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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): SAR279356	Study Identifiers: NCT01389700, UTN U1111-1118-6717 Study code: PKD11791
Title of the study: A randomized, double-blind, placebo-controlled trial to assess the pharmacokinetics, pharmacodynamics, and safety of a single dose of SAR279356 in patients hospitalized in intensive care unit and on mechanical ventilation	
Study center(s): 6 study centers in the United States	
Study period: Date first patient enrolled: 04/Oct/2011 Date last patient completed: 27/Dec/2012	
Phase of development: Phase 2a	
Objectives: *Primary objective:* To determine the pharmacokinetics (PK) of a single intravenous (IV) dose of SAR279356 administered to intensive care unit (ICU) patients on mechanical ventilation at the time of randomization. *Secondary objectives:* • To determine the safety and tolerability up to Day 90. • To evaluate the pharmacodynamics (PD) by the opsonophagocytic assay and opsonophagocytic killing assay. • To assess the immunogenicity by the human anti-human antibodies (HAHA). • To explore up to Day 28 efficacy of prevention of infections caused by poly-N-acetylglucosamine (PNAG)-expression pathogens. • To explore the duration of mechanical ventilation, ICU stay, hospital stay, 28-day and 90-day all-cause mortality.	
Methodology: Multinational, multicenter, parallel, randomized, double-blind, placebo-controlled	
Number of patients: Planned: 36 Randomized: 7 Treated: 6 Evaluated: Safety: 6 Pharmacokinetics: 4 (excluding 2 placebo patients)	
Diagnosis and criteria for inclusion: ICU patients on mechanical ventilation at the time of randomization	

Study treatments

Investigational medicinal product(s): SAR279356

Formulation: Concentrate solution for infusion: liquid at a concentration of 17.0 mg/mL

Route of administration: IV infusion administration in 250 mL of normal saline (0.9% sodium chloride [NaCl]) over 2 hours for both dose regimens

Dose regimen: Single administration of 8.6 mg/kg or 12.9 mg/kg

Investigational medicinal product(s): Placebo

Formulation: Saline solution (0.9% NaCl)

Route of administration: IV infusion of 250 mL over 2 hours

Dose regimen: Single administration

Duration of treatment: 2 hours

Duration of observation: 91 days (Screening: 1 day prior to dosing; Treatment period: one IV injection on Day 1; Follow-up: 90 days)

Criteria for evaluation:

Pharmacodynamics:

Primary Endpoint:

- Not applicable

Secondary Endpoint(s):

- Pharmacodynamic: opsonic titers over time.
- Immunogenicity: Human anti-human antibody (HAHA)
- Exploratory efficacy: Documented infections caused by Poly-N-Acetyl glucosamine (PNAG) expression pathogens up to Day 28.
- Exploratory efficacy: Duration of mechanical ventilation, ICU stay, hospital stay, 28-day, and 90-day all-cause mortality.

Safety: Acute infusion reactions, treatment-emergent adverse events (TEAEs) up to Day 90 and standard hematology and blood chemistry, blood cultures and endotracheal aspirate (ETA) cultures (for patients under mechanical ventilation).

Pharmacokinetics (Primary endpoint): the following PK parameters were calculated for SAR279356 using a non-compartmental method: Serum concentration at the end of infusion (C_{eoi}), area under the serum concentration versus time curve from time 0 to the real time t_{last} (AUC_{last}), time of last measured serum concentration (t_{last}), area under the serum concentration versus time curve extrapolated to infinity (AUC), terminal half-life ($t_{1/2z}$), total body clearance of a drug from the serum (CL), and volume of distribution at steady state (V_{ss}).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

PK:

- Sampling times: Blood samples were collected at predose, 1 hour, 2 hours (end of infusion), and 8 hours on Day 1, then on Days 2, 5, 7, 14, 21, 28, 56, 70, and 90 postdose.
- Bioanalytical methods: Serum concentrations of SAR279356 were determined by a validated enzyme-linked immmunosorbent assay with a lower limit of quantification of 0.0858 µg/mL.
- HAHA.
- Sampling times: Blood samples were collected at predose, then on Days 14, 28, 56, and 90 postdose.
- Bioanalytical methods: Serum HAHA was detected by a validated electrochemiluminescence immunoassay.

PD:

- Sampling times: Opsonophagocytic test (OPA): Day 1: Predose, 2 hours (end of infusion), Days 2, 7, 14, 28, 56, and 90; Killing test (OPK) samplings: Day 1: Predose, 2 hours (end of infusion), Day 14, Day 28, and Day 90.
- Bioanalytical methods OPA: Matrix: serum/Analytical technique: OPA/Lower limit of quantification: NA/Assay volume: NA/Site of bioanalysis: Flowapps/Method of reference: FA-440.
- Bioanalytical methods OPK: Matrix: serum/Analytical technique: OPA/Lower limit of quantification: NA/Assay volume: NA/Site of bioanalysis: Flowapps/Method of reference: FA-445.

Statistical methods:

- The primary analyses were summaries of PK variables (C_{eoi}, AUC_{last}, AUC, CL, V_{ss}, $t_{1/2z}$, and t_{last}) using descriptive statistics by dose. The analyses were based on the PK population consisting of all randomized patients with a least one PK-evaluable data.
- The safety population was defined as all patients who were randomized and administrated with infusion of the study medication regardless whether the infusion was completed or not. Safety data were summarized by the actual treatment or dose received, unless indicated otherwise. Adverse event incidence tables were presented by actual treatment or dose received system organ class (SOC) and preferred term.

Summary:

Population characteristics: Due to premature discontinuation of the study related to a very slow enrollment rate, a total of 7 patients were randomized out of the 36 planned. One patient did not receive the investigational medicinal product (IMP) because he was finally considered as noneligible for the study before receiving the IMP (meeting of at least one exclusion criterion). Overall, 6 patients received the IMP infusion: 2 received the placebo, 2 received 8.6 mg/kg SAR279356, and 2 received 12.9 mg/kg SAR279356. Only the patients who were administered the IMP infusion were considered for PK, safety, and other exploratory assessments. Since the number of patients is very small, only descriptive data are given. No PK or safety conclusion can be derived from this small data.

Pharmacodynamic results: Results are available upon request.

Safety results:

At least one TEAE was reported for all 6 patients. Most of the TEAEs were found in the "infections and infestations" SOC.

Three treatment-emergent serious adverse events (SAEs) were reported in 1 patient in the placebo group (cholecystitis, septic shock, urinary tract infection bacterial). One treatment-emergent SAE was reported in 1 patient in the 8.6 mg/kg SAR279356 group (swelling face). Six treatment-emergent SAEs were reported in 2 patients in the 12.9 mg/kg SAR279356 group (respiratory failure in 1 patient and pneumonia, sepsis, septic shock, respiratory failure, haematuria traumatic in 1 patient). None of the SAEs were judged as related to the IMP by the Investigator or the Sponsor.

No death or TEAE leading to permanent treatment discontinuation was reported during the study.

No acute infusion reaction-related event was reported in this study.

One patient in the 8.6 mg/kg SAR279356 group had an increase in alanine transaminase (ALT) resulting in an ALT >3 x ULN (4.2 x ULN), secondary to cytomegalovirus hepatitis and not related to the IMP.

One patient in the placebo and 12.9 mg/kg SAR279356 groups had at least one SAE related to infections and infestations, and none in the 8.6 mg/kg SAR279356 group.

No immunogenicity to SAR279356 was evidenced as no serum HAHA was detected in any patient in this study.

Pharmacokinetic results:

SAR279356 PK parameters after single IV doses are summarized in the following table.

Individual values of SAR279356 pharmacokinetic parameters (N=2/treatment)

Parameter	8.6 mg/kg	12.9 mg/kg
C_{eoi} (µg/mL)	147, NC [b]	268,184
t_{last} [a] (h)	643-1920	312-1410
AUC_{last} (µg.h/mL)	50600, 56800	27900, 67000
AUC (µg.h/mL)	69200, 71900	78000, NC [c]
$t_{1/2z}$ (h)	353, 632	275, 585
CL (mL/h/kg)	0.12, 0.12	0.17, NC [c]
V_{ss} (mL/kg)	61.0, 96.8	107, NC [c]

[a] range; PK samples were not collected beyond time point corresponding to t_{last} whereas it was planned to collect them up to Day 90 (T2160 h);

[b] Not calculated, due to no sampling at the end of infusion in one subject

[c] Not calculated, due to AUC extrapolation >30% in one subject

All values are expressed to three significant figures

Issue date: 24-Nov-2014