SYNOPSIS

Title of the study: Activity and safety of oral administration of SSR150106XB for the reduction of inflammation in patients with active rheumatoid arthritis (RA): A 4-week, multi-center, randomized, double-blind, placebo-controlled parallel group study of 90 µg administered once daily and 90 µg once every other day (ACT5488/ACCORD-RA).

Investigator(s): [redacted]

Study center(s): Patients were enrolled at 26 centers in 6 countries in Eastern Europe.

Publications (reference): Not applicable.

Study period:

Date first patient enrolled: 09-Oct-2007

Date last patient completed: 02-Jun-2008

Phase of development: IIa

Objectives: To assess the effect of SSR150106XB 90 µg once daily and SSR150106XB 90 µg once every other day to reduce systemic inflammation in patients with active RA, as measured by changes in the acute phase protein, C-reactive protein (CRP), over a 4-week treatment period.

Methodology: Multi-center, randomized, double-blind, placebo-controlled parallel group study.

Patients were randomly assigned to 1 of the 3 treatment groups and received SSR150106XB 90 µg once daily (OD), 90 µg once every other day (OEOD), or matching placebo for 4 weeks.

Number of patients: Planned: 75 (25 patients per treatment group)

Randomized: 79

Treated: 79

Evaluated: Efficacy/pharmacodynamic: Intent-to-treat (ITT) population: 79; Per-protocol (PP) population: 70

Safety : 79

Pharmacokinetics : 79

Diagnosis and criteria for inclusion: Men and women between 18 and 75 years of age, inclusive.
Patients with diagnosis of RA for at least 6 months based on the 1987 American Rheumatism Association (ARA) revised criteria for the classification of RA who are either treatment-naïve or who had previously discontinued their RA-directed medication due to either intolerability or insufficient efficacy.
Active disease at screening and baseline as defined by: i) at least 9 out of the 68 joints assessed as painful or tender on motion; ii) at least 6 out of the 66 joints assessed as swollen; iii) morning stiffness of at least 45 minutes in duration.
CRP >18 mg/L at screening and at CRP laboratory confirmation (pre-baseline) visit.
CYP2D6 non-poor metabolizer (non-PM) status, confirmed by genotyping, prior to randomization.

Investigational product: SSR150106XB 3.75 mL solution in vials containing a 90 µg unit dose.

Dose: 90 µg once daily (OD) or 90 µg once every other day (OEOD).

Administration: Oral route, with 200 mL of noncarbonated water, together with the morning meal.

Batch number(s): [redacted]

Duration of treatment: 28 days.

Duration of observation: Up to 10 weeks (screening period up to 4 weeks, double-blind treatment period of 4 weeks, and follow-up period of 2 weeks).

Reference therapy: Placebo 3.75 mL solution in vials.

Dose: 0 mg.

Administration: Oral route, with 200 mL of noncarbonated water, together with the morning meal. Placebo solution was taken either daily (in the placebo group) or alternatively with SSR150106XB every other day (in the SSR150106XB OEOD group)

Batch number(s): [redacted]

Criteria for evaluation: The current report is an abbreviated report, and as such, only the primary efficacy variable in the PP population and safety results in the ITT population are being presented in full. Secondary efficacy variables will be addressed when appropriate.

Primary variable – Efficacy:
The primary variable was mean change-from-baseline in CRP level at endpoint (Visit 7).

Secondary variables – Efficacy, safety, pharmacokinetics:
Efficacy: Main secondary efficacy endpoints were mean change-from-baseline in CRP level at Visits 4, 5 and 8; CRP responder rate (percentage of patients ≥ 50% decrease in serum CRP) at endpoint (Visit 7) and at Visits 4, 5 and 8 as compared to baseline; time to first CRP response (≥ 50% decrease in serum CRP).
Other secondary efficacy endpoints were ACR20/ACR50/ACR70 % improvement (composite index) responder rates; percent improvement for each component: swollen joint count, tender joint count, patient's global assessment (visual analogue scale – VAS), Investigator's global assessment (VAS), pain intensity (VAS), and Health Assessment Questionnaire (HAQ).

Safety: Adverse events (AEs) reported by the patient or noted by the Investigator, physical examination, vital signs, 12-lead electrocardiogram (ECG), and standard hematology, serum chemistry, and urinalysis.
Tolerability and safety of the study treatments were monitored by an external panel of experts (Data Monitoring Committee – DMC).

Pharmacokinetics (PK): Trough plasma concentrations (C_{trough}) of both SSR150106 and its metabolite, SSR150655, were to be documented after 2 dose regimens (90 µg OD or 90 µg OEOD).

Statistical methods:

Primary variable – Efficacy:
The primary efficacy criterion, the CRP absolute change between endpoint and baseline in the PP population, was analyzed by Analysis of Covariance (ANCOVA) using centered baseline CRP as covariate and treatment group as fixed effect. The adjusted means (SAS LSMEANS) were computed and the comparison test versus placebo was performed using a Student's test. There were no adjustments for multiplicity of doses. The primary population used for efficacy evaluation was the PP population.

Secondary variables – Efficacy, safety:
Efficacy: The analysis of the quantitative variables on changes versus baseline to endpoint followed the same model as the primary endpoint. For categorical data (including responders' analysis) at endpoint, pair-wise comparisons of active treatment dosages versus placebo were done with a chi-square or Fisher's exact test. Descriptive tables were presented by visit.
Analyses done on exploratory endpoints were only descriptive, without any test applied for treatment groups' comparison.

Safety: General evaluation of safety and tolerability of SSR150106XB was based on the review of individual values and summary statistics. Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 was used for AE coding. Treatment-emergent adverse events (TEAEs) were tabulated by counts and percentages. Changes in clinical laboratory tests, ECG, and vital signs were examined against pre-defined criteria for potentially clinically significant abnormalities (PCSA) and were tabulated by counts.

Summary:

Study disposition: A total of 79 patients at 26 centers in Eastern Europe (Croatia, Czech Republic, Romania, Russia, Slovakia, and Ukraine) were randomized into the double-blind phase of the trial and treated. Nine of them discontinued the 4-week study treatment period prematurely.

Demographics: Of the 79 patients who received either of the study drugs, 60 (75.9%) were females and 19 (24.1%) were males, but the fraction of males in the placebo group (38.5%) was greater than in the active treatment groups (14.8% and 19.2% in the SSR150106XB OEOD and OD groups, respectively). The mean (±SD) age for all patients was 51.8 ± 13.6 years. The overall age range for the study was 19 to 74 years. All the patients were Caucasian.

Baseline disease characteristics: The majority of the patients presented with a Class II (55.7%) or Class III (39.2%) ARA functional class, were diagnosed with RA from 1 to 5 years (40.5%) or >10 years (30.4%) , and were 44.0 ± 14.0 years old when diagnosed. The mean baseline CRP value was 49.8 ± 35.4 mg/L and was comparable within the 3 treatment groups.

Protocol deviations: In total, 9 patients presented with pre-defined major protocol deviations (6 patients had baseline CRP values ≤18 mg/L, 3 patients reported intake of prohibited RA-directed concomitant medication, and among the 3 who took forbidden concomitant medication, 1 patient was additionally exposed <7 days) and were excluded from the PP population.

Dosage and duration: Overall compliance with intake of study medication was good (99.8%). The mean extent of exposure was 26.6 ± 4.8 days.

Changes in the conduct of the study or planned analyses: One protocol amendment (Amendment No. 1, dated 9 July 2007) was issued prior to patients being enrolled in the study. There were no changes during the course of the study nor made with regard to the planned analyses.

Efficacy results:

Primary efficacy variable: The course of CRP change over time is presented in Figure 1. The CRP levels at endpoint remained stable in the placebo group, whereas a slight increase in the SSR150106XB OEOD group and a decrease in the SSR150106XB OD group was shown. However, no significant differences were observed between any dose of SSR150106XB and placebo (see Table 1). It is interesting to note that, after stop of treatment on Day 28, CRP levels decreased in both active treatment groups, resulting in change from baseline to Day 43 of -4.36 mg/L (-8.06%) in the SSR150106XB OEOD and -20.18 mg/L (-15.45%) in the OD group. These results are consistent when running the same analysis on the ITT population (data not shown here).

Figure 1 – CRP: absolute changes (mean ± SEM) from baseline (Observed Cases and LOCF) – PP population

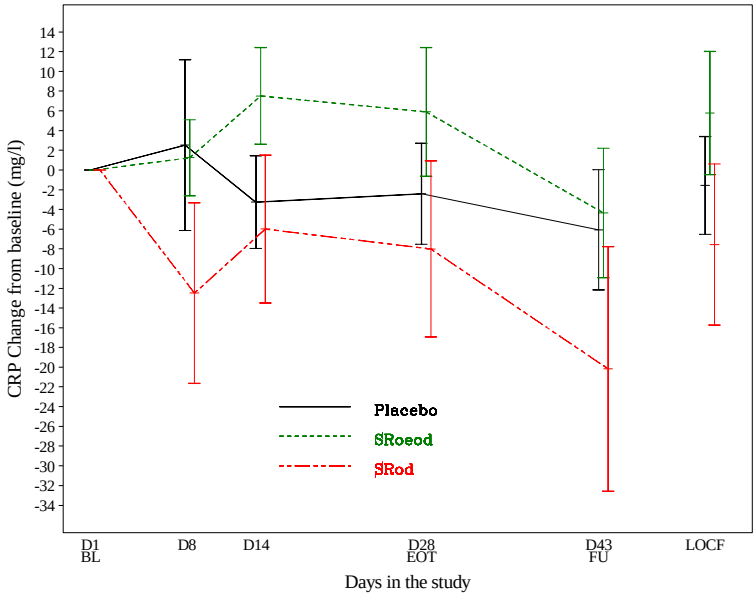

Table 1 – Summary of CRP (LOCF analysis) – PP population

CRP (mg/l)	Placebo (N=22)	SR oeod (N=24)	SR od (N=24)
Number	22	24	24
Baseline			
Mean (SD)	55.48 (29.66)	49.00 (26.30)	55.15 (48.08)
Median	44.15	41.83	39.08
Min : Max	19.8 : 138.7	18.1 : 144.5	20.6 : 258.6
Absolute change from baseline to endpoint (LOCF)			
LS Mean (SEM)	-0.26 (5.42)	3.47 (5.20)	-6.45 (5.19)
LS Mean Difference from Placebo (SEM)	-	3.74 (7.52)	-6.18 (7.50)
95% Confidence Interval	-	(-11.29 to 18.76)	(-21.16 to 8.80)
p-value vs. Placebo	-	0.6210	0.4130
% change from baseline to endpoint (LOCF)			
Mean (SD)	5.25 (45.29)	23.10 (69.74)	2.98 (61.46)
Median	2.18	15.67	-7.32
Min : Max	-77.4 : 119.7	-90.1 : 162.1	-83.1 : 192.2

Main secondary efficacy variable: In total, 9 patients (13%) were classified as CRP responders (CRP response defined as ≥50% decrease in serum CRP). No significant difference was observed between any dose of SSR150106XB and placebo (see Table 2).

Table 2 – Summary of CRP response (LOCF analysis) – PP population

	Placebo (N=22)	SR oeod (N=24)	SR od (N=24)
At endpoint (LOCF)			
Number	22	24	24
CRP responder	2 (9.1%)	4 (16.7%)	3 (12.5%)
CRP non responder	20 (90.9%)	20 (83.3%)	21 (87.5%)
p-value vs Placebo	-	0.6672	1.0000

CRP response defined as ≥ 50% decrease in serum CRP

Other secondary efficacy variables: The percent of ACR20 responders at endpoints in the PP population was 31.8% in the placebo group, 33.3% in the SSR150106XB OEOD group, and 50.0% in the SSR150106XB OD group. The observed differences in response rates between SSR150106XB and placebo groups did not reach statistical significance. Of note, 14 days after stop of the 4-week treatment, the ACR20 response rate in the SSR150106XB OD group remained at the 50% level, whereas it declined in the SSR150106XB OEOD group but even more in the placebo group, thus increasing the numerical difference between the SSR150106XB OD group and the placebo group.

Similarly, the analysis of individual ACR components showed a consistent numerical superiority of the SSR150106XB OD group over placebo, but none was significant.

The ACR50 response rates were 4.5%, 16.7% and 12.5% in the placebo, SSR150106XB OEOD and SSR150106XB OD groups, respectively, whereas the ACR70 response rates were 4.5%, 4.2% and 4.2% in the placebo, SSR150106XB OEOD and SSR150106XB OD groups, respectively. The validity of these figures, however, suffers from the small number of subjects in either of the treatment groups, ranging from 1 subject (4.2%) to 4 subjects (16.7%).

Safety results: Overall, 35.4% of patients experienced TEAEs during the study, but the number of TEAEs was equally distributed between the placebo and both active SSR150106XB groups (see Table 3). The most frequently reported TEAEs were from the following system organ classes: nervous system disorders (dizziness and headache), gastrointestinal disorders (nausea, dyspepsia, and vomiting), infections and infestations, and investigations.

Table 3 – Overview of safety profile: number (%) of patients – All treated population

	Placebo (N=26)	SR oeod (N=27)	SR od (N=26)
Patients with any TEAE (including SAEs)	9 (34.6%)	11 (40.7%)	8 (30.8%)
Patients with any serious TEAE (including SAEs leading to death)	0	0	3 (11.5%)
Deaths	0	0	0
Patients permanently discontinuing treatment due to AE	1 (3.8%)	3 (11.1%)	0

TEAE: Treatment Emergent Adverse Event, SAE: Serious Adverse Event
Adverse event coded in MedDRA version 10.0

In total, 3 patients presented with serious TEAEs, all occurring in the SSR150106XB OD group (see Table 4): one patient with a history of hypertension who developed a serious hypertensive stroke 1 week after completion of her treatment, and another who requested, for logistic reasons, hospitalization for differential diagnosis of her tinnitus (finally diagnosed as chronic earache). Both serious TEAEs resolved without sequelae.

The third serious TEAE (which was reported as a suspected unexpected serious adverse reaction – SUSAR) involved a 61-year old, Caucasian male patient with a medical history relevant for chronic cholelithiasis, who already showed elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) up to 6-fold upper limit of normal (ULN) prior to randomization, which was attributed to food poisoning a day before randomization. The patient restarted study medication, after a temporary discontinuation of 3 days duration due to transient neutropenia. At the day of final study visit and completion of study medication, the patient was clinically normal and there were no signs of liver or other organ systems involved. However, laboratory data showed a significant increase in transferases (ALT up to 12.2-fold ULN, AST up to 17.8-fold ULN), in alkaline phosphatase (ALP up to 3.0-fold ULN) and lactate dehydrogenase (LDH up to 2.6-fold ULN) together with a significant increase in total and direct bilirubin (up to 1.8-fold ULN). Conclusion of an abdominal ultrasound examination was calculous cholelithiasis and toxicoallergic hepatosis (possible medication) reactive hepatopathy. After laparoscopic cholecystectomy, the patient fully recovered from significant increase in ALT, AST and LDH and from significant increase in total and direct bilirubin whereas GGT and ALP improved substantially but were not yet within the normal range at the end of observation.

Table 4 – Number (%) of patients experiencing serious TEAE(s) presented by SOC and PT – All treated population

Primary system organ class Preferred term	Placebo (N=26)	SR oeod (N=27)	SR od (N=26)
Any serious TEAE	0	0	3 (11.5%)
Nervous system disorders	0	0	1 (3.8%)
Cerebrovascular accident	0	0	1 (3.8%)
Investigations	0	0	1 (3.8%)
Blood bilirubin increased	0	0	1 (3.8%)
Hepatic enzyme increased	0	0	1 (3.8%)
Ear and labyrinth disorders	0	0	1 (3.8%)
Ear pain	0	0	1 (3.8%)

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, PT: Preferred Term
Adverse events coded in MedDRA version 10.0
Primary SOC and preferred term sorted by decreasing frequency in SR od of all TEAE

Permanent discontinuation of study medication due to AEs occurred in 4 patients (see Table 5), 1 in the placebo group and 3 in the SSR150106XB OEOD group. In 3 cases it was the decision of the patient to discontinue the treatment due to the AE, whereas in the case of elevated transaminases (with peak levels up to 8.9-fold ULN or 6.2 times of baseline value for ALT, whereas total bilirubin remained always within the normal range) there were no clinical symptoms instead discontinuation had been requested by the investigator following the standard procedure described in the protocol; of notice, this specific patient presented with elevated transaminases (1.5-fold ULN for both ALT and AST) already at baseline.

Table 5 – Number (%) of patients experiencing AE(s) leading to study drug discontinuation presented by SOC and PT – All treated population

Primary system organ class Preferred term	Placebo (N=26)	SR oeod (N=27)	SR od (N=26)
Any AE leading to study drug discontinuation	1 (3.8%)	3 (11.1%)	0
Gastrointestinal disorders	1 (3.8%)	0	0
Abdominal pain upper	1 (3.8%)	0	0
Infections and infestations	0	1 (3.7%)	0
Bronchitis	0	1 (3.7%)	0
Investigations	0	1 (3.7%)	0
Transaminases increased	0	1 (3.7%)	0
Cardiac disorders	0	1 (3.7%)	0
Palpitations	0	1 (3.7%)	0

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, PT: Preferred Term
Adverse events coded in MedDRA version 10.0
Primary SOC and preferred term sorted by decreasing frequency in SR od of all TEAE

For clinical chemistry parameters, PCSAs in liver function tests were predominantly found in the SSR150106XB groups, with 2 cases of asymptomatic increases of transaminases up to 12.2-fold and 8.9-fold ULN for ALT, respectively (for more detailed case description, see above). None of them were qualified as potential Hy's law cases.

The analysis of categorical ECG parameters showed no noticeable effect in either treatment group. Specifically, there were no relevant findings with respect to QTc prolongation in any of the treatments groups.

Pharmacokinetic results: Trough concentrations of SSR150106 and its metabolite SSR150655 are available in the bioanalytical report.

Summary and conclusion: [redacted]

Date of report: 20-Nov-2008