SYNOPSIS

Title of the study:	A multicenter uncontrolled extension study evaluating the long term safety and efficacy of SAR153191 in patients with Ankylosing Spondylitis (AS) - LTS11298
Investigator(s):	[redacted]
Study center(s):	56 study centers in 12 countries in Europe, Canada, Australia, and the United States
Publications (reference):	None
Study period:	
Date first patient enrolled:	01 Jun 2010
Date last patient completed:	12 Dec 2011
Phase of development:	Phase 2

Objectives:

Primary

To evaluate the long-term safety of sarilumab in patients with AS

Secondary

The secondary objectives are all related to the long term efficacy of sarilumab as assessed by the following:

- ASAS 20
- ASAS partial remission
- disease activity (BASDAI)
- range of motion assessed by Bath AS Metrology Index (BASMI) (10-point scale)
- Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Magnetic Resonance Imaging (MRI) of the spine
- X-ray of the spine; cervical and lumbar spine lateral view.

Methodology: This was a multicenter, multinational, open-label, long-term study, only for patients with active AS who participated and completed the planned 12 weeks of treatment in the study DRI11073. Patients were to receive sarilumab 150 mg subcutaneously every week for up to 260 weeks (5 years) of treatment from the first intake of study drug, until commercially available, or until discontinuation of the project, whichever came first. The study was prematurely discontinued after approximately 1.5 years, when the AS development program was discontinued due to lack of efficacy in the DRI11073 study.

Number of patients:	Planned: 270 patients
	Treated: 223 patients
	Evaluated: 223 patients
	Safety : 223 patients

Diagnosis and criteria for inclusion: Male and female patients between 18 and 75 years of age inclusive, with active AS, who participated and completed the planned 12 weeks of treatment in Study DRI11073, not taking any biological agents other than sarilumab, with no event or laboratory abnormality at the screening visit (Screening corresponds to the end-of-treatment visit [Visit 8, Week 12] of Study DRI11073 that per Investigator judgment would adversely affect participation in this study.

Study treatments

Investigational medicinal product: Sarilumab

Formulation: Glass vials (75 mg/mL)

Route of administration: Subcutaneously, administered in a single injection

Dose regimen: 150 mg every week (qw); step-down dose (in case of safety issue) 150 mg every other week

Batch numbers: [redacted]

Duration of treatment: Up to 260 weeks (5 years)

Duration of observation (Planned): 267 weeks; up to 1 week of screening, 260-week open-label treatment period, and 6-week follow-up

Duration of observation (Actual): Approximately 1.5 years due to premature discontinuation of study

Criteria for evaluation: The study was prematurely discontinued after approximately 1.5 years of the planned 5-year duration, as a result of the discontinuation of the AS development program due to lack of efficacy in the DRI11073 study. The current report is an abbreviated report, and as such, only the safety results are being presented in full. 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:

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 Medical Dictionary for Regulatory Activities (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 t he protocol, were summarized. For the laboratory tests, vital signs, and ECG, incidences of potentially clinically significant abnormal (PCSA) values were summarized. The number of patients with neutropenia was listed by maximum grade during the TEAE period. The group means of absolute neutrophils counts (ANC) with standard error bars, were displayed graphically over time.

Summary:

Treatment-emergent adverse events

Infections and infestations were the most frequently-reported TEAEs per system organ class (SOC) classification, with nasopharyngitis being the most frequently reported TEAE (16 patients; 7.2%) within that SOC. Overall, neutropenia was the most frequently reported TEAE by preferred term (21 patients; 9.4%).

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

No deaths occurred during the study.

During treatment, 12 patients reported serious TEAEs, of whom 3 patients discontinued treatment as a result of the event. In addition to the 3 patients who experienced serious TEAEs that led to discontinuation, 15 patients experienced nonserious TEAEs that led to permanent discontinuation. The most frequently-reported TEAE that led to premature treatment discontinuation was neutropenia (n = 4).

Adverse events with prespecified monitoring

Adverse events with prespecified monitoring included autoimmune or lupus-like syndrome, DILI (increased liver function tests or elevated transaminases), gastrointestinal ulceration or confirmed diverticulitis, hypersensitivity reactions, neurological disorders, neutropenia (Grade 3 or 4), opportunistic infection, overdose, and thrombocytopenia.

The proportion of patients who experienced an AEPM during the study was 32.7% (73 of 223 patients). The most frequently reported AEPM was neutropenia.

Neutropenia was reported as an AEPM by the investigator for 21 patients. Of these, 5 patients experienced neutropenia during the initial DRI11073 study, recovered, and had a new occurrence of neutropenia in this LTS11298 study. No patient had neutropenia that was classified as a serious adverse event. Four patients were discontinued from treatment due to neutropenia. All 4 cases were reversible.

According to laboratory values, 14 of these 21 patients experienced Grade 3 ($\geq$500 to <1000/mm^3) and no patients experienced Grade 4 (<500/mm^3) neutropenia. The remaining 7 patients experienced Grade 2 neutropenia. Of the 14 patients who experienced Grade 3 neutropenia, 3 patients experienced 2 events of neutropenia. Of these, the first patient experienced both events by Week 8, the second patient experienced the first event by Week 6 and the second at Week 36, and the third patient experienced both events after Week 37. An additional patient experienced Grade 3 neutropenia, which began in the DRI11073 study (Days -7 and -3 of this LTS11298 study) and again at Week 12. Of the remaining 10 patients, 7 patients experienced neutropenia by Week 6, 1 patient experienced neutropenia by Week 8, 1 patient experienced neutropenia by Week 12, and 1 patient experienced neutropenia at Week 24. The duration of Grade 3 neutropenia from onset until ANC $\geq$1 Giga/L ranged from 4 to 44 days with no corrective treatment required. Eight of 17 events of neutropenia resolved by Day 7, 8 of 17 events resolved by Day 15, and 1 event resolved by Day 44.

No severe or serious infections were associated with intercurrent Grade 3 neutropenia. One patient experienced 2 intercurrent nonserious infections (urinary tract infection and sinusitis) with neutropenia and recovered with antibiotic treatment.

Thrombocytopenia was reported as an AEPM by the Investigator for 3 patients. According to laboratory values, thrombocytopenia (platelets <100 000/mm^3) was observed in 4 patients. None of these events were associated with any bleeding, and none required any corrective treatment. Of these, 2 patients were permanently discontinued from treatment.

There were no cases of potential Hy's Law (ALT >3 x ULN with concomitant total bilirubin >2 x ULN) reported. Increased ALT was reported as an AEPM by the Investigator in 11 (4.9%) patients. According to laboratory values, ALT >3 x ULN was observed in 6 of these 11 patients Two of these events led to permanent discontinuation of treatment.

Gastrointestinal AEPMs were mostly oral, with aphthous stomatitis reported most often, and leading to permanent discontinuation of treatment in 1 patient. Two cases of confirmed diverticulitis were reported, 1 of which was considered to be serious and resulted in permanent discontinuation of treatment. Neither patient required surgery, and both recovered with conservative treatment with antibiotics.

All but 1 of the 5 patients with autoimmune or lupus-like syndrome AEPMs were related to inflammatory conditions of the eye. No clinical cases of opportunistic infection were reported. Three cases of localized hypersensitivity reactions (2 cases of Injection site urticaria and 1 case of eye pruritus) were reported, all of which recovered without corrective therapy. One patient had an asymptomatic positive tuberculin test, for which tuberculosis was excluded by pulmonological evaluation. The patient was treated prophylactically with isoniazid and pyridoxine and recovered from the event.

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

Laboratory abnormalities and other safety

Any grade of neutropenia (by maximum grade) was observed in 112 patients (Grade 1 = 43, Grade 2 = 55, Grade 3 = 14, Grade 4 = 0). Neutrophil PCSA values (<1.5 Giga/L nonblack and <1.0 Giga/L black) were observed in 69 patients. Grade 3 neutropenia (neutrophils <1.0 Giga/L) was observed in 14 patients, and no patients reported Grade 4 neutropenia (neutrophils <0.5 Giga/L). A summary of neutropenia can be found in the discussion of "Adverse Events with Prespecified Monitoring" above.

Of the liver function values reported as PCSAs during the TEAE period, the greatest proportion of patients had ALT values >1 and ≤3 x ULN, and aspartate aminotransferase (AST) values >1 and ≤3 x ULN. Only 7 patients had total bilirubin PCSAs (>1.5 x ULN). Of these, 1 patient had total biliribun >2 x ULN, and was confirmed by genetic testing to have Gilbert's disease. A summary of elevated liver function tests and elevated transaminases, monitored for early detection of potential 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 low-density lipoprotein (LDL; ≥4.1 mmol). Three patients, who had normal total cholesterol levels at Baseline, increased to ≥7.74 mmol/L during treatment. 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 6 of 19 patients.

A similar trend to the changes from Baseline in total cholesterol levels was observed with respect to LDL. Few PCSAs with respect to triglyceride values and creatinine were reported and none were considered to be clinically significant. Potentially clinically significant abnormalities with respect to deficient glucose levels (≤3.9 mmol/L and < LLN) were observed in 10 patients and elevated glucose levels (≥11.1 mmol/L [unfasted]; ≥7 mmol/L [fasted]) in 23 patients. No PCSAs were reported with respect to creatine phosphokinase.

There were some vital sign and ECG PCSAs observed, none of which were considered to be clinically significant.

Conclusion

[redacted]

Date of report: 27-Apr-2012