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Sponsor: Sanofi	**Study Identifiers:** U1111-1207-8959, NCT03903016, 2018-003131-30
Drug substance(s): Insulin Lispro	**Study code:** BEQ15846

Title of the study: A randomized, double-blind, single-dose, 2-treatment, 2-period, 2-sequence crossover bioequivalence study comparing two different strengths formulations of insulin lispro using the euglycemic clamp technique, in patients with Type 1 diabetes mellitus (BEQ15846)

Study center: 1 center in Germany

Study period:

Date first patient enrolled: 26/Mar/2019

Date last patient completed: 19/Aug/2019

Phase of development: Phase 1

Objectives:

For clarity purposes, the wording used in the protocol for the reference formulation were changed from "insulin lispro 100 Units/mL" to "Insulin lispro Sanofi®100 Units/mL" throughout the clinical study report, including in the study objectives.

Primary:

- To demonstrate bioequivalence (expressed in terms of rate and extent of absorption) between insulin lispro given as SAR342434, 200 Units/mL test formulation (T) and Insulin lispro Sanofi® 100 Units/mL reference formulation (R) after a single subcutaneous (SC) dose.

Secondary:

- To assess the pharmacodynamic profiles and further pharmacokinetic characteristics of the SAR342434, 200 Unit/mL (insulin lispro) test formulation (T) in comparison to the Insulin lispro Sanofi® reference formulation (R) after a single SC dose.
- To assess safety and tolerability of the test and the reference formulation of insulin lispro.

Methodology:

This was single-center; double-blind, randomized, 2-sequence, 2-period, 2-treatment crossover euglycemic clamp study, with a wash-out duration between dosing occasions (5 to 18 days, preferred 7 days).

Number of patients:

Planned: 90 patients (45 patients in each sequence)

Randomized: 90

Treated: 90

Evaluated:

Pharmacodynamics: 89

Pharmacokinetics:89

Safety: 90

Diagnosis and criteria for inclusion:

Male or female patients between 18 and 64 years of age, inclusive, with diabetes mellitus Type 1 for more than 1 year, as defined by the American Diabetes Association (ADA). Body weight between 50.0 and 100.0 kg, inclusive, if male, and between 40.0 and 90.0 kg, inclusive, if female, and a body mass index between 18.0 and 30.0 kg/m^2, inclusive. Stable insulin regimen for at least 2 months prior to the study (day of insulin regimen switch, with respect to safety of the patient and scientific integrity of the study) and total insulin dose of <1.0 U/kg/day. Fasting serum C-peptide <0.30 nmol/L, glycohemoglobin (HbA1c) ≤75 mmol/mol (≤9%), and anti-insulin antibody titer ≤30.0 kU/L at screening.

Study treatments

Investigational medicinal product: Reference formulation (R): Insulin lispro Sanofi® 100 Units (U)/mL

Formulation: Solution for injection in a 3 mL cartridge, (100 U/mL [=U100] insulin lispro), commercially available.

Route(s) of administration: Subcutaneous injection in the abdominal wall (into alternate lower abdominal quadrants at an approximately 90-degree angle into a raised skinfold).

Dose regimen: Single dose of 0.3 U/kg on Day 1 of each period under fasting conditions.

Investigational medicinal product: Test formulation (T): SAR342434/insulin lispro 200 U/mL

Formulation: Solution for injection in a 3 mL cartridge (200 U/mL [=U200] insulin lispro).

Route(s) of administration: Subcutaneous injection in the abdominal wall (into alternate lower abdominal quadrants at an approximately 90-degree angle into a raised skinfold).

Dose regimen: Single dose of 0.3 U/kg on Day 1 of each period under fasting conditions.

Non investigational medicinal products:

Products used for preclamp and clamp procedure (insulin glulisine, glucose [20% solution for IV infusion], heparin [vial containing 5 mL solution, 5000 IU/mL] and 0.9% sodium chloride), and rescue medication for cases of uncontrolled high blood glucose (BG).

Duration of treatment: A single dose of Insulin lispro Sanofi 100 U/mL (R) or SAR342434/insulin lispro 200 U/mL (T) administered in a crossover design on Day 1 of 2 treatment periods with an overnight stay.

Duration of observation: Total study duration per patient: 18 to 62 days (minimum to maximum duration), including screening: 4 to 28 days before the first administration (Day -28 to Day -4); treatment Period 1 and 2: 2 days (1 overnight stay); in-house periods within each treatment period: Day 1 morning to Day 2 morning; wash-out duration between administration occasions (5 to 18 days, preferred 7 days); and End-of-Study visit (follow-up): between Day 7 and Day 14 after last administration of investigational medicinal product (IMP) in Period 2 (equal to: between Day 5 and Day 12 after the treatment Period 2).

Criteria for evaluation:

Pharmacokinetics:

Primary pharmacokinetics (PK) variables:

- Maximum serum insulin observed concentration (INS-C_{max}).
- Area under the serum insulin concentration-time curve from time 0 to time of last measurable concentration (INS-AUC_{last}).

Secondary PK variables:

- Area under the serum insulin concentration-time curve (INS-AUC).

- Time to reach INS-C_{max} (INS-t_{max}).
- Time corresponding to the last concentration above the limit of quantification, C_{last} (INS-t_{last}).
- Insulin terminal elimination half-life (INS-$t_{1/2z}$).

Pharmacodynamics:

- The area under the body weight standardized glucose infusion rate (GIR) versus time curve from 0 to 8 hours post administration (GIR-AUC_{0-8}).
- Maximum smoothed body weight standardized glucose infusion rate (GIR_{max}).
- Time to GIR_{max} (GIR-t_{max}).
- Time from start of IMP administration to end of glucose infusion (defined as the latest time after dosing with GIR above zero) (GIR-t_{last}) (hours).
- Duration of BG control under clamp conditions with smoothed BG smaller/equal to the 4 levels of 105, 110, 130, and 150 mg/dL.
- Time to x% of the GIR-AUC_{0-8} (Tx%-GIR-AUC_{0-8}) (x = 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%).

Further supplemental secondary endpoints for PK and pharmacodynamic (PD) could be derived as appropriate.

Safety and tolerability:

Safety and tolerability were assessed by: adverse events (AEs), physical examinations, 12-lead electrocardiograms (ECGs), vital signs, clinical laboratory tests, injection site reactions, aural temperature, and hypoglycemia.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetics:

Blood samples for the determination of serum concentrations of insulin glulisine were collected on Day 1 of each treatment period at the following time points: 0 (predose) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 8, 9, and 10 hours after dose.

Plasma concentrations of SAR342434/insulin lispro were determined using a validated bioanalytical method with a lower limit of quantification of 100 pg/mL.

Pharmacodynamics:

Arterialized venous blood was continuously drawn at a rate of 2 mL/h for determination of arterial BG concentration from about 1.5 to 6.5 hours prior to the IMP administration to the end of the clamp up to 8 hours after the IMP administration.

Arterialized venous blood samples (approximately 0.1 mL) for concurrent clamp device adjustment (using SuperGL) was collected approximately in 30 minute-intervals (more often if required) after connection to the clamp device until end of the clamp.

Statistical methods:

Pharmacokinetics:

Primary:

Pharmacokinetic parameters were summarized by formulation using descriptive statistics.

Bioequivalence between the 2 formulations was assessed by using a linear mixed effects model for log-transformed INS-C_{max}, and INS-AUC_{last}. Estimate and 90% confidence interval (CI) for the ratio of treatments geometric means (T/R) between the 2 formulations were computed for INS-C_{max}, and INS-AUC_{last} within the mixed effect model framework. Bioequivalence was concluded in a confirmatory manner if the 90% CI for the formulation ratios of the geometric means (T/R) between the 2 formulations of INS-C_{max} and INS-AUC_{last} were entirely within the acceptance reference range (0.80; 1.25).

Secondary:

For the secondary PK parameters descriptive statistics were presented. The INS-t_{max} was analyzed non-parametrically based on Hodges-Lehmann method for paired treatment comparisons.

Pharmacodynamics:

Pharmacodynamic parameters were summarized, by treatment, using descriptive statistics. For log-transformed GIR-AUC_{0-8} and GIR_{max}, the PD profiles between the 2 products were assessed using a linear mixed effects model. Estimates, 90% and 95% CIs for the ratios of geometric means (T/R), were computed for GIR-AUC_{0-8} and GIR_{max} within the linear mixed effects model framework. The GIR-t_{max} was analyzed non-parametrically based on Hodges-Lehmann method for paired treatment comparisons.

Safety and tolerability:

The safety evaluation was based on the review of the individual data (clinically significant abnormalities), descriptive statistics (summary tables, graphics), and if needed, on statistical analysis (appropriate estimations). All safety analyses were performed using the safety population. Adverse events were coded according the Medical Dictionary for Regulatory Activities (MedDRA, v22.0), and the number of patients with treatment - emergent adverse events (TEAEs) was summarized by treatment. For vital signs and ECGs, the number of patients with abnormalities and/or potentially clinically significant abnormalities (PCSAs) was summarized in frequency tables by treatment, where appropriate. The number of patients with injection site reactions and the number of patients with hypoglycemia were tabulated by treatment.

Summary:

Population characteristics: Ninety patients (26 females and 64 males) were randomized and were exposed to the IMP. All patients completed both treatment periods. One patient was excluded from PK and PD evaluation due to wrong dosing in Treatment Period 2.

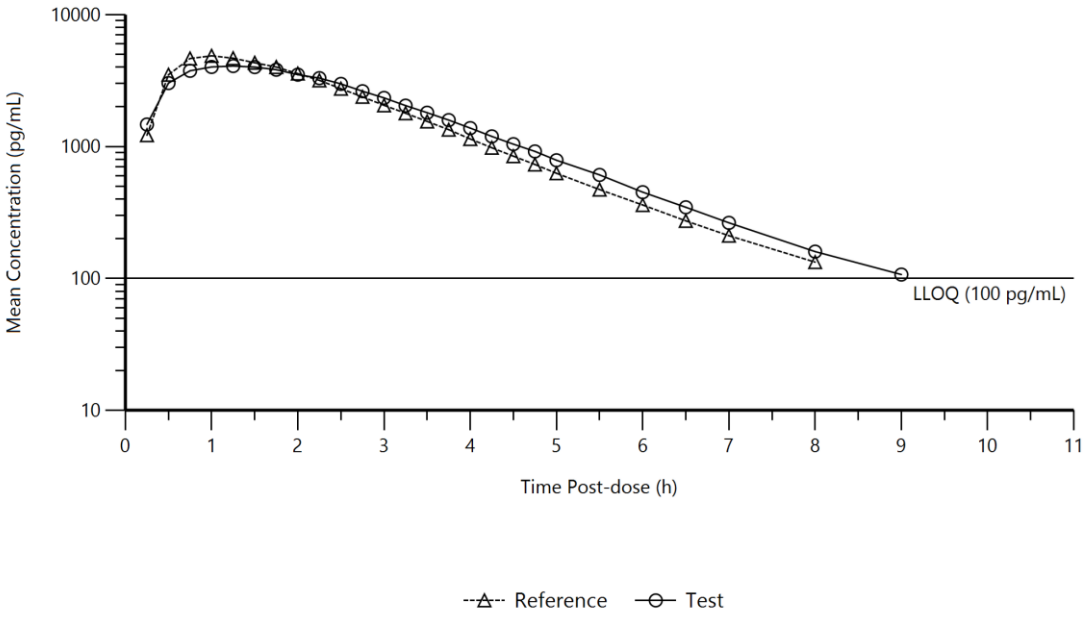
Pharmacokinetic results:

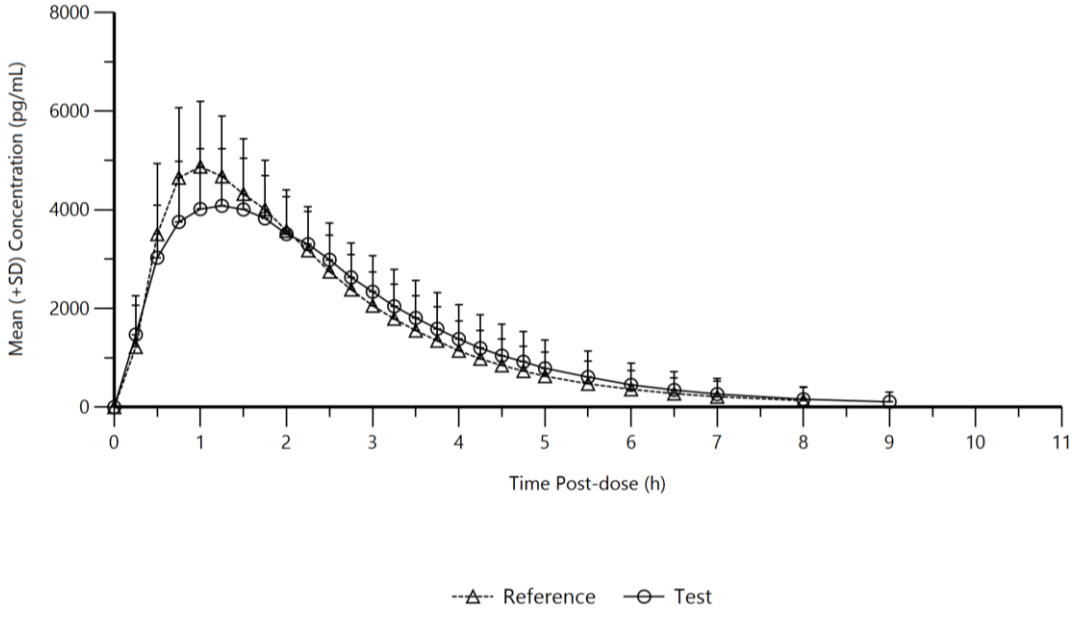
Eighty-nine patients were evaluable for PK in both periods in which they received treatments.

Following single SC dose administration (0.3 U/kg) of SAR342434/insulin lispro 200 U/mL (T) and Insulin lispro Sanofi 100 U/mL (R), maximum plasma concentrations of SAR342434/insulin lispro occurred at a median time of 1.25 and 1.00 hours, respectively, with a slightly wider t_{max} range observed for Test versus Reference (0.50 to 3.50 hours versus 0.50 to 2.25 hours). Following INS-C_{max}, concentrations of SAR342434 declined rapidly in a generally monophasic manner, with similar mean INS-$t_{1/2z}$ values for Test and Reference (1.28 and 1.27 hours, respectively).

Between-patient variability based on coefficient of variation (CV%) was moderate for INS-C_{max} and INS-AUC_{last} with values ranging from 24% to 27% across treatments.

Mean (+SD) plasma SAR342434/insulin lispro concentration-time profiles after a single subcutaneous dose (0.3 U/kg) of SAR342434 (insulin lispro) 200 U/mL (Test) and Insulin lispro Sanofi 100 U/mL (Reference) are shown in following figures (linear and semi-logarithmic scales):





Pharmacokinetic parameters of SAR342434/insulin lispro are summarized in the table below:

Pharmacokinetic parameters of SAR342434/insulin lispro following a single subcutaneous dose (0.3 U/kg) of SAR342434 (insulin lispro) 200 U/mL (T) and Insulin lispro Sanofi 100 U/mL (R)

	Plasma SAR342434/insulin lispro	
Mean ± SD (Geometric Mean) [CV%]	**SAR342434 (insulin lispro) 200 U/mL (T)**	**Insulin lispro 100 U/mL (R)**
N	89	89
INS-C_{max} (pg/mL)	4400 ± 1150[b] (4250) [26]	5190 ± 1420 (5000) [27]
INS-t_{max}[a] (h)	1.25[b] (0.50 - 3.50)	1.00 (0.50 - 2.25)
INS-AUC_{last} (pg.h/mL)	13700 ± 3310[b] (13400) [24]	13600 ± 3370[b] (13200) [25]
INS-AUC (pg.h/mL)	14000 ± 3690[b] (13700) [26]	13900 ± 3790 (13500) [27]
INS-t_{last}[a] (h)	8.00 (4.75 - 10.00)	7.00[b] (4.75 - 10.25)
INS-$t_{1/2z}$ (h)	1.28 ± 0.624 (1.15) [49]	1.27 ± 0.594 (1.16) [47]

a Median (min-max); b n=88

Subject 276000100003 was excluded from descriptive statistics for both treatments following a dosing error in TP2 (R treatment).

INS-AUC, INS-AUClast, INS-Cmax and INS-tmax for Subject 276000100023, T treatment (TP1) were excluded from descriptive statistics as the 1.75-hour PK sample was not collected, which may have resulted in underestimation of these parameters

INS-AUClast and INS-tlast for Subject 276000100024, R treatment (TP1) were excluded from descriptive statistics as the 9-hour PK sample did not have a reportable concentration result, which may have resulted in underestimation of these parameters.

The point estimate (90% CI) of the formulation ratio comparing T treatment versus R treatment was 1.01 (1.00 to 1.03) for INS-AUC_{last} and 0.85 (0.81 to 0.88) for INS-C_{max}, respectively. For both INS-AUC_{last} and INS-C_{max}, the 90% CIs were completely covered by the accepted bioequivalence range of 0.80 to 1.25, therefore bioequivalence can be concluded for the primary PK parameters as shown in table below:

Formulation effect on INS-AUC_{last} and INS-C_{max} of SAR342434/insulin lispro: point estimates of formulation ratios with 90% confidence intervals - primary analysis

Formulation ratio	Parameter	Estimate	90% CI
Test vs Reference	AUC_{last}	1.01	(1.00 to 1.03)
	C_{max}	0.85	(0.81 to 0.88)

Test = Test formulation SAR342434 (Insulin lispro) 200 Units/mL

Reference = Reference formulation Insulin lispro 100 Units/mL

PGM=PRODOPS/DVC201501/BEQ15846/CSR/REPORT/PGM/pk_estim_krm.sas

OUT= REPORT/OUTPUT/pk_mix_k_t_2_i.rtf (26SEP2019 18:11)

Pharmacodynamic results:

Eighty-nine patients were evaluable for PD in both treatment periods.

The 90% and 95% CIs of the formulation ratios of the PD parameters GIR-AUC_{0-8} and GIR_{max} were within the 0.80 to 1.25 range as shown in the table below:

Results of statistical analysis of pharmacodynamic data - Estimate and 90% - 95% CI of Treatment ratio - GIR-AUC_{0-8} and GIR_{max}

Treatment ratio	Parameter	Estimate	90% CI	95% CI
T (200 U/mL)[b]/R (100 U/mL)[a]	GIR-AUC_{0-8}	1.05	(1.01 to 1.10)	(1.00 to 1.11)
	GIRmax	1.00	(0.95 to 1.06)	(0.94 to 1.07)

a R: Reference formulation Insulin lispro (100 U/mL)

bT: Test formulation SAR342434 (Insulin lispro) (200 U/mL)

GIR-AUC0-8 = Area under the body weight standardized glucose infusion rate time curve

GIRmax = Maximum smoothed body weight standardized glucose infusion rate

PGM=PRODOPS/DVC201501/BEQ15846/CSR/REPORT/PGM/pd_iequivstat_d.sas

OUT=REPORT/OUTPUT/pd_eq_k_t_2_i.rtf (19SEP2019 17:20)

The BG profiles of Insulin lispro Sanofi 100 U/mL (R) and SAR342434/insulin lispro 200 U/mL (T) were comparable up to 8 hours postdose (mean BG profile) and until 7 hours postdose (median BG profile).

Safety results:

There were no deaths, serious AEs, or severe TEAEs reported during the study. All patients completed the study.

Treatment-emergent AEs were reported in 10 out of 90 patients following administration of SAR342434/insulin lispro 200 U/mL (T) and 4 out of 90 patients following administration of Insulin lispro Sanofi 100 U/mL (R). The TEAEs observed in a higher number (%) of patients were vomiting and headache. Vomiting was reported for 5 (5.6%) patients following administration of SAR342434/insulin lispro 200 U/mL (T) and in 3 (3.3%) patients following administration of Insulin lispro Sanofi 100 U/mL (R).

Headache was reported in 5 (5.6%) patients following administration of SAR342434/insulin lispro 200 U/mL (T) and in no patients following administration of Insulin lispro Sanofi 100 U/mL (R). In intensity, most of the TEAEs of vomiting were moderate while most of the TEAEs of headache were mild; all of these were assessed by the Investigator as not related to the IMP. Only 1 local site reaction TEAE of injection site pain was reported following administration of Insulin lispro Sanofi 100 U/mL (R), which was assessed as related to the IMP by the Investigator.

There were no observed severe/serious hypoglycemic events during the conduct of the study. There were a few PCSAs reported in vital signs and ECG parameters, but none of those were recorded as AEs. No patient had a corrected QT (QTc) interval >480 msec or a QTc interval change from baseline of >60 msec.

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