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Sponsor / Company: sanofi-aventis **Drug substance(s):** SAR161271	**Study Identifier:** NCT01053728 **Study code:** TDU10948
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 healthy subjects, Part 1.***	
Study center(s): Profil GmbH, Hellersbergstraße 9, 41460 Neuss, Germany	
Study period: Date first subject enrolled: 07 January 2010 Date last subject completed: 29 January 2010	
Phase of development: 1	
Objectives: Part 1 TDU10948: 1. Establish initial safety/tolerability and pharmacodynamic (PD) and pharmacokinetic (PK) profiles of two formulations of SAR161271, one with and one without 80 µg/mL added zinc, in healthy subjects. ***This study in healthy subjects was followed by the study, TDU10987 (Part 2), performed in patients.***	
Methodology: Single-center, randomized, double-blind, comparator-controlled, single-dose, parallel-group, euglycemic glucose clamp in healthy young male subjects.	
Number of subjects:	Planned: 16
	Randomized: 16
	Treated: 16
Evaluated:	
	Pharmacodynamic: 16
	Safety: 16
	Pharmacokinetics: 16 (6 on SAR161271 and 2 on insulin glargine per cohort)
Diagnosis and criteria for inclusion: Healthy, male subjects, between 18 and 45 years.	

Investigational product: SAR161271 with zinc 0 μg/mL (Zn0) 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 U/kg, single

Administration: subcutaneous (SC)

Duration of treatment: A single dose on Day 1.

Duration of observation: Between 10 and 37 days.

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

Dose: 0.3 U/kg, single

Administration: SC

Criteria for evaluation:

Pharmacodynamic:

The glucose utilization over a euglycemic clamp set at 5.5 mmol/L (100 mg/dL) after an injection of SAR161271 or insulin glargine was assessed based on the following criteria:

- Area under the curve for body-weight-standardized glucose infusion rate (GIR) between time of dosing and end of clamp, based on the linear rectangular rule for a time scale in minutes: GIR-$AUC_{0\text{-}end}$ [mg/kg];
- Maximum of the smoothed body-weight-standardized glucose infusion rate: GIR_{max} [mg/kg/min];
- Time to maximum of the smoothed body-weight-standardized glucose infusion rate: GIR-t_{max} [hours].
- Fractional areas under the curve for the body-weight-standardized GIR between x and y hours after dosing, based on the linear rectangular rule: GIR-$AUC_{x\text{-}y}$ [mg/kg].
- Duration of bulk activity was to be derived as the time in hours with GIR above 0.2 mg/kg/min (GIR duration [hours]).
- Percentage fractional GIR-AUCs derived as percentage ratios of fractional GIR-$AUC_{x\text{-}y}$ relative to GIR-$AUC_{0\text{-}end}$: GIR% $AUC_{x\text{-}y}$ [%].
- First time to reach at least x% of GIR-$AUC_{0\text{-}end}$ [tx%-GIR-AUC0-end, hours] was derived for x=10, 20, 30, 40, 50, 60, 70, 80, 90.

Safety:

The following safety criteria were evaluated, and analyzed using descriptive statistics: adverse events (AEs) reported by the subject or noted by the Investigator, standard hematology and blood chemistry, urinalysis, physical examination, vital signs (VS), standard 12-lead electrocardiogram (ECG) and ECG telemetry, and any concomitant medications. In addition, local tolerability at the injection site was assessed. Serum C-peptide as a measure of endogenous insulin was used to assess a potential interference with GIR.

Pharmacokinetic:

SAR161271 (parent compound) 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}, $t_{x\%}$-$AUC_{0\text{-}end}$, $AUC_{0\text{-}6}$, $AUC_{6\text{-}12}$, $AUC_{12\text{-}18}$, $AUC_{18\text{-}24}$, $AUC_{24\text{-}30}$, $AUC_{30\text{-}36}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}end}$, 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 1, 2, 3, 4, 6, 8, 10, 14, 18, 24, 30, 36, 48, and 168 hours post dose. Free SAR161271 (parent compound) in plasma was 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. Total insulin glargine (parent compound) in plasma was determined using IAE followed by an enzyme-linked immunosorbent assay (ELISA) with a LOQ of 0.5 ng/mL. Total insulin glargine metabolites M1 and M2 in plasma were determined using IAE followed by LC-MS/MS with a LOQ of 0.2 ng/mL for each analyte.

Statistical methods:

Pharmacodynamic: All PD analyses were based on the PD analysis population.

Glucose infusion rate was divided by individual body weight to standardize on units of insulin dosed. The derivation of GIRmax and of the time to GIRmax, was based upon a LOESS (locally weighted regression in smoothing scatter plots) smoothing technique for the raw GIR data. A smoothing factor of 6% was used (SAS®, PROC LOESS, factor 0.06).

Pharmacodynamic parameters were summarized by treatment using descriptive statistics. Mean raw and mean smoothed GIR profiles, and individual blood glucose profiles were plotted per treatment.

In addition to the descriptive analyses, supplemental comparative analyses were performed for GIR-$AUC_{0\text{-end}}$, selected fractional GIR-AUCs and GIR_{max} as described below. However, these analyses were of fully explorative character, had low statistical power and were only to be considered to deliver supplemental information.

The aim of the pairwise comparisons was to derive explorative estimators for the treatment ratios:

- SAR161271 Zn0 / Insulin glargine

- SAR161271 Zn80 / Insulin glargine

- SAR161271 Zn80 / SAR161271 Zn0

Prior to the analysis described below, the GIR-$AUC_{0\text{-end}}$ were log-transformed (natural log). The log-transformed GIR-$AUC_{0\text{-end}}$ were analyzed with a linear fixed effect model with fixed term for treatment as follows:

- log(parameter) = treatment + error,

using SAS® PROC MIXED.

Confidence interval (CI) for the pairwise ratios of treatment geometric means were obtained by computing the estimate, 90% CI, and 95% CI for the difference between treatment means within the linear fixed effects model framework, and then by converting to the ratio of geometric means by the antilog transformation.

Due to the explorative character of the study, no adjustment of error level for multiple statistical analyses was performed.

Safety: The safety evaluation was based on the review of the individual values (potentially clinically significant abnormalities [PCSA]) and descriptive statistics (summary tables). The safety analysis was conducted on all subjects who received at least one dose of the study drug (safety population). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 12.1). Subjects with treatment-emergent adverse events (TEAEs) were summarized by system-organ classes (SOC) and preferred term (PT). Individual hematology and biochemistry, VS and ECG (standard and telemetric) data were flagged when reaching the limit for potentially clinically significant abnormality (PCSA) criteria.

Pharmacokinetics: SAR161271 (parent compound) and insulin glargine (parent compound and metabolites M1 and M2) PK parameters were to be summarized by treatment using descriptive statistics.

Summary:

Pharmodynamic results: Mean GIR-$AUC_{0\text{-}end}$ over the 30 hours of the clamp procedure was higher after treatment with 0.3 U/kg insulin glargine (2303 mg/kg) than after treatment with 0.3 U/kg SAR161271 Zn0 (1411 mg/kg) and 0.3 U/kg SAR161271 Zn80 (1042 mg/kg). The mean smoothed GIRs of the treatments with SAR161271 Zn0 and Zn80 were almost permanently lower than those with insulin glargine during the 30 hours of the clamp.

The GIR profiles showed a trend for insulin glargine having an earlier and higher maximum than SAR161271 Zn0 and Zn80 (mean GIR_{max} 2.89, 2.53, and 2.18 mg/kg/min and mean GIR-t_{max} 16.76, 17.62, 19.15 hours for insulin glargine, SAR161271 Zn0, and SAR161271 Zn80, respectively).

Assessing the 6-hour fractions of the mean GIR-$AUC_{x\text{-}y}$, insulin glargine showed a crescendo-decrescendo pattern with an apparent maximum in the period from 12 to 18 hours after dosing, which was not seen in the 2 treatment groups with SAR161271.

Subjects having received SAR161271 Zn0 or Zn80 showed a feeble, not persistent reduction in C-peptide concentration over the 30 hours of the clamp, whereas C-peptide concentrations decreased from baseline and remained lower in the group treated with insulin glargine, pointing at the suppression of the endogenous insulin release.

Safety results: Single SC doses of 0.3 U/kg insulin glargine, SAR161271 without zinc or SAR161271 with 80 µg/mL zinc were well tolerated in healthy young male subjects. There were no SAEs and no AEs leading to treatment discontinuation in the study.

Three TEAEs were reported for 2 subjects, all classified as not drug related by the Investigator. One subject in the SAR161271 Zn0 group experienced a moderate headache during the clamp procedure. One subject in the SAR161271 Zn80 group experienced headache and diarrhea during the clamp procedure, both of mild intensity.

Another subject of the group treated with SAR161271 Zn0 showed a decrease in platelet count from 266 Giga/L at baseline to 76 Giga/L after dosing on Day 3, however, without any related clinical symptoms. On his EOS visit, the platelet count was normal (273 Giga/L).

There were more subjects with potential clinically significant abnormalities (PCSAs) in ECG parameters in the treatment group of SAR161271 Zn80 than in the other 2 treatment groups. However, all abnormalities in ECGs were classified as not clinically significant by the Investigator.

There were no injection site findings in any of the subjects in this study.

Pharmacokinetic results:

Following a SC administration of 0.3 U/kg SAR161271 Zn0, SAR161271 Zn80 or insulin glargine in HS, mean SAR161271 (free parent compound), mean insulin glargine (total parent compound), and mean insulin glargine metabolite (total M1 or M2) plasma concentrations were below the LOQ of 0.2, 0.5, and 0.2 ng/mL, respectively. Very few individual samples had SAR161271 parent compound or insulin glargine M1 plasma concentrations above the LOQ (between 0.2 and 0.3 ng/mL or between 0.2 and 0.4 ng/mL, respectively). Therefore, PK parameters could not be calculated for any analyte and no statistical analysis could be performed.

Issue date: 04 June 2012