2. SYNOPSIS

Name of Sponsor: 4SC AG	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: SC12267	Volume:	
Name of active ingredient: Vidofludimus	Page:	

Title of study:	A Randomized, Double Blind, Placebo-controlled, Phase II Study to Evaluate Efficacy, Safety, and Pharmacokinetics of SC12267 (35 mg) in Combination with Methotrexate compared to Methotrexate Alone in Patients with Rheumatoid Arthritis ("COMPONENT")
Investigators:	Coordinating Principal Investigator: Prof. Dr. Stanislaw Sierakowski A list of investigators is provided in Appendix 16.1.4.
Study centre(s):	Information regarding study centers is provided in Appendix 16.1.4.
Publication (reference):	None.
Studied period (years):	Date of first patient enrolment: 06 November 2009 Date of last patient completed: 20 April 2011
Phase of development:	Phase II
Objectives:	
Primary:	To evaluate the efficacy of SC12267 (35 mg) in combination with methotrexate (MTX) compared to that of MTX alone in patients with rheumatoid arthritis (RA) after a 13-week therapy
Secondary:	To evaluate the safety profile of SC12267 in combination with MTX in patients with RA at doses of 35 mg per day To evaluate the plasma concentrations (trough value) of SC12267 in patients with RA after once daily application when given in combination with MTX once weekly
Methodology:	Randomized, double blind, placebo-controlled, parallel-group, multicentre study performed in 29 sites in Bulgaria, Czech Republic, Poland, and Romania
Number of patients (planned and analyzed):	planned: 244 randomized: 266 withdrawn: 53 completed: 213 analyzed (safety): 241 analyzed (efficacy): 236
Diagnosis and main criteria for inclusion:	Male and female patients aged ≥ 18 years with active RA and a 28-joint count disease activity score with erythrocyte sedimentation rate (DAS28[ESR]) ≥ 4.5, who had been taking weekly, stable doses of MTX (10-25 mg) for at least 3 months before Day 1 without any change to route or change in folic acid intake for at least 6 weeks prior to Day 1 and complied with the specified washout periods for prohibited medication were eligible for enrolment into the study.
Test products, dose and mode of administration, batch number:	SC12267 (35 mg) po, once daily, batch number: 88048G004, 90292G005, 88047G003, 90701G006.
Duration of treatment:	The estimated duration of the study for each patient was approximately 17 weeks, including a 2-week screening period, 13-week treatment period, and 2-week follow-up period.
Reference therapy, dose and mode of administration, batch number:	Placebo po, once daily, batch number: 88049G001, 90291G003, 92931G002, 88050G002 Methotrexate 2.5, 7.5, or 10 mg, po, once weekly, batch number: 0909000140, 0909000142, 0909000144, 0909000145, 0909000146, 0909000148, 1001000140, 1001000141, 1001000144, 1001000145, 1001000146, 1001000148, 1005000058, 1009000242, 1009000243, 1009000244, 1010000146, 1010000148, 1011000105, 1102000010, 1102000011 Folic acid 5 mg, po, once weekly (after MTX dosing), batch number: EC0060, 1011000233/GF0071, 1011000034/GF0071, M99049A

Name of Sponsor: 4SC AG	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: SC12267	Volume:	
Name of active ingredient: Vidofludimus	Page:	

Criteria for evaluation:

Efficacy:

This study used the criteria defined by the American College of Rheumatology (ACR). The primary efficacy criterion was the ACR_{20} defined as 20% improvement in tender joint count (TJC), swollen joint count (SJC) and 3 of the last 5 items listed below:

- Acute phase reactant: C-reactive protein (CRP)
- Patient's pain on a visual analogue scale (VAS)
- Patient's global assessment of disease activity on a VAS
- Physician's global assessment of disease activity on a VAS
- Health Assessment Questionnaire-Disability Index (HAQ-DI)

The primary efficacy analysis was based on the ACR_{20} responder rate after 13 weeks of treatment.

Secondary efficacy criteria are as follows:

- ACR_{50}
- ACR_{70}
- Disease Activity Scores (28 joint count) with CRP *(*DAS28[CRP]) and 28-joint count DAS with erythrocyte sedimentation rate (DAS28[ESR])
- Responder rates for DAS28 (CRP) and DAS28 (ESR)
- Morning stiffness
- Patient's assessment of pain and patient's assessment of disease activity obtained from diary data using a VAS, measured at the end of treatment period over 7 days, and change from first week
- Rheumatoid factor (RF)
- Patient's global assessment of efficacy (end of study)
- Physician's global assessment of efficacy (end of study)
- Number of withdrawals due to lack of efficacy

The pharmacokinetic endpoint was the plasma concentration of SC12267 (trough values) at steady state when administering a single daily dose.

The concentration of interleukin-17 (IL-17) in blood samples was evaluated as a biomarker for RA disease activity.

Safety:

The criteria to evaluate safety were as follows:

- Adverse events (AEs)
- Changes from baseline in safety laboratory values (hematology, clinical chemistry, urinalysis)
- Changes from baseline in vital signs (blood pressure, heart rate)
- Findings on 12-lead electrocardiogram (ECG)
- Patient's global assessment of tolerability (end of study)
- Physician's global assessment of tolerability (end of study)

Name of Sponsor: 4SC AG	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: SC12267	Volume:	
Name of active ingredient: Vidofludimus	Page:	

Statistical methods:

The following 4 analysis population sets were planned for this study:

- **Safety set**: The safety set (SAF) included all patients who were randomized and received any amount of planned study drug.
- **Full analysis set:** The full analysis set (FAS) included all patients who were randomized and received any amount of study drug and who had minimum efficacy data available. Minimum efficacy data was defined as at least 1 post-baseline efficacy observation of any of the primary or secondary efficacy parameters (including global assessment of efficacy) at Visit 3 or later with the exception of diary data.
- **Completer set:** The completer set (Completers) included all patients in the FAS who completed the study and had all efficacy assessments at Visit 8 which were required to calculate the primary efficacy parameter.
- **Per protocol set:** The per-protocol set (PPS) included all patients in the FAS who were either treated for the full treatment period or who were discontinued due to lack of efficacy. These patients must not have had a major protocol violation.

Descriptive summaries were provided where appropriate for each of the primary and secondary variables. In general, baseline and safety summaries were completed for the SAF. Efficacy summaries were completed for the FAS. Summaries of the primary efficacy variable were repeated for the PPS and Completers. All summaries were stratified by treatment arm.

Continuous, quantitative, variable summaries included the number of patients (N) (with non-missing values), mean, standard deviation (SD), median, minimum, maximum, and 1st and 3rd quartiles.

Categorical, qualitative, variable summaries included the frequency and percentage of patients in each particular category. In general, the denominator for the percentage calculation was based upon the total number of patients in the study population for the treatment arms unless otherwise specified.

Where applicable, changes from baseline were presented quantitatively as defined above, or in shift tables for categorical variables. All raw data were presented as listings.

Imputation of missing values was used only in special cases for deriving the ACR criteria. If centers became too small, they were pooled (eg, by country) for analysis. Rules for pooling were decided at the blinded data review meeting and described in the minutes of the meeting.

For all inferential analyses, a 2-sided *P* value and a significance level of 0.05 were used.

SUMMARY OF RESULTS

EFFICACY RESULTS:

The following conclusions can be made regarding the efficacy findings of this study:

- The primary efficacy analysis was based on the ACR_{20} responder rate after 13 weeks of treatment (Visit 8). At Visit 8, the difference between the SC12267 and placebo arms in ACR_{20} response rate was not statistically significant based on analyses using the FAS ($p = 0.365$ and $p = 0.379$ for Fisher's Exact and Cochran-Mantel-Haenszel [CMH] tests, respectively), the PPS ($p = 0.331$ and $p = 0.256$ for Fisher's Exact and CMH tests, respectively), or the Completers ($p = 0.273$ and $p = 0.252$ for Fisher's Exact and CMH tests, respectively).
- At Visit 3, the ACR_{20} response rate for the SC12267 arm was significantly higher compared to placebo based on analyses using CMH and the FAS and Completers but not using Fisher's Exact test or the PPS.
- At Visit 5 the difference between the SC12267 and placebo arms in ACR_{20} response rate was not statistically significant.
- At Visit 7, the ACR_{20} response rate for the SC12267 arm was significantly higher compared to placebo based on analyses using the FAS ($p = 0.024$ and $p = 0.022$ for Fisher's Exact and CMH tests, respectively), the PPS ($p = 0.018$ and $p = 0.014$ for Fisher's Exact and CMH tests, respectively) and the Completers ($p = 0.013$ and 0.011).
- A statistically significant earlier ACR_{20} response was observed for the SC12267 arm compared to placebo based on Kaplan-Meier estimates and Log-Rank-test.

Name of Sponsor: 4SC AG	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: SC12267	Volume:	
Name of active ingredient: Vidofludimus	Page:	

- No statistically significant differences were observed between treatment arms for the ACR_{50} or ACR_{70} response.
- The frequency of 'good' and 'moderate' responses for DAS28(CRP) (summarized into 1 category of responders) was significantly higher in the SC12267 arm compared to placebo at Visit 5 (difference between SC12267 and placebo response rates = 0.136, p = 0.038) and the frequency of 'good' and 'moderate' responses for DAS28(ESR) (summarized into 1 category of responders) was significantly higher in the SC12267 arm compared to placebo at Visit 3 (difference between SC12267 and placebo response rates = 0.145, p = 0.009).
- Although statistical significance was not demonstrated, the mean percentage changes from baseline for TJC, SJC, the pain assessment performed at study visits, physician's assessment of disease activity, and HAQ-DI were numerically greater (indicating greater reductions from baseline) for the SC12267 arm compared to placebo at the majority of study visits.
- Although statistical significance was not demonstrated, the mean changes from baseline for CRP and ESR were numerically superior for the SC12267 arm compared to placebo at the majority of study visits.
- Although statistical significance was not demonstrated, the difference between post-baseline means and baseline mean for TJC, SJC, ESR, patient's assessment of disease activity, physician's assessment of disease activity, and HAQ-DI were numerically greater (indicating greater reductions from baseline) at Visits 3, 5, 7, and 8 for the SC12267 arm compared to placebo. The difference between post-baseline means and baseline mean for CRP and the pain assessment performed at study visits were numerically greater (indicating greater reductions from baseline) at Visits 3, 5, and 8 for the SC12267 arm compared to placebo.
- Although statistical significance was not demonstrated, the frequency of morning stiffness greater than 1 hour duration was numerically lower for the SC12267 arm compared to placebo at all study visits.
- No statistically significant treatment effect was observed for changes from the beginning (Days 2-7) to end (last 7 days) of treatment in mean values for the patients diary assessment of pain and the patient's assessment of disease activity.
- Although statistical significance was not demonstrated, the mean value and values for frequencies of responses of 'very good' and 'good' for the patient's global assessment of efficacy and the physician's global assessment of efficacy were numerically superior for the SC12267 arm compared to placebo.
- A statistically significant correlation between increasing SC12267 plasma concentration and increased probability of an ACR_{20} response was noted at Visit 3 in an analysis using the SC12267 arm of the FAS (p = 0.021). This correlation of increasing SC12267 plasma concentration with increased probability of ACR20 response remained stable in an analysis that used both the placebo and the SC12267 arms (combined) of the FAS, with statistical significance achieved at Visit 3 (p = 0.002) and Visit 7 (p = 0.006).
- A statistically significant effect of weekly MTX dose on SC12267 plasma concentration was noted; plasma concentration of SC12267 decreased as weekly MTX dose increased (p = 0.026).
- The interpretation of results using IL-17 plasma concentration data was confounded by the large number of plasma samples with values that fell below the LLQ. Statistically significant results were noted infrequently, and the large numbers of samples with values below the LLQ suggest the model was not appropriate.

SAFETY RESULTS: The following conclusions can be made regarding the safety findings of this study:

- No deaths occurred during the study. Two patients experienced serious adverse events (SAEs): Patient 2916 in the SC12267 arm (pneumonia, renal amyloidosis, and chronic renal failure) and Patient 0406 in the placebo arm (hypertensive crisis and hemiparesis). All 5 SAEs reported for these 2 patients were considered unlikely to be related to any study drug.
- The most frequently experienced treatment-emergent adverse event (TEAE) overall was headache, reported by 19 (15.6%) and 20 (16.8%) patients in the SC12267 and placebo arms, respectively.
- Of the patients who experienced at least 1 TEAE, most experienced TEAEs of mild or

Name of Sponsor: 4SC AG	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: SC12267	Volume:	
Name of active ingredient: Vidofludimus	Page:	

moderate severity. Five patients in each treatment arm reported severe TEAEs: those reported in the SC12267 arm included rheumatoid arthritis, pneumonia, viral infection, arthralgia, renal amyloidosis, and chronic renal failure; those in the placebo arm included headache, herpes zoster, rheumatoid arthritis, dysuria, hematuria, and uterine dilation and curettage.

- Of the patients who experienced at least 1 TEAE, 22 (18.0%) patients in the SC12267 arm and 30 (25.2%) patients in the placebo arm experienced an AE that was considered related (ie, possibly or probably related) to any study drug.
- No pattern was noted with regard to TEAE frequency and MTX dose group.
- The numbers of patients reporting TEAEs in the system organ classes (SOCs) of renal and urinary disorders and hepatobiliary disorders were similar in both treatment arms.
- Eight patients experienced a TEAE that led to discontinuation of any study drug, including 3 (2.5%) patients in the SC12267 arm and 5 (4.2%) patients in the placebo arm.
- No remarkable differences in hematology and urinalysis results were noted between the 2 treatment arms. The percentage of patients with hematuria was not higher in the SC12267 arm compared to the placebo arm.
- Vital sign values remained generally stable over time, and no consistent differences or trends between treatment groups were observed. Similar numbers of patients in each treatment arm experienced vital sign abnormalities reported as AEs.
- Electrocardiogram values remained stable over time, and no consistent differences or trends between the treatment groups were noted. Similar numbers of patients in each treatment arm had abnormal ECG results.
- The patient's global assessment of tolerability showed that most patients in both treatment arms considered the treatment tolerability as very good (49 [40.2%] in the SC12267 arm and 34 [28.6%] in the placebo arm) or good (48 [39.3%] in the SC12267 arm and 59 [49.6%] in the placebo arm). Most physician's assessments of tolerability were also very good (54 [44.3%] in the SC12267 arm and 37 [31.1%] in the placebo arm) or good (47 [38.5%] in the SC12267 arm and 58 [48.7%] in the placebo arm). The results for the physician's global assessment of tolerability were significantly better in the SC12267 arm than in the placebo arm.

CONCLUSION:

The primary efficacy analysis, based on the ACR_{20} responder rate after 13 weeks of treatment (Visit 8), was not statistically significantly different across treatments.

This study, however, provided statistically significant results showing treatment with SC12267 shortened the time to achieve ACR_{20}, improved the ACR_{20} response rate at Visit 7, and improved the frequencies of DAS28(CRP) and DAS28(ESR) responses (at 1 visit each) compared to placebo. The results for the majority of the efficacy parameters consistently showed a trend of numerically better values in the SC12267 arm compared to placebo, although in most of the analyses the effect was not sufficient to reach statistical significance.

A statistically significant correlation between increasing SC12267 plasma concentration and increased probability of an ACR20 response was noted at Visit 3. Study results revealed a statistically significant effect of weekly MTX dose on SC12267 plasma concentration; plasma concentration of SC12267 decreased as weekly MTX dose increased.

These correlations as well as the numerically and at some time points also statistically significant superiority of SC12267 over placebo in some secondary endpoints suggests the possibility that the dose of SC12267 used in this study might have been too low.

The interpretation of results using IL-17 plasma concentration data was confounded by the large number of plasma samples with IL-17 values that fell below the LLQ.

The results of most safety assessments were unremarkable. Overall, the results of this study indicate SC12267 is safe and very well-tolerated, suggesting that the use of higher SC12267 doses in further studies may be an option to improve efficacy.

Date of the report: 04 January 2012