SYNOPSIS

Title of the study: A randomized, double-blind, parallel-group, placebo- and active calibrator-controlled study assessing the clinical benefit of SAR153191 subcutaneous (SC) on top of methotrexate (MTX) in patients with active rheumatoid arthritis (RA) who have failed previous TNF-α antagonists (ACT11575)

Coordinating Investigator: [redacted]

Study centers: 10 active centers in North and South America and Europe

Publications (reference): None

Study period:

Date first patient enrolled: 15/Nov/2010

Date last patient completed: 15/Sep/2011

The study was discontinued as a result of the delays incurred in the study and impact to timelines for completing the study. At time of study discontinuation, 16 patients had been randomized, of whom 13 completed the study as planned per protocol and 3 discontinued. No efficacy analyses were performed due to insufficient data as a result of the low enrollment relative to the initially planned study sample size. Safety analyses were performed as planned in the statistical analysis plan and the results are presented through a synopsis-style report.

Phase of development: 2

Objectives:

Primary objective

- To demonstrate that SAR153191 (sarilumab) on top of methotrexate (MTX) is superior in efficacy to placebo, for the relief of signs and symptoms of RA, in patients with active RA who have failed up to 2 tumor necrosis factor α (TNF-α) antagonists

Secondary objectives

- To assess the safety of sarilumab;
- To document the pharmacokinetic profile of sarilumab.

Methodology: This was a multicenter, multinational, randomized, double-blind, parallel group, placebo-and active calibrator-controlled study intending to compare the efficacy and safety of sarilumab subcutaneous (SC) with placebo on top of MTX in patients with active RA who had failed previous TNF-α antagonists. Golimumab, an anti-TNF-α monoclonal antibody, was to be used as the active calibrator. Eligible patients were to be centrally randomized via an interactive voice response system in a 2:1:2 ratio to one of the 3 treatment groups (sarilumab 150 mg/2 mL weekly + placebo 0.5 mL every 4 weeks; matching placebo 2 mL weekly + placebo 0.5 mL every 4 weeks; matching placebo 2 mL weekly + golimumab 50 mg/0.5 mL every 4 weeks) and treated double-blind for approximately 12 weeks. Randomization was stratified by region and by the number of prior anti-TNF-α biologic agents. All patients were to continue to receive MTX as background therapy.

Patients who completed the 12-week treatment period were offered enrollment in a separate long-term extension study (LTS11210).

Number of patients:

Planned: Approximately 250 patients (100 patients in the sarilumab arm; 50 patients in the placebo arm; 100 patients in the active calibrator arm)

Randomized: 16 Treated: 16 Efficacy: NA Safety : 16 Pharmacokinetics : 16

Diagnosis and key criteria for inclusion: Male and female patients between 18 and 74 years of age inclusive with moderate-to-severe active RA for at least 6 months and American College of Rheumatology (ACR) Class I-III functional status at screening and baseline, with continuous treatment with MTX for at least 12 weeks prior to screening and on stable dose for at least 6 weeks prior to the screening visit, and who were primary TNF-α blocker nonresponders (up to 2 agents).

Investigational medicinal product: sarilumab

Formulation: vials (75 mg/mL), 2 mL

Dose: 150 mg weekly (qw) (or 150 mg every other week if dose reduced)

Administration: SC in abdomen, injection volume 2.0 mL

Batch number: [redacted]

Investigational medicinal product: golimumab (Simponi®)

Formulation: Prefilled syringe (50 mg/ 0.5 mL)

Dose: 50 mg every 4 weeks (q4w)

Administration: SC in abdomen, injection volume 0.5 mL

Batch numbers: [redacted]

Duration of treatment: 12 weeks

Duration of observation: 22 weeks, including screening, a 12-week treatment period, and a 6-week posttreatment observation

Reference therapy: placebo (matched for sarilumab)

Formulation: vials, 2 mL

Dose: Not applicable

Administration: SC in abdomen, injection volume 2.0 mL

Batch numbers: [redacted]

Noninvestigational medicinal product:	methotrexate	folic acid
Formulation:	2.5 mg tablet or 10 mg/ 5 mL (liquid)	1 mg or 2.5 mg (tablet)
Dose:	15 to 25 mg qw (≥10 mg qw, minimum based on tolerability)	5 to 7 mg per week (or as per regional prescribing practice)
Administration:	Oral (tablet) or SC, intramuscular (liquid)	Oral
Batch number(s):	Not applicable	Not applicable

Criteria for evaluation:

Safety was to be assessed throughout the study, by recording of adverse events (AEs), and by clinical and laboratory (biochemistry, hematology, anti-nuclear antibody/ anti-double-stranded DNA antibody**,** and urinalysis) examinations, vital signs (including temperature, blood pressure, heart rate) and electrocardiogram (ECG), at selected visits.

Blood samples for clinical laboratories were taken at Visits 1 to 7, and vital signs were collected at Visits 1 to 8. ECGs were performed at screening and at the end-of-treatment visit. Additional blood samples were taken at various specified time-points to measure sarilumab concentrations, anti-sarilumab antibody, C-reactive protein, interleukin-6 (IL-6), and soluble IL-6 receptor.

Statistical methods:

The baseline value was defined as the last available value prior to the first dose of the study medication.

Demographic characteristics and disease characteristics at baseline were summarized by treatment group on the randomized population, which included all patients who had been allocated to a randomized treatment.

All medications taken within a certain period of time before randomization and until the end of the study were coded using the World Health Organization-Drug Dictionary Version 2011MAR. These medications were reported as prior medications (used prior to first investigational medicinal product [IMP] intake) and concomitant medications (received by the patient concomitantly to the/any IMP, from the first IMP intake to the end of the follow-up period), which were summarized by treatment group.

The extent of IMP exposure and compliance were assessed and summarized by actual treatment group within the safety population (included all randomized patients who received at least one dose of the study medication).

Duration of study treatment exposure was defined as: last dose (injection) date – first dose (injection) date + 7/28 day (7 days for placebo and sarilumab treatment patients, 28 days for golimumab treatment patients), regardless of unplanned intermittent discontinuations.

Percentage of compliance for a patient was defined as the number of administrations (injections) the patient was compliant divided by the total number of administrations (injections) the patient was planned to take during the treatment period (ie, from the first to the last administration).

Safety

Safety data were analyzed descriptively by treatment group using the safety population, which included all randomized patients who received at least one dose of the study medication. All patients were analyzed according to the treatment which they actually received. The analyses mainly focused on AE data and the potentially clinically significant abnormality (PCSA) values, which were defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, vital signs and ECG (PCSA version dated January 2009).

The same observation period was used for all safety observations defined as follows:

- Screening observation period was defined as the time from signed informed consent to randomization, and;
- Treatment emergent adverse event (TEAE) observation period was defined as the time from first dose of IMP up to the end of the follow-up period (Visit 8, Week 18), for patients not electing to enter the extension study and up until randomization (first dosing) in the extension study for patients electing to participate.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0).

Adverse events were classed as follows:

- Pretreatment AEs are AEs that developed or worsened or became serious from the signed informed consent date up to first dose of IMP;
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the TEAE observation period.

Adverse events requiring prespecified monitoring (AEPM) were adverse events (serious or nonserious) that needed to be monitored, documented, and managed in a prespecified manner described in the protocol. The following adverse events required prespecified monitoring: opportunistic infections including but not limited to herpes zoster infection, confirmed diverticulitis and gastrointestinal perforation, systemic hypersensitivity reactions or anaphylaxis, autoimmune or lupus-like syndrome, drug-induced liver injury, neutropenia, thrombocytopenia, neurological disorders, pregnancy, overdose.

AEPMs could have been reported by the Investigator or identified by the Sponsor through searches using specific event terms. Following identification of these cases, further medical review identified relevant terms to include in the list of AEPMs.

All AEs (including serious adverse events and AEPMs were coded to a “Lower Level Term (LLT)”, “Preferred Term (PT)”, “High Level term (HLT)”, “High Level Group Term (HLGT)” and associated primary “System Organ Class (SOC)”.

For clinical laboratory, vital sign, and ECG parameters, PCSAs observed during the TEAE observation period were flagged and summarized for each treatment group, irrespective of baseline level and/or according to the baseline status.

Summary:

Patient disposition

Of 41 screened patients, 25 were screen failures (61%) and 16 were randomized and treated in the study: 4 in the placebo group, 5 in the golimumab 50 mg q4w group, and 7 in the sarilumab 150 mg qw group. Three patients did not complete the treatment period: 1 patient each in the placebo and golimumab groups discontinued due to AE, and 1 patient in the sarilumab group discontinued due to lack of efficacy. Four of 7 patients in the sarilumab group and 3 of 5 patients in the golimumab group rolled over to the long-term extension study versus 0 of 4 patients in the placebo group. Further information on patient disposition can be found in (appendix reference not disclosed).

There were no randomization or dosing irregularities. However, 6 patients had protocol deviation concerning inclusion/exclusion criteria.

Demographic and baseline characteristics

Randomized patients were mostly female (14 of 16 patients, 87.5%), Caucasian (9 of 16, 56.3%), and less than 65 years old (12 of 16, 75%). The mean (standard deviation [SD]) duration of RA at baseline was 6.75 (4.39) years in the placebo group, 4.41 (4.87) years in the golimumab group, and 16.27 (10.22) years in the sarilumab group. Almost half the patients had Class II RA (7 of 16, 43.8%) and half Class III RA (7 of 16, 43.8%), and most were positive for rheumatoid factor (11 of 16, 68.8%) or anti-cyclic citrullinated protein (13 of 15, 86.7%), and had not previously used a disease-modifying anti-rheumatic drug other than MTX (14 of 16, 87.5%). All patients took concomitant MTX and most patients took concomitant folic acid, as planned in the protocol. Further information on patient demographic and baseline characteristics as well as prior and concomitant medication can be found in (appendix reference not disclosed).

Safety

The safety population included all 16 randomized and treated patients. Treatment compliance was 100% in the placebo and golimumab groups, and 98.1% in the sarilumab group. The mean (SD) duration of study treatment was 67.8 (31.2) days in the placebo group, 75.8 (27.5) days in the golimumab group, and 82.9 (13.8) days in the sarilumab group.

No serious adverse events were reported during the study. There were 2 treatment discontinuations due to AE: 1 in the placebo group due to TEAE (urticaria) and 1 in the golimumab group due to pretreatment AE (grade 3 neutropenia) (see patient narratives in 15.3.3-narratives). Overall, TEAEs were reported in 3 of 4 patients in the placebo group, 1 of 5 patients in the golimumab group, and 3 of 7 patients in the sarilumab group. There were no investigator-reported AEPMs, but clinical review by the Sponsor based on MedDRA terms identified 4 potential AEPMs: 1 event of urticaria in the placebo group (as mentioned above), 2 events of asymptomatic accidental overdose (defined as at least twice the dose during less than a 6-day interval), 1 each in the placebo and sarilumab groups, and 1 event of increased transaminases less than 3 x upper limit of normal [ULN] with normal bilirubin, in the sarilumab group; only the event of urticaria qualified as an AEPM.

A summary of the number (%) of patients with TEAE(s) by primary system-organ class and preferred term is provided in (appendix reference not disclosed). In the placebo group, 1 patient had urticaria, 1 had nasopharyngitis, and 1 had urinary tract infection, sinusitis and accidental overdose. In the golimumab group, 1 patient had diarrhea, vomiting, and dermatitis. In the sarilumab group, 1 patient had influenza, muscle spasm, and application site reaction (erythema); 1 patient had hypertension, cough, chills, and increased transaminases (less than 3 x ULN); and 1 patient had accidental overdose. All TEAEs were mild with the exception of urticaria, which was moderate.

Across all treatment groups, few PCSAs were reported for hematology parameters. One of 7 patients in the sarilumab group had neutrophils <1.5 Giga/L (grade 2 neutropenia) versus none in the placebo and golimumab groups. The patient was found to have decreased neutrophil count at 1.32 Giga/L at Visit 4 versus 6.55 Giga/L at baseline, and which returned to normal at the next visit with no interruption to dosing.

For liver function tests, 3 of 7 patients in the sarilumab group were found to have PCSAs in alanine aminotransferase and aspartate aminotransferase (values between 1 and 3 x ULN) versus 1 of 5 patients in the golimumab group and none in the placebo group.

For metabolism tests, 4 of 7 patients in the sarilumab group had PCSAs in total cholesterol with values increasing to ≥6.2 and <7.74 mmol/L and 1 of 7 had total cholesterol ≥7.74 mmol/L. Also in the sarilumab group, 3 of 7 patients had PCSAs in low density lipoprotein (LDL) ≥4.1 mmol/L. All patients with postbaseline PCSAs had normal or missing values at baseline, except for the patient with total cholesterol ≥7.74 mmol/L who had elevated values at baseline. No PCSAs in total cholesterol or LDL were observed in the placebo and golimumab groups. In the sarilumab group, 2 of 4 patients with normal values for creatinine clearance

at baseline had transient PCSA at ≥ 50 - ≤ 80 mL/min (73.06 and 79.67 mL/min) versus 1 of 3 patients in the golimumab group (77.99 mL/min) and none in the placebo group.

There were no clinically significant abnormalities in vital signs or ECGs across treatment groups (appendix reference not disclosed).

None of the patients were positive for anti-sarilumab antibodies during the study (appendix reference not disclosed).

Based on the limited available data for autoantibodies (ie, anti-nuclear antibody and anti-double-stranded DNA antibody), no seroconversion was observed in any of the treatment arms (including sarilumab) of the ACT11575 study during the study treatment period (appendix reference not disclosed).

Listings of C-reactive protein, interleukin-6 (IL-6), and soluble IL-6 receptor data are presented in (appendix reference not disclosed).

Pharmacokinetics

Listings of serum sarilumab concentrations are provided in (appendix reference not disclosed). Due to the limited number of blood samples collected in this study, no meaningful pharmacokinetic analysis could be performed.

Overall conclusion

[redacted]

Date of report: 02-Feb-2012