These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert in the country of prescription*

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00563849
		Study Code:	HWA486_4021
Generic drug name:	Leflunomide	**Date:**	03/Dec/2007

Title of the study:	An open-label, multi-center study to evaluate Leflunomide plus Methotrexate for the treatment of rheumatoid arthritis in DMARDs (Disease-Modifying anti rheumatic drugs) naïve or restart (skip DMARDs more than 4 weeks) subjects.		
Investigator(s):	Dr. Shin Seok Lee 8, Hak 1-dong, Dong-gu, Gwangju, 501-840, Chonnam, Korea		
Study center(s):	ChonNam national university hospital, Korea		
Publications (reference):	NA		
Study period: **Date first patient/subject enrolled:** 23-May-2003 **Date last patient/subject completed:** 27-Aug-2004		**Phase of development:** Phase IV	
Objectives:	To determine the efficacy and safety of the combination of leflunomide and methotrexate for treating active rheumatoid arthritis (RA) in an open non-comparative multicenter trial.		
Methodology:	Open-label, Multi-center, Non-comparative		
Number of patients:	**Planned**: 74	**Randomized**: NA	**Treated:** 74
Evaluated:	**Efficacy/Pharmacodynamics**: NA	**Safety**: 74	**Pharmacokinetics**: NA

Diagnosis and criteria for inclusion:	>Male or female between ages of 18 and 75 years old. >Female subjects must be of non childbearing potential (i.e., surgically sterile or at least 2 years postmenopausal) OR their participation is contingent upon the following: - they are practicing a medically accepted contraceptive regimen (acceptable methods must include one of the following: systemic contraceptive, oral or implanted estrogen/progestin; diaphragm with intravaginal spermicide; cervical cap; intrauterine device; or condom with intravaginal spermicide) AND - they are demonstrated not to be pregnant (by serum pregnancy test) or breastfeeding at the time of study entry AND - they intend to continue the contraceptive regimen and remain not pregnant throughout the study AND - they are willing to undergo pregnancy testing (serum) at screening and (urine) monthly thereafter AND - they are fully informed as to the risks of entering the trial and provide written consent to enter the trial; female patients not sexually active should also be adequately informed about appropriate methods of contraception AND - they agree to not get pregnant for 24 months after discontinuation of treatment with study medication or they undergo a washout procedure with cholestyramine or charcoal. >Male subjects must consent to practice contraception during the study. The subject needs to have clinically diagnosed rheumatoid arthritis including diagnosis of RA by ACR criteria = 6 months prior to enrollment active disease by ACR criteria. Men wishing to father a child should consider discontinuing use of study drug and taking cholestyramine 8 gm 3 times daily for 11 days. In addition, males should consider discontinuation of methotrexate treatment and waiting an additional three months. >Active disease by ACR criteria despite methotrexate therapy for three of the following four criteria: - -=9 tender joints - =6 swollen joints - =45 minutes of morning stiffness - ESR = 28mm/hr >Subject must remain on unchanged doses of NSAIDs for at least 4 weeks prior to study drug administration and throughout the time course of the study. >Concomitant therapy will be permitted with corticosteroids at a dose of =10 mg prednisone daily (or the steroid equivalent administered orally), provided the dose has been stable for at least 4 weeks prior to the study drug administration; dose must remain constant throughout the time course of the study. >Subjects must not receive intramuscular, intra-articular or intravenous corticosteroids within 4 weeks prior to initiating study participation or during the study. >Subjects must be able and willing to comply with the terms of this protocol. Informed consent must be obtained for all subjects before enrollment in the study.
Investigational product: Dose: Administration:	Arava® (Leflunomide) 10 mg/day Seventy-four RA patients who had received no previous treatment with disease-modifying anti-rheumatic drugs (DMARDs) were enrolled to receive concomitantly leflunomide (no loading dose, 10 mg/day) and methotrexate (starting at 7.5 mg/week and titrating up to 15 mg/week) for 20 weeks. During the study period folate 1mg/day was administered regularly. If ALT or AST elevated two times over upper normal limit for two consecutive months, leflunomide might be stopped and begin elimination process
Duration of treatment: 16 weeks	**Duration of observation:** 4 weeks

Reference therapy: Dose: Administration:	NA NA NA
Criteria for evaluation:	
Efficacy:	The primary end point was a 20% improvement in the American College of Rheumatology criteria (ACR 20) at 20 weeks
Safety:	Safety measurement included evaluation of adverse events at each visit and laboratory data, including hematology and liver function tests. Analyses were done by intention to treat
Pharmacokinetics	NA
Pharmacokinetics and sampling times and bioanalytical methods	NA
Statistical methods:	The primary end point was the ACR success rate in the ITT population.

Summary:	*Subjects demographics* The median age of the patients at the time of enrollment was 52.0 years (range 24.0–75.0 years) and the median disease duration was 0.21 years (range 0.0-30.9 years); 81.1% were female. When classifying the enrolled subject's rheumatoid arthritis status according to ARA functional class, a majority, 40 subjects (54.1%) was Class II, 29 subjects (39.2%) were Class III, and 5 subjects (6.8%) were Class I. Class IV subjects were not enrolled in this study. The median age of subject at the time of rheumatoid arthritis diagnosis was 48.6, and the median disease duration was 2.4 years. At the time of enrollment, the subjects' average duration of morning stiffness was 2.6 hours. *Results- Efficacy* Sixty-five patients completed 20 weeks of treatment and 71.6% were responders according to ACR 20. (95% CI: 61.3%, 81.9%) After 20 weeks, the mean changes were –16.3 for tender joint count, –12.0 for swollen joint count, –4.4 for physician global assessment, and 3.4 for patient global assessment, 22.7 for erythrocyte sedimentation rate, and –0.65 for Health Assessment Questionnaire scores. This study was according to ACR 20, 71.6% in the ITT group (95% confidence interval: 61.3%, 81.9%) and 81.6% in the PP group (95% confidence interval: 70.8%, 92.5%). After taken the drug, the mean changes were –16.3 for tender joint count, –12.0 for swollen joint count, and the patient global assessment on rheumatoid arthritis symptoms was -34.3, the physician global assessment, –44.0. In addition, mean changes were -35.0 for pain, -0.62 for Korean HAQ, and of the acute phase reactant, mean changes were -22.7mm/hr for erythrocyte sedimentation rate and -5.69mg/dl for CRP. *Results- Safety* Adverse events occurred at a rate of 32.4% (24 out of 74 subjects), and adverse events with causality occurred at a rate of 8.1% (6 out of 74 subjects). Of the 24 reported adverse events, 8 subjects (10.8%) showed symptoms related to gastrointestinal disorder, 5 subjects each (6.8%) showed respiratory and chest related symptoms, and liver related adverse events. Serious adverse events were reported in 3 subjects, but did not lead to death. In other hematology/biochemistry clinical values, vial signs, and other tests, in the report of adverse events, there were no abnormalities found relating to safety.
Efficacy results:	Sixty-five patients completed 20 weeks of treatment and 71.6% were responders according to ACR 20. (95% CI: 61.3%, 81.9%) After 20 weeks, the mean changes were –16.3 for tender joint count, –12.0 for swollen joint count, –4.4 for physician global assessment, and 3.4 for patient global assessment, 22.7 for erythrocyte sedimentation rate, and –0.65 for Health Assessment Questionnaire scores. This study was according to ACR 20, 71.6% in the ITT group (95% confidence interval: 61.3%, 81.9%) and 81.6% in the PP group (95% confidence interval: 70.8%, 92.5%). After taken the drug, the mean changes were –16.3 for tender joint count, –12.0 for swollen joint count, and the patient global assessment on rheumatoid arthritis symptoms was -34.3, the physician global assessment, –44.0. In addition, mean changes were -35.0 for pain, -0.62 for Korean HAQ, and of the acute phase reactant, mean changes were -22.7mm/hr for erythrocyte sedimentation rate and -5.69mg/dl for CRP.
Safety results:	Adverse events occurred at a rate of 32.4% (24 out of 74 subjects), and adverse events with causality occurred at a rate of 8.1% (6 out of 74 subjects). Of the 24 reported adverse events, 8 subjects (10.8%) showed symptoms related to gastrointestinal disorder, 5 subjects each (6.8%) showed respiratory and chest related symptoms, and liver related adverse events. Serious adverse events were reported in 3 subjects, but did not lead to death. In other hematology/biochemistry clinical values, vial signs, and other tests, in the report of adverse events, there were no abnormalities found relating to safety.
Date of report:	14-Sep-2005