SYNOPSIS

Title of the study:	A randomized double blind placebo controlled dose ranging study to evaluate the efficacy and safety of SAR153191 in patients with Ankylosing Spondylitis (AS)
Investigator(s):	[redacted]
Study center(s):	68 study centers in Europe, Canada, and the United States
Publications (reference):	None
Study period:	
Date first patient enrolled:	04 Feb 2010
Date last patient completed:	21 Jun 2011
Phase of development:	Dose ranging (Phase 2)

Objectives:

Primary:

To evaluate the efficacy by ASAS20 (Assessment in Ankylosing Spondylitis Working Group responses criteria) of SAR153191 in patients with AS at Week 12 and to define the best dose/dosage regimen for further development

Secondary

The secondary objectives were:

- assessment of higher level of response ASAS40
- ASAS partial remission
- disease activity (BASDAI) at Week 12
- range of motion assessed by (BASMI) (11-point scale)
- Ankylosing Spondylitis Disease Activity Score (ASDAS)
- safety and tolerability of SAR153191 in patients with AS
- to document PK profile of SAR153191 in patients with AS
- MRI of the spine

Note: A typographical error in the secondary objective "range of motion assessed by (BASMI) (10-point scale)" was inadvertently overlooked in the protocol. In fact, the BASMI is based on an 11-point scale and has been corrected for this Abbreviated Clinical Study Report.

Exploratory

To collect DNA blood sample for the purpose of discovery; and serum sample for the purpose of biomarkers discovery

Methodology: This was a multicenter, multinational, double-blind, placebo-controlled, randomized, parallel-group, 12-week study in patients with active AS. Patients were randomized in a ratio of 1:1:1:1:1:1 (5 SAR153191 [sarilumab], 1 placebo), and stratified according to screening high-sensitivity C-Reactive Protein (CRP [≤1.5 mg/dL or >1.5 mg/dL]) and region as stratification factors.

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

Number of patients:	Planned: 300 (50 patients per arm with a randomized ratio of 1:1:1:1:1:1)
	Randomized: 301 patients
	Treated: 300 patients

	Efficacy: 301 patients
	Safety : 300 patients Pharmacokinetics :151 patients
Diagnosis and criteria for inclusion: Male and female patients between 18 and 74 years of age inclusive, with active AS for at least 3 months, with Bath AS Disease Activity Index and total back pain score ≥4 at screening and baseline, without complete fusion of the spine, and who were not responding adequately to, or were intolerant of, nonsteroidal anti-inflammatory drug**.**	
Investigational product: SAR153191 50 mg/mL, 75 mg/mL, or 100 mg/mL Dose: 100 mg or 150 mg of SAR153191 weekly (qw) OR 100 mg every other week (q2w [alternating with placebo]), 150 mg q2w (alternating with placebo), or 200 mg q2w (alternating with placebo) Administration: Subcutaneously, administered in a single injection Batch numbers: [redacted]	
Duration of treatment: 12 weeks **Duration of observation:** 22 weeks: up to 4 weeks screening, 12-week double-blind treatment period, and 6-week follow up	
Reference therapy: placebo for SAR153191 (matched placebo) Dose: Matching placebo 2 mL (to 100 or 150 mg SAR153191) q2w OR Matching placebo 2 mL qw (alternating with SAR153191 100 mg, 150 mg, or 200 mg) OR Placebo qw for 12 weeks Administration: Subcutaneously, administered in a single injection Batch numbers: [redacted]	
Criteria for evaluation: The current report is an abbreviated report, and as such, only the safety results are being presented in full. Only partial efficacy results are presented. The following safety criteria were evaluated, and analyzed using descriptive statistics: • adverse events reported by the subject or noted by the Investigator Note: Adverse events with prespecified monitoring (AEPM) were defined in the protocol and were reported by the Investigator in the e-CRF. Additional adverse events that should have been reported as AEPMs were identified through searches that were based on Standard MedDRA Query (SMQ) or modified SMQ (if standard not available), and/or prespecified event terms. Further medical review identified additional relevant terms to include in the list of AEPMs. • clinical laboratory parameters • 12-lead electrocardiograms (ECGs) • vital signs.	
Statistical methods: **Efficacy:** The primary efficacy variable was analyzed using the 2-sided Cochran-Mantel-Haenszel test, stratified by screening CRP and region, using the intent-to-treat population, which included all randomized patients. Pair-wise comparisons of the response rates and the 95% confidence interval (CI) for the odds ratios between each dose of sarilumab and placebo were derived by testing each active dose group versus placebo separately. The Mantel-Haenszel estimate of the odds ratio and the corresponding 95% CI were derived by testing each active dose group versus placebo separately. A last	

observation carried forward (LOCF) procedure was used to impute any missing AS International Working Group Criteria for Improvement (ASAS20) components for patients who missed at least 1 ASAS component at Week 12. However, patients who discontinued study treatment due to lack of efficacy before Week 12 were considered as nonresponders.

Safety: Safety analyses were performed on the safety population. Safety summaries were descriptive and no hypothesis testing was conducted**.**

The primary focus of adverse event reporting was on treatment-emergent adverse events (TEAEs). Summary of TEAEs was based on MedDRA coding of verbatim terms reported by the Investigators. Treatment-emergent adverse events were defined as any adverse event that was newly developed or worsened or became serious on or after the day of the first dose of study drug, up to the end of study. Adverse events with prespecified monitoring, as defined in the protocol, were summarized by treatment group. For the laboratory tests, vital signs, and ECG, incidences of potentially clinically significant abnormal (PCSA) values were summarized by treament group. The number of patients with neutropenia was listed by maximum grade during the TEAE period for each treatment group. The group means of absolute neutrophils counts (ANC) with standard error bars, were displayed graphically over time.

Summary:

Efficacy

The study failed to demonstrate a statistically significant efficacy for any of the sarilumab treatment groups in any of the primary or secondary efficacy measures. For the primary endpoint, the ASAS20 response at Week 12, a higher treatment response was observed in the highest (150 mg qw) dose group (38%) compared with placebo (24%). However, the difference was not statistically significant.

Safety

Treatment-emergent adverse events

The proportion of patients who experienced at least 1 TEAE was approximately 2-fold higher in the sarilumab treatment groups (69% to 78%) compared with the placebo group (36%). There was no clear dose response for TEAEs in the sarilumab treatment groups; 69% of patients in the lowest dose group (100 mg q2w), 64% in the 100 mg qw dose group, 78% in the 150 mg q2w dose group, 71% in the 200 mg q2w dose group, and 74% in the highest dose group (150 mg qw) reported TEAEs.

Treatment-emergent adverse events were most frequently reported in the Infections and infestations system organ class (SOC) by both sarilumab- and placebo-treated patients, with URTI being the most frequently reported TEAE. The proportion of patients who reported TEAEs in the Infections and infestations SOC were approximately the same in the placebo (18%) and 200 mg q2w groups (18.4%), and ranged from 21.6% (150 mg q2w) to 28.6% (150 mg qw) in the other sarilumab groups. Neutropenia was the most frequently-reported TEAE among sarilumab-treated patients, and ranged from 3.8% (100 mg qw) to 16.3% (150 mg qw).

Serious adverse events and treatment-emergent adverse events leading to discontinuation

No deaths occurred during the study.

During 12 weeks of treatment, 7 patients reported serious TEAEs, of whom 5 patients discontinued treatment as a result of the event. All serious TEAEs occurred in patients who received sarilumab; no serious TEAEs were experienced by placebo patients.

In addition to the 5 patients who experienced serious TEAEs that led to discontinuation, 15 patients experienced nonserious TEAEs that led to permanent discontinuation. These discontinued patients were evenly distributed across the 100 mg qw, 150 mg q2w, and 150 mg qw treatment groups (10%, 10%, and 12%, respectively), and 4% in each of the remaining sarilumab treatment groups. The majority of the TEAEs that led to premature treatment discontinuation were neutropenia (n = 6), gastrointestinal disorders (n = 5), and increased alanine aminotransferase [(ALT), n = 4]. No placebo-treated patients permanently discontinued the Investigational Medicinal Product due to a TEAE.

Adverse events with prespecified monitoring

The proportion of patients who experienced an AEPM during the study ranged from 23.1% to 40.8% among the sarilumab treatment groups, and 6% in the placebo group. The most frequently reported AEPMs for sarilumab-treated patients were neutropenia, aphthous stomatitis, and increased ALT ($\geq$3 x ULN). One case of aphthous stomatitis was reported in a placebo patient. No neutropenia or increased ALT($\geq$3 x ULN) was reported among placebo patients.

Neutropenia was experienced by 21 sarilumab-treated patients. Of these, 1 patient experienced a Grade 3 neutropenia that was classified as a serious adverse event (SAE) and led to discontinuation of treatment. An additional 5 patients experienced Grade 3

neutropenia that led to discontinuation of treatment.

Nineteen of these 21 patients experienced Grade 3 (≥500 to <1000/mm^3; 16 patients) or 4 (<500/mm^3; 3 patients) neutropenia, based on the maximum grade during the TEAE period. Of these, 15 patients experienced the neutropenia by Week 6, 2 patients experienced the neutropenia by Week 8, and 2 patients experienced the neutropenia between Weeks 10 and 12. The duration of Grade 3/4 neutropenia from onset until the neutrophil count was $\geq 1000\ \mathrm{mm}^3$ ranged from 3 to 34 days with no corrective treatment required. Nine of 19 patients recovered by Day 7 and 16 of 19 patients recovered by Day 15. The 3 cases of Grade 4 neutropenia lasted from 5 to 14 days.

No severe or serious infections were associated with Grade 3 or Grade 4 neutropenia. Two patients experienced intercurrent nonserious infections (1 patient with mild genital herpes and 1 patient with moderate tooth infection) with Grade 3 neutropenia, both of which recovered with corrective treatment.

A sarilumab dose response was observed with respect to mean reduction of ANC by visit. Decreases were apparent by Week 2 for all doses except 100 mg q2w, which was apparent by Weeks 4 to 6, and remained relatively stable for the duration of the study.

Thrombocytopenia was reported by 1 patient (platelets 109 Giga/L) in the 150 mg qw dose group. The thrombocytopenia was not associated with any bleeding events and did not require any corrective treatment. No patients experienced platelet counts <50 Giga/L.

Elevated liver function enzyme (ALT $\geq$3 xULN) was reported in sarilumab-treated patients and not in placebo-treated patients. Among patients who had increased ALT, 1 case was classified as an SAE (ALT >10 x ULN) and was identified during routine laboratory safety monitoring; this patient was asymptomatic and recovered. Three additional patients had increased ALT that led to discontinuation. No dose response was demonstrated.

Gastrointestinal AEPMs were observed in all dose groups, including placebo. Among the gastrointestinal AEPMs, aphthous stomatitis was reported most often. Incidence of aphthous stomatitis was reported more often among sarilumab-treated patients (2% to 6%) compared with placebo (2%; 1 patient). Of these, 2 patients had aphthous stomatitis that led to discontinuation of treatment. No dose response was observed.

Of the other protocol-defined AEPMs, no opportunistic infections, neurological events suspicious of demyelination or PML, confirmed diverticulitis, acute renal failure, or pregnancy were reported during the study.

Laboratory abnormalities

Neutrophil PCSA values (<1.5 Giga/L nonblack and <1.0 Giga/L black) were reported across all sarilumab treatment groups, with a dose-response rate that ranged from 2% in the 100 mg q2w to 46.9% in the 150 mg qw group. Grade 3 neutropenia (neutrophils <1.0 Giga/L) ranged from 0 in the 100 mg q2w to 9.8% in the 150 mg q2w group. Grade 4 neutropenia (neutrophils <500 Giga/L) was reported in 3 patients, of which 2 patients received 150 mg q2w and 1 patient received 150 mg qw. No patients in the placebo group reported neutrophil PCSAs. A summary of neutropenia can be found in the discussion of "Adverse Events with Prespecified Monitoring" above.

There was a trend for patients with neutropenia (including Grade 3 and 4) to have higher serum drug levels. However, there was a significant number of patients with serum drug levels in higher ranges, for whom the neutrophil counts were maintained within normal limits.

Of the liver function values reported as PCSAs during the TEAE period, the greatest proportion of patients had ALT and aspartate aminotransferase (AST) values >1 and ≤3 x ULN. Only 3 patients, all of whom received 200 mg q2w, had total bilirubin PCSAs. Of these, 2 patients had total biliribun >2 x ULN, and were both confirmed by genetic testing to have Gilbert's disease. A summary of elevated liver function and drug-induced liver injury can be found in the discussion of 'Adverse Events with Prespecified Monitoring' above.

Among metabolic parameters, PCSAs were most frequently observed in total cholesterol (≥6.2 mmol/L and <7.74 mmol/L) and LDL (≥4.1 mmol) in all treatment groups, including placebo. No dose response was observed.

Among patients with normal baseline values of total cholesterol, PCSAs (≥6.2 and <7.74 mmol/L) during treatment were reported more often in sarilumab-treated (11.1% to 34.1%) compared with placebo-treated (8.9%) patients. Only 2 patients in the 100 mg qw dose group, who had normal total cholesterol levels at Baseline, increased to ≥7.74 mmol/L during treatment. Since few patients had elevated levels (≥6.2 and <7.74 mmol/L) at Baseline, meaningful conclusions cannot be drawn.

For patients with baseline total cholesterol PCSAs (≥6.2 mmol/L and <7.74 mmol/L), total cholesterol increased to ≥7.74 mmol/L

in close to half (3/7, 2/5, and 3/6) of the patients in the 100 mg q2w, 150 mg q2w, and 100 mg qw dose groups, respectively, and in 1 of 4 placebo-treated patients.

A similar trend to the changes from Baseline in total cholesterol levels was observed with respect to low-density lipoprotein (LDL).

Few PCSAs with respect to glucose, triglyceride values, creatine phosphokinase (CPK), and creatinine were reported. Among metabolic parameters, no dose response was observed and PCSAs were not considered to be clinically significant.

There were some vital sign and ECG PCSAs observed, none of which demonstrated a dose response or were considered to be clinically significant.

Date of report: 10-Dec-2011