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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00451971
		Study Code:	HWA486_4020
Generic drug name:	Leflunomide	**Date:**	26 June 2008

Title of the study:	Objectives Study in Rheumatoid Arthritis (OSRA) HWA486_4020
Investigator(s):	Prof John Edmonds & A/Prof Marissa Lassere Department of Rheumatology, St George Hospital, Kogarah, NSW 2217, AUSTRALIA
Study center(s):	Royal Prince Alfred (Bleasel, McGill, Youssef, Vaile, Richards) South West (White, Riordan, Patapanian, Gotis-Graham) Westmead (Howe, Spencer, Manolios, Liew) North East (Portek, Lawford, Shenstone, Sturgess) Central Coast / Northern (Baume, Podgorski) Monash Medical Centre / VIC (Littlejohn, Leech) St Vincent's Hospital / VIC (Clemens, Moran, Romas) Australian Capital Territory (Tymms, Dorai Raj, Khoo, Brook) Tasmania (Jones, Graham, Francis, Cooley) (32 rheumatologists)

Publications (reference):	OSRA: what are the hidden drivers of rheumatologists' 'usual care' management? Marissa Lassere, Kent Johnson, Kerrie Carlton et al. Oral Presentation – ARA Annual Scientific Meeting, Adelaide, 2008 Objectives Study in RA (OSRA): A RCT Defining the Best Clinical Target Control in RA John P. Edmonds[1], Marissa N. Lassere[1], John T. Sharp[2], Paul Bird[1], Kerrie Carlton[1], OSRA Study Group. [1]St George Hospital, Sydney, Australia; [2]University of Washington, Seattle, WA Oral Presentation. American College of Rheumatology – November 2007 Objectives Study in RA (OSRA): A RCT Defining the Best Clinical Target Control in RA. John P. Edmonds[1], Marissa N. Lassere[1], John T. Sharp[2], Paul Bird[1], Kerrie Carlton[1], OSRA Study Group. [1]St George Hospital, Sydney, Australia; [2]University of Washington, Seattle, WA Poster EULAR – Barcelona June 2007 Objectives Study in RA (OSRA): A RCT Defining the Best Clinical Target Control in RA John P. Edmonds[1], Marissa N. Lassere[1], John T. Sharp[2], Paul Bird[1], Kerrie Carlton[1], OSRA Study Group. [1]St George Hospital, Sydney, Australia; [2]University of Washington, Seattle, WA Oral presentation. ARA Sydney May 2007 OSRA-An Outcomes Driven RCT in RA: Adverse event/safety profile during combination DMARD therapy. John P. Edmonds[1], Marissa N. Lassere[1], Kerrie Carlton[1], OSRA Study Group. [1]St George Hospital, Sydney, Australia Poster American College of Rheumatology San Antonio Nov 2004 OSRA-An Outcomes Driven RCT in RA: Adverse event/safety profile during combination DMARD therapy. John P. Edmonds[1], Marissa N. Lassere[1], Kerrie Carlton[1], OSRA Study Group. [1]St George Hospital, Sydney, Australia Poster EULAR Berlin June 2004 Rheumatoid Arthritis: Time for Trials of Therapeutic Targets, J. Edmonds, M. Lassere, Journal of Rheumatology Volume 29: No. 9 October 2002, 2041-2044

Study period: Date first **patient** enrolled: 04-Mar-2002 Date last **patient** completed: 20-Sep-2005			**Phase of development:** IV
Objectives:	**PRIMARY OBJECTIVE** 1. To test the feasibility, in patients with active rheumatoid arthritis, of using an 'aggressive' treatment algorithm to bring a short term treatment objective (STO) within the normal or an arbitrarily defined 'desirable' range. This aim asks the research question: Do patients with active RA randomly assigned to a particular treatment strategy to bring a target short-term objective (STO) within the normal or desirable range succeed in attaining that objective? It examines the *feasibility* of bringing the STO within a normal or desirable range. 2. To determine whether patients with active rheumatoid arthritis randomly allocated to a particular STO show a reduced rate of MRI damage progression at two years compared to those randomly allocated to usual care. This aim asks the question: Is allocation to a particular STO associated with a reduced rate of MRI progression at two years. It drives the *study power.* **SECONDARY OBJECTIVES** 1. To establish the relationship between achieving a given STO or combination of STOs and damage progression. 2. To identify the characteristics of responders and non-responders with respect to STO achievement and predictors of greater and lesser degrees of damage progression. These aims are based on the notion that an STO, which is not within the normal/desirable range is a risk factor for radiological/MRI damage progression, or conversely, that achieving the STO is protective. They ask the following questions: Is achieving the STO (or a combination of STOs) associated with a lower rate of MRI progression than not achieving it? Is a combination of responders associated with a reduced rate of MRI progression? These could provide the *clinically relevant* results of the study.		
Methodology:	Two year randomised controlled target biomarker trial - Arm 1: STO 1 - target was swollen joint count <3 (double-blind) - Arm 2: STO 2 - target was normal CRP (double-blind) Arm 3: usual care (no target – unblinded)		
Number of patients:	Planned: 333	Randomized: 249	Treated: 249
Evaluated:		Safety: 249	

Diagnosis and criteria for inclusion:	**Inclusion criteria** ▪ Rheumatoid Arthritis as defined by the ACR criteria, with active disease defined as **either** ▪ ≥ 6/28 swollen joints **or** ▪ ESR > normal **or** ▪ CRP > normal **or** ▪ DAS ≥ 3.2 ▪ Age 18 yrs to ≤ 75 yrs **except patients older than 75 yrs permitted if physically robust and well** ▪ Disease duration ≤ 15 yrs **except patients with disease duration greater than 15 yrs permitted provided that they did not have end-stage disease or were not physically frail because of their disease** ▪ Any therapy ▪ Females of child-bearing potential must have adequate contraception. Informed consent was obtained in writing for all patients at enrolment into the study. **EXCLUSION CRITERIA** ▪ Frailty, limiting co-morbidity ▪ Obesity limiting ability to have MRI ▪ Geographical difficulty preventing follow-up and visits ▪ Women at risk of becoming pregnant ▪ Patients unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study
Investigational product:	None
Dose:	Not applicable
Administration:	Not applicable
Duration of treatment: Not applicable	**Duration of observation:** Not applicable

Reference therapy:	Rheumatologists were free to use any drugs, doses or combinations to bring the STO within the target range, provided they considered therapy appropriate to good management. Treatment escalation, step-wise as dictated by the STO remaining above the target, was undertaken according to the following pathway: 1. current treatment levels maximized Prednisolone 10 mg daily Methotrexate 25 mg p.o., s.c. or i.m. once weekly Sulphasalazine 3.0 G daily Leflunomide 20 mg daily Cyclosporin A 3 mg/Kg/day Hydroxychloroquine 6 mg/Kg/day D-penicillamine 750 mg daily Gold 50 mg weekly Azathioprine 2.5 mg/Kg/day Etanercept 25 mg twice weekly Doses of other new therapies were discussed if they became available. 2. leflunomide added, according to published protocol (i.e. loading with 2x100 mg, then 10 mg daily, increasing to 20 mg daily if necessary and if no adverse reaction to the combination) allowing 3 months without further increase to achieve STO 3. use of combination therapy such as: ▪ MTX, leflunomide ▪ MTX, sulphasalazine, hydroxychloroquine ▪ Sulphasalazine, leflunomide ▪ MTX, etanercept ▪ Additional of prednisolone to any of the above at any time For safety reasons, the study protocol did not endorse the following combinations: ▪ Leflunomide, cyclosporine A ▪ MTX, azathioprine

Dose:	Not applicable
Administration:	Not applicable
Criteria for evaluation:	
Safety:	Adverse events reported by the patient or noted by the investigator were recorded from the time the patient gave informed consent until the final visit and procedures had taken place. If an adverse event was considered serious it had to be reported to the sponsor within 24 hours or at the latest on the following working day. Routine safety blood tests including FBC and ESR, UEC, LFT were evaluated.
Statistical methods:	DATA ANALYSIS The primary and secondary aims of the study require different modes of analysis. PRIMARY AIMS 1. To compare the success rates of the two STOs in achieving the normal or specified target range entails a comparison of the proportions of patients attaining target. For a difference between STOs to be significant, it would have to be of magnitude at least 20%, with the sample sizes envisaged for this study. Comparisons for this analysis of variance will be made using a logistic model to allow for the widely differing variances between groups. 2. To compare the mean rate of MRI damage progression across the three arms (STO 1, STO 2 and usual care) a one-way analysis of variance for a random effects model with Bonferroni, Sidak and Scheffe multiple-comparison tests will be performed. Analysis of covariance will be used to adjust for: patient disease duration, baseline disease activity using an equally weighted pooled index (incorporating the 28 tender joint count, 28 swollen joint count, VAS patient global, ESR and CRP), number of prior DMARDs, baseline HAQ and baseline Sharp radiographic score. The analysis has a power of at least 80%. SECONDARY AIMS To determine (i) the relationship between achieving a given STO or combination of STOs and damage progression and (ii) identify the characteristics of responders and non-responders with respect to STO achievement and predictors of greater and lesser degrees of damage progression various multivariate models will be used including repeated analysis of variance and covariance, multiple linear regression, logistic regression, log-linear analysis depending on the specific question asked. No interim analysis is planned for this study.

Summary:

Results: 249 RA patients, recruited by 32 rheumatologists, were randomised to 3 study arms: 85 to STO 1 (SJC<3); 82 to STO 2 (normal CRP); 82 to 'UC'. Mean age 56±12 yrs; disease duration 7.2 ± 6.6 yrs.

	STO 1 (SJC)		STO 2 (CRP)		Usual Care	
	Baseline n=85	24 months n= 75	Baseline n=82	24 months n=66	Baseline n=82	24 months n=72
SJC	12±5	5±5	11.6±5	5±5	11.8±5	5±6
CRP	12±11	6±6	20.7±28	12±23	17.7±25	12±25
DAS28	5.1±1.2	3.4	4.9±1.3	3.7	5.07± 1.5	3.8

The target STO was met in 29% of 1845 visits of patients in STO 1, and in 41% of 1663 visits of patients in STO 2. Across all arms, the average (AUC) CRP met the target in 28% of patients, but average (AUC) SJC was <3 in only 12%.
MRI progression scores (209 patients) were low and did not differ significantly between arms.

Radiographic progression scores (211 patients) showed a significant difference in erosion progression 0.19±0.97 v 0.99±2.49 (p< 0.03), joint space narrowing 0.33±1.27 v 1.16±2.63 (p<0.03), and total score 0.53±1.57 v 2.15±4.18 (p<0.005) in patients who met the AUC CRP target compared to those who did not. These differences were not seen for SJC or DAS28 at cut-off levels of 3.2 or 2.6. Correlations with Sharp score progression were 0.41 for CRP, 0.25 for ESR, 0.12 for DAS28, 0.11 for SJC.

Safety results:	78 SAEs reviewed in total ▪ 18 infections o 11 lungs o 2 sepsis o 1 abscess o 1 frontal lobe o 3 UK ▪ 8 neoplasm o 1 seminoma o 1 lung o 3 breast o 1 hepatoma o 1 ? melanoma or BCC o 1 ? recurrence of NHL ▪ 5 severe abnormal blood tests/allergic reactions ▪ 47 other hospitalizations (including for RA) 6 deaths ▪ 1 MI prior to randomisation ▪ 4 post study o 1 Ca lung o 1 MI (known heart problems) o 1 cerebral toxoplasmosis o 1 breast Ca with secondaries (outcome UK) ▪ 1 during study o 1 primary hepatoma
Date of report:	25-May-2008