The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: RA4104917
Title: A randomised, double-blind, placebo-controlled, parallel group study to investigate the safety and tolerability, pharmacokinetics (PK) and effect on synovial thickness and vascularity of 28 days repeat dosing of investigational product or 7.5 mg prednisolone in rheumatoid arthritis (RA) subjects.
Rationale: This was an exploratory study to assess the effect of investigational product or 7.5 mg prednisolone in RA subjects.
Phase: IIa
Study Period: 09 Jan 2006- 19 Dec 2007.
Study Design: A randomised, double-blind, placebo-controlled, parallel group study.
Centres: The study was conducted at 3 centres in Serbia and 1 centre in the United Kingdom.
Indication: Rheumatoid arthritis.
Treatment: Subjects were randomised to receive one of the following treatments for 28 days: investigational product, prednisolone 7.5 mg once daily or placebo once daily. At the completion of the treatment phase, subjects who were randomised to receive 7.5 mg prednisolone received tapering doses of prednisolone for a further 2 weeks (Day 29 to Day 42). On Day 29 to Day 35, subjects received prednisolone 5 mg, and on Day 36 to Day 42 subjects received prednisolone 2.5 mg. In order to maintain the study blind, subjects who were randomised to receive investigational product or placebo in the treatment phase received placebo medication for further 2 weeks.
Objectives: The primary objective was to investigate the effect of the investigational product on synovial vascularity after 28 days repeat dosing.
Statistical Methods: The sample size calculation was based on an estimate of between-subject variability of the power Doppler total vascularity score seen in a previous study. Based on this estimate, a study with 15 subjects per treatment arm was to detect a decrease of 60% in total vascularity score for investigational product versus placebo, with 90% power at the two-sided 5% level. There was no formal interim analysis. The final planned analyses were performed after all subjects had completed the study and after the database freeze and treatment code unblinding. The Modifi ed ITT'a nd the Sa fety'p opulation included the same subjects, therefore these two populations were defined as the 'All Subjects'p opulation. This population was used for all study population, safety and efficacy outputs. The PK'p opulation was used for all listings, figures, summaries and analyses of pharmacokinetic concentrations and parameters. Formal statistical analysis was carried out on the $\log_e$-transformed imaging endpoints, i.e. total vascularity score, power Doppler area (PDA) and total thickness score using a repeated measures model. As the recruitment was carried out in two different countries, i.e. in the UK and in Serbia, a country variable was fitted as a covariate in the analysis model to explore a potential country effect. In case there was a suggestion of a country effect, the country by treatment interaction was explored. No formal statistical analysis was performed on safety data.
Study Population: Adult males and females (females of childbearing and non-childbearing potential) ≥18 years of age with body weight ≥50 kg for males and ≥45 kg for females, who were not morbidly obese, were considered for this study. The subjects had a diagnosis of rheumatoid arthritis (according to the revised 1987 criteria of the American College of Rheumatology (ACR)) with DAS28 ≥4.0 and at least one metacarpal phalangeal joint with either detectable vascularity or thickness and were on stable doses of disease modifying anti-rheumatic drugs [DMARDs] (which included but were not restricted to methotrexate, sulphasalazine and hydroxychloroquine in any combination) for 8 weeks prior to enrolment.

Number of Subjects:	**Placebo**	**7.5 mg prednisolone**
Planned N	15	15

Dosed N	17	14
Completed n (%)	14 (82)	14 (100)
Total Number Subjects Withdrawn N (%)	3 (18)	0
Withdrawn due to Adverse Events n (%)	1 (6)	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for Other Reasons n (%)	2 (12)	0
Demographics		
N (All subjects)	17	14
Females: Males	15: 2	10: 4
Mean Age in Years (Range)	57.1 (34 – 74)	53.8 (25 – 68)
Mean Weight in Kg (Range)	68.53 (46.0 – 95.0)	75.76 (63.7 – 93.0)
White n (%)	14 (82)	13 (93)

Efficacy Endpoints: The primary efficacy endpoint analysed was power Doppler ultrasonographic measurement (pre-dose Day 28) of synovial vascularity. The secondary efficacy endpoint analysed was high frequency ultrasound measurement of synovial thickness.

Summary of results from the statistical analysis for total vascularity score:

Time point	**Adjusted geometric means**		**Ratio of adjusted geometric means (95% CI) p-value**
	Placebo (N=17)	**Prednisolone 7.5 mg (N=14)**	**Prednisolone 7.5 mg-Placebo**
Day 15	7.76	5.77	0.74 (0.43, 1.29) p=0.279
Day 28	7.03	3.75	0.53 (0.30, 0.96) p=0.036

CI= confidence interval

Summary of results from the statistical analysis of power doppler area (PIXEL):

Day 15	8065.43	3884.35	0.48 (0.11, 2.11) p=0.322
Day 28	10317.68	2244.96	0.22 (0.07, 0.66) p=0.008

Summary of results from the statistical analysis of total thickness score:

Day 15	10.35	6.83	0.66 (0.42, 1.04) p=0.073
Day 28	11.67	6.40	0.55 (0.35, 0.85) p=0.009

Pharmacokinetics Endpoints: No pharmacokinetic data are available for prednisolone 7.5 mg.

Safety results: From the time a subject received their first dose until he or she completed the study (including any Follow-up period), all adverse events (AEs) were recorded. Any serious adverse event (SAE) reported after a subject consented to participate in the study but before receiving their first dose and also after the final Follow-up visit and considered related to the investigational product by the Investigator would also be reported. The number of subjects reporting AEs are summarised in the table below.

Adverse Events:	**Placebo**	**7.5 mg prednisolone**
N (All subjects)	17	14
No. subjects with AEs n (%)	8 (47)	4 (29)
Most Frequent AEs		

Headache	5 (29)	0

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: There were no deaths, no SAEs or pregnancies reported in this study

Publications: No publication

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