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Sponsor: Sanofi **Drug substance(s):** SAR342434	**Study Identifiers:** U1111-1134-4816, NCT02273258 & 2012-004453-86 **Study code:** PDY12704

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

Study center(s): 1 center in Germany

Study period:

Date first subject enrolled: 12/Mar/2013

Date last subject completed: 08/Jul/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

Investigational medicinal product (Reference 1): SAR342434 (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

Investigational medicinal product (Reference 2): SAR342434 (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

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 Clast (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.

Pharmacodynamics 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-tmax 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-Cmax (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-AUClast (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

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Secondary variables:

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

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

Parameter	Treatment ratio	Estimate	90% CI
INS-AUC0-2 (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-AUC4-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-t1/2z (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-t_{max} (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)

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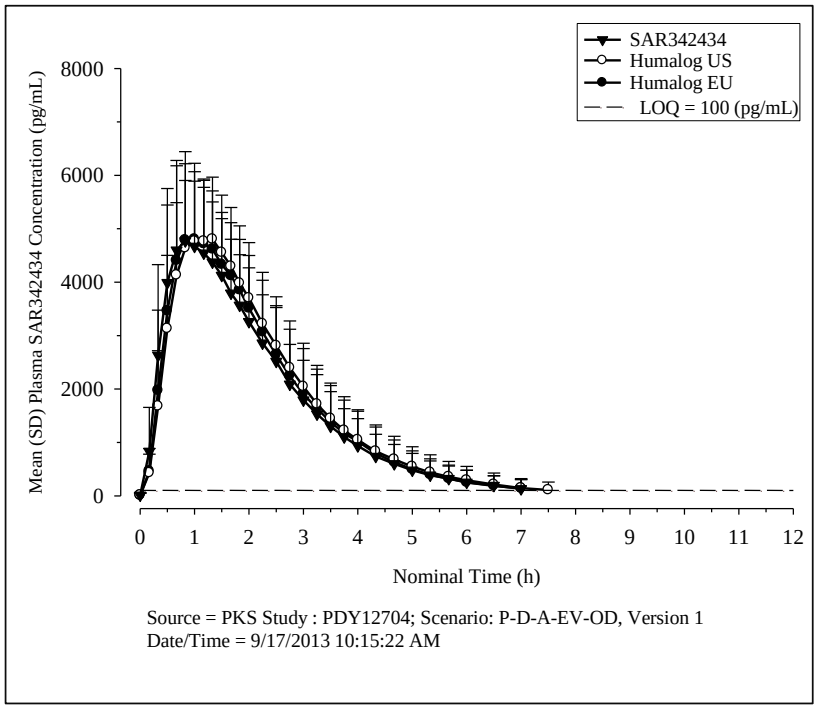
Mean concentration versus time profiles for SAR342434, Humalog US, and Humalog EU are presented in the figure below. The PK profiles were generally similar for SAR342434 and the 2 Humalog treatments.

Pharmacokinetic Profiles for SAR342434, Humalog US and Humalog EU



Pharmacodynamic results:

Primary variables:

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

Treatment effect on GIR-AUC$_{0\text{-}12}$.
Point estimates of treatment ratio with 90% and 95% confidence intervals

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC0-12h (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)
GIR$_{max}$ (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)

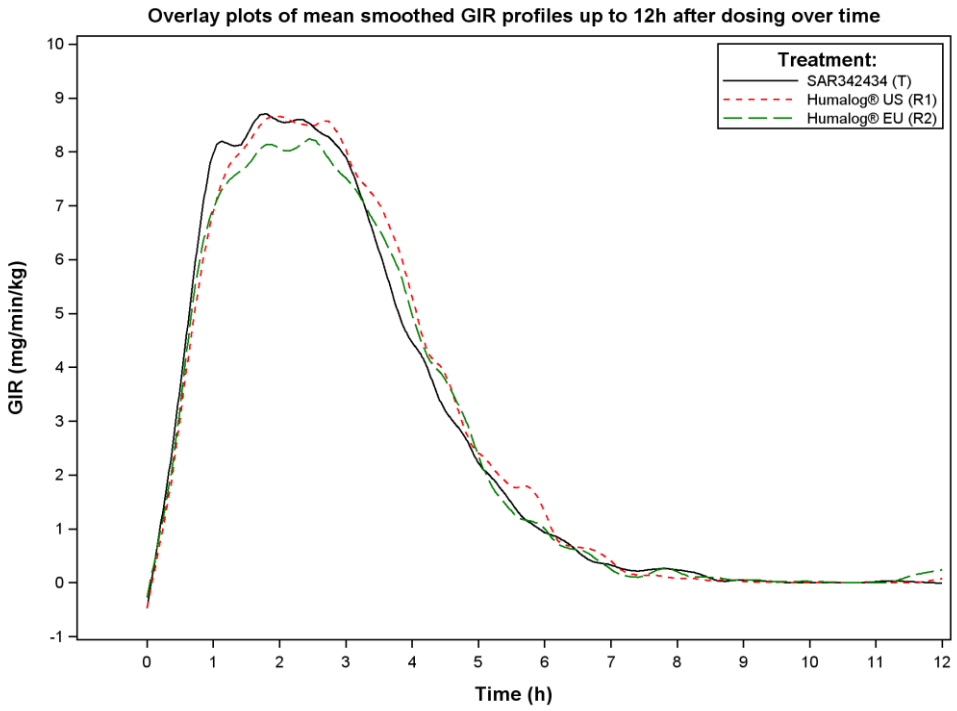
The Hodges-Lehmann point estimates for the median of the treatment difference between SAR342434 to Humalog US and Humalog EU for Tx% GIR-AUC0-12 (where x = 10, 20, 50, and 90) and GIR-tmax are provided in the table below.

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)
GIR-t_{max} (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.



GIR = body weight standardized Glucose Infusion Rate
LOESS smoothing using factor = 0.06
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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.

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