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Sponsor / Company: sanofi-aventis **Drug substance(s):** SAR161271, Insulin glargine	**Study Identifier:** NCT01053728 **Study code:** TDU10987

Title of the study: Randomized, double-blind, euglycemic glucose clamp study of four formulations of SAR161271, in single doses in healthy subjects and single ascending doses in patients with Type 1 diabetes mellitus

This report presents the study part in patients with Type 1 diabetes mellitus, Part 2.

Study center(s): Profil GmbH, Hellersbergstraße 9, 41460 Neuss, Germany.

Study period:

Date first patient enrolled: 05 February 2010

Date last patient completed: 26 May 2010 (last poststudy visit for assessment of anti-insulin antibodies - 18 November 2010)

Phase of development: exploratory, dose escalation

Objectives:

1. Establish initial safety/tolerability and pharmacodynamic (PD) and pharmacokinetic (PK) profiles of up to four formulations of SAR161271, with 0, 10, 30, or 80 µg/mL added zinc in patients with Type 1 diabetes mellitus (T1DM);
2. To establish relative potency of up to 4 formulations of SAR161271 compared with insulin glargine in patients with T1DM.

This is the second part of the study, performed in patients. The first part in healthy subjects is reported in TDU10948.

Methodology: single-center, randomized, double-blind, euglycemic glucose clamp study with single ascending doses of 0.3, 0.6 or 1.2 U/kg of SAR161271 with 0, 10, 30 or 80 µg/ml zinc (Zn0, Zn10, Zn30, Zn80) and of insulin glargine in patients with Type 1 diabetes mellitus, with incomplete crossover (4 periods, 5 treatments in each dose cohort) in a 5-sequence balanced incomplete block design.

Number of patients:	Planned: 45
	Randomized: 46
	Treated: 46
	Pharmacodynamic: 37
	Safety : 46
	Pharmacokinetics : 46

Diagnosis and criteria for inclusion: Male patients aged 18-60 years who have T1DM and are in otherwise reasonable health

Investigational product: SAR161271 with zinc 0 µg/mL (Zn0), SAR161271 with zinc 10 µg/mL (Zn10), SAR161271 with zinc 30 µg/mL (Zn30), and SAR161271 with zinc 80 µg/mL (Zn80), in the form of solution for injection (100 U/mL) in 3 mL cartridges.

Dose: 0.3, 0.6 or 1.2 U/kg, single

Administration: subcutaneous (SC)

Duration of treatment: 4 days (a single dose at the beginning of each of the 4 treatment periods [TPs]; depending on the sequence, each patient received 4 single doses of SAR161271 or 3 single doses of SAR161271 and 1 single dose of insulin glargine).

Duration of observation: 15 (in a dropout) to 103 (in a rescreen) days (normally, including screening on Day-27 to Day-3; doses on Days 1, 8, 15, and 22; and EOS on Day 29).

Reference therapy: Insulin glargine in the form of solution for injection (100 U/mL; Lantus®) in 3 mL cartridges.

Dose: 0.3, 0.6 or 1.2 U/kg, single

Administration: SC

Criteria for evaluation:

Pharmacodynamic

Area under the body-weight-standardized glucose infusion rate (GIR) versus time curve calculated between the time of dosing and end of clamp (GIR-$AUC_{0\text{-}end}$ [mg/kg]); area under the body-weight-standardized GIR versus time curve calculated up to 24 hours after dosing (GIR-$AUC_{0\text{-}24}$ [mg/kg]); maximum of the smoothed body-weight-standardized GIR (GIR_{max} [mg/kg/min]); time to GIR_{max} (GIR-t_{max} [hours]); 6-hour fractions of GIR-$AUC_{0\text{-}end}$ (mg/kg); first time to reach at least x% of GIR-$AUC_{0\text{-}end}$ ($T_{x\%}$-GIR-$AUC_{0\text{-}end}$) and of GIR-$AUC_{0\text{-}24}$ ($T_{x\%}$-GIR-$AUC_{0\text{-}24}$) (hours); and duration of controlled (smoothed) blood glucose within a predefined margin above the clamp level (hours).

Safety

Treatment-emergent adverse events (TEAEs); local tolerability/reaction at the SC injection site; clinical laboratory evaluations; vital signs, physical examination, body temperature; ECG (12-lead and telemetry).

Assessment of anti-insulin antibodies prior to the first dose, following the fourth treatment, and at 3 months after the last treatment.

Pharmacokinetic

SAR161271 (parent compound and metabolites M1, M2, M3 and M4) and insulin glargine (parent compound and metabolites M1 and M2) plasma concentrations were to be used to determine the following PK parameters using standard non compartmental techniques: C_{max}, t_{max}, $T_{x\%}$-$AUC_{0\text{-}24}$, $T_{x\%}$-$AUC_{0\text{-}end}$, $AUC_{0\text{-}6}$, $AUC_{6\text{-}12}$, $AUC_{12\text{-}18}$, $AUC_{18\text{-}24}$, $AUC_{24\text{-}30}$, $AUC_{30\text{-}36}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}end}$, and AUC_{last}, and if applicable due to the low plasma concentrations, also AUC and $t_{1/2z}$.

Pharmacokinetic sampling times and bioanalytical methods

Blood samples were collected before dosing and at 3, 6, 12, 18, 24, 30, 36, 48, 120, and 168 hours post dose (n=10). The sample at 120 hours was introduced by Amendment 03, during Cohort 3. From the time this amendment was in place, the PK sample at 30 hours was omitted, in order not to increase the number of PK samples over 10 per period.

Free SAR161271 (parent compound), free SAR161271 metabolites M1, M2, M3 and M4, free insulin glargine (parent compound) and free insulin glargine metabolites M1 and M2 in plasma were determined using immunoaffinity extraction (IAE) followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a lower limit of quantification (LOQ) of 0.2 ng/mL.

Statistical methods:

Pharmacodynamic

- Glucose infusion rate was divided by individual body weight to standardize on units of insulin dosed.
- Pharmacodynamic parameters were summarized by treatment using descriptive statistics.
- Descriptive analyses were performed separately for test treatments in each dose cohort (formulations of SAR161271 Zn0, Zn10, Zn30, and Zn80) and insulin glargine.
- Bar charts for the 6-hour fractions of GIR-$AUC_{0\text{-}end}$, overlay plots of the mean smoothed GIR profiles and scatter plots of GIR-$AUC_{0\text{-}24}$ versus bicarbonate and absolute dose were provided.

Safety and tolerability

- The safety analysis was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics by treatment.
- For adverse events (AEs), frequencies of TEAEs classified by Medical Dictionary for Regulatory Activities (MedDRA version 13.0) system organ class and preferred term were tabulated by treatment.
- For clinical laboratory data, vital signs and ECG, frequency of patients with abnormalities and Potentially Clinically Significant Abnormalities (PCSAs) were summarized by treatment.

Pharmacokinetics

SAR161271 (parent compound and metabolites M1, M2, M3 and M4) and insulin glargine (parent compound and metabolites M1 and M2) PK parameters were summarized by dose and, if applicable, by treatment (formulation) using descriptive statistics.

PK / PD

Scatter plots of GIR-$AUC_{0\text{-}24}$ and GIR-$AUC_{0\text{-}end}$ over the area under the plasma concentration versus time curve ($AUC_{0\text{-}24}$ and $AUC_{0\text{-}end}$) were provided.

Summary:

Pharmacodynamic results:
With single SC doses of 4 formulations of SAR161271 with 0, 10, 30 and 80 µg/mL zinc, blood glucose control over 24 and 30 hours during the glucose clamp period showing a smoothed blood glucose profile not exceeding 150 mg/dL was not achieved in all patients at any of the dose levels of 0.3, 0.6 or 1.2 U/kg.

The fraction of patients controlled at this blood glucose threshold ranged, depending on SAR161271 formulation, from 2 (n=12) to 6 (n=11) at 0.6 U/kg, and from 3 (n=12) to 9 (n=11) at 1.2 U/kg, whereas it was 11 (n=11) for insulin glargine at both of these dose levels. At the 0.3 U/kg dose level, only 1 out of 12 patients could be controlled with SAR161271 Zn10, Zn30 and Zn80, whereas it was none with SAR161271 Zn0. A dose of 0.3 U/kg insulin glargine could control blood glucose in 8 (n=12) of the patients for 24 hours and in 7 (n=12) for 30 hours.

The number of patients being controlled for blood glucose below the threshold of 150 mg/dL with SAR161271 increased with dose and decreased with increasing zinc concentration within a dose level.

The number of glucose clamps having required a restart of the insulin glulisine infusion within 24 hours after investigational product (IP) administration because of exceeding a blood glucose level of 200 mg/dL was lower for insulin glargine at all dose levels than for SAR161271 in all formulations. Within the periods with SAR161271 of dose cohorts 0.6 and 1.2 U/kg, this number became higher with increasing zinc concentration.

This number of clamp periods having required a restart of the insulin glulisine infusion within 24 hours after dosing was 3 (n=12) for 0.3 U/kg insulin glargine and 8 (n=13), 6 (n=12), 8 (n=12), and 6 (n=12) for the same dose of SAR161271 with 0, 10, 30, and 80 µg/mL zinc, respectively. In the 0.6 U/kg group, the numbers were 0 (n=11) for insulin glargine and 1 (n=11), 4 (n=12), 5 (n=12), and 6 (n=12) for SAR161271 with 0, 10, 30, and 80 µg/mL zinc, respectively. In the 1.2 U/kg group, the numbers were 0 (n=11) for glargine and 1 (n=11), 5 (n=12), 5 (n=12), and 8 (n=12) for SAR161271 with 0, 10, 30 and 80 µg/mL zinc, respectively.

Within the evaluable clamp periods without restart of insulin infusion, the individual variability of the blood glucose profiles over the first 24 hours after dosing decreased slightly with increasing dose of the SAR161271 formulations with 0 and 10 µg/mL zinc, but no such trend was obvious for the other 2 formulations of SAR161271 or insulin glargine. Insulin glargine had at each dose level a markedly lower individual variability of the blood glucose profile than any of the SAR161271 formulations.

The mean GIR-AUC (GIR-$AUC_{0\text{-}end}$ and GIR-$AUC_{0\text{-}24}$) was higher and had a lower variability under insulin glargine than under SAR161271 in any formulation at each dose level. Within each dose level, there was an overall trend for the mean GIR-AUC to decrease with increasing zinc concentration.

At 0.6 U/kg, the mean GIR-$AUC_{0\text{-}24}$ (in brackets, the coefficient of variation, CV%) over 24 hours was 2525.52 mg/kg (37%) for glargine, whereas it was 414.65 mg/kg (95%), 378.95 mg/kg (111%), 267.48 mg/kg (110%), and 183.27 mg/kg (142%) for SAR161271 with 0, 10, 30, and 80 µg/mL zinc, respectively. The means and CV% in the 1.2 U/kg cohort were 5421.63 mg/kg (28%) for glargine and 1004.16 mg/kg (127%), 664.90 mg/kg (101%), 466.29 mg/kg (90%), and 562.25 mg/kg (80%) for SAR161271 with 0, 10, 30, and 80 µg/mL zinc, respectively. In the 0.3 U/kg group, there were only 1 or 2 patients per formulation of SAR161271 interpretable, thus not enabling any relevant descriptive analysis. Insulin glargine had a mean GIR-$AUC_{0\text{-}24}$ of 664.45 mg/kg with a CV% of 64% at this dose level.

Safety results:

Overall, SAR161271 given as singles doses in formulations with 0, 10, 30 and 80 µg/mL zinc, as well as insulin glargine in its commercial formulation Lantus®, were well tolerated. There were no serious adverse events (SAEs) in this study. Two patients were withdrawn from treatment due to TEAEs that in both cases were considered by the investigator as nonserious and not drug-related.

There were more patients with TEAEs in the dose cohorts of 0.6 and 1.2 U/kg than in the low dose cohort of 0.3 U/kg, but with no clear trend from 0.6 U/kg to 1.2 U/kg. Within each dose level, there was no substantial difference in the number of patients with TEAEs between insulin glargine treatment periods and those periods with the 4 formulations of SAR161271. Most of the patients at 0.3 U/kg with TEAEs reported headache; in the 2 higher dose cohorts, most patients with TEAEs had events of hypoglycemia recorded. The latter were mostly self-reported outside the clamp procedures by means of the diary in Cohorts 2 and 3 (0.6 and 1.2 U/kg) and were of mild intensity in all cases but 1 in the 0.3 U/kg cohort.

A 45-year-old male patient (276 001 002) had a nonsustained (7 beats) ventricular tachycardia recorded by ECG telemetry during his first clamp period, about 1 hour after dosing with 0.3 U/kg SAR161271 Zn0. The event was classified by the investigator as not drug-related, due to its occurrence early after dosing (at a time when no detectable PD effect was present as concluded from GIR and no SAR161271 was detected in plasma). The patient was withdrawn from the study due to the TEAE.

A 48-year-old male patient (276 001 020) with a 30-year history of T1DM and no history of ketoacidosis or macro- or microvascular diabetic complications developed ketoacidosis of moderate intensity at the end of a clamp (Day 1) in TP2 with 0.6 U/kg SAR161271 Zn80. The diagnosis was confirmed by laboratory measurements. The event was classified by the investigator as not drug-related, but rather related to the clamp procedure. The patient was withdrawn from the study due to the TEAE. By TP2 Day 8 (the patient's EOS), pH and ketone levels had entirely normalized.

Pharmacokinetic results:

Following a single SC administration of 0.3, 0.6 or 1.2 U/kg SAR161271 as Zn0, Zn10, Zn30 or Zn80 formulation in T1DM patients, the majority of plasma samples had SAR161271 parent compound concentrations below the LOQ of 0.2 ng/mL with a clear tendency of increasing number of samples above LOQ with dose while decreasing number of samples above LOQ with higher zinc concentrations within a dose cohort. A reasonable PK profile was observed in the highest dose group (1.2 U/kg) for the Zn0 and Zn10 formulations only. Mean plasma concentrations were up to approximately 0.5 ng/mL between 3 and 24 hours for the Zn0 and up to approximately 0.3 ng/mL between 3 and 18 hours for the Zn10 formulation. A formal dose proportionality or zinc formulation effect assessment of PK parameters was not possible due to the high number of treatment profiles below LOQ.

Following a single SC administration of 0.3, 0.6 or 1.2 U/kg insulin glargine, in the majority of T1DM patients, neither insulin glargine parent compound nor metabolite M2 were detectable in plasma (LOQ of 0.2 ng/mL). In most patients, mean plasma concentrations of parent compound and metabolite M2 were below LOQ over the entire observation period (168 hours). In those patients, where parent compound and/or metabolite M2 were detected in less than 10% of individual samples, parent and metabolite M2 concentrations ranged from 0.2 to 0.8 ng/mL. The exposure to insulin glargine parent or metabolite M2 did not increase with increasing dose. In contrast, insulin glargine metabolite M1 was the predominant analyte in plasma. For all patients, a reasonable M1 PK profile with maximum plasma concentrations approximately 12 hours post dose was observed. The exposure to M1 increased with dose in a supra-dose-proportional manner for the increase from 0.3 to 0.6 U/kg and in a less than dose-proportional manner from 0.6 to 1.2 U/kg. Scatter plots of GIR-AUC_{0-24} over AUC_{0-24} showed that an increase in insulin glargine metabolite M1 exposure correlated with an increased efficacy as measured by GIR-AUC.

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