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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00596206
		Study Code:	LEFLU_R_01143
Generic drug name:	Leflunomide	**Date:**	11 Octobre 2010

Title of the study:	Assessment of the early efficacy response rate of leflunomide according to the initial dosing regimen in the treatment of naïve-DMARD (Disease Modifying Antirheumatic Drug) early RA (Rheumatoid Arthritis)-patients.
Investigator(s):	The multinational study was coordinated by a steering committee made up of Pr M. Cutolo and Pr H. Bolosiu.
Study centre(s):	Multinational study conducted in 24 centres in five countries (Czech Republic, Italy, Korea, Portugal and Romania), of which nineteen were active.
Publications:	*Cutolo et al.* Efficacy and safety of leflunomide in DMARD-naïve patients with recently-diagnosed rheumatoid arthritis: comparison of a loading and a fixed dose regimen in the LEADER study. Ann Rheum Dis 2010;69(Suppl3):214. (*poster*).
Study period: Date first patient was enrolled: Date last patient completed main trial:	 20th December 2007 16th October 2009
Phase of development:	Phase IIIb
Objectives:	The primary objective of the study was to assess the clinical efficacy response rate in patients with early RA treated with leflunomide, using the ACR20 criteria evaluated at three months as the primary endpoint in two initial dosing treatment regimen groups (with and without loading dose). **Secondary Objectives** were to assess the clinical efficacy of leflunomide at one and three months using complementary efficacy criteria, to assess the clinical and biological safety of treatment and to evaluate treatment modifications.
Methodology:	This was a multicentre, international phase IIIb, double blind, double dummy, randomised study. During the initial three day double-blind period, two parallel groups received either 20 mg or 100 mg of leflunomide with matching placebo. The three day double-blind period was followed by an open label maintenance period of three months, during which both groups received leflunomide 20 mg daily
Number of patients:	Planned: 200 (100 per treatment group)
	Randomised: 124
	Treated: 121
	Evaluated: 121 (safety analysis population) 120 (intent to treat population) 116 (per protocol population)

Diagnosis and criteria for inclusion: The study included patients of either sex aged over 18 years old with a diagnosis of active rheumatoid arthritis assigned in the previous six months, with current active disease demonstrated by clinical (tender and swollen joint count, morning stiffness and pain) and biological (CRP > 2.0mg/dl or ESR>28mm/Hg) criteria, who were starting DMARD treatment for the first time.

Investigational product: Leflunomide

Dose: 20 mg or 100 mg once a day for three days (double-blind phase); 20 mg once a day (maintenance phase).

Administration: oral

Duration of treatment: Double-blind phase: 3 days; open-label phase: 90 days.

Duration of observation: 120 days.

Reference therapy: Not applicable

Criteria for evaluation:

Efficacy: Treatment efficacy was primarily assessed using the ACR20 response rate at three months. Secondary outcome measures were the ACR50 and ACR70 response rates, the individual components of the ACR, the DAS28 response rate, duration of morning stiffness, changes in concomitant RA treatments (corticosteroids, analgesics and NSAIDs). Quality of life was determined with the SF-36.

Safety: The safety evaluation consisted of reporting of adverse events and systematic monitoring of haematology, blood chemistry and vital signs.

Statistical methods: For the primary efficacy variable (ACR20 response rates), responder rates were determined in each treatment group together with their 95% confidence intervals. The between-group hazard ratio was determined together with its 95% confidence intervals, and the two groups compared using the χ^2 or Fisher's exact test. A similar procedure was followed for the ACR50, ACR70 and DAS28 responder rates. Other data are presented descriptively only.

The efficacy analysis was conducted in an intent-to-treat population, corresponding to all patients who had received at least one dose of study medication and had been evaluated at least once following inclusion. The safety analysis was conducted on all patients with at least one intake of study medication

Study population:

120 patients (54 in the 100 mg initial dose group and 66 in the 20 mg initial dose group) were randomised, treated with study medication and evaluated at least once since baseline (ITT population).

Six major protocol violations were detected, leaving 96.7% of the ITT population eligible for the per protocol population.

109 patients (90.8% of the ITT population) were available for evaluation at the planned 90-day study visit; 92 patients in all (76.7% of the ITT population) completed the entire study as planned.

The two groups were well balanced with respect to age, gender and all RA-related clinical variables with the exception of the duration of morning stiffness, which was longer in the 20 mg initial dose group.

The mean age of the included patients was 53.4 ± 13.3 years and 79.2% were female.

At inclusion, the median time since first symptoms was 6 months and the median time since RA diagnosis was 1 month.

The mean DAS28 score at baseline was 6.07 ± 0.99. The median swollen and tender joint counts were 8 and 11 respectively. Anti-CCP antibodies could be detected in 62.7% of patients and radiographic changes to joints observed in 40.0%.

Efficacy results: The primary efficacy variable was the ACR20% response rate at study endpoint (Visit 3 or last observation) in the ITT population. This was 58.5% in the 100 mg initial dose group and 77.8% in the 20 mg initial dose. The between-group difference was -19.3% with a confidence interval of -36.1% to -2.5%, corresponding to a risk ratio of 0.752 [(-19.9 [95% CI: 0.578 to 0.978] and a significant between-group difference (p = 0.025; χ^2 test).

	100 mg initial dose	**20 mg initial dose**	**Total**
	N = 54	**N = 66**	**N = 120**
Missing data	*1*	*3*	*4*
Responders (n; %)	31 (58.5%)	49 (77.8%)	80 (69.0%)
95% Confidence Interval	[45.2% – 71.8%]	[67.5% – 88.0%]	[60.5% – 77.4%]
Between-group difference [95%CI)	-19.3% [-36.1% to -2.5%]		
Risk ratio [95%CI)	0.752 [0.578 to 0.978]		
Probability (χ^2 test)	0.025		

In the PP population, a similar between-group difference was observed (-19.9 [95% CI: -36.8 to -2.9]), corresponding to a risk ratio of 0.748 [(-19.9 [95% CI: 0.574 to 0.974] and a significant between-group difference (p = 0.023; χ^2 test).

Secondary efficacy variables evaluated in the ITT population were ACR20% response rates evaluated Day 30 and Day 90, ACR50% and ACR70% response rates and DAS28 response rates. Between-group risk ratios for these variables are provided in the Table below. No significant between-group differences were observed for any of these secondary outcome variables.

	Risk ratio (ITT population)	***p***
ACR20% response rate at 30 days	1.121 [0.827;1.520]	0.465
ACR20% response rate at 90 days	0.771 [0.589;1.010]	0.050
ACR50% response rate at study end	0.972 [0.629;1.501]	0.896
ACR70% response rate at study end	0.960 [0.431;2.135]	0.920
DAS28 response rate at study end	0.905 [0.757;1.081]	0.261

Concomitant medication with NSAIDS, analgesics and corticosteroids during the treatment phase was also evaluated:

	100 mg initial dose	**20 mg initial dose**	**Total**	***p***
	N = 54	**N = 66**	**N = 120**	
At least one concomitant medication	36 (66.7%)	51 (77.3%)	87 (72.5%)	0.195
Taken for RA	26 (72.2%)	45 (88.2%)	71 (81.6%)	0.058
Corticosteroid	18 (69.2%)	31 (68.9%)	49 (69.0%)	0.976
Nonsteroidal antiflammatory drugs	21 (80.8%)	34 (75.6%)	55 (77.5%)	0.612
Analgesic	3 (11.5%)	6 (13.3%)	9 (12.7%)	1.000
Taken for any other indication	14 (38.9%)	11 (21.6%)	25 (28.7%)	0.079

Percentages for subcategories are calculated on number of subjects with at least one concomitant. Individual patients can be counted in more than one subcategory, which are not mutually exclusive.

Efficacy conclusions: At Study End, the overall ACR20% response rate was 69.0%, and this rate was significantly higher (p <0.025; χ^2 test) in the 20 mg initial leflunomide dose group (77.8%) than in the group receiving the loading dose of 100 mg. For the secondary outcome variables, no significant differences in outcome between the two treatment groups were observed at a probability threshold of 0.05. A clinical response was observable during the first month of treatment in more than half the subjects. Overall ACR50%, ACR70% and DAS28 response rates at Study End were 41.4%, 17.7% and 81.7% respectively. The proportion of randomised patients evaluated at the final efficacy assessment at ninety days was high, contributing to the strength of the findings.
Safety results: Treatment-emergent adverse events (TEAEs) were reported in 29 (53.7%) of patients in the 100 mg initial dose group and in 33 (49.3%) in the 20 mg initial dose group. The most commonly reported individual adverse event was diarrhoea (14.8% of patients in the 100 mg initial dose group and 6.0% in the 20 mg group). Diarrhoea and elevated hepatic enzymes were reported more frequently in the 100 mg initial dose group. Around half the TEAEs (56 out of 113) were considered to be possibly related to treatment, in particular gastrointestinal disorders and elevated hepatic enzymes. Serious adverse events were reported by three patients in each group. None of these was considered to be possibly related to treatment. No deaths were reported during the study. Treatment discontinuation due to an adverse event was reported in seven (13.0%) patients in the 100 mg initial dose group and eight patients (11.9%) in the 20 mg initial dose group. Possible clinically abnormal laboratory results were reported in >95% of patients, most frequently related to leukocyte count, haemoglobin or to hepatic enzymes. There was a tendency for serum aminotransferase levels to rise over the treatment period.
Safety conclusions: The safety data obtained are consistent with the known safety profile of leflunomide. The most frequently reported adverse event was diarrhoea. The incidence of gastrointestinal side-effects and of elevated liver enzymes reported as adverse events tended to be higher in the patients receiving the loading dose of 100 mg leflunomide. However, systematic monitoring of liver function failed to reveal any clear differences in transaminase levels between the two treatment groups. The most frequent laboratory abnormality observed was changes in white blood cell count, which is to be expected given the mechanism of action of leflunomide. The rate of treatment discontinuation due to adverse events was low, around 12%. None of the six serious adverse events reported were considered to be possible related to leflunomide treatment.
Quality of life data: At the inclusion visit, all SF-36 quality of life dimension scores were low, ranging from 35.29 for the Bodily Pain dimension to 43.99 for the Vitality dimension. After three months of treatment with leflunomide, mean scores had increased on all dimensions by up to seven points. The Physical Component Summary rose from 36.35 to 42.85 and the Mental Component Summary from 43.46 to 47.07. Improvements appeared similar in both treatment arms. At the inclusion visit, 38 patients (31.9%) considered their health to be somewhat or much worse than one week previously, compared to 22 (18.5%) who considered it to be somewhat or much better. At Visit 2, the proportion of patients who considered their health to be somewhat or much better than one week previously had risen to 51.2% (61 patients) and the proportion who considered it to be somewhat or much worse had declined to 5.9% (7 patients). At Visit 3, 62 patients (54.4%) considered their health to be stable, 38 (33.4%) to be somewhat or much better and 14 (12.3%) to be somewhat or much worse.
Date of report: 21st July 2010