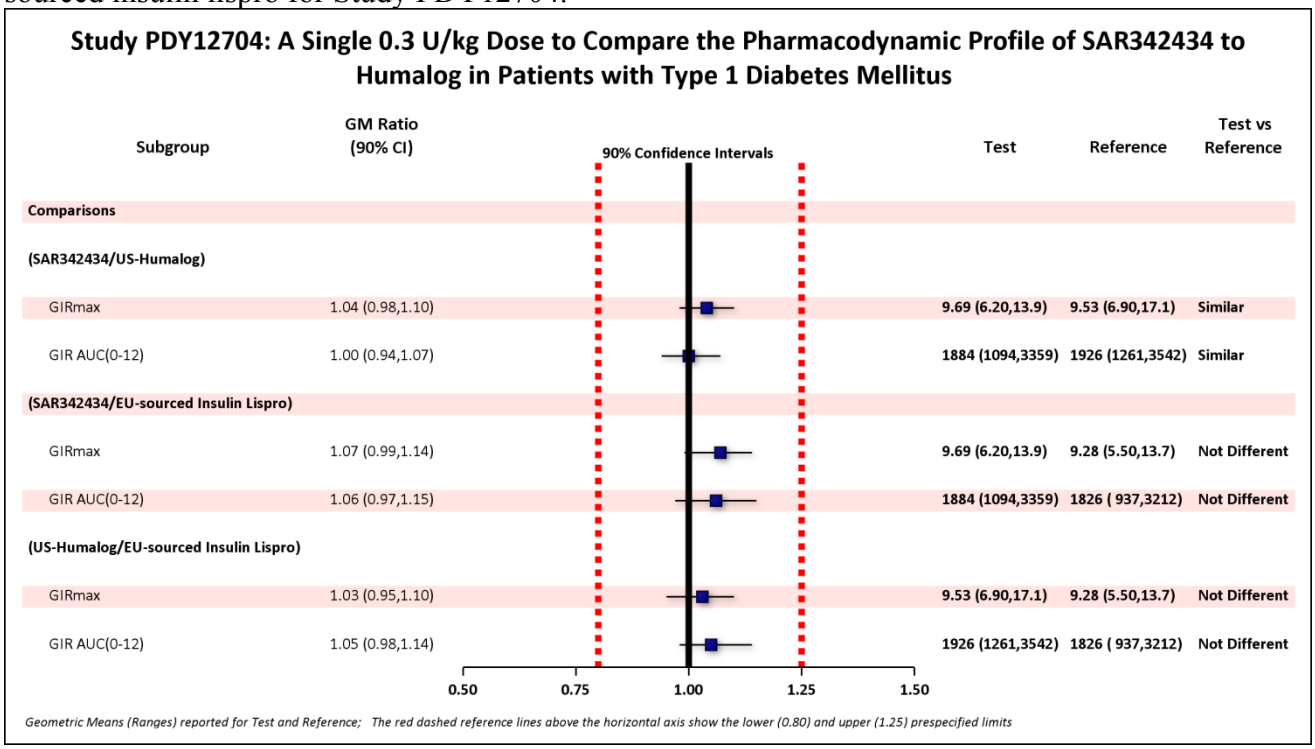
Source: Reviewer's analysis

Figure 2. Forest plot of primary PK parameter comparisons between SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



Source: Reviewer's analysis

Figure 3. Forest plot of primary PD parameter comparisons between SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



Source: Reviewer's analysis

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the formulation of the to-be-marketed SAR342434?

Table 1 details the formulation of the to-be-marketed SAR342434.

Table 1. The to-be-marketed SAR342434 insulin lispro solution for injection 100 units/mL.

Components	Composition			Function	Reference to standards
	Percentage	Per mL	Per unit (3 mL		
Insulin lispro *[equivalent to U of insulin]*	(b) (4)	*[100]*	*[300]*	Drug substance	Ph. Eur., USP
Metacresol	1.88	(b) (4)			Ph. Eur.,
Glycerol (b) (4)	(b) (4				USP Ph.
Dibasic sodium phosphate					Eur.
Zinc oxide					USP
Sodium hydroxide					Ph. Eur.,
Hydrochloric acid, (b) (4)					USP Ph.
(b) (4) Water for injection					Eur., NF
					Ph. Eur.,

Source: Modified from Sponsor's Quality Overall Summary – 2.3.P Table 1.

2.1.2 Is there any difference between the clinically-tested formulation of SAR342434 and the to-be-marketed formulation of SAR342434?

The SAR342434 solution formulation used throughout the clinical development program is identical to the final to-be-marketed formulation. The SAR342434 product also has the same pharmaceutical composition and strength as Humalog 100 units/mL.

2.2 Key Clinical Pharmacology Questions

2.2.1 What are the design features of Study PDY12704?

Study PDY12704 was a double-blind, controlled, crossover (3-treatment, 3-period, and 6-sequence), euglycemic clamp study in 30 male patients with T1DM. Randomized patients received 1 of the 6 treatment sequences for single doses of 0.3 unit/kg for SAR342434, US-Humalog, and EU-sourced insulin lispro in 3 separate treatment periods. The SC injection site was the periumbilical area (through a standardized skin-fold technique). A washout of 5 – 18 days (for resuming their routine insulin treatment) separated each treatment period (TP).

During the euglycemic clamp, the GIR, blood glucose concentration, and amount necessary to keep a patient's blood glucose concentration at its target concentration were continuously measured and recorded via the Biostator device. After dosing SAR342434, US-Humalog, or EU-sourced insulin lispro, blood glucose concentrations of the patients were maintained within a range of 5.5 mmol/L (100 mg/dL) ± 20% for the last hour prior to dosing and ± 10% in the last 30 minutes prior dosing via the intravenous infusion of 20% glucose solution with the Biostator (euglycemic clamp) until 12 hours postdose (clamp end). GIR is a measure of the PD response.

The amount of glucose required (area under the body weight standardized GIR versus time curve [GIR-AUC]) is a measure of insulin mediated glucose uptake into tissues (glucose disposal or glucose lowering activity). Biostator determined blood glucose concentrations in 1-minute intervals and adjusted the GIR in response to changes in blood glucose via a predefined algorithm. During the clamp, arterialized venous blood glucose concentrations, which reflected the supply for total glucose utilization of all tissues, as well as GIRs were continuously monitored. The clamp visit occurred 2 to 28 days after the screening visit. Patients were admitted to the clinic in the morning of Day 1 (dosing day) in TP1, TP2, and TP3, having fasted since 10:00 PM the evening before (except if slight intake of rapidly absorbable carbohydrates [≤ 20 g carbohydrate] was necessary to prevent hypoglycemia).

The sponsor collected serial plasma samples at predose and up to 12 hours postdose for the determination of SAR342434 or insulin lispro concentration via a validated liquid chromatography with tandem mass spectrometry bioanalytical assay. The sponsor collected the GIR rates and the blood glucose concentration data during the entire glucose clamp study.

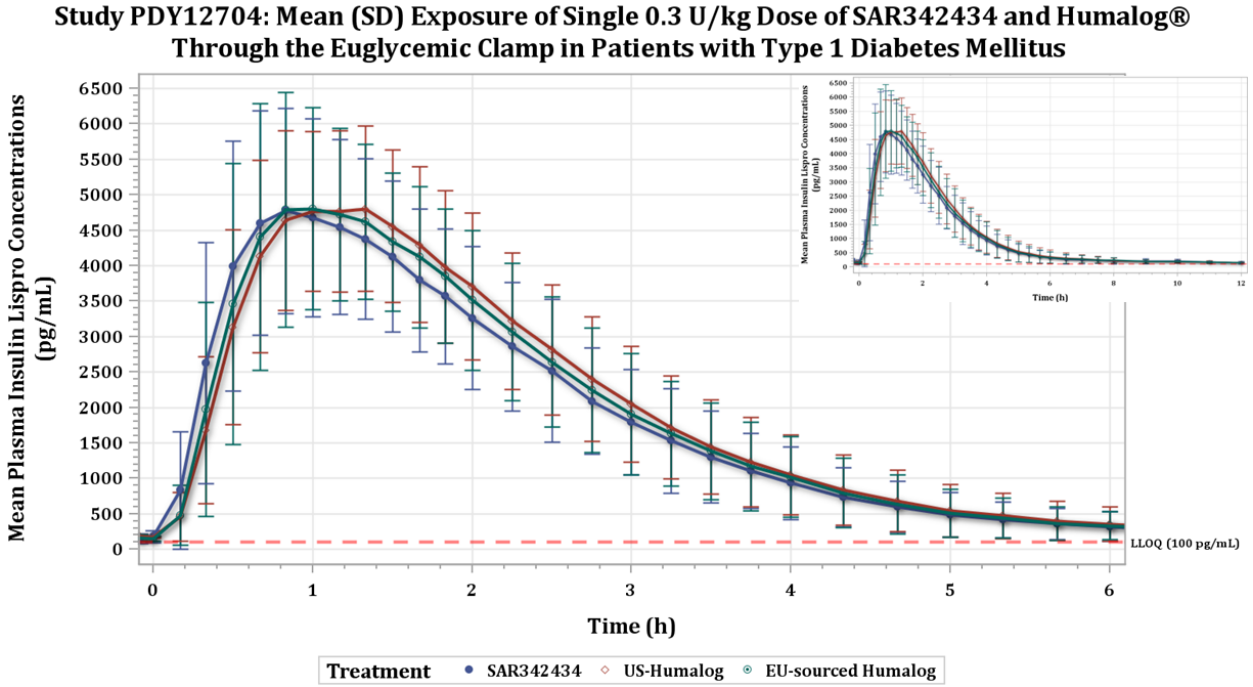
Overall, Study PDY12704's design was acceptable.

2.2.2 Are the PK and PD characteristics of SAR342434 similar to those of the US-Humalog? Are the PK and PD characteristics of SAR342434 similar to those of the EU-sourced insulin lispro? Are the PK and PD characteristics similar between US-Humalog and EU-sourced insulin lispro?
Yes, Study PDY12704 showed the PK and PD data:

- are similar between SAR342434 and US-Humalog
- are not different between SAR342434 and EU-sourced insulin lispro
- are not different between US-Humalog and EU-sourced insulin lispro

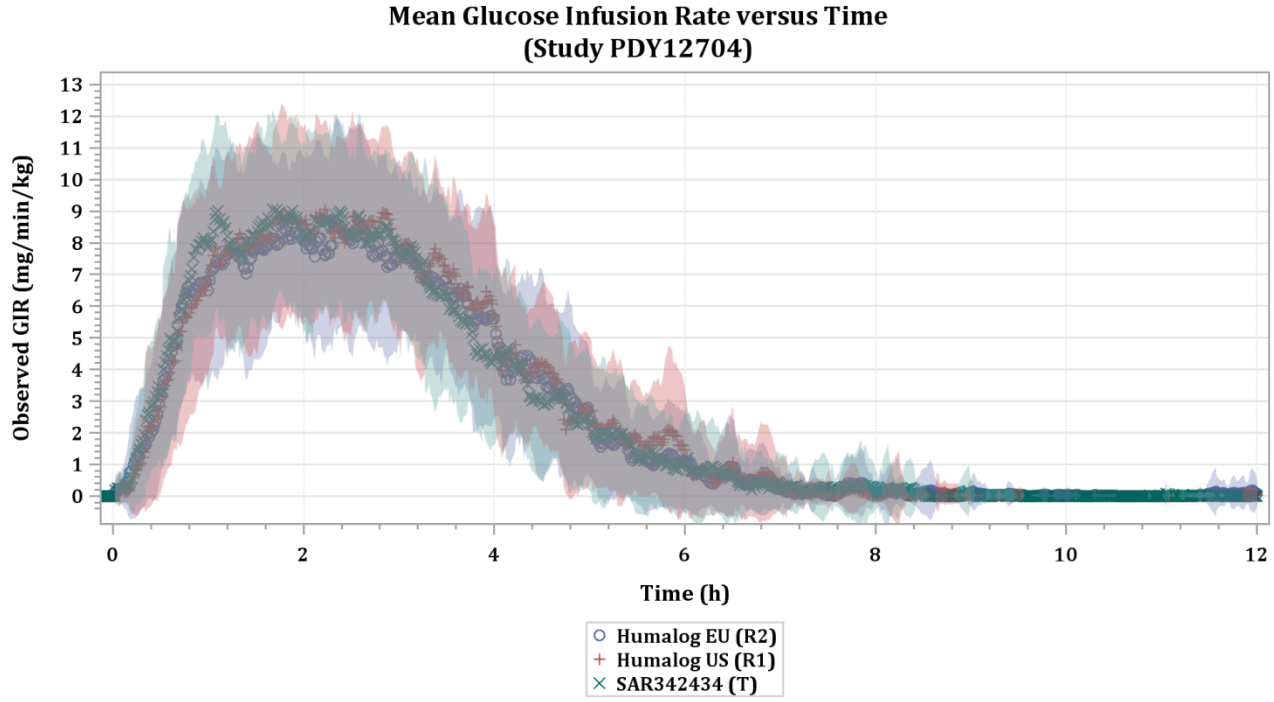
Figure 4 shows the mean (SD) plasma insulin lispro concentration versus time profiles of single dose 0.3 unit/kg of SAR342434, US-Humalog, and EU-sourced insulin lispro in patients with T1DM. Upon SC injection of 0.3 unit/kg, maximum plasma insulin lispro concentrations occurred at about 1 hour postdose for SAR342434, US-Humalog, and EU-sourced insulin lispro and then decline to about 8 hours within quantitation limit (Figure 2). In general, the mean plasma insulin lispro concentration versus time profiles of SAR342434, US-Humalog, and EU-sourced insulin lispro are similar.

Figure 4. Mean (SD) plasma insulin lispro concentration versus time profiles following single 0.3 unit/kg SC doses of SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



The main figure shows the first 6 hours of plasma insulin lispro concentration-time profile for the ease of viewing early time points, whereas the insert shows the plasma insulin lispro concentration-time profile for the full 12 hours of sample collection.
Source: Reviewer's analysis

Figure 5. Mean raw GIR versus time profiles upon single doses SC administration of 0.3 unit/kg SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



Humalog EU = EU-sourced insulin lispro; Humalog US = US-Humalog
Source: Reviewer's analysis

Figure 6. Mean smoothed GIR versus time profiles upon single doses SC administration of 0.3 unit/kg SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.

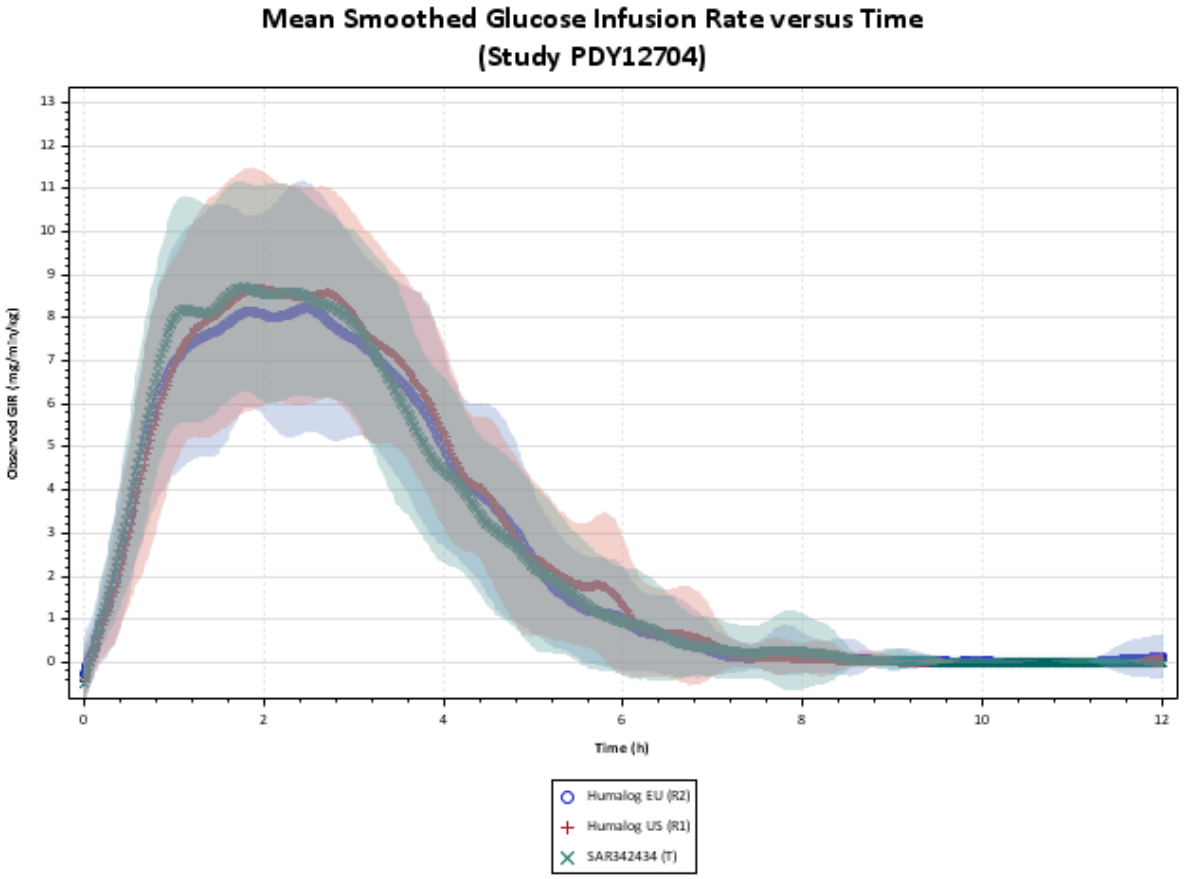
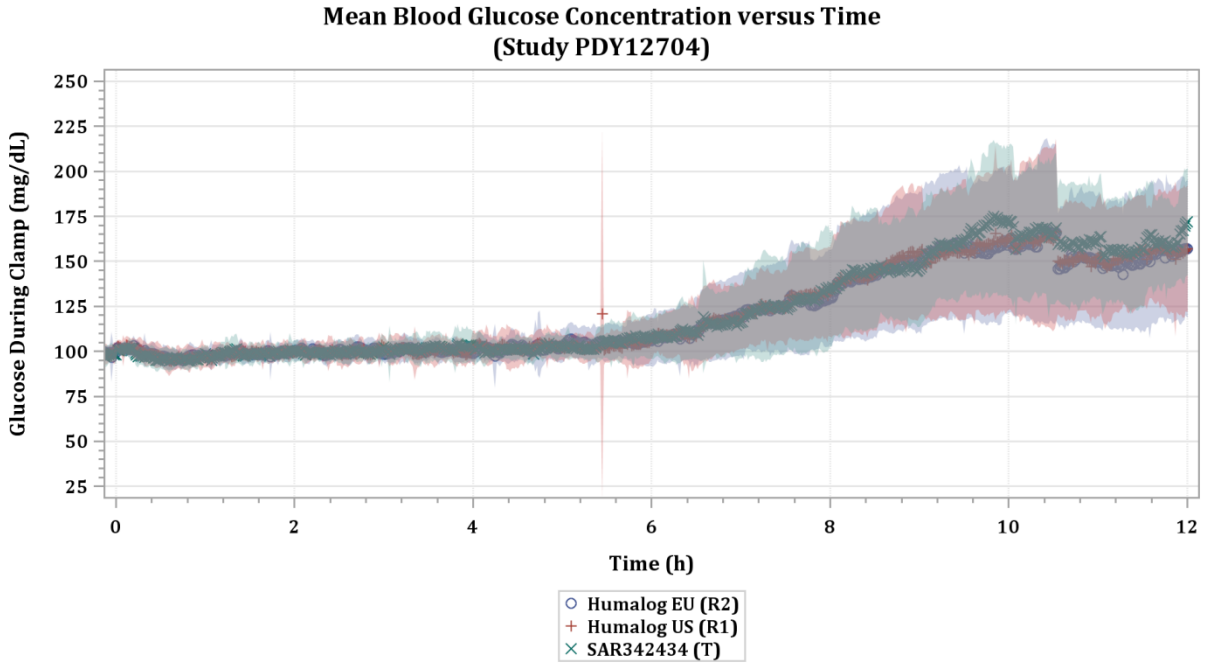


Figure 7. Mean blood glucose concentration versus time profiles upon single doses SC administration of 0.3 unit/kg SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



Humalog EU = EU-sourced insulin lispro; Humalog US = US-Humalog
Source: Reviewer's analysis

Table 2. Summary statistics for PK and PD parameters of Study PDY12704

Type	Parameter	SAR342434	US-Humalog	EU-sourced insulin lispro
PK	C_{max} (pg/mL)	4860 (1950 – 7910)	5020 (3310 – 7870)	5090 (2700 – 9590)
	$AUC_{0\text{-}last}$ (pg·h/mL)	12100 (7720 – 24700)	12700 (9060 – 22000)	12400 (9030 – 23200)
	$AUC_{0\text{-}inf}$ (pg·h/mL)	12400 (8020 – 25600)	13000 (9160 – 22700)	12700 (9180 – 24200)
	$AUC_{0\text{-}2}$ (pg·h/mL)	6960 (2950 – 11800)	7010 (5050 – 10300)	6960 (3200 – 13100)
	$AUC_{4\text{-}last}$ (pg·h/mL)	1030 (155 – 5730)	1140 (182 – 5290)	1050 (132 – 5150)
	T_{max} (hr)[a]	0.83 (0.5 – 1.5)	1.17 (0.5 – 1.67)	1.00 (0.5 – 1.83)
PD	$GIRAUC_{0\text{-}12}$ (mg/kg)	1883.55 (1093.9 – 3359.2)	1925.5 (1260.6 – 3541.8)	1825.56 (936.5 – 3212.4)
	$GIRAUC_{0\text{-}2}$ (mg/kg)	696.23 (349.8 – 1133.1)	639.42 (345.8 – 1281.6)	633.84 (312.5 – 1161.3)
	$GIRAUC_{4\text{-}12}$ (mg/kg)	260.7 (44.6 – 1385.7)	324.3 (72.9 – 1300.9)	275.28 (12.5 – 1132.8)
	GIR_{max} (mg/kg/min)	9.69 (6.2 – 13.9)	9.53 (6.9 – 17.1)	9.28 (5.5 – 13.7)
	Time to GIR_{max} (hr)[a]	2.07 (0.8 – 4.0)	2.35 (0.9 – 4.0)	2.45 (0.8 – 4.1)

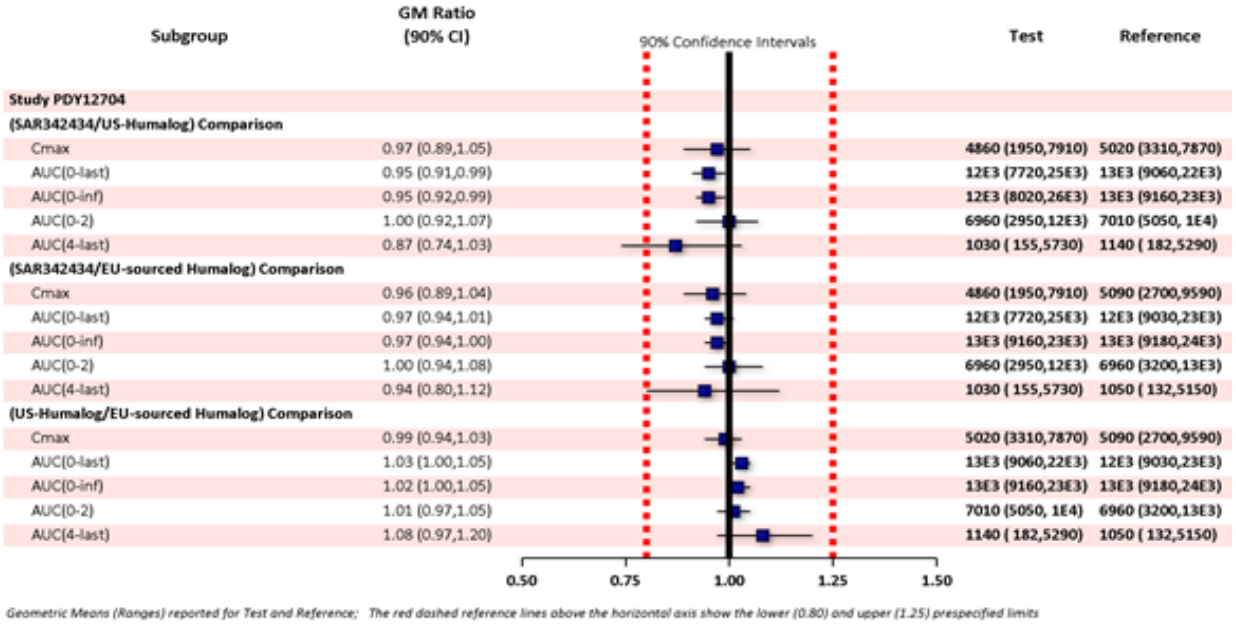
PK and PD parameters reported as geometric mean (range); [a]Calculated from LOESS smoothed data as median (range)
Source: Reviewer's compilation of Tables 8 – 10 and Tables 16 – 18 in Study PDY12704's report

Table 3. Statistical analysis results for PK and PD parameters of Study PDY12704

Type (PK)	Parameter	GMR (90% CI)		
		(SAR342434/US-Humalog)	(SAR342434/EU-sourced insulin lispro)	(US-Humalog/EU-sourced insulin lispro)
	C_{max} (pg/mL)	0.97 (0.89 – 1.05)	0.96 (0.89 – 1.04)	0.99 (0.94 – 1.03)
	$AUC_{0\text{-}last}$ (pg·h/mL)	0.95 (0.91 – 0.99)	0.97 (0.94 – 1.01)	1.03 (1.00 – 1.05)
	$AUC_{0\text{-}inf}$ (pg·h/mL)	0.95 (0.92 – 0.99)	0.97 (0.94 – 1.00)	1.02 (1.00 – 1.05
	$AUC_{0\text{-}2}$ (pg·h/mL)	1.00 (0.92 – 1.07)	1.00 (0.94 – 1.08)	1.01 (0.97 – 1.05)
	$AUC_{4\text{-}last}$(pg·h/mL)	0.87 (0.74 – 1.03)	0.94 (0.80 – 1.12)	1.08 (0.97 – 1.20)
Type (PD)	$GIRAUC_{0\text{-}12}$ (mg/kg)	1.00 (0.94 – 1.07)	1.06 (0.97 – 1.15)	1.05 (0.98 – 1.14)
	$GIRAUC_{0\text{-}2}$ (mg/kg)	1.13 (1.05 – 1.21)	1.13 (1.02 – 1.27)	1.01 (0.9 – 1.12)
	$GIRAUC_{4\text{-}12}$ (mg/kg)	0.81 (0.61 – 1.06)	0.94 (0.72 – 1.24)	1.17 (0.92 – 1.48)
	GIR_{max} (mg/min)	1.04 (0.98 – 1.10)	1.07 (0.99 – 1.14)	1.03 (0.95 – 1.10)

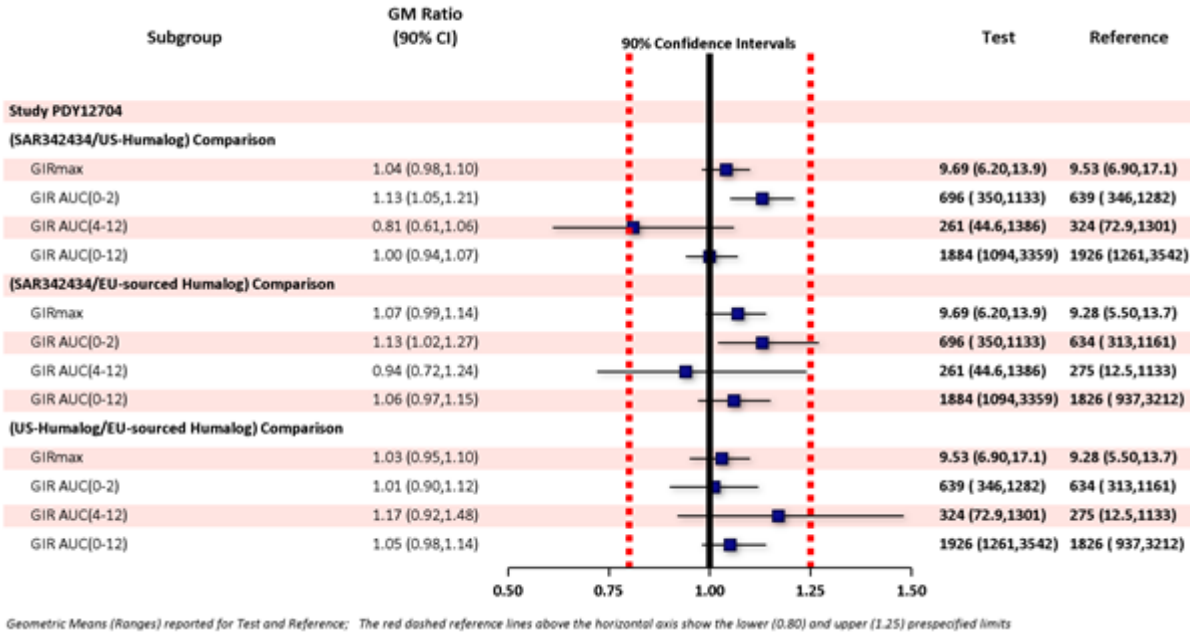
Source: Reviewer's compilation of Tables 8 – 10 and Tables 16 – 18 in Study PDY12704's report

Figure 8. Forest plot of PK parameter comparisons between SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



EU-sourced Humalog = EU-sourced insulin lispro
Source: Reviewer's analysis

Figure 9. Forest plot of PD parameter comparisons between SAR342434, US-Humalog, and EU-sourced insulin lispro for Study PDY12704.



EU-sourced Humalog = EU-sourced insulin lispro
Source: Reviewer's analysis

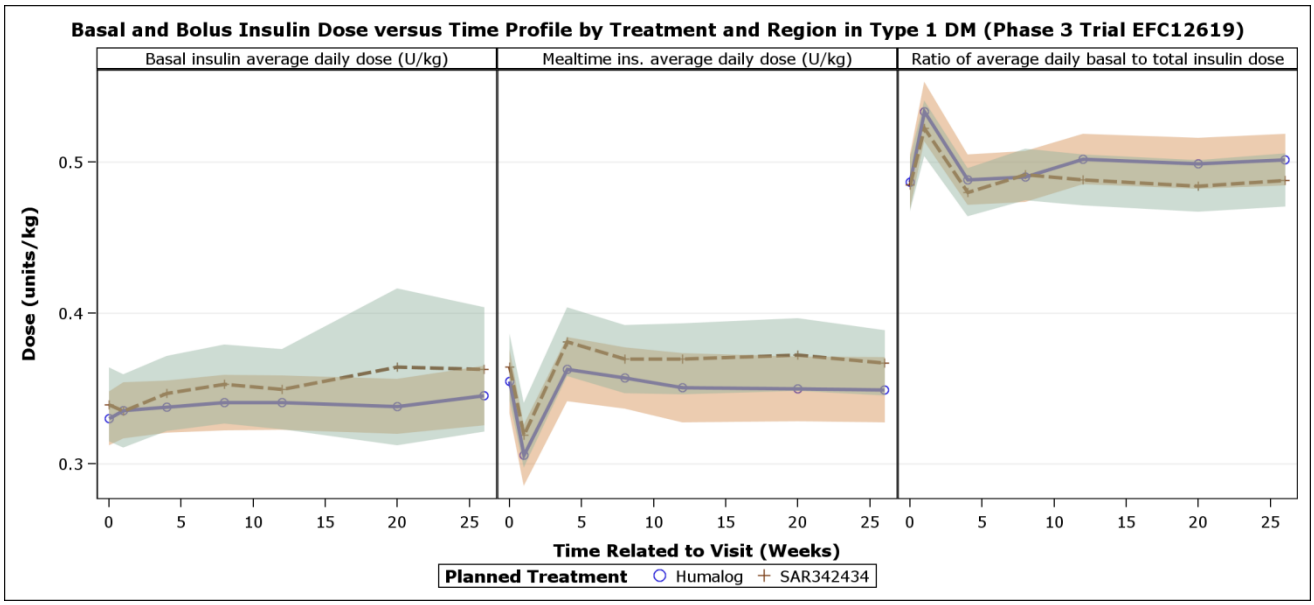
2.2.3 How are the results of PK and PD study of SAR342434 related to the efficacy comparison of SAR342434 versus US-Humalog or EU-sourced insulin lispro?

The sponsor conducted 2 randomized, active-control, Phase 3, multinational clinical studies to support the efficacy and safety of SAR342434 to Humalog in patients with T1DM (Study EFC12619) and T2DM (Study EFC13403). The primary objective of these two Phase 3 studies was to test the hypothesis that SAR342434 is non-inferior to Humalog according to the change in HbA1c from baseline to the 26-week endpoint. In these studies, patients in the control treatment group randomly received either US-Humalog or EU-sourced insulin lispro. Patients enrolled in sites in Europe, Turkey, Korea, Argentina, Chile, and Colombia received EU-sourced insulin lispro, whereas patients enrolled in sites in the United States and Japan received US-Humalog. See Dr. Sonia Doi's Clinical Review and Dr. Robero Crackel's statistical review for detailed assessment of efficacy and safety of SAR342434 in DARRTS.

The non-inferiority comparison in the clinical efficacy and safety studies assumes similar unit dose definition for the test and reference products, which is determined relying on the PK and PD similarity between SAR342434 and Humalog.

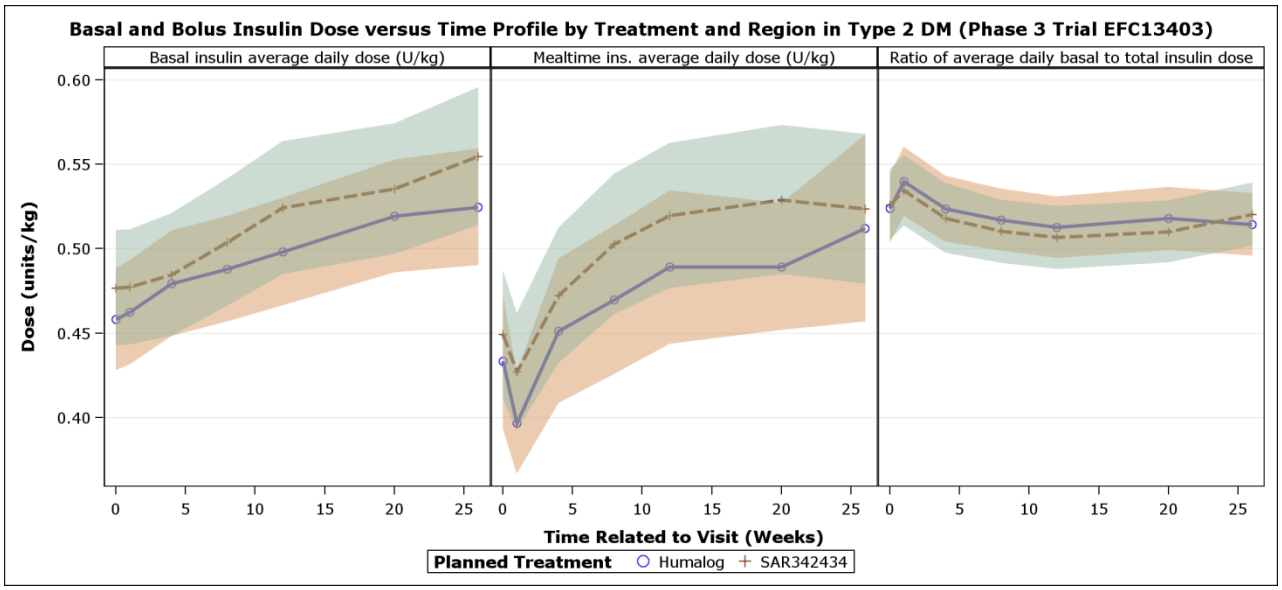
According to the overall dose-time profile for the basal and prandial insulins used in the 2 clinical efficacy and safety studies, the trends of dose utilization were not different between SAR342434 and Humalog. The dose-time data for the reference in Figures 10 and 11 represent both US-Humalog and EU-sourced insulin lispro.

Figure 10. Overall daily mean (95% CI) basal insulin dose (left panel), mealtime insulin dose (central panel), and ratio of basal to total insulin dose (right panel) by treatment in patients with T1DM.



Source: Reviewer's analysis

Figure 11. Overall daily mean (95% CI) basal insulin dose (left panel), mealtime insulin dose (central panel), and ratio of basal to total insulin dose (right panel) by treatment in patients with T2DM.



Source: Reviewer's analysis

2.3 Bioanalytical

2.3.1 Is the bioanalytical method properly validated to measure SAR342434 and insulin lispro?

The sponsor used a liquid chromatography-tandem mass-spectrometry (LC-MS/MS) bioanalytical assay to measure insulin lispro concentration in plasma samples. Briefly, the sponsor treated the plasma samples for protein precipitation and followed by solid phase extraction. The sponsor used bovine insulin as the internal standard. The volume is 0.25 mL per sample. The sponsor used a linear calibration regression with a weighting factor of $1/x^2$ to quantitate insulin lispro. The lower limit of quantification of

the assay is 100 pg/mL. See Table 4 for the assay validation such as within-run and between-run precision and accuracy for SAR342434, US-Humalog, and EU-sourced insulin lispro. The sponsor confirmed via Serial 0013 submitted on April 20, 2017 that there was no difference in preparation for the calibration standards, quality control (QC) samples, and the clinical samples. Clinical samples went through the same sample processing steps as the standards and the QC samples.

Table 4. Summary of validation for SAR342434 and insulin lispro bioanalytical assay for Study PDY12704.

Methods Report (Report Location)	Matrix (Anticoagulant)	Analytes	Type of Method	Calibration Range (pg/mL)	Precision CV%		Accuracy A%		Clinical Studies
					Within run	Between run	Within run	Between run	
DOH1221 inVentiv Health Clinique no. 125084AHEG/AILX 5.3.1.4 [DOH1221]	Plasma (K_2EDTA)	SAR342434 Cross-validation to Humalog US and Humalog EU	LC-MS/MS	100 - 8000	SAR342434 (AHEG) 4.26% - 5.84% Humalog US 3.78% - 6.78% Humalog EU 5.08% – 11.54%	SAR342434 (AHEG) 3.29% - 6.49% SAR342434 (AILX) 4.49% - 6.76% Humalog US 3.13% - 7.25% Humalog EU 4.14% - 7.41%	SAR342434 (AHEG) 92.87% - 98.74% Humalog US 91.17% - 95.19% Humalog EU 89.86% - 99.74%	SAR342434 (AHEG) 94.58% - 98.12% SAR342434 (AILX) 96.23% - 99.31% Humalog US 92.32% – 97.39% Humalog EU 91.79% - 97.64%	PDY12704

Humalog US and Humalog EU in this table are US-Humalog and EU-sourced insulin lispro, respectively, in this review.
Source: Modified from the sponsor's Section 2.7.1 Table 1.

SAR342434 was stable in human K_2EDTA plasma at 4°C for up to 21 hours 55 minutes, and at room temperature for up to 22 hours 46 minutes. In whole blood, SAR342434 was stable at 4°C for at least 1 hour 51 minutes. In the presence of hemolyzed blood (1%) in human K_2EDTA plasma, SAR342434 was stable at room temperature for at least 8 hours. Processed samples were stable at room temperature for at least 97 hours 16 minutes.

SAR342434, US-Humalog, and EU-sourced insulin lispro were stable in human K_2EDTA plasma at about -20°C and at about -80°C for 286 days, and after 4 freeze-thaw cycles in matrix at about -20°C and at about -80°C.

The bioanalytical assay for measuring SAR342434 and insulin lispro are acceptable with reasonable accuracy and precision.

2.3.2 Was an Office of Study Integrity and Surveillance (OSIS) inspection requested for the clinical study?

The Division of Metabolism and Endocrinology Products requested an OSIS inspection for the clinical and bioanalytical sites of Study PDY12704 through Callie Cappel-Lynch dated February 6, 2017 (Reference ID: 4052004 in DARRTS).

The Division of New Drug Bioequivalence Evaluation within OSIS recommended accepting the bioanalytical data without an on-site inspection because OSIS recently inspected the clinical and bioanalytical sites of Study PDY12704. The outcome of the inspections was classified as No Action Indicated. See memorandum by Shila Nkah dated April 4, 2017 (Reference ID: 4079722 in DARRTS).

3 Preliminary Labeling Recommendations

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

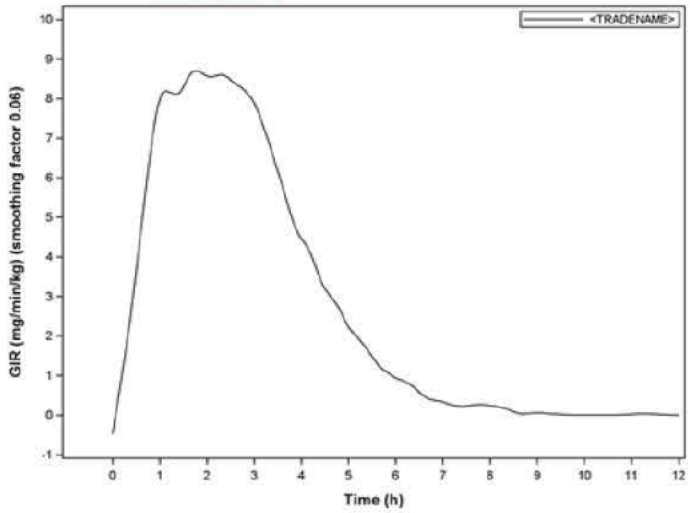
Regulation of glucose metabolism is the primary activity of insulins and insulin analogs, including insulin lispro. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

12.2 Pharmacodynamics

Subcutaneous Administration

The pharmacodynamic profile of a single 0.3 unit (b) (4)/kg dose of TRADENAME administered subcutaneously was (b) (4) evaluated in a euglycemic clamp study enrolling 30 patients with type 1 diabetes. In this study, the mean (SD) time to maximum effect of TRADENAME (measured by the peak rate of glucose infusion) was approximately 2.07 (0.78) hours. The mean (SD) area under the glucose infusion rate curves (measure of overall pharmacodynamic effect) and mean (SD) maximum glucose infusion rate were 1953.5 (547.3) mg/kg and 9.97 (2.37) mg/min/kg, respectively (b) (4) (b) (4) see Figure 1).

Figure 1: Mean Smoothed Glucose Infusion Rate after Subcutaneous Injection of TRADENAME (0.3 unit- (b) (4) /kg) in Patients with Type 1 Diabetes.



TRADENAME has been shown to be equipotent to human insulin on a molar basis. One unit of TRADENAME has the same glucose-lowering effect as one unit of regular human insulin.

Studies in normal volunteers and patients with diabetes demonstrated that another rapid-acting insulin lispro product, 100 units/mL, has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

The time course of action of insulin and insulin analogs, such as TRADENAME, may vary considerably in different individuals or within the same individual. The rate of insulin absorption, and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables *[see Warnings and Precautions (5.2)]*.

Intravenous Administration

The glucose lowering effect of intravenous administration of another (b) (4)-insulin lispro product, 100 units/mL, was tested in 21 patients with type 1 diabetes. For the study, the patients' usual doses of insulin were held and blood glucose concentrations were allowed to reach a stable range of 200 to 260 mg/dL during a one to three hours run-in phase. The run-in phase was followed by a 6-hour assessment phase. During the assessment phase, patients received intravenous infusion of another (b) (4)-insulin lispro product, 100 units/mL, at an initial infusion rate of 0.5 units/hour. The infusion rate of another (b) (4)-insulin lispro product, 100 units/mL, could be adjusted at regular timed intervals to achieve and maintain blood glucose concentrations between 100 to 160 mg/dL.

The mean blood glucose levels during the assessment phase for patients on another (b) (4) insulin lispro product, 100 units/mL, therapy are summarized below in Table 2. All patients achieved the targeted glucose range at some point during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 17 of 20 patients treated with another (b) (4)-insulin lispro product, 100 units/mL. The average time (±SE) required to attain near normoglycemia was 129 ± 14 minutes for another (b) (4)-insulin lispro product, 100 units/mL.

Table 2: Mean Blood Glucose Concentrations (mg/dL) During Intravenous Infusions of Another (b) (4) Insulin Lispro Product, 100 units/mL

Time from Start of Infusion (minutes)	Mean Blood Glucose (mg/dL) Intravenous[a]
0	224 ± 16
30	205 ± 21
60	195 ± 20
120	165 ± 26
180	140 ± 26
240	123 ± 20
300	120 ± 27
360	122 ± 25

[a] Results shown as mean ± SD

(b) (4)

(b) (4)

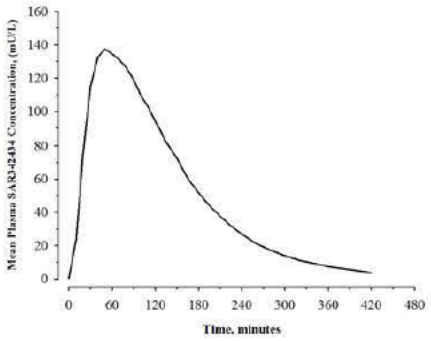
12.3 Pharmacokinetics

Absorption and Bioavailability

The pharmacokinetic profile of a single 0.3 unit/kg dose of TRADENAME administered subcutaneously was (b) (4) evaluated in a study enrolling 30 patients with type 1 diabetes. In this study, the mean observed area under the (b) (4) plasma insulin lispro concentration-time curve from time zero to infinity and peak (b) (4) lasma insulin lispro

concentration were 12800 pg·hr/mL and 5070 pg/mL, respectively. The median time to maximum (b) (4) lasma insulin lispro concentration was 0.83 hours after injection (b) (4) (b) (4) see Figure 2).

Figure 2: Mean (b) plasma Concentrations of TRADENAME after a Single Subcutaneous Administration of TRADENAME (0.3 U/kg) in Patients with Type 1 Diabetes.



Studies in healthy volunteers and patients with diabetes demonstrated that another (b) (4) (b) (4)–product, 100 units/mL, is absorbed more quickly than regular human insulin. In healthy volunteers given subcutaneous doses of another (b) (4)–insulin lispro product, 100 units/mL, ranging from 0.1 to 0.4 unit/kg, peak serum levels were seen 30 to 90 minutes after dosing. When healthy volunteers received equivalent doses of regular human insulin, peak insulin levels occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes.

Another (b) (4)–insulin lispro product, 100 units/mL, was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 unit/kg at abdominal, deltoid, or femoral subcutaneous sites. After another (b) (4)–insulin lispro product, 100 units/mL, was administered in the abdomen, serum drug levels were higher and the duration of action was slightly shorter than after deltoid or thigh administration. Bioavailability of another (b) (4) insulin lispro product, 100 units/mL, is similar to that of regular human insulin. The absolute bioavailability after subcutaneous injection ranges from 55% to 77% with doses between 0.1 to 0.2 unit/kg, inclusive.

The mean observed area under the serum insulin concentration-time curve from time zero to infinity was 2360 pmol hr/L [redacted] for another [redacted]-insulin lispro product, 100 units/mL, respectively. The corresponding mean peak serum insulin concentration was 795 pmol/L [redacted]

for another [redacted]-insulin lispro product, 100 units/mL [redacted] The median time to maximum concentration was 1.0 hour [redacted]

Distribution

When administered intravenously as bolus injections of 0.1 and 0.2 U/kg dose in two separate groups of healthy subjects, the mean volume of distribution of another [redacted]-insulin lispro product, 100 units/mL, appeared to decrease with increase in dose (1.55 and 0.72 L/kg, respectively) in contrast to that of regular human insulin for which, the volume of distribution was comparable across the two dose groups (1.37 and 1.12 L/kg for 0.1 and 0.2 U/kg dose, respectively).

Metabolism

Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of another [redacted]-insulin lispro product, 100 units/mL, is identical to that of regular human insulin.

Elimination

After subcutaneous administration of another [redacted] (b) (4)–insulin lispro product, 100 units/mL, the $t_{1/2}$ is shorter than that of regular human insulin (1 versus 1.5 hours, respectively).

When administered intravenously, another insulin lispro product, 100 units/mL, and regular human insulin demonstrated similar dose-dependent clearance, with a mean clearance of 21.0 mL/min/kg and 21.4 mL/min/kg, respectively (0.1 unit/kg dose), and 9.6 mL/min/kg and 9.4 mL/min/kg, respectively (0.2 unit/kg dose). Accordingly, another insulin lispro product, 100 units/mL, demonstrated a mean $t_{1/2}$ of 0.85 hours (51 minutes) and 0.92 hours (55 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses, and regular human insulin mean $t_{1/2}$ was 0.79 hours (47 minutes) and 1.28 hours (77 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses.

Specific Populations

The effects of age, gender, race, obesity, pregnancy, or smoking on the pharmacokinetics of TRADENAME have not been studied.

Renal Impairment - Type 2 diabetic patients with varying degree of renal impairment showed no difference in pharmacokinetics of regular insulin and another [redacted] (b) (4)–insulin lispro product, 100 units/mL. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including TRADENAME, may be necessary in patients with renal dysfunction.

Hepatic Impairment - Type 2 diabetic patients with impaired hepatic function showed no effect on the pharmacokinetics of another [redacted] (b) (4)–insulin lispro product, 100 units/mL, as compared to patients with no hepatic dysfunction. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including TRADENAME, may be necessary in patients with hepatic dysfunction.

4.1 Individual Study Synopsis

SYNOPSIS

Title of the study:	A randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence crossover study to compare exposure and activity of SAR342434 to Humalog® using the euglycemic clamp technique, in subjects with type 1 diabetes mellitus (PDY12704)
Investigator:	Christoph Kapitza MD, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstrasse 9, D-41460 Neuss, Germany
Study center:	1 center in Germany
Publications (reference):	Not applicable
Study period:	
Date first subject enrolled:	12 March 2013
Date last subject completed:	08 July 2013
Phase of development:	Phase 1
Objectives:	The primary objective was to compare exposure and activity of SAR342434 to Humalog. The secondary objective was to assess the safety and tolerability of SAR342434.
Methodology:	Single-center, randomized, double-blind, controlled, 3-treatment, 3-period, 6-sequence, crossover study in adult male and female subjects with type 1 diabetes mellitus.
Number of subjects:	Planned: 30 Randomized: 30 Treated: 30
Evaluated:	Pharmacodynamics: 30 Safety: 30 Pharmacokinetics: 30
Diagnosis and criteria for inclusion:	Male and female subjects, aged 18 to 65 years old, with type 1 diabetes mellitus for more than 1 year, receiving a total insulin dose of <1.2 U/kg/day and with glycohemoglobin ≤9%.
Study treatments	
Investigational medicinal product (Test):	SAR342434 (insulin lispro)
Formulation:	Solution for injection containing 100 U/mL insulin lispro
Route of administration:	Subcutaneous (SC)
Dose regimen:	Single dose of 0.3 U/kg in 1 of 3 treatment periods (TPs), randomized to 1 of 6 sequences
Batch number:	C1024625

Investigational medicinal product (Reference 1): US-approved Humalog (insulin lispro)

Formulation: Solution for injection containing 100 U/mL insulin lispro

Route of administration: SC

Dose regimen: Single dose of 0.3 U/kg in 1 of 3 TPs, randomized to 1 of 6 sequences

Batch number: C084899D

Investigational medicinal product (Reference 2): EU-approved Humalog (insulin lispro)

Formulation: Solution for injection containing 100 U/mL insulin lispro

Route of administration: SC

Dose regimen: Single dose of 0.3 U/kg in 1 of 3 TPs, randomized to 1 of 6 sequences

Batch number: C086784

Noninvestigational medicinal product (1): Glucose (for euglycemic clamp)

Formulation: 20% solution for infusion

Route of administration: Intravenous (IV) infusion

Dose regimen: As required to maintain the glucose clamp level at 100 mg/dL

Noninvestigational medicinal product (2): Intramed heparin sodium (for maintenance of catheter permeability)

Formulation: 5000 IU/mL solution

Route of administration: IV infusion

Dose regimen: 10 000 IU heparin in 100 mL 0.9% sodium chloride solution infused at approximately 2 mL/hour

Noninvestigational medicinal product (3): Sodium chloride (to keep the line patent)

Formulation: 0.9% solution

Route of administration: IV infusion

Dose regimen: Infused at approximately 2 mL/h to keep the catheter patent

Noninvestigational medicinal product (4): Apidra® (insulin glulisine; for euglycemic clamp)

Formulation: Solution for injection containing 100 U/mL insulin glulisine

Route of administration: IV infusion

Dose regimen: 0.3 U/mL infused as required to maintain glucose clamp

Duration of treatment: The 3 treatments (test [T], reference 1 [R1], and reference 2 [R2]) were each administered in a crossover design in 3 TPs using 6 sequences.

Duration of observation: Up to a maximum of 8 weeks (excluding screening) which includes 3 TPs (2 days each including 1 treatment day), washout period (5 to 18 days between TPs, preferentially 7 days), and an end-of-study visit (5 to 14 days after last administration).

Criteria for evaluation:

Pharmacokinetics:

The following pharmacokinetic (PK) parameters were calculated using noncompartmental methods from plasma SAR342434 or insulin lispro concentrations: maximum observed concentration (INS-C_{max}), time to reach C_{max} (INS-t_{max}), area under the concentration versus time curve (AUC) calculated using the trapezoidal method from time 0 to 2 hours (INS-AUC_{0-2}), AUC calculated using the trapezoidal method from time 4 hours to the time corresponding to the last concentration above the limit of quantification C_{last} (t_{last}) (INS-$AUC_{4-tlast}$), AUC calculated using the trapezoidal method from time 0 to the real time t_{last} (INS-AUC_{last}), AUC extrapolated to infinity (INS-AUC) time to reach x% of AUC (Tx%-INS-AUC) where x = 10, 20, 50, and 90, time corresponding to the last concentration above the limit of quantification (INS-t_{last}), and terminal half-life (INS-$t_{1/2z}$).

Pharmacodynamics:

Blood glucose concentration and glucose infusion rate (GIR) were recorded using a euglycemic clamp. The following pharmacodynamic parameters were calculated: area under the body weight standardized GIR versus time curve from 0 to 12 hours post-investigational medicinal product (IMP) administration (GIR-AUC_{0-12}), the time to x% of GIR-AUC_{0-12} (Tx% GIR-AUC_{0-12}) where x = 10, 20, 50, and 90, the maximum smoothed body weight standardized GIR (GIR_{max}), the time to GIR_{max} (GIR-t_{max}), the area under the body weight standardized GIR versus time curve from 0 to 2 hours post-IMP administration (GIR-AUC_{0-2}) and from 4 to 12 hours post-IMP administration (GIR-AUC_{4-12}). The duration of blood glucose control was also assessed (that is, the time to elevation of smoothed blood glucose profile above clamp level [+5 mg/dL] and to elevation above prespecified blood glucose levels).

Safety:

Adverse events (AEs) spontaneously reported by the subject or observed by the Investigator; 12-lead electrocardiogram (ECG) recordings; vital sign assessments (heart rate, systolic blood pressure, and diastolic blood pressure); aural temperature; physical examination; clinical laboratory tests (hematology, coagulation, biochemistry, and urinalysis); urine drug screen; anti-insulin antibodies; injection site reaction (ISR) assessments (including injection site pain, erythema, and edema); and, if any, assessment of the incidence of hypoglycemia. It was the Investigator's responsibility to decide if any of ISR assessments, as well as any other spontaneously reported symptoms, should be captured as AEs.

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples for the determination of SAR342434 or insulin lispro in plasma were collected at the following time points: -0H10, -0H05 (pre-dosing), 0H00, 0H10, 0H20, 0H30, 0H40, 0H50, 1H00, 1H10, 1H20, 1H30, 1H40, 1H50, 2H00, 2H15, 2H30, 2H45, 3H00, 3H15, 3H30, 3H45, 4H00, 4H20, 4H40, 5H00, 5H20, 5H40, 6H00, 6H30, 7H00, 7H30, 8H00, 9H00, 10H00, 11H00 and 12H00 post-dosing of each TP.

Plasma concentrations of insulin lispro were determined using a validated specific liquid chromatography with tandem mass spectrometry assay with a lower limit of quantification of 100 pg/mL.

Pharmacodynamic sampling times and bioanalytical methods:

Arterialized venous blood was drawn continuously at a rate of 2 mL/h for the determination of arterial blood glucose concentration every minute. In addition, blood samples were collected in 30-minute intervals for concurrent calibration of the Biostator clamp device.

Statistical methods:

Pharmacokinetics: Pharmacokinetic parameters were summarized and tabulated by treatment using descriptive statistics. Scatter plots were used to present individual and mean (standard deviation) PK parameters.

A linear mixed effects model with fixed terms for sequence, period, and treatment and random term for subject-within-sequence was used on log-transformed INS-C_{max}, INS-AUC_{last}, INS AUC, the fractional INS-AUCs and INS-$t_{1/2z}$. The 90% confidence intervals (CIs) for the ratio of treatments geometric means were computed.

Bioequivalence for INS-C_{max}, INS-AUC_{last}, and INS-AUC were concluded if the 90% CIs for the treatment ratios were entirely contained within 0.80 to 1.25.

The Tx%-INS-AUC and INS-t_{max} were analyzed non-parametrically based on the Hodges-Lehmann method for paired treatment comparisons and 90% CIs for medians of pair-wise treatment differences were derived.

Pharmacodynamics: Pharmacodynamic parameters were summarized by treatment using descriptive statistics.

For log-transformed GIR-AUC_{0-12}, GIR-AUC_{0-2}, GIR-AUC_{4-12}, and GIR_{max} the relative activity between the 3 IMPs was assessed using a linear mixed effects model with fixed terms for sequence, period, and treatment and with an unstructured R matrix of treatment (i,j) variances and covariances for subject within sequence blocks. The 90% and 95% CIs for the ratios of geometric means (T/R1 and T/R2) were computed within the linear mixed effects model framework. Bioequivalence for the primary PD parameter GIR-AUC_{0-12} was concluded if the 90% CIs for the treatment ratios were entirely contained within 0.80 to 1.25.

The Tx% GIR-AUC_{0-12} and GIR-t_{max} were analyzed non-parametrically based on the Hodges-Lehmann method for paired treatment comparisons and 90% CIs for pair-wise medians of treatment differences were derived.

Safety: The safety evaluation was based on the review of individual values and descriptive statistics by treatment. For AEs, frequencies of treatment-emergent AEs (TEAEs) classified by Medical Dictionary for Regulatory Activities system-organ class and preferred term were tabulated by treatment. All AEs were listed.

For biochemistry and hematology, vital signs, and ECGs, counts of subjects with abnormalities and potentially clinically significant abnormalities (PCSA) were summarized by treatment for each type of parameter.

Counts of subjects with signs of local intolerance and hypoglycemia were tabulated by treatment.

Summary:

Population characteristics:

Thirty male subjects were randomized and treated: 28 subjects completed all 3 TPs. Two subjects prematurely discontinued the study: 1 subject withdrew informed consent after TP2 (not due to an AE) and 1 subject was withdrawn after TP1 because the maximal washout period could not be respected due to sinusitis and concomitant medication.

Pharmacokinetic results:

Primary variables:

The INS-C_{max}, INS-AUC_{last}, and INS-AUC, were equivalent for SAR342434, Humalog US, and Humalog EU as shown for the 90% CI. The INS-C_{max}, INS-AUC_{last}, and INS-AUC treatment ratios are provided in the table below.

Statistical analyses of primary pharmacokinetic variables INS-C_{max}, INS-AUC_{last}, and INS-AUC
Point estimates of treatment ratio with 90% CIs

Parameter	Treatment ratio	Estimate	90% CI
INS-C_{max} (pg/mL)	SAR342434 vs Humalog US	0.97	(0.89 to 1.05)
	SAR342434 vs Humalog EU	0.96	(0.89 to 1.04)
	Humalog US vs Humalog EU	0.99	(0.94 to 1.03)
INS-AUC_{last} (pg.h/mL)	SAR342434 vs Humalog US	0.95	(0.91 to 0.99)
	SAR342434 vs Humalog EU	0.97	(0.94 to 1.01)
	Humalog US vs Humalog EU	1.03	(1.00 to 1.05)
INS-AUC (pg.h/mL)	SAR342434 vs Humalog US	0.95	(0.92 to 0.99)
	SAR342434 vs Humalog EU	0.97	(0.94 to 1.00)
	Humalog US vs Humalog EU	1.02	(1.00 to 1.05)

T: SAR342434 ; R1: Humalog® US ; R2: Humalog® EU
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pk_equivstat_k.sas OUT=REPORT/OUTPUT/pk_eq_pp_int_k_t_2_i.rtf (19SEP2013 - 15:07)

Secondary variables:

The INS-AUC_{0-2}, INS-AUC_{4-last}, and INS-$t_{1/2z}$ treatment ratios are provided in the table below.

Statistical analyses of secondary pharmacokinetic variables INS-AUC_{0-2}, AUC_{4-last} and $t_{1/2z}$
Point estimates of treatment ratio with 90% CIs

Parameter	Treatment ratio	Estimate	90% CI
INS-AUC_{0-2} (pg.h/mL)	SAR342434 vs Humalog US	1.00	(0.92 to 1.07)
	SAR342434 vs Humalog EU	1.00	(0.94 to 1.08)
	Humalog US vs Humalog EU	1.01	(0.97 to 1.05)
INS-AUC_{4-last} (pg.h/mL)	SAR342434 vs Humalog US	0.87	(0.74 to 1.03)
	SAR342434 vs Humalog EU	0.94	(0.80 to 1.12)
	Humalog US vs Humalog EU	1.08	(0.97 to 1.20)
INS-$t_{1/2z}$ (h)	SAR342434 vs Humalog US	1.05	(0.95 to 1.16)
	SAR342434 vs Humalog EU	1.08	(0.98 to 1.19)
	Humalog US vs Humalog EU	1.02	(0.94 to 1.12)

T: SAR342434 ; R1: Humalog® US ; R2: Humalog® EU
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pk_equivstat_k.sas OUT=REPORT/OUTPUT/pk_eq_sp_int_k_t_2_i.rtf (19SEP2013 - 15:09)

The Hodges-Lehmann point estimates for the median of the treatment differences between SAR342434, Humalog US, and Humalog EU for INS-t_{max} and Tx%-INS-AUC (x = 10, 20, 50 and 90) are provided in the table below.

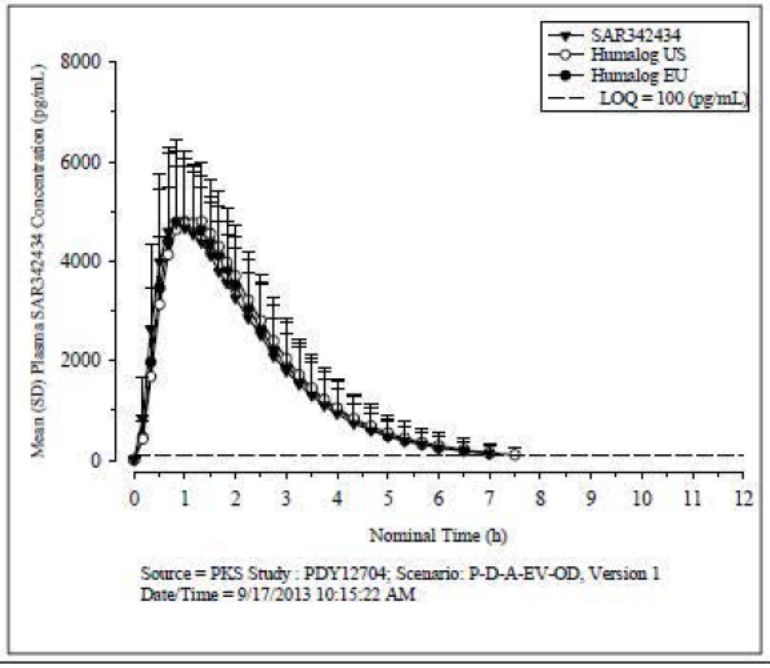
Hodges-Lehmann estimates for the median of treatment differences

	Point estimate (90% CI) in hours		
Parameter	**SAR342434 (T) - Humalog® US (R1)**	**SAR342434 (T) - Humalog® EU (R2)**	**Humalog® US (R1) - Humalog® EU (R2)**
INS-tmax (h)	-0.17	-0.17	0.08
	(-0.25 , -0.08)	(-0.25 , -0.09)	(-0.00 , 0.17)
T10%-INS-AUC (h)	-0.10	-0.08	0.02
	(-0.13 , -0.08)	(-0.12 , -0.04)	(-0.00 , 0.05)
T20%-INS-AUC (h)	-0.11	-0.09	0.03
	(-0.15 , -0.08)	(-0.13 , -0.04)	(0.00 , 0.06)
T50%-INS-AUC (h)	-0.13	-0.10	0.05
	(-0.20 , -0.08)	(-0.17 , -0.01)	(-0.01 , 0.08)
T90%-INS-AUC (h)	-0.15	-0.12	0.01
	(-0.37 , 0.08)	(-0.28 , 0.09)	(-0.13 , 0.22)

Point estimate method: Hodges-Lehmann - CI method: Moses (exact)
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pk_hl_k.sas OUT=REPORT/OUTPUT/pk_hl_k_t_i.rtf (20SEP2013 - 11:29)

Mean concentration versus time profiles for SAR342434, Humalog US, and Humalog EU are presented in the figure below. The PK profiles were generally similar for SAR342434 and the 2 Humalog treatments.

Pharmacokinetic Profiles for SAR342434, Humalog US and Humalog EU



Pharmacodynamic results:

Primary variables:

The GIR-AUC_{0-12} was equivalent for SAR342434, Humalog US-approved and Humalog EU-approved as shown for the 90% CI. The GIR-AUC_{0-12} treatment ratios are provided in the table below.

Treatment effect on GIR-AUC_{0-12}.
Point estimates of treatment ratio with 90% and 95% confidence intervals

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC_{0-12h} (mg/kg)	SAR342434 vs Humalog US	1.00	(0.94 to 1.07)	(0.93 to 1.08)
	SAR342434 vs Humalog EU	1.06	(0.97 to 1.15)	(0.95 to 1.17)
	Humalog US vs Humalog EU	1.05	(0.98 to 1.14)	(0.96 to 1.15)

GIR = body weight standardized glucose infusion rate.
T: SAR342434 ; R1: Humalog® US ; R2: Humalog® EU
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pd_equivstat_intext_d.sas
OUT=REPORT/OUTPUT/pd_eq_pp_d_t_2_i.rtf (16SEP2013 - 11:30)

Secondary variables:

The treatment ratios for GIR-AUC_{0-2}, GIR-AUC_{4-12}, and GIR_{max} are provided in the table below.

Treatment effect on GIR-AUC_{0-2}, GIR-AUC_{4-12} and GIR_{max}
Point estimates of treatment ratio with 90% and 95% confidence intervals

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC_{0-2h} (mg/kg)	SAR342434 vs Humalog US	1.13	(1.05 to 1.21)	(1.04 to 1.23)
	SAR342434 vs Humalog EU	1.13	(1.02 to 1.27)	(0.99 to 1.29)
	Humalog US vs Humalog EU	1.01	(0.90 to 1.12)	(0.88 to 1.15)
GIR-AUC_{4-12h} (mg/kg)	SAR342434 vs Humalog US	0.81	(0.61 to 1.06)	(0.58 to 1.12)
	SAR342434 vs Humalog EU	0.94	(0.72 to 1.24)	(0.68 to 1.31)
	Humalog US vs Humalog EU	1.17	(0.92 to 1.48)	(0.88 to 1.55)
GIRmax (mg/kg/min)	SAR342434 vs Humalog US	1.04	(0.98 to 1.10)	(0.96 to 1.12)
	SAR342434 vs Humalog EU	1.07	(0.99 to 1.14)	(0.98 to 1.16)
	Humalog US vs Humalog EU	1.03	(0.95 to 1.10)	(0.94 to 1.12)

GIR = body weight standardized glucose infusion rate. GIRmax is based on smoothed GIR profiles.
T: SAR342434 ; R1: Humalog® US ; R2: Humalog® EU
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pd_equivstat_intext_d.sas
OUT=REPORT/OUTPUT/pd_eq_sp_d_t_2_i.rtf (16SEP2013 - 11:31)

The Hodges-Lehmann point estimates for the median of the treatment difference between SAR342434 to Humalog US and Humalog EU for Tx% GIR-AUC_{0-12} (where x = 10, 20, 50, and 90) and GIR-t_{max} are provided in the table below.

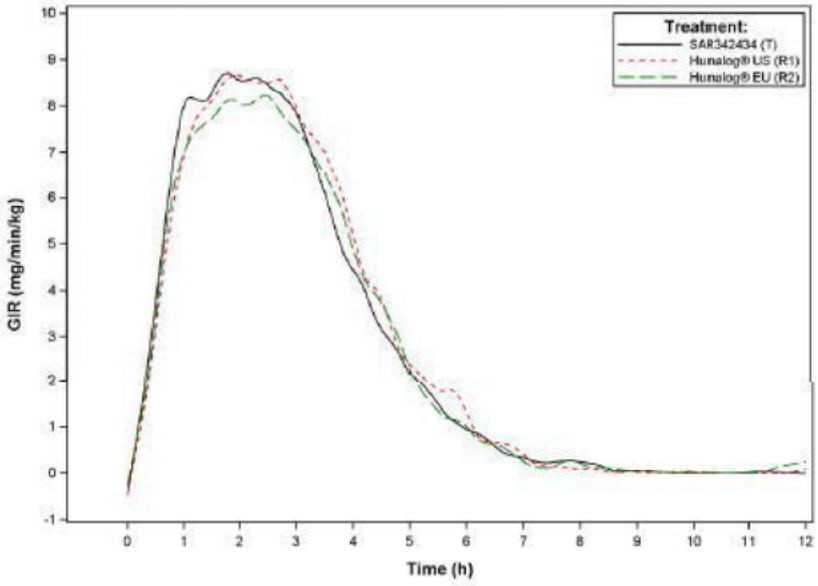
Hodges-Lehmann estimates for the median of treatment differences

Parameter	Point estimate (90% CI) in hours		
	SAR342434 (T) - Humalog® US (R1)	SAR342434 (T) - Humalog® EU (R2)	Humalog® US (R1) - Humalog® EU (R2)
GIR-tmax (h)	-0.30	-0.26	-0.07
	(-0.56 , -0.03)	(-0.61 , 0.00)	(-0.42 , 0.28)
T10% GIR-AUC_{0-12h} (h)	-0.10	-0.04	0.05
	(-0.15 , -0.03)	(-0.09 , 0.01)	(-0.00 , 0.10)
T20% GIR-AUC_{0-12h} (h)	-0.15	-0.06	0.07
	(-0.21 , -0.09)	(-0.14 , 0.03)	(0.01 , 0.12)
T50% GIR-AUC_{0-12h} (h)	-0.18	-0.12	0.04
	(-0.28 , -0.07)	(-0.23 , -0.00)	(-0.07 , 0.12)
T90% GIR-AUC_{0-12h} (h)	-0.22	-0.02	0.05
	(-0.46 , 0.02)	(-0.22 , 0.19)	(-0.20 , 0.30)

Point estimate method: Hodges-Lehmann - CI method: Moses (exact)
GIR = body weight standardized glucose infusion rate. GIR-tmax is based on smoothed GIR profiles.
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pd_ihl_d.sas OUT=REPORT/OUTPUT/pd_ihl_d_t_i.rtf (13AUG2013 - 15:27)

Mean smoothed GIR profiles for SAR342434, Humalog US and Humalog EU are presented in the figure below. The GIR profiles were similar for all 3 insulin lispro treatments.

Overlay plots of mean smoothed GIR profiles up to 12h after dosing over time



GIR = body weight standardized Glucose Infusion Rate
LOESS smoothing using factor = 0.06
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pd_igirmeanover_d_g.sas OUT=REPORT/OUTPUT/pd_igirmeanover_d_g_i.rtf (09AUG2013 - 14:45

Safety results:

There were no serious adverse events reported during the study.

Treatment-emergent adverse events were reported in 6 out of 29 subjects following administration of SAR342434, 6 out of 29 subjects following administration of Humalog US-approved, and 3 out of 29 subjects following administration of Humalog EU-approved. Irrespective of the treatment given, the most frequent TEAE observed during the study was headache (11 events in 8 subjects), followed by nausea (2 cases in 2 subjects). All other TEAEs were single occurrences. No ISRs were reported as AEs during the study.

There were only a few PCSAs in vital signs, none of which were clinically relevant and with no relevant differences between the 3 insulin lispro formulations. Potentially clinically significant abnormalities for ECG parameters occurred infrequently with no trend observed for the 3 different insulin lispro products. One subject in the SAR342434 group, 2 in the Humalog US group, and 3 subjects in the Humalog EU group had a prolonged QTc interval (>450 ms). No subject had a QTc ≥500 ms or delta QTc >60 ms.

Conclusions:

Similar pharmacokinetic exposure and pharmacodynamic activity were demonstrated for SAR342434 to both Humalog US and Humalog EU, as well as between both Humalog US and Humalog EU.

All treatments were well tolerated with no relevant difference in safety related parameters between treatments.

Date of report: 23-Sep-2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
07/28/2017

MANOJ KHURANA
07/28/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	209-196	**SDN**	1
Applicant	sanofi-aventis U.S. LLC	**Submission Date**	November 1, 2016
Generic Name	SAR342434 Insulin lispro [rDNA origin]	**Brand Name**	To be determined
Drug Class	Rapid acting insulin		
Indications	Improve glycemic control in adults and children with diabetes mellitus		
Dosage Regimen	Individualized based on the route of administration and the individual's metabolic needs, blood glucose monitoring results and glycemic control goal		
Dosage Form	Solution	**Route of Administration**	Subcutaneous
OCP Division	2	**OND Division**	DMEP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	S.W. Johnny Lau	Manoj Khurana
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/31/2016	**74-Day Letter Date**	1/10/2017
Review Due Date	7/28/2017	**PDUFA Goal Date**	9/1/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

Study PDY127040 is a pivotal clinical pharmacology study to claim PK/PD similarity. Thus, an inspection of the bioanalytical and clinical sites is in order.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		1	Bioequivalence criteria followed to support pharmacokinetic and pharmacodynamic similarity claim in Study PDY12704 in Type I Diabetes Mellitus (see Pharmacokinetics/Pharmacodynamics section below)
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		3	Studies EFC12619 and EFC13403 (efficacy and safety) , Study PDY13502 (safety)
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		3	Conducted to support pharmacokinetic and pharmacodynamic similarity claim in Study PDY12704 in Type I Diabetes Mellitus
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	4
Total Number of Studies to be Reviewed				4

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☑No ☐N/A	See Filing Memo on this review's last page.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Refers to the innovator's product label
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No',	☑Yes ☐No ☐N/A	

has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Background

The SAR342434 solution formulation used throughout the clinical program is identical to the final to-be-marketed formulation. The SAR342434 product also has the same pharmaceutical composition and strength as Humalog 100 U/mL (Page 12/74 Section 2.5 Clinical Overview).

Depending on the geographical location of the investigational sites, patients randomized to Humalog received the regionally approved product, Humalog US or Humalog EU: patients in the US and Japan received Humalog US and patients in Europe and other regions received Humalog EU (Page 12/74 Section 2.5 Clinical Overview).

Table 1 - Overview of clinical studies supporting SAR342434 registration

	PDY1270 4 Euglycemic clamp study	**EFC1261 9 Efficacy/safety Phase 3 study**	**EFC1340 3 Efficacy/safety Phase 3 study**	**PDY13502 Safety study**
Design	3x1 day cross-over study	Randomized, active-controlled, open-label, parallel group study	Randomized, active-controlled, open-label, parallel group study	Randomized, active-controlled, open-label, 2x4 weeks cross-over study
Population	Patients with **T1DM**	Patients with **T1DM** on Lantus in combination with mealtime insulin analog for at least 6 months prior to	Patients with **T2DM** on Lantus in combination with mealtime insulin analog for at least 6 months prior to	Patients with **T1DM** on Continuous Subcutaneous Insulin Infusion (CSII)
Comparator and regions	• Humalog US • Humalog EU	Humalog • Humalog US: US, Japan • Humalog EU: Europe	Humalog • Humalog US: US • Humalog EU: Europe, Turkey, South Korea, Argentina, Chile,	Humalog US
Randomization	1:1:1	1:1	1:1	1:1
Route of administration and injection device for IMP	SC injection syringes	SC injection before each main meal or snack; or immediately after meal intake (if allowed per local label)	SC injection before each main meal or snack; or immediately after meal intake (if allowed per local label)	External pump for CSII (Medtronic with 3 mL reservoir or Animas Vibe or OneTouch Ping pump)
Objectives	PK and PD (euglycemic clamp	Efficacy and safety	Efficacy and safety	Safety
Primary endpoint	• PK: AUC, AUC_{last} $C_{max,}$ • PD: GIR-AUC_{0-12}	HbA1c (%), change from baseline to Week 26	HbA1c (%), change from baseline to Week 26	Incidence of infusion set occlusions defined as failure to correct hyperglycemia (plasma glucose ≥300 mg/dL) by
Safety	General safety	Immunogenicity and general safety	Immunogenicity and general safety	Infusion set occlusions and general safety
Number of patients randomiz	N=30	SAR342434: N=253 Humalog:	SAR342434: N=253 Humalog:	N=27

Duration of treatment	3x1 day	6 months (main study period) 6 months comparative safety	6 months	2x4 weeks	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
02/17/2017

MANOJ KHURANA
02/17/2017