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Sponsor: Sanofi	**Study Identifiers:** U1111-1124-1425, 2011-005481-37, NCT01529853
Drug substance: Romilkimab	**Study code:** TDR11326

Title of the study:

Randomized, double-blind, placebo-controlled study of the safety, tolerability, pharmacokinetics and pharmacodynamics of ascending repeated doses of SAR156597 in patients with idiopathic pulmonary fibrosis (IPF)

Study centers: 12

Study period:

Date first participant enrolled: 09/Jan/2012

Date last participant completed: 15/Oct/2013

Study Status: Completed

Phase of development: 1b/2a

Objectives:

Primary: To assess in patients with IPF the safety and tolerability of ascending doses of SAR156597 administered subcutaneously (SC) once weekly over a 6-week period.

Secondary: To assess in patients with IPF:

- The pharmacodynamic effects of SAR156597, as measured on pulmonary function tests, pulse oximetry, patient reported outcome, and biomarkers isolated from peripheral blood
- The trough plasma concentrations of SAR156597
- The potential immunogenicity of SAR156597

Methodology:

Randomized, double-blind, placebo-controlled, 6 weeks, repeated doses ascending in 3 sequential cohorts of patients with IPF.

Number of participants:

Planned: 24

Randomized: 24

Treated: 24

Evaluated:

pharmacodynamics: 24

Safety: 24

Pharmacokinetics: 17 patients who completed the study treatments and 6 placebo patients

Diagnosis and criteria for inclusion:

Documented diagnosis of IPF according to the current ATS/ERS/JRS/ALAT guidelines and over 18 years of age

Study Products

Investigational medicinal product(s): SAR156597

Formulation: SAR156597 in lyophilized form (each vial containing 185 mg of SAR156597 plus excipients, reconstituted with sterile, nonpyrogenic distilled water to achieve a final concentration of 100 mg/mL of SAR156597)

Route(s) of administration: Subcutaneous

Dose regimen:

- Cohort 1 SAR156597 dose 1 or placebo once weekly
- Cohort 2 SAR156597 dose 2 or placebo once weekly
- Cohort 3 SAR156597 dose 3 or placebo once weekly

Duration of treatment: Six weeks

Duration of observation: Up to 22 weeks

Criteria for evaluation:

Safety:

Safety and tolerability as measured on:

- Adverse events (AEs)/treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs)/adverse events of special interests (suspicion of vasculitis [based on nonclinical data], ALT increase, increase in cardiac troponin I, prolongation of QTc, injection site reaction, overdose, and pregnancy)
- Standard hematology and blood chemistry, and autoimmune/inflammatory markers, when indicated;
- Physical examination, vital signs, and 12-lead electrocardiogram;
- Tolerability at the investigational medicinal product (IMP) injection site;
- Immunogenicity:

  Testing for anti-drug antibodies (ADA).

Pharmacokinetics:

SAR156597 trough plasma concentrations (C_{trough}) and plasma concentrations at selected timepoints after the last dose. Predicted C_{max}, t_{max}, $t_{1/2z}$, and AUC_{0-168} by pharmacokinetic of population approach.

Pharmacodynamics:

- Pulmonary function test parameters including FVC, forced expiratory volume over 1 second (FEV1), total lung capacity (TLC), DLCO (corrected for hemoglobin), and residual volume (RV).
- Oxygen saturation by pulse oximetry (SpO2, %)
- Impact on quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ)
- Biomarkers from peripheral whole blood:

  Protein biomarkers: Biomarkers including but not limited to Chemokine (C-C motif) ligand 18 (CCL18), Krebs von den Lundgen-6 (KL-6), surfactant protein A (SP-A), and surfactant protein D (SP-D), mammalian chitinase-like protein (YKL-40), Interleukin 4 (IL-4), Interleukin 13 (IL-13), Interleukin 8 (IL-8), immunoglobulin E (Ig-E), inter-cellular adhesion molecule 1 (ICAM1), periostin, and eotaxin (CCL11)

  RNA biomarkers: Messenger- and micro-RNAs

DNA biomarkers: Blood DNA for pharmacogenomics

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Samples for pharmacokinetic analysis were collected at predose (within 2 hours before each dose administration) during Visits 2 (predose first administration) to 8 (predose of last administration). Pharmacokinetics samples during Visits 9, 11, and 14 were collected in the morning. Samples for ADA analysis were collected during Visit 2 (predose of first administration) then on Visit 8 (predose last administration), Visit 11, and Visit 14. Pharmacokinetic assay: SAR156597 plasma concentrations were determined using a validated enzyme linked immunosorbent assay (ELISA) method (DOH0850) with a lower limit of quantification (LLOQ) of 0.05 µg/mL. ADA assay: immunogenicity testing for anti-drug antibodies (ADA) in plasma was performed using a validated ELISA method (DOH0851). All samples were first evaluated using a screening assay. Samples found to be positive in the screening assay were then tested in a confirmatory assay followed by titer determination.

Two pulmonary functions tests (PFTs) were performed within 3 weeks prior to dosing. The first PFT was performed to screen the patient and the data from the second PFT was averaged with the first one to establish a baseline value; these tests were performed on separate days. A PFT was also performed at Visit 8 (Week 6/end of treatment [EOT]) and Visit 14 (Week 18/12 weeks following the last dose of study treatment).

Oxygen saturation was assessed using pulse oximetry (SpO2) at screening, baseline, at Week 6/ET, and at Week 18 (12 weeks following the last dose of study treatment). The first pulse oximetry measurement was performed at the screening and the data from the second measurement was averaged with the first one to establish a baseline value; these tests were performed on separate days.

Impact of IPF on quality of life was assessed using the SGRQ at baseline, at Week 6/EOT, and on Week 18 (12 weeks following the last dose of study treatment).

Selected biomarkers from whole blood were assessed at screening, baseline, Week 6/EOT, and at the end of the follow-up period (Week 18). Serum and plasma samples were collected at screening, baseline (prior to first dosing), Week 6/EOT, and at the end of the follow-up period (Week 18). All samples were analyzed at the designated central laboratories by following the laboratory manuals.

Statistical methods:

Safety:

The safety analysis was based on the review of descriptive statistics (summary tables) and individual data for adverse events, clinical laboratory, vital signs, and ECG parameters. The on-treatment period was defined as the time from the first dose of IMP administration up to the Week 18 visit. Adverse events were coded using Medical Dictionary for Regulatory Activities version 16.1, and the number of patients with TEAEs was summarized by treatment. Potentially clinically significant abnormalities (PCSAs; definitions according to version dated 14 September 2009) for clinical laboratory, vital signs, and ECG data were flagged and summarized in frequency tables by treatment. Supplementary tests for vasculitis were performed at baseline and then at postdose only for patients exhibiting hsCRP >10 mg/L and >2x baseline value for $\geq$72 hours. Tolerability at the IMP injection site was summarized by treatment group.

Pharmacokinetics:

Assayed SAR156597 C_{trough} concentrations and predicted C_{max}, $AUC_{0\text{-}168h}$, and $t_{1/2z}$ were summarized by descriptive statistics.

Prior to all statistical analyses, C_{max}, $AUC_{0\text{-}168h}$, and $t_{1/2z}$ were log-transformed. The occurrence of steady state was assessed by fitting C_{trough} values with a non-linear mixed effects model. Dose effect for $t_{1/2z}$ was assessed with a linear fixed effect model. Dose proportionality for C_{max} and $AUC_{0\text{-}168h}$ was assessed using a power model.

Pharmacodynamics:

The change from baseline in PFT parameters on Week 6 and Week 18 was analyzed using a linear mixed effects model with fixed

terms for treatment, time, sex, treatment-by-time as fixed terms, and patient as random effects including the respective baseline values of PFTs as covariate. Mean estimates and confidence interval [CI]) of pairwise comparisons at each time-point were obtained within the mixed model framework. The same analysis was also performed for each component and total score of SGRQ and SpO2 using change from baseline.

All pharmacodynamic parameters were summarized using descriptive statistics by treatment group and by time of measurement. Summary plots are provided for each parameter.

Summary Results:

Population characteristics:

Overall, 24 patients (8 patients per cohort: 6 patients on active and 2 patients on placebo) were randomized and treated with SAR156597 or placebo and represented the safety population.

Patients across treatment groups have comparable baseline demographic and disease characteristics, most were Caucasian, male, and former smokers, with ages between 45 and 81 years old. Across treatment groups, mean baseline carbon monoxide diffusion capacities (DLco) were approximately 50% of predicted, and mean forced vital capacities (FVC) were around the mid-70% of predicted, consistent with mild to moderate impaired lung function. All patients have definite or possible usual interstitial pneumonia (UIP) pattern on either high resolution computed tomography (HRCT) or histopathology from surgical lung biopsy. All were confirmed by the investigators to have disease characteristics consistent with IPF diagnosis.

Safety:

All patients completed the 6-week treatment period with the exception of 1 patient in the SAR156597 SC weekly dose 2 group who had to be discontinued from study treatment after the administrations of 3 doses of study drug due to an SAE of tuberculosis.

The number of patients with at least 1 TEAE was comparable among the treatment groups (5 of 6 patients in the placebo and dose 3 groups, 6 of 6 patients in the dose 1 and dose 2 groups); most TEAEs were mild to moderate in intensity. The most common reported TEAE was infections, which was balanced among the treatment groups (3 of 6 patients in the placebo, dose 1, and dose 3 groups, 2 of 6 patients in dose 2 group). Serious adverse event (SAE) was reported in 3 patients, 1 in each of the 3 SAR156597 dose groups (1 patient with SAEs of fall and femur fracture in the dose 1 group, 1 patient with SAE of tuberculosis in the dose 2 group, and 1 patient with SAE of pneumonia bacterial in the dose 3 group).

There was no death reported at any time of the study period. None of the potentially clinically significant abnormalities (PCSAs) from the hematology and biochemistry laboratory results, vital signs, and electrocardiogram (ECG) were associated with any clinical manifestations. While there were more patients with QTcB prolonged in the active treatment groups, this was not consistently observed when the QT interval was corrected with the Fridericia method. None of the QTcB or QTcF prolongations were associated with any clinical manifestations, and none were considered clinically significant. Although only patients on active treatments had measured orthostatic blood pressures, the total sample size was relatively small in all treated groups, and all patients with orthostatic blood pressures were on concomitant medications that could have contributed to the orthostatic findings. Furthermore, given the general older age of the study population and various medical co-morbidities in many of these patients, this was not unexpected.

In general, elevated hsCRP level was a nonspecific marker of inflammation that could be due to a wide variety of causes and has not been validated as a measure for diagnosis or screening of vasculitis. Most of the abnormal values of hsCRP measured during the study were only mild or moderately elevated, and were either of no clinical consequence or were uninterpretable in the context of this generally older study population that has multiple medical co-morbidities that might have contributed to the elevations in hsCRP. All patients with transient elevations of hsCRP were either associated with clinical events, such as

infections (which occurred in 3 of the 4 cases of adverse events of special interests related to suspicions for vasculitis), or were judged to be not clinically relevant by the investigators. There were no confirmed cases of vasculitis in this study.

Overall, the 3 doses of SAR156597 were generally safe and well tolerated.

Pharmacokinetic:

All 18 patients randomized to SAR156597 were exposed to SAR156597 and 17 patients were eligible for PK evaluation. No SAR156597 was detected in plasma from the 6 placebo patients. Bayesian pharmacokinetic analysis predicted that 89% to 94.8% of steady state was reached after 7 doses of SAR156597 on Week 6. The $t_{1/2z}$ ranged between 260 hours (approximately 11 days) to 348 hours (approximately 15 days) with unexpected significant dose effect on $t_{1/2z}$ (p=0.049). On Week 1 and on Week 6, SAR156597 exposure increased slightly more than dose proportionally. A 4-fold increase in SAR156597 dose demonstrated a 5.21- to 5.92-fold increase in C_{max} and a 5.17- to 5.83-fold increase in $AUC_{0\text{-}168}$. No significant treatment-emergent ADA reactivity developed as a consequence of treatment with SAR156597.

No significant treatment-emergent ADA reactivity developed as a consequence of treatment with SAR156597. Post-treatment ADA status of 1 patient from the dose 3 cohort is unknown, as no ADA samples were collected from this patient.

Pharmacodynamics:

There are insufficient data from this study to draw any definitive conclusions on all the pharmacodynamic assessments. However, an indication of SAR156597 dose related expression of TARC (CCL-17) could confirm the IL-4/IL-13 target engagement.

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