2. SYNOPSIS

Name of Sponsor/Company 4SC AG **Name of Finished Product** SC12267 film coated tablets **Name of Active Ingredient** SC12267	**Individual Trial Table** **Referring to Part of the Dossier** **Volume** **Page**	***(For National Authority Use only)***

Title of Trial:	A Randomized, Double Blind, Placebo-controlled, Proof of Concept Study to Evaluate Efficacy, Safety, and Pharmacokinetics of two Different Doses of SC12267 (20 mg, 35 mg) in Patients with Rheumatoid Arthritis.	
Investigators	Co-ordinating/Principal Investigator ('Leiter der Klinischen Prüfung', §40 AMG) was Prof. Dr. med. B. Manger, Department of Internal Medicine III and Institute for Clinical Immunology, Clinic of Friedrich-Alexander University, Erlangen, Germany. For a complete list of investigators see Section 6 and Appendix 16.1.4.	
Trial Centers	13 centers selected, 12 active centers (2 in Germany, 8 in Poland, 2 in Serbia), 1 inactive center (Germany)	
Publication	Not applicable	
Studied Period	Date of first enrollment: 26-Feb-2007 Date of last follow-up: 08-Oct-2007	**Phase of Development:** Phase IIa
Objectives	Primary objective: • To evaluate the efficacy of SC12267 in patients with RA. Secondary objectives: • To evaluate the safety profile of SC12267 in patients with RA, • To evaluate the plasma concentration of SC12267 in patients with RA after once daily application (trough value).	
Methodology	Randomized, double blind, placebo-controlled, multicenter clinical trial; screening visit, efficacy/safety assessments at baseline, after 1 to 12 weeks of treatment with either SC12267 or placebo, and at a follow-up visit.	

No. of Patients	planned			analyzed		
	SC 20 mg	SC 35 mg	placebo	SC 20 mg	SC 35 mg	placebo
Randomized	n=40	n=40	n=40	n=36	n=41	n=44
Evaluable - safety	n=40	n=40	n=40	n=36	n=41	n=44
- full analyis set	-	-	-	n=35	n=38	n=43
- per-protocol set	n=35	n=35	n=35	n=32	n=35	n=40

Diagnosis and Main Criteria for Inclusion	Diagnosis: • Active rheumatoid arthritis of functional class I, II or III Inclusion Criteria: • Male and female Caucasian patients with active RA, age ≥18 years, BMI 19-30 kg/m2, written informed consent Major Exclusion Criteria: • Class IV RA; history of treatment with leflunomide, gold, cyclophosphamide, biologicals; pretreatment within last 4 weeks with methotrexate (MTX), sulfasalazine (SUL), hydroxychloroquine, azathioprine, cyclosporine, specific corticosteroids; physical therapy; relevant history/concomitant diseases (e.g. arrhythmia, heart failure, uncontrolled asthma or hypertension, renal disease, malignancy, immunodeficiency, active tuberculosis, psychiatric illness, HIV, hepatitis, serious drug sensitivity, alcohol or drug dependence); vaccination; relevant abnormalities in Hb, WBC, platelets, liver enzymes, creatinine, or GFR; inadequate contraception, pregnancy, heavy smoking, participation in another trial within last 3 months.
Test Product, Dose, Mode of Administration, Batch-No.	SC12267 20 mg (batch No. 79156G002, expiry date 10-Feb-2007 and batch No. 79155G003, expiry date 13-Oct-2007) and 35 mg (batch No. 76275G001, expiry date 10-Feb-2007 and batch No. 79156G002, expiry date 13-Oct-2007) film coated tablets for oral administration once daily

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Duration of Treatment:	12 weeks
Reference Therapy, Dose, Mode of Administration, Batch-No.	Placebo (batch No. 75930G001, expiry date 10-Feb-2007 and batch No. 79154G002, expiry date 13-Oct-2007) film coated tablets for oral administration once daily
Criteria for Evaluation Efficacy	**Primary efficacy variable:** • Difference last visit versus baseline in DAS28 (CRP) (Disease Activity Score 28 joints) calculated from the 4 variables (see below) TJC, SJC, CRP and HAQ according to EULAR **Secondary efficacy variables:** • DAS 28 based on ESR = DAS 28(ESR) • Tender (TJC) and Swollen Joint Count (SJC) of 28 joints (0=no, 1=yes) • Acute phase reactant (CRP and ESR) • DAS28 (CRP) and DAS28 (ESR) responder rates • ACR20, ACR50, ACR70 responder rates as defined by American College of Rheumatology • Patient's pain (Visual Analogue Scale, VAS) • Patient's and physician's global assessment of disease activity (VAS) • Physical disability (Health Assessment Questionnaire, HAQ) • Morning stiffness • Laboratory parameters: RF, Anti-CCP • Patient's and physician's global assessment of efficacy (end of study) • Use of rescue medication
Safety	• Adverse events • Vital signs, 12-lead ECG • Safety laboratory (hematology, coagulation, clinical chemistry, urinalysis) • Patient's and physician's global assessment of tolerability (end of study)
Pharmacokinetics	• SC12267 trough plasma concentration at steady state
Statistical Methods	Efficacy: A confirmatory analysis of the primary efficacy variable was conducted for the highest dose vs. placebo using 2-factorial ANOVA with pairwise contrasts of both doses vs. placebo. Two-sided confidence intervals (95 % CI) were given. All components of DAS28 (CRP and ESR) were described by summary statistics. DAS28 and ACR responder rates as well as global assessments were summarized by appropriate frequency tables. DAS28 and ACR responder classifications were analyzed by Cochran-Mantel-Haenszel (CMH)-tests. Confidence intervals for the treatment differences of the ACR responder rates were separately calculated for each dose versus placebo A-posteriori efficacy analyses after unblinding: Subgroup analyses by RA classes I to III, by RA pretreatment (MTX, SUL, others, and all disease modifying drugs (DMARDS)), cortison comedication, and baseline anti-CCP level were performed on DAS28 (CRP) values, DAS28 (CRP) responders, and ACR responders. Safety: Treatment emergent AEs (from first up to 14 days after last dosing, TEAEs) were analyzed globally as well as on MedDRA preferred term (PT) and system
Statistical Methods (cont).	organ class (SOC) level. Vital signs, ECG variables, and laboratory data were analyzed by summary statistics for each time point and for the differences to baseline. Additionally, clinically significant laboratory data and global assessments were described by frequency tables. Pharmacokinetics: Trough plasma concentrations were analyzed by 2-factorial ANOVA for time and dose effects. Summary statistics were applied in addition.

SUMMARY – CONCLUSIONS

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EFFICACY RESULTS

Primary efficacy analysis:

The statistical analysis of the primary efficacy variable DAS28 (CRP) based on the FAS population and the PPS population indicated comparable results. DAS28 (CRP) decreased in all 3 treatment groups during the 12 weeks course of the trial as can be seen from the following table:

DAS28 (CRP)	**SC12267 20 mg** (n=34, FAS)		**SC12267 35 mg** (n=38, FAS)		**Placebo** (n=43, FAS)	
	Mean±SD	Median, Min-Max	Mean±SD	Median, Min-Max	Mean±SD	Median Min-Max
Day 1	5.49±0.88	5.49, 3.8-7.5	5.62±0.81	5.60, 3.6-8.1	5.75±0.92	5.87, 3.5-7.7
Week 2	5.23±1.03	5.40, 2.6-7.4	5.40±1.17	5.46, 1.3-7.8	5.45±1.11	5.45, 2.9-8.0
Week 4	4.96±1.01	5.12, 2.6-7.3	5.26±1.09	5.03, 2.1-7.5	5.11±1.19	5.05, 1.8-7.7
Week 8	4.62±1.14	4.73, 1.3-7.2	4.74±1.27	4.66, 1.8-7.4	4.81±1.08	4.73, 1.9-7.1
Week 12	4.53±1.24	4.56, 1.8-7.2	4.50±1.23	4.41, 2.0-6.9	4.65±1.33	4.69, 1.8-7.0
Last value	4.57±1.20	4.58, 1.8-7.2	4.62±1.23	4.57, 2.0-6.9	4.67±1.32	4.65, 1.8-7.0
Difference last value to baseline	-0.91±0.92	-0.88, -3.1-0.8	-1.01±1.07	-1.02, -4.1-1.0	-1.08±1.15	-1.02, -3.6-2.2

Due to a high response to placebo, statistically significant differences between SC12267 20 mg and SC12267 35 mg versus placebo were not observed for the entire FAS and PPS populations.

Subgroup analyses indicated more prominent effects of SC12267 20 mg and 35 mg on DAS28 (CRP) than placebo in patients who had received DMARDSs prior to enrollment (differences between Week 12 and baseline; FAS, mean: placebo (n=15): -0.69, SC12267 20 mg (n=8) -0.94, SC12267 35 mg (n=10) -1.50; PPS: placebo (n=14): -0.89, SC12267 20 mg (n=8) -0.94, SC12267 35 mg (n=9) -1.60).

Likewise, SC12267 35 mg showed a trend towards a higher efficacy than placebo in patients with RA class III (mean decrease in DAS28 (CRP) between Week 12 and placebo: SC12267 35 mg -1.04, placebo -0.62).

Subgroup analyses lacked adequate power to reveal statistically significant differences between the treatments due to the small number of patients per group.

Secondary efficacy analyses:

DAS28 (ESR): The treatment effects on the DAS28 (ESR) score resembled those observed for the DAS28 (CRP) score. The DAS28 (ESR) score decreased continuously between baseline and Week 12 in all 3 random groups (mean±SD

Secondary efficacy analyses (cont.):

changes last value versus baseline: SC12267 20 mg -0.97±1.00; SC12267 35 mg -1.00±1.07; placebo: -1.00±1.25). Statistically significant differences between the treatment groups were not observed.

Tender joint count (TJC): The number of tender joints decreased in all 3 treatment groups during the course of the trial. The active treatments and placebo attained quite similar effects (mean±SD changes Week 12 versus baseline: SC12267 20 mg -4.30±7.60; SC12267 35 mg -6.68±6.74; placebo: -6.85±7.42).

Swollen joint count (SJC): The number of swollen joints decreased continuously between baseline and Week 12 following active treatment as well as following placebo (mean±SD changes Week 12 versus baseline: SC12267 20 mg -4.12±4.90; SC12267 35 mg -4.56±5.00; placebo: -4.65±4.69).

DAS28 responder rates: About 40 to 60 % of patients showed a moderate treatment response to the active treatments and placebo alike as assessed by the DAS28 classifications. The highest percentage of moderate responders (61.8 %) was observed based on the DAS28 (CRP) score in the SC12267 35 mg group. CMH-tests demonstrated no statistically

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significant differences between active treatments and placebo.

ACR20, ACR50, ACR70 responder rates: ACR20 responder rates indicated a positive treatment effect in 32.5 % of patients on placebo, 39.4 % of patients on SC12267 20 mg and 47.1 % of patients on SC12267 35 mg. Active treatment with SC12267 35 mg was associated with a clearly higher ACR20 response rate than placebo. Statistical significance was not reached for rate differences in CMH tests. In the subgroup of DMARDS pretreated patients, ACR20 responder rates at Week 12 were higher in the SC12267 20 mg (25 %) and 35 mg (50 %) group than in the placebo group (13.3 %). There were no consistent differences between mean plasma concentration levels in ACR20 responders and non-responders to treatment.

Acute phase reactants: Baseline CRP (mg/L) and ESR (mm/h) were highest in the placebo and lowest in the SC12267 35 mg group. After 12 weeks of treatment, mean values decreased on SC12267 20 mg and on placebo and remained nearly unchanged on SC12267 35 mg (mean±SD: SC12267 20 mg: CRP -3.772±13.434, ESR -1.8±20.0; SC12267 35 mg: CRP -0.106±16.407, ESR -0.2±11.2; placebo: CRP -3.246±20.193, ESR -1.5±24.7).

Patient's pain: The patient's subjective experience of pain (VAS, mm) decreased nearly continuously throughout the course of treatment in all 3 random groups. Due to a high placebo response, active treatments and placebo did not differ to a clinically relevant extent (mean±SD decrease between baseline and Week 12: SC12267 20 mg: -19.73±23.74; SC12267 35 mg: -18.26±27.97; placebo: -15.43±24.07).

Global assessment of disease activity: Patients' and physicians' assessment of global disease activity demonstrated an improvement following all treatments without prominent differences between the 3 random groups.

Physical disability (HAQ): Health assessment questionnaires indicated a comparable, continuous decrease in the patients' physical disability between baseline and Week 12 in all 3 treatment groups.

Morning stiffness: Morning stiffness (min) decreased continuously throughout the course of the trial in all 3 random groups (mean±SD decrease between baseline and Week 12: SC12267 20 mg: -39.39±58.95; SC12267 35 mg: -47.00±52.49; placebo: -61.05±68.03).

RA specific laboratory parameter: RF and anti-CCP levels showed a high variability between patients. Mean anti-CCP data indicated a small increase in the placebo group and slight decreases in the active treatment groups after 12 Weeks of treatment.

Global assessment of efficacy: In all 3 treatment groups was the global efficacy judged as 'very good', 'good' or 'moderate' by the majority of patients (SC12267 20 mg n=29/34; SC12267 35 mg n=27/38; placebo n=34/43) and physicians (SC12267 20 mg n=30/35; SC12267 35 mg n=30/38; placebo n=35/43) alike.

Use of rescue medication: The mean number of paracetamol tablets used per day did not change relevantly throughout the course of the trial in any of the random groups. After 12 weeks of treatment, patients on SC12267 20 mg required 0.78 tablets/day as compared to 1.01 in the SC12267 35 mg and 1.03 in the placebo group.

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SAFETY RESULTS

Adverse events: Overall, TEAE occurred in 16/36 (44.4 %) patients in the SC12267 20 mg group, 23/41 (56.1 %) patients in the SC12267 35 mg group, and 14/44 (31.8 %) patients in the placebo group. The majority of TEAE were mild to moderate in severity, TEAE of severe intensity occurred in all 3 treatment groups in 1 patient each.

AE leading to permanent treatment discontinuation were observed in 1 patient on SC12267 20 mg and 3 patients on SC12267 35 mg.

The most frequent TEAEs (incidence>10 % in any one group) were (i) nervous system disorders (most prominent PT headache, incidences: SC12267 20 mg 5.6 %, SC12267 35 mg 29.3 %, placebo 15.9 %), (ii) infections and infestations (no specific PT prevailed), (iii) gastrointestinal disorders (most prominent PT abdominal pain; incidences: SC12267 20 mg 8.3 %, SC12267 35 mg 14.6 %, placebo 6.8 %), and (iiii) musculoskeletal disorders (no specific PT prevailed).

In 9/36 (25 %) patients on SC12267 20 mg, 15/41 (36.6 %) patients on SC12267 35 mg, and in 7/44 (15.9 %) patients on placebo, TEAEs were judged as not unlikely related to treatment. Headache (24.4 %, SC12267 35 mg group) and (upper) abdominal pain (14.6 %, SC12267 35 mg group) were the most frequently observed, not unlikely related TEAE (PT).

No deaths occurred during the study. A total of 3 patients experienced SAE (SC12267 20 mg: not related severe acute renal failure in 1 patient; SC12267 35 mg: not related moderate pyrexia, dyspnea, and bronchopneumonia in 1 patient, possibly related severe hospitalization for further investigation in 1 patient (see below)). All SAEs recovered completely.

A patient with Morbus Meulengracht, who was erroneously included in the clinical trial and randomized to SC12267 35 mg by the investigator despite mild to moderate increases in GGT and ASAT, developed hepatitis (up to CTC grade 3) and was withdrawn after 24 days of treatment. He was hospitalized for further investigation. Liver biopsy identified toxic reaction, autoimmune reaction, or viral disease as potential causes of the event. The event resolved completely 6 months after the end of treatment. The investigator assessed the event as possibly related and the sponsor as unlikely related.

Vital signs: Day 1 median BP and HR were 126.5/80 mmHg, 74.5 bpm in the SC12267 20 mg group, 130/80 mmHg, 72 bpm in the SC12267 35 mg group, and 122.5/80 mmHg, 71 bpm in the placebo group. There were no treatment induced, statistically significant and clinically relevant changes in the vital signs from baseline during the entire course of the trial.

ECG: QTc data did not indicate any specific changes following active treatment with SC12267 as compared to placebo.

Safety laboratory: Mean lab data of main interest did not indicate any consistent, treatment induced changes on active treatment and placebo alike. Exploratory statistical analyses of changes versus baseline located isolated significant findings ($p<0.05$) only. The frequency of clinically relevant abnormal findings did not systematically increase between baseline and Week 12 in any of the 3 treatment groups. Deviations in relevant hepatic or renal laboratory parameter NCI CTC grades 2 and 3) were observed in 6 patients on SC12267 (n=1 on 20 mg and n=5 on 35 mg). These were assessed as clinically not relevant by the investigator or resolved during ongoing treatment / further follow-up. Urinalysis indicates AEs in 2 cases.

Tolerability: In all 3 groups, the majority of patients judged the treatment tolerability as either ‘very good’ or ‘good’ (31/36 (86 %) patients on SC12267 20 mg, 26/41 (63 %) patients on SC12267 35 mg, 36/44 (82 %) patients on placebo. The tolerability assessments of the physicians were quite similar.

PHARMACOKINETIC ANALYSES

The mean±SD trough plasma concentrations at steady state (corrected for weight) reached 3.023±2.524 µg/mL (median 2.357) following 12 weeks of treatment with SC12267 20 mg and 5.466±3.746 µg/mL (median 4.755) following SC12267 35 mg and thus were indicative of dose proportionality.

CONCLUSION

In this randomized, double-blind, placebo-controlled clinical trial in patients with RA classes I to III, 12 weeks of treatment with SC12267 20 or 35 mg proved to be safe and well tolerated by the vast majority of patients. All 3 treatments

favorably affected the primary efficacy variable, the DAS28 (CRP) score, to a comparable extent. Likewise, most of the secondary efficacy variables improved during the course of the study in all treatment groups. Due to the high placebo response observed for the DAS28 (CRP) parameter, significant differences between the active treatments and placebo were not observed taking into account the entire study population. However, the ACR20 responder rates indicated a clear trend for the dose dependent efficacy of SC12267. A-posteriori subgroup analyses indicated a higher treatment efficacy of SC12267 than placebo as observed from DAS28 (CRP) score and ACR response rates in patients pretreated with disease modifying drugs and in patients with RA functional class III.

Date of the Report: 21-Dec-2011