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Sponsor / Company: Sanofi **Drug substance(s):** SAR113945	**Study Identifiers:** NCT01511549, UTN U1111-1121-4499 **Study code:** TDU11333
Title of the study: A randomized, double-blind, placebo-controlled ascending single dose study to evaluate the safety, tolerability and pharmacokinetics of SAR113945 (IKK inhibitor) following intra-articular administration in Japanese patients with knee osteoarthritis (TDU11333)	
Study center(s): 1 center in Japan	
Study period: Date first patient enrolled: 08/Jan/2012 Date last patient completed: 04/Sep/2012	
Phase of development: Phase 1	
Objectives: To assess in Japanese patients with knee osteoarthritis (OA): - The safety and tolerability of SAR113945 after ascending single intra-articular doses. - The pharmacokinetics (PK) of SAR113945 after ascending single intra-articular doses.	
Methodology: Single-center, double-blind, randomized, placebo-controlled, ascending single dose study in 3 sequential groups (8 patients per group).	
Number of patients**:**	Planned: 24 Randomized: 24 Treated: 24
Evaluated:	Pharmacodynamics: 24 Safety: 24 Pharmacokinetics: 18
Diagnosis and criteria for inclusion: Japanese patients aged 40 years or older, diagnosed with primary knee OA based upon X-ray or magnetic resonance imaging (MRI) evidence for joint space narrowing and osteophyte formation (Kellgren Lawrence Grades II or III), a total Western Ontario MacMaster (WOMAC) score ≤72, and patients who fulfilled the American College of Rheumatology Clinical and Radiographic criteria for OA.	

Study treatments

Investigational medicinal product(s): SAR113945

Formulation: 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).

Route(s) of administration: Intra-articular injection (knee)

Dose regimen: Single dose administration of 3 mL SAR113945 injection 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.

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

Criteria for evaluation:

Pharmacodynamics:

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

Secondary Parameter: Biomarkers related to OA.

- Markers relating to pain: prostaglandin E2 measured in synovial fluid (SF)
- Markers of inflammation: matrix metalloproteinase-13, interleukin-6, and tumor necrosis factor α measured in SF and high-sensitivity C-reactive protein (measured as part of the routine laboratory tests).

Safety: Adverse events (AEs); standard clinical laboratory (biochemistry, hematology, urinalysis); physical examination; vital signs; electrocardiogram (ECG); ophthalmologic examination; 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], warmth [yes/no], pain [100 mm visual analog scale]).

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}), terminal half-life associated with the terminal slope ($t_{1/2z}$), time corresponding to the last concentration above the limit of quantification (t_{last}), lag time, interval between administration time and the sampling time preceding the first concentration above the limit of quantification (t_{lag}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to 24 hours postdose (AUC_{0-24}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to t_{last} (AUC_{last}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), apparent total body clearance of a drug from the plasma (CL/F), apparent volume of distribution at the steady state, using single dose data (V_{ss}/F), and mean time a molecule resides in body (MRT).

Pharmacokinetic/Pharmacodynamics 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 synovial samples were not taken on Days 28 and/or 84, then they were collected on Days 112 and/or 168.

SAR113945 concentrations in plasma were determined by a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification (LLOQ) of 20 pg/mL.

Statistical methods:

Safety: The safety analysis was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics. For AEs, frequencies of treatment-emergent adverse events (TEAEs) classified by the Medical Dictionary for Regulatory Activities (version 15.0) system-organ class (SOC) and preferred term were tabulated by dose level. All AEs were listed.

Frequency of patients with abnormalities and/or potentially clinically significant abnormalities (PCSAs), were summarized per dose level by counts for each type of parameter.

Individual clinical laboratory data, vital signs and 12-lead ECGs data were listed and flagged for PCSAs and for lower and upper clinical laboratory limits. Raw data and changes from baseline for selected parameters, including local tolerability at injection site, were summarized by descriptive statistics and summary plots.

Pharmacokinetics: Pharmacokinetic parameters for SAR113945 were summarized for each dose level by descriptive statistics. Dose proportionality was assessed for C_{max}, AUC_{last}, and AUC using a log-transformed power model. Estimates with 90% confidence intervals (CIs) for the parameter increase associated with an r-fold (r = 2 and highest dose/lowest dose only) increase in dose were computed.

For $t_{1/2z}$, the dose effect was assessed using a linear fixed effects model on log-transformed $t_{1/2z}$ values. Estimates and 90% CIs for the geometric mean were provided by dose level and all pooled doses.

Pharmacodynamics: The total WOMAC score and WOMAC subscore for pain, stiffness, and physical function were analyzed as raw data and change from baseline and summarized using descriptive statistics and plots.

The biomarkers related to OA were listed.

Summary:

Pharmacodynamic results: WOMAC scores and subscores suggested a trend for a positive effect of the treatment, as all active treatment groups showed a greater improvement (change) from baseline compared with placebo. There was no clear dose relationship and the placebo group had lower WOMAC scores and subscores at baseline; however, the highest dose (60 mg) showed the largest improvement.

No conclusions could be drawn from the biomarker data concerning the effect of treatment with SAR113945 since it was not possible to collect many paired samples (ie, baseline and following treatment) from enough patients in order to be able to observe any treatment or dose-related trends.

Safety results: Twenty-one of the 24 patients (16/18 patients receiving SAR113945 and 5/6 patients receiving placebo) experienced at least 1 TEAE. No serious TEAEs were reported during the study, and no patients discontinued the study due to TEAEs. Treatment-emergent AEs were evenly reported across all treatment groups, including placebo, and no dose relationship was identified. The most frequently reported TEAEs by SOC were gastrointestinal disorders (mostly nausea [1/6 patients each for placebo, SAR113945 30 mg and SAR113945 60 mg] and stomatitis [1/6 patients each for placebo, SAR113945 15 mg, and SAR113945 60 mg]) and musculoskeletal and connective tissue disorders (mainly arthralgia [1/6 patients each for SAR113945 15 mg and SAR113945 30 mg, 2/6 patients each for placebo and SAR113945 60 mg]). Injection site pain (1/6 patients each for placebo, SAR113945 15 mg, and SAR113945 60 mg) and swelling (1/6 patients for SAR113945 15 mg) were reported as injection site-related TEAEs in this study. Knee joint effusion was reported by 1 patient in the SAR113945 30 mg and 1 patient in the SAR113945 60 mg dose groups. All TEAEs were of mild or moderate intensity and no severe TEAEs were observed during the study.

A few PCSA values, evenly distributed across the treatment groups, were reported for clinical laboratory parameters, vital signs, and ECG parameters. There were no PCSAs for liver function parameters. An increase in alkaline phosphatase in 1 female patient who received SAR113945 30 mg (not meeting the PCSA criterion [>1.5 x upper limit of normal range]) was considered clinically significant and reported as an AE by the Investigator. No PCSAs for C-reactive protein were reported. No patient had a prolonged QT interval corrected for heart rate ([QTc] >450 ms for males, >470 ms for females) or an increase in QTc from baseline of >30 ms.

The visual analogue scale data showed decreases in knee pain for all treatment groups, including placebo, with no overall dose-related trends. Decreases from baseline in the SAR113945 treated groups were greater than placebo up to Day 14 for the 15 mg and 30 mg doses, and up to Day 28 for the 60 mg dose. Following this, the decreases were comparable to the placebo group.

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

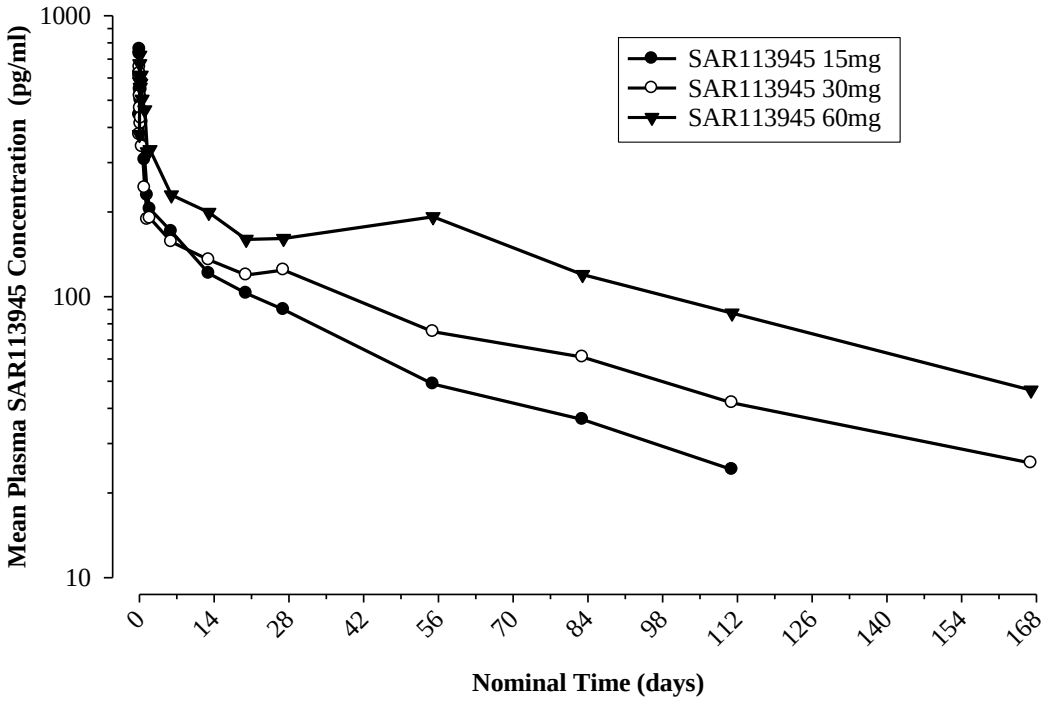
Pharmacokinetic results:

Summary of SAR113945 pharmacokinetic parameters after single intra-articular doses of 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}	765 ± 488	709 ± 408	749 ± 753
(pg/ml)	(578) [63.9]	(597) [57.6]	(480) [100.5]
t_{max}[a]	2.02	1.50	2.00
(hr)	(1.50 - 2.03)	(1.00 - 2.00)	(1.50 - 8.00)
t_{last}[a]	2665.04	4009.08	4009.19
(hr)	(673.68 - 4009.15)	(2615.98 - 4009.47)	(4008.33 - 4009.58)
$t_{1/2z}$	63.7 ± 31.3	79.2 ± 30.2	83.3 ± 40.7
(day)	(57.8) [49.1]	(73.4) [38.2]	(74.0) [48.8]
AUC_{last}	8150 ± 4960	11900 ± 6280	21900 ± 13000
(pg•day/mL)	(6280) [60.9]	(10700) [52.7]	(18400) [59.3]
AUC_{0-24}	442 ± 320	367 ± 265	525 ± 584
(pg•day/mL)	(323) [72.3]	(289) [72.2]	(299) [111.2]
AUC	12000 ± 4160	19700 ± 4310	32800 ± 15800
(pg•day/mL)	(11400) [34.8][b]	(19400) [21.9][c]	(29200) [48.1][b]
MRT	1390 ± 367	2010 ± 1080	2340 ± 846
(hr)	(1350) [26.4][b]	(1840) [53.8][c]	(2220) [36.1][b]

[a] Median (Min - Max)
[b] n=4; [c] n=3

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 1.5 to 2.0 hours.

For a 2-fold increase between the 15 and 30 mg dose, estimates for C_{max} and AUC increases were 1.03 (90% CI: 0.42 2.57) and 1.70 fold (90% CI: 0.91-3.15), respectively. Between the 30 and 60 mg doses, C_{max} and AUC increased with estimates of 0.80 (90% CI: 0.32-2.00) and 1.50 (90% CI: 0.81-2.79), respectively. SAR113945 concentrations in plasma increased roughly dose proportionally over the investigated dose range for AUC.

The variability of C_{max} values was high (60% to 90%), to very high (>90%) but did not exceed 2.01 ng/mL as seen for a patient in the 60 mg group. For AUC the variability was low (<30%) to moderate (30% to 60%).

No statistically significant effect of the dose on $t_{1/2z}$ was seen (p = 0.628). Point estimates for $t_{1/2z}$ ranged between 57.8 days (90% CI: 40.45-82.48 days) for the 15 mg dose and 74.04 days (90% CI: 51.85-105.73 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 1/6 patients in the 15 mg group, in 5/6 patients in the 30 mg group, and 6/6 patients in the 60 mg group.

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