These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance:** SAR113945	**Study Identifiers:** NCT01113333, EudraCT 2009-017502-36, UTN U1111-1116-5630 **Study code:** TDU10820
Title of the study: A double blind, placebo controlled ascending single dose study to evaluate the safety, tolerability, and pharmacokinetics of the IKK inhibitor, SAR113945, following intra-articular administration in patients with knee osteoarthritis. (TDU10820)	
Study center(s): 1 center in Germany	
Study period: Date first patient enrolled: 06/Apr/2010 Date last patient completed: 11/Feb/2011	
Phase of development: Phase 1	
Objectives: • To assess in patients with knee osteoarthritis (OA), the safety and tolerability of single intra-articular doses of SAR113945. • To assess any systemic exposure of SAR113945 following intra-articular delivery.	
Methodology: Single center, double blind, placebo controlled, randomized, single dose escalation, sequential group study	
Number of patients**:**	Planned: 40 Randomized: 40 Treated: 40
Evaluated:	Pharmacodynamics: 40 Safety: 40 Pharmacokinetics: 30
Diagnosis and criteria for inclusion: Patients aged 40 years or older, diagnosed with primary knee OA based upon X-ray/magnetic resonance imaging evidence for joint space narrowing and osteophyte formation (Kellgren-Lawrence Grades II or III), a Western Ontario McMaster (Index) (WOMAC) score ≤72, and American College of Rheumatology clinical and radiographic criteria.	

Study treatments

Investigational medicinal product(s): SAR113945 suspension for injection

Formulation: 3 mL at concentrations of 25 µg/mL, 100 µg/mL, 250 µg/mL, 1 mg/mL, 5 mg/mL, and 5 mL at maximum administered or maximum tolerated dose (5 mg/mL), corresponding to doses of 0.075, 0.3, 0.75, 3, 15, and 25 mg, respectively.

Route of administration: Intra-articular injection (knee)

Noninvestigational medicinal product:(s) Placebo (0.9% saline solution)

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

Route of administration: Intra-articular injection (knee)

Duration of treatment: Single dose

Duration of observation: 5 to 17 weeks (including screening, treatment, and follow-up)

Criteria for evaluation:

Pharmacodynamics: Western Ontario and McMaster Universities Osteoarthritis Index scores evaluating pain, stiffness, and physical function using a 5-point Likert scale; biomarkers of inflammation and cartilage turnover related to OA.

Safety: Adverse events (AEs); standard clinical laboratory (biochemistry, hematology, urinalysis); vital signs; electrocardiogram (ECG); automatic readings; ophthalmological examinations (subjective refraction, perimetry, color vision [Farnworth test and anomaloscope for red-green vision], and funduscopy); local tolerability at site of injection (assessments for skin/soft tissue: erythema, edema, pain, papules, and hematoma [graded none, mild, moderate, or severe]; assessments for knee joint: effusion/worsening of effusion [yes/no], warm [yes/no], and pain [100 mm visual analog scale]).

Pharmacokinetics: The following pharmacokinetic (PK) parameters were to be calculated using noncompartmental methods for SAR113945 in plasma: C_{max}, t_{max}, t_{lag}, AUC_{last}, AUC_{0-24}, AUC_{0-648}, AUC, $t_{1/2z}$, t_{last}, V_{ss}/F, CL/,F, and mean residence time (MRT).

Pharmacokinetic sampling times and bioanalytical methods: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dose, and on Days 7, 14, 21, and 28 (morning). Further samples were taken beyond Day 28 if SAR113945 plasma concentrations at Day 28 were still above the lower limit of quantification (LLOQ) of 20 pg/mL, and until concentrations <LLOQ were reached, with a maximum of 4 further samples until Day 112. SAR113945 plasma concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with an LLOQ of 20 pg/mL. Synovial fluid samples were collected on Day 1 pre dose and on Day 28 (not available for knee rheumatoid synovitis [KRS]). Spot urine samples were collected pre dose and on Days 2, 7, 14, 21, and 28 (morning urine).

Statistical methods:

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

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. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0, and the numbers of patients with treatment-emergent adverse events (TEAEs) were summarized by treatment group (placebo, SAR113945 0.075, 0.3, 0.75, 3, 15, and 25 mg). Potentially clinically significant abnormalities (PCSAs; definitions according to version dated 14 September 2009) for clinical laboratory, vital sign, and ECG data and out of normal range values for clinical laboratory data were flagged and summarized in frequency tables by treatment.

Local tolerance/tolerability at the site of injection was summarized by descriptive statistics. Comments from the individual ophthalmological examinations (normal/abnormal) at baseline and end of study were summarized in a frequency table.

Pharmacokinetics: Concentrations and all PK parameters for SAR113945 in plasma were listed by patient and dose group and summarized for each dose group using descriptive statistics.

For C_{max}, AUC, AUC_{last}, AUC_{0-648}, 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 pair wise dose increases were computed. For $t_{1/2z}$, the dose effect was assessed using a linear fixed effect model on log-transformed parameter. Estimates and 90% CI for the geometric mean were provided.

Summary:

Pharmacodynamic results:

WOMAC Index

Assessment of effect upon the WOMAC Index was not a primary objective for this First into Man study. Decreases in total WOMAC scores were seen in all groups including placebo, without a clear dose relationship. All groups showed a decrease in score from baseline to the 7 day measurement point (34% for placebo; for active treatment, the decrease at Day 7 ranged from 9%-38%). At Day 28 for placebo, the decrease in total WOMAC score was 24%; the corresponding values for active ranged from 11%-49%, without dose relationship. Decreases in score were also seen at Day 84, where data were available (the decreases were 49% and 38% at Day 28, and 33% and 29% at Day 84 for the 15 mg and 25 mg groups, respectively). A similar pattern of results was observed in pain and physical function sub-scores.

Safety results:

No serious TEAEs were reported during the study, and no patients discontinued the study due to TEAEs. TEAEs were commonly reported for all treatment groups including placebo - overall no dose relationship was identified (see Table below).

The most frequently reported TEAEs were those relating to “musculoskeletal/connective tissue disorders” (mostly arthralgia and joint swelling) and “general disorders and administration site conditions” for the injected knee (mostly injection site edema, injection site pain, and sensation of pressure). Except for joint swelling, these events were reported in patients receiving both SAR113945 and placebo; no dose relationship was identified (see Table below).

Number of patients with TEAEs overall, plus number with TEAEs observed in a total of >5 patients by preferred term - safety population

Primary system organ class Preferred term [n]	Placebo (N=10)	SAR113945 (mg) 0.075 (N=3)	0.3 (N=3)	0.75 (N=3)	3 (N=3)	15 (N=9)	25 (N=9)
Any class	8	2	3	3	3	9	6
Musculoskeletal and connective tissue disorders							
Arthralgia	3	1	1	3	3	6	1
Joint swelling	0	1	1	2	2	0	1
General disorders and administration site conditions							
Injection site pain	1	1	1	1	2	4	3
Injection site oedema	1	1	1	1	2	3	3
Sensation of pressure	4	0	1	2	2	1	2

MedDRA 14.0

N = Number of patients treated within each group, n = number of patients with at least 1 TEAE in each category

Note: An AE is considered as treatment-emergent if it occurred from the time of the first investigational product (IP) administration up to Day 84 visit (included).

Note: All patients from last cohort (dose level of 25 mg) received an injection volume of 5 mL instead of 3 mL in the other cohorts

The above TEAEs were generally of mild or moderate intensity, appeared a few hours, after dosing and usually lasted for no more than 48 hours. The only TEAE with a maximum intensity recorded as severe was arthralgia at the target knee reported for 1 patient in the SAR113945 0.75 mg treatment group; the event lasted for 27 days after injection.

Overall, there were few PCSAs for clinical laboratory parameters, vital signs, or ECGs. There were no PCSAs for liver function parameters. There were isolated increases in CRP meeting the PCSA criterion. Such increases were seen for placebo, 0.3 mg, 0.75 mg (1 patient each), and 25 mg (2 patients). One of the patients with increased CRP at 25 mg had an abnormal baseline; the other one (normal baseline) was notable in showing an increase to 28.4 mg/L (5.7 x ULN), the value returned to baseline value (1mg/L) at Day 28. Other increases in CRP were $\leq$2 x ULN. No patient had a QT interval automatically corrected by the ECG machine (QTc) ≥500 ms or an increase in QTc by >60 ms.

From the review of ophthalmologic evaluations, there was no indication of any adverse effect within the eye.

Pharmacokinetic results:

Summary of SAR113945 pharmacokinetic parameters after single intra-articular doses of 0.075 to 25 mg for an observation period up to Day 84 (post administration)

Mean ± SD (CV%) [Geometric Mean]	Plasma SAR113945					
	0.075 mg	**0.300 mg**	**0.750 mg**	**3 mg**	**15 mg**	**25 mg***
N	3	2	3	3	9	9
C_{max} (pg/mL)	65.9 ± 63.4 (96.3) [49.0]	23.7 ± 2.47 (10.5) [23.6]	38.7 ± 14.3 (36.9) [36.6]	351 ± 225 (64.2) [277]	1030 ± 572 (55.8) [893]	844 ± 455 (53.9) [745]
t_{max}[a] (hr)	2.02 (0.75 - 3.00)	1.51 (1.50 - 1.52)	2.00 (1.50 - 2.00)	3.00 (1.50 - 4.02)	2.00 (1.00 - 4.02)	3.00 (1.52 - 8.02)
t_{last}[a] (hr)	4.68 ± 2.30 (2.02 - 6.02)	1.76 ± 0.368 (1.50 - 2.02)	5.01 ± 2.64 (3.02 - 8.00)	479 ± 168 (312 - 647)	1710 ± 481 (647 - 1990)	1900 (816 - 2180)
$t_{1/2z}$ (day)	0.177 ± 0.0615 (34.8) [0.172][b]	NC ± NC (NC) [NC]	0.222 ± 0.154 (69.4) [0.193][c]	25.3 ± 16.8 (66.6) [22.1]	25.3 ± 5.87 (23.2) [24.7]	77.7 ± 76.3 (98.2) [52.2]
AUC (pg•day/mL)	NC ± NC (NC) [NC]	NC ± NC (NC) [NC]	NC ± NC (NC) [NC]	NC ± NC (NC) [NC]	10000 ± 3350 (33.5) [9520][d]	13500 ± 7660 (56.6) [11800][e]
AUC_{0-24} (pg•day/mL)	19.8 ± 14.5 (73.4) [16.9][b]	NC ± NC (NC) [NC]	14.8 ± 8.47 (57.0) [13.6][c]	122 ± 84.2 (68.8) [99.2]	465 ± 169 (36.4) [432]	442 ± 197 (44.7) [406]
AUC_{0-648} (pg•day/mL)	20.2 ± 17.6 (70.0) [17.6][b]	NC ± NC (NC) [NC]	16.5 ± 10.7 (64.9) [14.6][c]	990 ± 400 (40.4) [938]	5050 ± 2270 (44.8) [4550]	4720 ± 2520 (53.4) [4190]

* 7 patients were followed up to Day 112, additional data point not included in calculation of summary statistics

a Median (Min - Max)

b n=2

c n=2

d n=8,

NC = Not calculated

Plasma: SAR113945 appeared quickly in plasma with a mean time to peak (t_{max}) of 1.51 - 3.0 hours. In the dose groups 75 µg to 750 µg, SAR113945 was detectable in plasma only transiently, with a mean t_{last} of 5 hours in the 750 µg dose group. In contrast, sustained concentrations of SAR113945 in plasma were observed in the 3 mg and higher dose groups with t_{last} of several weeks. Plasma concentrations did not increase with strict dose proportionality. Geometric mean elimination half-lives ($t_{1/2z}$) generally increased with dose to approximately 52 days in the 25 mg dose group. The durable presence of SAR113945 in the plasma of the 25 mg dose group resulted in the highest mean AUC of 13500 pg*day/mL calculated for Study TDU10820. The variability (CV%) in C_{max} and AUC values was moderate (30% to 60%).

Urine: Excretion of unchanged SAR113945 was determined in spot urine samples in the highest dose group of 25 mg and the fraction excreted was estimated to not exceed more than 5% of the administered dose over an observation period of 84 days.

Synovial fluid: In the 25 mg dose group synovial fluid samples taken on Day 84 confirmed the presence of SAR113945 in the knee joint. Based on the limited number of synovial fluid samples available, the synovial fluid/plasma exposure ratio was roughly estimated in a range of 100 to 2000; there was a large variability in synovial fluid concentrations.

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