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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00280644
		Study Code:	HWA486_4022
Generic drug name:	Leflunomide	**Date:**	10/Dec/2007

Title of the study:	Efficacy of Leflunomide on the Prevention of Joint Inflammation and Damage in Patients with Early Rheumatoid Arthritis.		
Investigator(s):	Prof.Dr. Fikret Tüzün (MD) Istanbul University, Cerrahpasa School of Medicine, Department of Physical Medicine and Rehabilitation, ISTANBUL/TURKEY		
Study center(s):	6		
Publications (reference):	NA		
Study period: Date first patient enrolled: 05/May/2004 Date last patient completed: 27/Oct/2005		**Phase of development:** IV	
Objectives:	Primary objectives: • Evaluation of the efficacy of leflunomide therapy on inflammation modulation, and serum - urine matrix degradation products in patients with early active rheumatoid arthritis • Confirmation of the sensitivity of the DEMRI (Dynamic Enhanced Magnetic Resonance Imaging) technique to identify the inflammatory changes with response to leflunomide therapy in patients with active rheumatoid arthritis Secondary objective: Evaluation of the effects of leflunomide therapy on physical functions and quality of life in patients with rheumatoid arthritis.		
Methodology:	National, multi-center, open label, prospective, non-comparative clinical study		
Number of patients:	Planned: 60	Randomized: 63	Treated: 63
Evaluated:	63	Safety:	
Diagnosis and criteria for inclusion:	• Patients diagnosed as rheumatoid arthritis according to “American Rheumatism Association” (ARA) diagnostic criteria. • Patients with rheumatoid arthritis functional staging grade I, II and III according to “American College of Rheumatology” (ACR) (1991) • Patients who have “Modified Disease Activity Score” (DAS28) > 3.2		

Investigational product: Dose: Administration:	Leflunomide 100 mg/day for the first 3 days and than 20 mg/day for 6 months Oral	
Duration of treatment: 6 months		**Duration of observation:** 6 months
Reference therapy: Dose: Administration:	NA NA NA	
Criteria for evaluation:		
Efficacy:	Primary: • Percentage of responsive patients according to DAS28 criteria • C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) • Serum MMP-3, IL-6 and PIIINP levels • Urine CTx II and GLc-Gal-Pyd levels • Evaluation of the wrist by DEMRI technique Secondary: • SF-36 quality of life parameters	
Safety:	• Adverse events reported by the patient or noted by the investigator • Standard hematology and blood chemistry	
Statistical methods:	Efficacy and safety parameters were analyzed by using descriptive (mean, percentage, standard deviation, safety intervals) statistics. The variations observed during the therapy period, compared to the pre-treatment period, and various sub-group analyses were performed with parametric or non-parametric tests according to the character of the data.	

Summary:	
Efficacy results:	Six months duration leflunomide therapy; significantly improved (p=0.000) all the clinical outcome parameters, determined by ACR. Although not stated as a response criteria by the study protocol, ACR 20 response was also calculated for the study treatment. A minimum of 66.6 % percentage reduction in tender joint count and a minimum of 81.6 % reduction in swollen joint count were achieved with leflunomide treatment during the first visit after treatment initiation along with at least 3 additional criteria. DAS28 score, calculated as 6.31 (+1.22) at baseline (indicative of high disease activity) decreased to 4.10 (+1.25) at endpoint (indicative of medium disease activity) (p=0.000). Although not statistically significant, decreases on evaluated DEMRI parameters were observed. Inflammatory parameters which include ESR and CRP; serum–urine matrix degradation factors which include S-MMP-3, S-IL-6, S-PIIINP, U-CTX-II, U-Glc-Gal-Pyd gradually decreased during six months treatment period, but not statistically significant except U-CTX-II (p=0.005). Statistically significant differences were observed on all 8 parameters of Health Assessment Questionnaire at the end of the one month treatment period (p<0.001). Improvements continued gradually for the rest of the five months therapy.
Safety results:	Four of the patients were dropped out from the study because of treatment related AE's and SAE's. Two of them withdrew due to liver enzyme elevation, one of them due to decrease in blood parameters (anemia and leucopenia) and one of them due to rash. All these events were assessed as related to study drug by the investigators. Infections were the most common adverse events occurred during the six months leflunomide therapy (20.6 %). The less common adverse events were rash and liver enzyme elevations (14.2 % and 12.6 % respectively). Other adverse events were: diarrhea (7.9%), pruritus (7.9%), palpitation (7.9%) and loss of appetite (6.3%). Leucopenia, anemia and mouth ulcers were noted as adverse events at a rate of each 4.7%. There were no deaths reported during the study.
Date of report:	12-Nov-2007