SYNOPSIS

Title of the study:	A 2-part protocol to assess, using double blind placebo control, the safety, tolerability, and pharmacokinetics of ascending single doses of new intra-articular administration formulation of SAR113945 (IKK inhibitor) followed by assessment of efficacy, safety, tolerability, and pharmacokinetics of a single dose in patients with knee osteoarthritis (TDU11685-ACT12505) This document reports the results from Part 2 (ACT12505), the evaluation of the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of a single dose administration at the maximum tolerated dose selected from Part 1 of the study (TDU11685)
Investigators:	[redacted]
Study centers:	2 centers in Germany
Publications (reference):	Not applicable
Study period:	
Date first patient enrolled:	26 April 2012
Date last patient completed:	05 February 2013
Phase of development:	Phase 1
Objectives:	To assess in patients with knee osteoarthritis (OA), the efficacy, safety, and tolerability of a single intra-articular dose of SAR113945
Methodology:	Double-blind, randomized, placebo-controlled, single dose, parallel group study
Number of patients:	Planned: 130 Randomized: 130 Treated: 130
Evaluated:	Efficacy: 130 Safety: 130 Pharmacokinetics: 64
Diagnosis and criteria for inclusion:	Patients aged 40 years or older, diagnosed with primary knee OA based upon X-ray/magnetic resonance imaging evidence within the last 6 months for joint space narrowing and osteophyte formation (Kellgren-Lawrence Grades II or III), a Western Ontario MacMaster (WOMAC) score of 24 to 72, and American College of Rheumatology Clinical and Radiographic criteria.
Study treatments	
Investigational medicinal product:	SAR113945 suspension for injection
Formulation:	Vials of lyophilized suspensions of SAR113945 for intra-articular injection containing 80 mg/4 mL (equivalent to 20 mg/mL)
Dose regimen:	Single dose administration of 3 mL SAR113945 at a concentration of 20 mg/mL, corresponding to a dose of 60 mg
Administration:	Intra-articular injection (knee)
Batch number:	[redacted]

Reference therapy: Placebo (0.9% saline solution)

Dose: 0 mg/mL, volume matching the corresponding SAR113945 treatment

Administration: Intra-articular injection (knee)

Batch numbers: [redacted]

Duration of treatment: Single dose

Duration of observation: Up to 28 weeks (including screening, study period, and follow-up)

Criteria for evaluation:

Efficacy: WOMAC index scores evaluating pain, stiffness, and physical function using a 5-point Likert scale (measured at Screening, Days 1 [predose], 7, 14, 28, 56, 84, 112, and 168)

Safety: Adverse events (AEs) assessed up to end of study, Day 168; standard clinical laboratory (biochemistry, hematology, urinalysis); physical examination; vital signs; electrocardiogram (ECG); local tolerability at site of injection (assessments for skin/soft tissue: erythema, edema, pain, hematoma [graded none, mild, moderate, or severe]; assessments for knee joint: effusion/worsening of effusion [yes/no], warm [yes/no], pain [100 mm visual analog scale])

Pharmacodynamics:

Biomarkers related to OA:

- Markers of inflammation: matrix metalloproteinase-13, interleukin-6, and tumor necrosis factor α measured in synovial fluid (SF) and C-reactive protein (CRP) measured in serum
- Markers relating to pain: prostaglandin E_2 measured in SF

Pharmacokinetics: Concentrations of SAR113945 in plasma and SF. The following plasma PK parameters were calculated: terminal half-life associated with the terminal slope ($t_{1/2z}$) and time corresponding to the last concentration above the limit of quantification (t_{last}).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Plasma was collected: predose, 3 hours postdose; and on Days 28, 56, 84, 112, and 168. A maximum of 3 SF samples were collected on Day 1 (predose) and if possible Days 28 and 84 or otherwise at later visits. If the patient showed presence of an effusion by ultrasound examination at the above timepoints, then a SF sample was taken.

SAR113945 plasma concentrations were determined by a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantitation (LLOQ) of 20 pg/mL. SAR113945 SF concentrations were determined by an exploratory assay method with an LLOQ of 1 ng/mL.

Statistical methods:

Efficacy: The primary endpoint, the reduction (absolute change from baseline) in WOMAC pain subscore at Day 56 was analyzed using an analysis of covariance including the corresponding baseline as covariate and treatment, sex, and site investigator as fixed effects. The primary analysis consisted of a 1-sided pairwise comparison for SAR113945 60mg versus placebo, at the 5% alpha level. The mean estimates from each treatment, the mean estimate of the difference and the effect size of the absolute change from baseline with the 90% confidence interval (CI) were calculated from the fixed effect model framework. The WOMAC pain subscore at Days 84, 112 and 168, and total WOMAC score and WOMAC subscores for stiffness and physical function were analyzed in the same way.

The total WOMAC scores and WOMAC subscore for pain, stiffness and physical function raw data and absolute change from baseline were summarized using descriptive statistics by treatment group and day. Time profile plots of mean ± standard error of mean were provided.

Safety: The safety analysis was based on the review of descriptive statistics (summary tables) and individual data for AEs, clinical laboratory, vital signs, and ECG parameters. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 15.1) and the numbers of subjects with treatment-emergent AEs (TEAEs) were tabulated (counts and percents). For clinical laboratory, vital signs, and ECG data, the analyses of abnormalities were based on the definitions of potentially clinically significant abnormalities (PCSAs; definitions according to version 2.0 dated 14 September 2009). Local tolerance/tolerability at the site of injection was summarized by descriptive statistics.

Pharmacodynamic: The biomarkers related to OA were analyzed as raw data and change from baseline and summarized using descriptive statistics by treatment group and day.

Pharmacokinetic: SAR11395 plasma concentrations and PK parameters were listed by patient and summarized using descriptive statistics.

Summary:

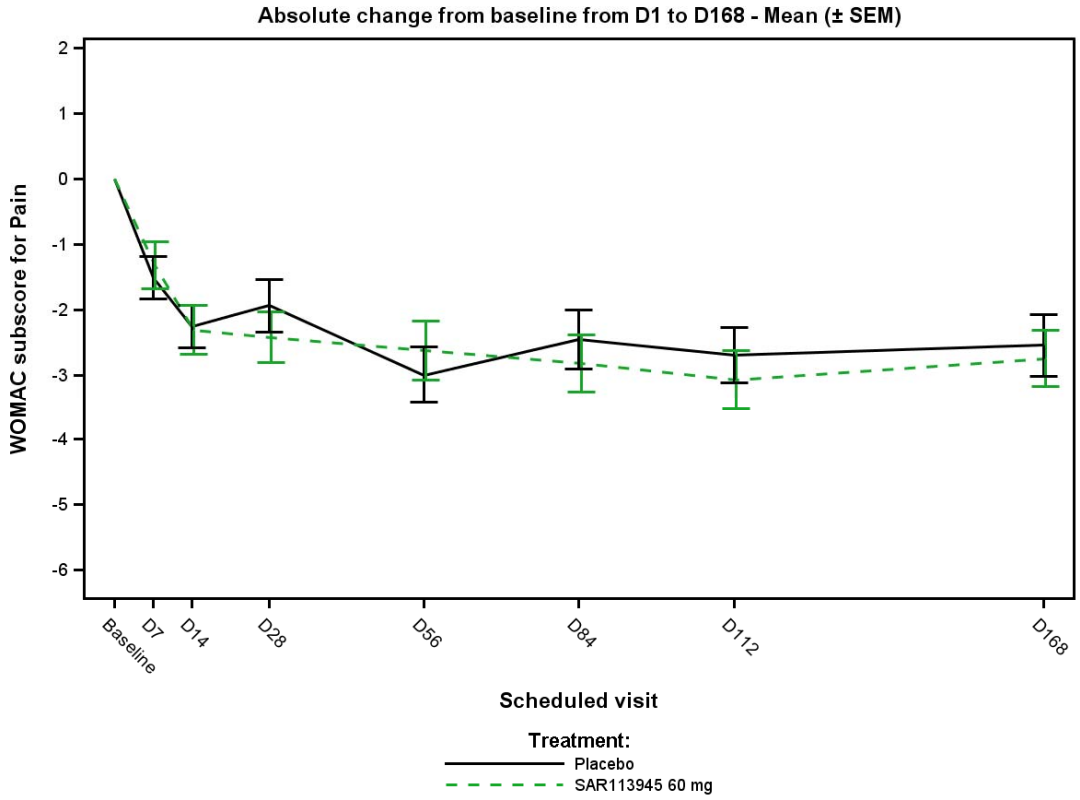
Population characteristics:

From the total of 130 patients admitted into this study, 64 patients received SAR113945 (60 mg) and 66 patients received placebo. All patients completed the study up to Day 168.

	SAR113945 (n=64)	Placebo (n=66)
Age (years)		
Mean (SD)	61.9 (7.5)	62.6 (8.2)
Sex		
M	29	30
F	35	36
Weight (kg)		
Mean (SD)	82.5 (17.5)	86.3 (15.6)
BMI Group (kg/m^2)		
<30	43	36
>30	21	30
Total WOMAC Score at Baseline (SD)	46.5 (10.4)	46.0 (11.4)

Efficacy results: The primary efficacy endpoint for the study was the effect upon the WOMAC Pain subscore at Day 56. SAR113945 had neither a clinically significant nor a statistically significant effect on either the WOMAC Pain subscore or the other WOMAC subscores or Total score. The effect sizes for WOMAC subscores ranged from 0.12 to -0.04 (negative indicates a positive effect of drug against placebo).

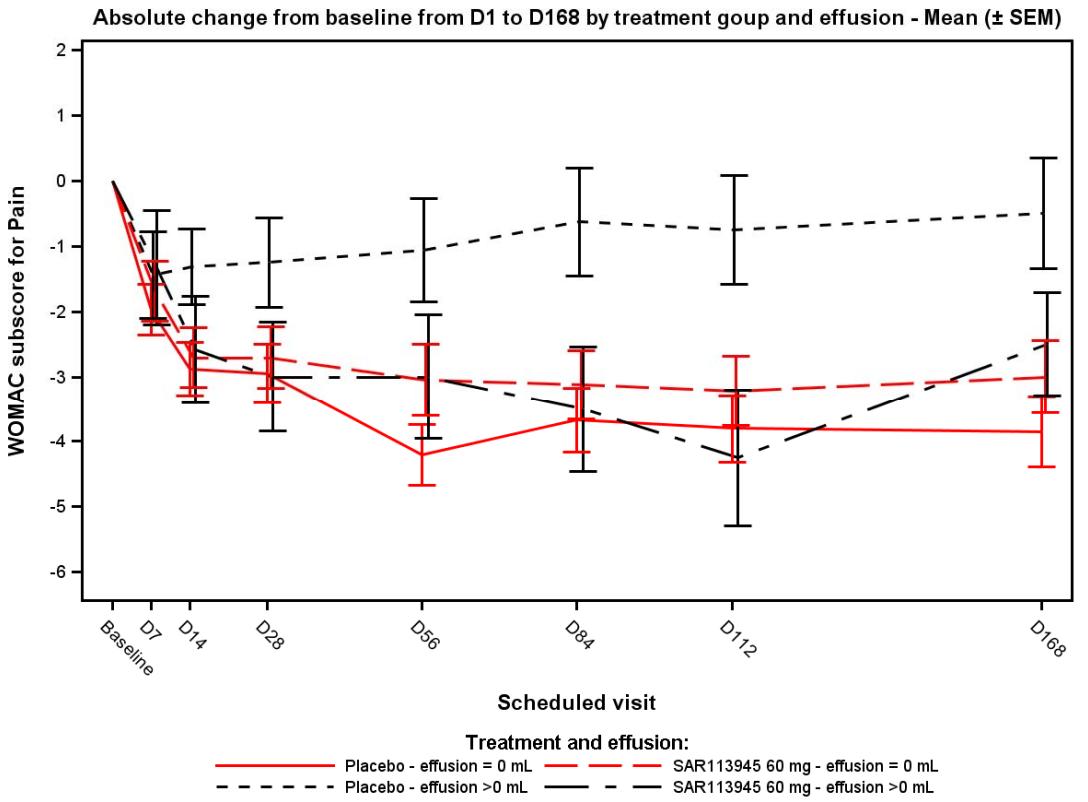
Summary plot of WOMAC subscore for pain (absolute change from baseline) by treatment - efficacy population



Additional statistical analyses showed a statistically significant effect of gender and also for baseline WOMAC score upon the change in WOMAC subscores (greater decreases seen in females and in those with higher baseline total WOMAC, >48), however the interaction with treatment was not statistically significant.

An additional analysis was carried out for this study in those patients who had an effusion, those from whom SF was removed (varying between 0.2 mL and 113 mL). Analysis of the patients with an effusion at baseline (28 patients from the total of 130 [21.5%]; 16 patients administered placebo and 12 patients administered SAR113945) showed a significant effect of SAR113945 upon WOMAC Pain score, Total WOMAC score, and WOMAC Physical Function scores at Day 56, corresponding to effect sizes of 0.55, 0.66, and 0.66 respectively (corresponding p-values 0.07, 0.04, and 0.04 respectively). However, it should be noted that the placebo response for the effusion subgroup for WOMAC Pain subscore appeared to differ from that for placebo in the total population showing a lower response. This subgroup contained relatively more males (68.8%) by comparison with the overall population – 45.5% males for placebo as a whole.

Summary plot of WOMAC subscore for pain (absolute change from baseline) by treatment and effusion at baseline - efficacy population



Safety results:

Intra-articular administration of SAR113945 at a dose of 60 mg was well tolerated in this study and this was apparent from the severity of the reported AEs and their incidence relative to placebo. During the study period, a total of 95 patients experienced at least 1 TEAE: in 45 patients (70.3%) who received SAR113945 60 mg and in 50 patients (75.8%) who received placebo.

Five serious AEs were reported in the study, all of which were unrelated to administration of the investigational medicinal product. Four serious AEs were reported in the placebo group: 1 case of hypertonic bladder; 2 cases of arthralgia, and 1 case of joint effusion. These 3 latter AEs required replacement surgery for the target knee. One case of arthralgia also requiring target knee replacement surgery was reported in the SAR113945 group. No patient discontinued the study due to TEAEs.

The most frequently reported TEAEs by system organ class were:

- musculoskeletal and connective tissue disorders, mainly arthralgia (23.4% for SAR113945 60 mg, 18.2% for placebo) and joint warmth (1.6% for SAR113945 60 mg, 10.6% for placebo);
- general disorders and administration site conditions
    - injection site hematoma (7.8% for SAR113945 60 mg, 10.6% for placebo);
    - injection site pain (7.8% for SAR113945 60 mg, 19.7% for placebo);
    - injection site edema (7.8% for SAR113945 60 mg, 1.5% for placebo);
- infections and infestations, mainly nasopharyngitis (10.9% for SAR113945 60 mg, 18.2% for placebo);
- nervous system disorders, mainly headache (7.8% for SAR113945 60 mg, 3.0% for placebo).

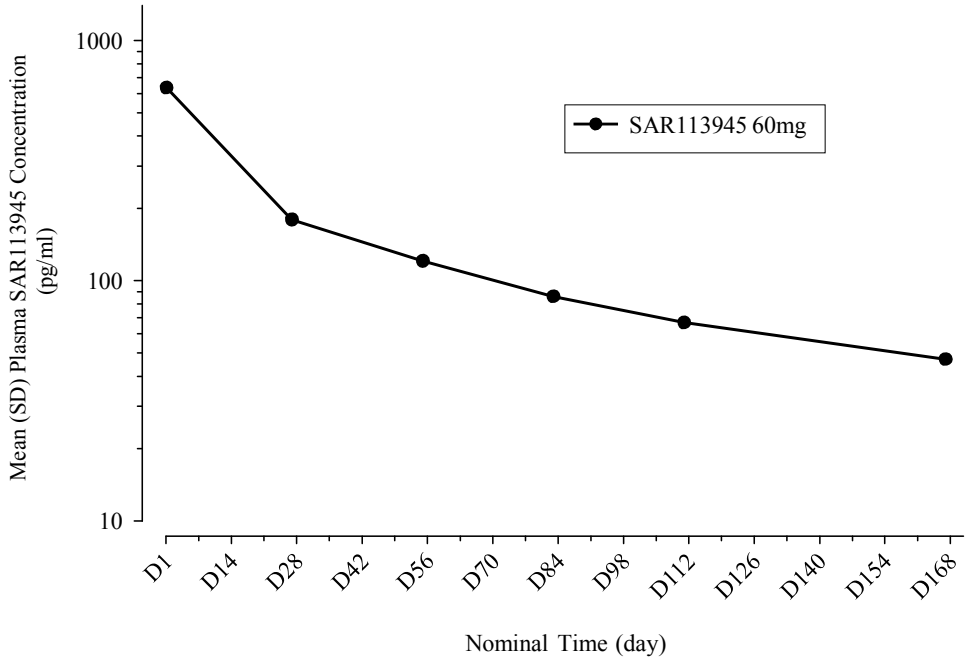
Safety results (cont'd):

All but 2 TEAEs were of mild or moderate intensity; the severe TEAEs reported were arthralgia at target knee on Day 51 (placebo) and an increase in creatine phosphokinase (50 x the upper limit of normal [ULN]) at the Day 84 visit due to intense physical activity (SAR113945). The increase in creatine phosphokinase level was accompanied by PCSAs for increases in aspartate aminotransferase (>5 x ULN) and alanine aminotransferase (>2 x ULN).

Occasional PCSA values, evenly distributed between the 2 treatment groups, were reported for clinical laboratory parameters, vital sign, and ECG parameters; this was not unexpected given the patient population.

Pharmacokinetic results:

Mean SAR113945 plasma concentration-time profile (semi-log scale)



A median terminal plasma $t_{1/2z}$ of 83.6 days was calculated.

Conclusions:

[redacted]

Date of report: 19-Aug-2013