SYNOPSIS

Title of the study:	A two part protocol to assess, using double blind placebo control, the safety, tolerability, and pharmacokinetics of ascending single doses of a 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 ascending single doses part of the study (TDU11685)
Investigator:	[redacted]
Study center:	1 center in Germany
Publications (reference):	Not applicable
Study period:	
Date first patient enrolled:	11 November 2011
Date last patient completed:	01 August 2012
Phase of development:	Phase 1
Objectives:	To assess in patients with knee osteoarthritis (OA), the safety, tolerability, and pharmacokinetics (PK) of single intra-articular doses of SAR113945.
Methodology:	Single center, double-blind, randomized, placebo-controlled, single ascending dose study in sequential groups.
Number of patients:	Planned: 24 Randomized: 24 Treated: 24 (placebo, N = 6; SAR113945 at 15 mg, 30 mg and 60 mg N = 6 each).
Evaluated:	Safety: 24 Pharmacodynamics: 24 Pharmacokinetics: 18
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 20 mg/4 mL (equivalent to 5 mg/mL), 40 mg/4 mL (equivalent to 10 mg/mL), and 80 mg/4 mL (equivalent to 20 mg/mL).
Dose regimen:	Single dose administration of 3 mL SAR113945 at concentrations of 5 mg/mL, 10 mg/mL, and 20 mg/mL corresponding to doses of 15 mg, 30 mg, and 60 mg, respectively.
Administration:	Intra-articular injection (knee).
Batch numbers:	[redacted]

Reference therapy: Placebo (0.9% saline solution).

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

Administration: Intra-articular injection (knee).

Batch number: [redacted]

Duration of treatment: Single dose.

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

Criteria for evaluation:

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:

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

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: The following PK parameters were calculated using noncompartmental methods for SAR113945 in plasma: maximum plasma concentration observed (C_{max}), first time to reach C_{max} (t_{max}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the last quantifiable concentration (AUC_{last}), partial areas under the plasma concentration versus time curve calculated using the trapezoidal method ($AUC_{0\text{-}24h}$, $AUC_{0\text{-}648h}$, $AUC_{0\text{-}1320h}$, $AUC_{0\text{-}1992h}$, $AUC_{0\text{-}2664h}$, and $AUC_{0\text{-}4008h}$), area under the plasma concentration versus time curve extrapolated to infinity (AUC), terminal half-life associated with the terminal slope ($t_{1/2z}$), time corresponding to the last concentration above the limit of quantification (t_{last}), apparent volume of distribution at the steady state (V_{ss}/F), apparent total body clearance of a drug from the plasma (CL/F), and mean time a molecule resides in body (MRT).

Pharmacokinetic sampling times and bioanalytical methods: Plasma was collected: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose; and on Days 7, 14, 21, 28, 56, 84, 112, and 168. A maximum of 3 SF samples were collected on Day 1 (predose) and if possible on Days 28 and 84. If the patient showed presence of an effusion by ultrasound examination at the above time points, 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.

Statistical methods:

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 15.0) and the numbers of subjects with treatment-emergent AEs (TEAEs) were summarized by treatment group (placebo, SAR113945 15, 30, and 60 mg). 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.

Pharmacodynamics: The total WOMAC score and WOMAC subscale scores for pain, stiffness, and physical function were analyzed as raw data and change from baseline (absolute and percentage) using descriptive statistics by treatment group and day. The biomarkers related to OA were listed.

Pharmacokinetics: All PK parameters and concentrations of SAR11395 in plasma were listed by patient and dose group and summarized by dose group, using descriptive statistics.

For C_{max}, AUC_{last}, and AUC, dose proportionality was evaluated using a linear fixed effect model on log-transformed parameters. Estimates with 90% confidence intervals (CI) for the parameter increases associated with pairwise dose increases were computed. For $t_{1/2z}$, dose effect was assessed with a linear fixed effects model on the log-transformed parameter. Estimate and 90% CI for the geometric mean were provided pooled across dose levels and separately for each dose group.

Summary:

Safety results: Sixteen of the 24 patients (13/18 patients receiving SAR113945) experienced at least 1 TEAE. One serious, unrelated TEAE (anaphylactic reaction to nuts) was reported in a patient in the SAR113945 30 mg group. There were no severe TEAEs. Treatment-emergent AEs were evenly reported across all treatment groups, including placebo, and no dose relationship was identified. The most common TEAEs were nasopharyngitis, procedural pain, arthralgia, injection site edema, and injection site pain. Arthralgia was only reported at the SAR113945 15 mg dose.

A few PCSA values, evenly distributed across both the placebo and the SAR113945 groups, were reported for laboratory parameters, vital signs, and ECG parameters. An increase in CRP level >2 x the upper limit of normal was reported in 3 patients in the placebo group and in 1 patient each at the 15 and 60 mg dose (the 2 patients on SAR113945 had abnormal baseline values). Concomitant nasopharyngitis was a potential explanation for CRP elevation in all but 1 patient (placebo group). No changes in liver enzymes were reported.

The visual analogue data showed that the lowest pain scores were observed at Day 3 for the SAR113945 30 mg and 60 mg groups. For the SAR113945 15 mg dose group, the maximum pain relief was initially observed at 4 hours postdose. From Day 3, no differences were observed across treatment groups, including the placebo group, for the assessment of pain using visual analogue data.

Pharmacodynamic results: Results of WOMAC index score or subscores for all treatment groups showed the expected decrease in symptoms following arthrocentesis. WOMAC scores also suggested a trend for a positive effect of SAR113945 treatment, with all doses showing a consistently larger improvement (change) from baseline than placebo. No dose-effect relationship was apparent for the effect of SAR113945 upon the WOMAC Index, although this could be due to the small sample sizes.

No conclusions could be drawn from the biomarker data concerning the effect of treatment with SAR113945.

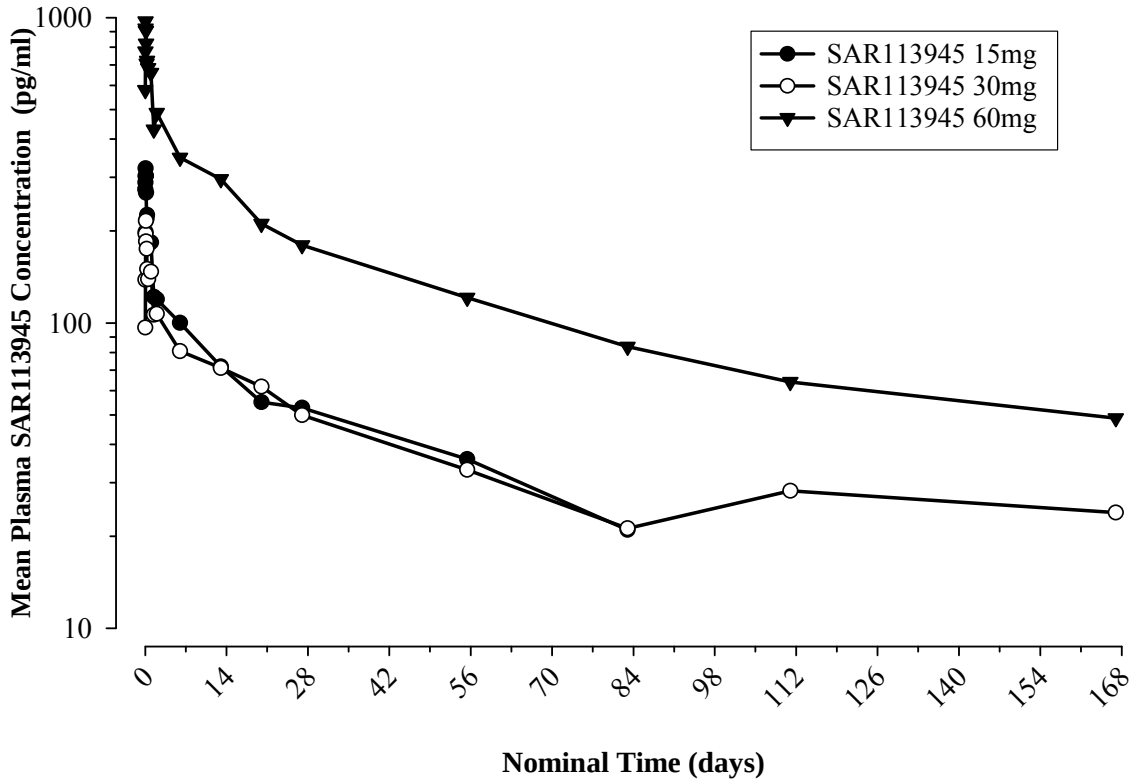
Pharmacokinetic results:

Summary of SAR113945 pharmacokinetic parameters after single intra-articular doses of 15 to 60 mg for an observation period up to Day 168 post administration

Mean ± SD (Geometric Mean) [CV%]	**Plasma SAR113945**		
	SAR113945 15mg	SAR113945 30mg	SAR113945 60mg
N	6	6	6
C_{max} (pg/ml)	358 ± 349 (251) [97.5]	244 ± 149 (207) [61.3]	986 ± 805 (681) [81.7]
t_{max}[a] (hr)	1.75 (0.50 - 3.00)	3.01 (2.00 - 24.15)	2.26 (1.50 - 4.05)
t_{last}[a] (hr)	2663.99 (142.53 - 4008.02)	4007.43 (647.77 - 4198.92)	4007.89 (4007.50 - 4008.18)
$t_{1/2z}$ (day)	54.4 ± 31.9 (39.7) [58.7]	133 ± 108 (90.5) [81.5]	78.9 ± 25.4 (75.7) [32.2]
AUC_{last} (pg•day/mL)	5640 ± 5340 (2770) [94.8]	6210 ± 3260 (5230) [52.5]	20500 ± 13600 (16700) [66.1]
AUC (pg•day/mL)	13700 ± NC (13400) [NC][b]	6430 ± 4020 (5160) [62.5][c]	31200 ± 17300 (26300) [55.3][d]
AUC_{0-24h} (pg•day/mL)	210 ± 216 (142) [103.0]	152 ± 80.4 (135) [52.8]	708 ± 571 (485) [80.6]
$AUC_{0-1992h}$ (0-Day 84) (pg•day/mL)	4500 ± 3740 (2840) [83.0]	4040 ± 1880 (3700) [46.5]	15300 ± 11100 (11900) [72.6]
$AUC_{0-4008h}$ (0-Day 168) (pg•day/mL)	6100 ± 4960 (3690) [81.3]	6260 ± 3110 (5500) [49.6]	20500 ± 13600 (16700) [66.1]

[a] Median (Min - Max); NC = Not calculated
[b] n=2; [c] n=3; [d] n=4

Mean SAR113945 plasma concentration-time profiles in semi-log scale



SAR113945 appeared rapidly in plasma following a single intra-articular administration, with median t_{max} values of 1.75 to 3.01 hours.

For a 2-fold increase between the 15 and 30 mg dose, no linear increase was seen for C_{max} and AUC, with estimates of 0.82 (90% CI: 0.34-1.99) and 0.39 fold (90% CI: 0.08-1.90), respectively. Between the 30 and 60 mg doses, C_{max} and AUC increased greater than dose proportionally, with estimates of 2.75 (90% CI: 1.09-6.94) and 5.11 (90% CI: 1.25-20.8), respectively.

The variability of C_{max} values was high (60% to 90%), to very high (>90%) but did not exceed 2.3 ng/mL as seen for a subject in the 60 mg group.

No statistically significant effect of the dose on $t_{1/2z}$ was seen. Point estimates for $t_{1/2z}$ ranged between 29.13 days (90% CI: 14.96-56.72 days) for the 15 mg dose and 75.75 days (90% CI: 41.34-138.80 days) for the 60 mg dose. After single intra-articular administration, SAR113945 was detectable (above LLOQ of 20 pg/mL) in the systemic circulation up to Day 168 in 3/6 patients in the 15 mg group, in 5/6 patients in the 30 mg group, and 6/6 patients in the 60 mg group.

Conclusions: [redacted]
Date of report: 27-Nov-2012