CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-905 / S-012

Trade Name: **Arava**

Generic Name: **leflunomide**

Sponsor: **Aventis Pharmaceuticals Inc**

Approval Date: **March 5, 2004**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-905/S-012

Aventis Pharmaceuticals Inc.
Attention: Kerry Rothschild, JD
Director, Regulatory Affairs
200 Crossing Boulevard, PO Box 6890
Bridgewater, NJ 08807-0890

Dear Mr. Rothschild:

Please refer to your supplemental new drug application dated September 4, 2003, received September 5, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arava® (leflunomide) 10 mg, 20 mg and 100 mg tablets.

We acknowledge receipt of your submissions dated September 30, 2003 and March 4, 2004.

This supplemental new drug application provides for additional language to the **CLINICAL PHARMACOLOGY, CLINICAL STUDIES** and **ADVERSE REACTIONS** sections of the label.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert submitted March 4, 2004). These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved supplement NDA 20-905/S-012.**" Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, MD, PhD
Acting Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Deputy Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brian Harvey
3/5/04 05:05:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

LABELING

Rev. xxx

ARAVA® Tablets
(leflunomide)
10 mg, 20 mg, 100 mg

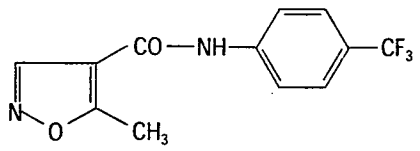
Rx only

CONTRAINDICATIONS AND WARNINGS

PREGNANCY MUST BE EXCLUDED BEFORE THE START OF TREATMENT WITH ARAVA. ARAVA IS CONTRAINDICATED IN PREGNANT WOMEN, OR WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT USING RELIABLE CONTRACEPTION. (SEE CONTRAINDICATIONS AND WARNINGS.) PREGNANCY MUST BE AVOIDED DURING ARAVA TREATMENT OR PRIOR TO THE COMPLETION OF THE DRUG ELIMINATION PROCEDURE AFTER ARAVA TREATMENT.

DESCRIPTION

ARAVA® (leflunomide) is a pyrimidine synthesis inhibitor. The chemical name for leflunomide is N-(4′-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. It has an empirical formula $C_{12}H_9F_3N_2O_2$, a molecular weight of 270.2 and the following structural formula:



ARAVA is available for oral administration as tablets containing 10, 20, or 100 mg of active drug. Combined with leflunomide are the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talc, titanium dioxide, and yellow ferric oxide (20 mg tablet only).

CLINICAL PHARMACOLOGY

Mechanism of Action

Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-inflammatory effect.

Pharmacokinetics

Following oral administration, leflunomide is metabolized to an active metabolite A77 1726 (hereafter referred to as M1) which is responsible for essentially all of its activity *in vivo*. Plasma

levels of leflunomide are occasionally seen, at very low levels. Studies of the pharmacokinetics of leflunomide have primarily examined the plasma concentrations of this active metabolite.

Absorption

Following oral administration, peak levels of the active metabolite, M1, occurred between 6 - 12 hours after dosing. Due to the very long half-life of M1 (~2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of M1. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional.

Table 1. Pharmacokinetic Parameters for M1 after Administration of Leflunomide at Doses of 5, 10, and 25 mg/day for 24 Weeks to Patients (n=54) with Rheumatoid Arthritis (Mean ± SD) (Study YU204)

Maintenance (Loading) Dose			
Parameter	5 mg (50 mg)	10 mg (100 mg)	25 mg (100 mg)
C_{24} (Day 1) (μg/mL)[1]	4.0 ± 0.6	8.4 ± 2.1	8.5 ± 2.2
C_{24} (ss) (μg/mL)[2]	8.8 ± 2.9	18 ± 9.6	63 ± 36
$t_{1/2}$(DAYS)	15 ± 3	14 ± 5	18 ± 9

[1] Concentration at 24 hours after loading dose
[2] Concentration at 24 hours after maintenance doses at steady state

Relative to an oral solution, ARAVA tablets are 80% bioavailable. Co-administration of leflunomide tablets with a high fat meal did not have a significant impact on M1 plasma levels.

Distribution

M1 has a low volume of distribution (Vss = 0.13 L/kg) and is extensively bound (>99.3%) to albumin in healthy subjects. Protein binding has been shown to be linear at therapeutic concentrations. The free fraction of M1 is slightly higher in patients with rheumatoid arthritis and approximately doubled in patients with chronic renal failure; the mechanism and significance of these increases are unknown.

Metabolism

Leflunomide is metabolized to one primary (M1) and many minor metabolites. Of these minor metabolites, only 4-trifluoromethylaniline (TFMA) is quantifiable, occurring at low levels in the plasma of some patients. The parent compound is rarely detectable in plasma. At the present time the specific site of leflunomide metabolism is unknown. *In vivo* and *in vitro* studies suggest a role for both the GI wall and the liver in drug metabolism. No specific enzyme has been identified as the primary route of metabolism for leflunomide; however, hepatic cytosolic and microsomal cellular fractions have been identified as sites of drug metabolism.

Elimination

The active metabolite M1 is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. In a 28 day study of drug elimination (n=3) using a single dose of radiolabeled compound, approximately 43% of the total radioactivity was eliminated in the urine and 48% was eliminated in the feces. Subsequent analysis of the samples revealed the primary urinary metabolites to be leflunomide glucuronides and an oxanilic acid derivative of M1. The primary fecal metabolite was M1. Of these two routes of elimination, renal elimination is more significant over the first 96 hours after which fecal elimination begins to predominate. In a study involving the intravenous administration of M1, the clearance was estimated to be 31 mL/hr. In small studies using activated charcoal (n=1) or cholestyramine (n=3) to facilitate drug elimination, the *in vivo* plasma half-life of M1 was reduced from >1 week to approximately 1 day (see PRECAUTIONS - General - Need for Drug Elimination). Similar reductions in plasma half-life were observed for a series of volunteers (n=96) enrolled in pharmacokinetic trials who were

given cholestyramine. This suggests that biliary recycling is a major contributor to the long elimination half-life of M1. Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that M1 is not dialyzable.

Special Populations

Gender. Gender has not been shown to cause a consistent change in the *in vivo* pharmacokinetics of M1.

Age. Age has been shown to cause a change in the *in vivo* pharmacokinetics of M1. (See PEDIATRICS).

Smoking. A population based pharmacokinetic analysis of the phase III data indicates that smokers have a 38% increase in clearance over non-smokers; however, no difference in clinical efficacy was seen between smokers and nonsmokers.

Chronic Renal Insufficiency. In single dose studies in patients (n=6) with chronic renal insufficiency requiring either chronic ambulatory peritoneal dialysis (CAPD) or hemodialysis, neither had a significant impact on circulating levels of M1. The free fraction of M1 was almost doubled, but the mechanism of this increase is not known. In light of the fact that the kidney plays a role in drug elimination, and without adequate studies of leflunomide use in subjects with renal insufficiency, caution should be used when ARAVA is administered to these patients.

Hepatic Insufficiency. Studies of the effect of hepatic insufficiency on M1 pharmacokinetics have not been done. Given the need to metabolize leflunomide into the active species, the role of the liver in drug elimination/recycling, and the possible risk of increased hepatic toxicity, the use of leflunomide in patients with hepatic insufficiency is not recommended.

Pediatrics

The pharmacokinetics of M1 following oral administration of leflunomide have been investigated in 73 pediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) ranging in age from 3 to 17 years. The results of a population pharmacokinetic analysis of these trials have demonstrated that pediatric patients with body weights ≤40 kg have a reduced clearance of M1 (see Table 2) relative to adult rheumatoid arthritis patients.

Table 2: Population Pharmacokinetic Estimate of M1 Clearance Following Oral Administration of leflunomide in Pediatric Patients with Polyarticular Course JRA Mean ±SD [Range]

N	Body Weight (kg)	CL (mL/h)
10	<20	18 ± 9.8 [6.8-37]
30	20-40	18 ± 9.5 [4.2-43]
33	>40	26 ± 16 [9.7-93.6]

Drug Interactions *In vivo* drug interaction studies have demonstrated a lack of a significant drug interaction between leflunomide and tri-phasic oral contraceptives, and cimetidine.

In vitro studies of protein binding indicated that warfarin did not affect M1 protein binding. At the same time M1 was shown to cause increases ranging from 13 - 50% in the free fraction of diclofenac, ibuprofen and tolbutamide at concentrations in the clinical range. *In vitro* studies of drug metabolism indicate that M1 inhibits CYP 450 2C9, which is responsible for the metabolism of phenytoin, tolbutamide, warfarin and many NSAIDs. M1 has been shown to inhibit the formation of 4′-hydroxydiclofenac from diclofenac *in vitro*. The clinical significance of these findings with regard to phenytoin and tolbutamide is unknown, however, there was extensive concomitant use of NSAIDs in the clinical studies and no differential effect was observed. (see PRECAUTIONS – Drug Interactions).

Methotrexate. Coadministration, in 30 patients, of ARAVA (100 mg/day x 2 days followed by 10 - 20 mg/day) with methotrexate (10 - 25 mg/week, with folate) demonstrated no pharmacokinetic interaction between the two drugs. However, co-administration increased risk of hepatotoxicity (see PRECAUTIONS - Drug Interactions–Hepatotoxic Drugs).

Rifampin. Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to receive both ARAVA and rifampin.

CLINICAL STUDIES

A. Adults

The efficacy of ARAVA in the treatment of rheumatoid arthritis (RA) was demonstrated in three controlled trials showing reduction in signs and symptoms, and inhibition of structural damage. In two placebo controlled trials, efficacy was demonstrated for improvement in physical function.

1. Reduction of signs and symptoms

Relief of signs and symptoms was assessed using the American College of Rheumatology (ACR)20 Responder Index, a composite of clinical, laboratory, and functional measures in rheumatoid arthritis. An "ACR20 Responder" is a patient who had ≥ 20% improvement in both tender and swollen joint counts and in 3 of the following 5 criteria: physician global assessment, patient global assessment, functional ability measure [Modified Health Assessment Questionnaire (MHAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein. An "ACR20 Responder at Endpoint" is a patient who completed the study and was an ACR20 Responder at the completion of the study.

2. Inhibition of structural damage

Inhibition of structural damage compared to control was assessed using the Sharp Score (Sharp, JT. Scoring Radiographic Abnormalities in Rheumatoid Arthritis, Radiologic Clinics of North America, 1996; vol. 34, pp. 233-241), a composite score of X-ray erosions and joint space narrowing in hands/wrists and forefeet.

3. Improvement in physical function

Improvement in physical function was assessed using the Health Assessment Questionnaire (HAQ) and the Medical Outcomes Survey Short Form (SF-36).

In all Arava monotherapy studies, an initial loading dose of 100 mg per day for three days only was used followed by 20 mg per day thereafter.

US301 Clinical Trial in Adults

Study US301, a 2 year study, randomized 482 patients with active RA of at least 6 months duration to leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week increasing to 15 mg/week (n=182), or placebo (n=118). All patients received folate 1 mg BID. Primary analysis was at 52 weeks with blinded treatment to 104 weeks.

Overall, 235 of the 508 randomized treated patients (482 in primary data analysis and an additional 26 patients), continued into a second 12 months of double-blind treatment (98 leflunomide, 101 methotrexate, 36 placebo). Leflunomide dose continued at 20 mg/day and the methotrexate dose could be increased to a maximum of 20 mg/week. In total 190 patients (83 leflunomide, 80 methotrexate, 27 placebo) completed 2 years of double-blind treatment.

The rate and reason for withdrawal is summarized in Table 3.

Table 3: Withdrawals in US301

	n(%) patients		
	Leflunomide 190	Placebo 128	Methotrexate 190
Withdrawals in Year-1			
Lack of efficacy	33 (17.4)	70 (54.7)	50 (26.3)
Safety	44 (23.2)	12 (9.4)	22 (11.6)
Other[1]	15 (7.9)	10 (7.8)	17 (9.0)
Total	92 (48.4)	92 (71.9)	89 (46.8)
Patients entering Year 2	98	36	101
Withdrawals in Year-2			
Lack of efficacy	4 (4.1)	1 (2.8)	4 (4.0)
Safety	8 (8.2)	0 (0.0)	10 (9.9)
Other[1]	3 (3.1)	8 (22.2)	7 (6.9)
Total	15 (15.3)	9 (25.0)	21 (20.8)

[1] Includes: lost to follow up, protocol violation, noncompliance, voluntary withdrawal, investigator discretion.

MN301/303/305 Clinical Trial in Adults

Study MN301 randomized 358 patients with active RA to leflunomide 20 mg/day (n=133), sulfasalazine 2.0 g/day (n=133), or placebo (n=92). Treatment duration was 24 weeks. An extension of the study was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulfasalazine (study MN303). Of the 168 patients who completed 12 months of treatment in MN301 and MN303, 146 patients (87%) entered a 1-year extension study of double blind active treatment (MN305; 60 leflunomide, 60 sulfasalazine, 26 placebo/ sulfasalazine). Patients continued on the same daily dosage of leflunomide or sulfasalazine that they had been taking at the completion of MN301/303. A total of 121 patients (53 leflunomide, 47 sulfasalazine, 21 placebo/sulfasalazine) completed the 2 years of double-blind treatment.

Patient withdrawal data in MN301/303/305 is summarized in Table 4.

Table 4: Withdrawals in study MN301/303/305

	n(%) patients		
	Leflunomide 133	Placebo 92	Sulfasalazine 133
Withdrawals in MN301 (Mo 0-6)			
Lack of efficacy	10 (7.5)	29 (31.5)	14 (10.5)
Safety	19 (14.3)	6 (6.5)	25 (18.8)
Other[1]	8 (6.0)	6 (6.5)	11 (8.3)
Total	37 (27.8)	41 (44.6)	50 (37.6)
Patients entering MN303	80		76
Withdrawals in MN303 (Mo 7-12)			
Lack of efficacy	4 (5.0)		2 (2.6)
Safety	2 (2.5)		5 (6.6)
Other[1]	3 (3.8)		1 (1.3)
Total	9 (11.3)		8 (10.5)
Patients entering MN305	60		60
Withdrawals in MN305 (Mo 13-24)			
Lack of efficacy	0 (0.0)		3 (5.0)
Safety	6 (10.0)		8 (13.3)
Other[1]	1 (1.7)		2 (3.3)
Total	7 (11.7)		13 (21.7)

[1] Includes: lost to follow up, protocol violation, noncompliance, voluntary withdrawal, investigator discretion.

MN302/304 Clinical Trial in Adults

Study MN302 randomized 999 patients with active RA to leflunomide 20 mg/day (n=501) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n=498). Folate supplementation was used in 10% of patients. Treatment duration was 52 weeks.

Of the 736 patients who completed 52 weeks of treatment in study MN302, 612 (83%) entered the double-blind, 1-year extension study MN304 (292 leflunomide, 320 methotrexate). Patients continued on the same daily dosage of leflunomide or methotrexate that they had been taking at the completion of MN302. There were 533 patients (256 leflunomide, 277 methotrexate) who completed 2 years of double-blind treatment.

Patient withdrawal data in MN302/304 is summarized in Table 5.

Table 5: Withdrawals in MN302/304

	n(%) patients	
	Leflunomide 501	Methotrexate 498
Withdrawals in MN302 (Year-1)		
Lack of efficacy	37 (7.4)	15 (3.0)
Safety	98 (19.6)	79 (15.9)
Other[1]	17 (3.4)	17 (3.4)
Total	152 (30.3)	111 (22.3)
Patients entering MN304	292	320
Withdrawals in MN304 (Year-2)		
Lack of efficacy	13 (4.5)	9 (2.8)
Safety	11 (3.8)	22 (6.9)
Other[1]	12 (4.1)	12 (3.8)
Total	36 (12.3)	43 (13.4)

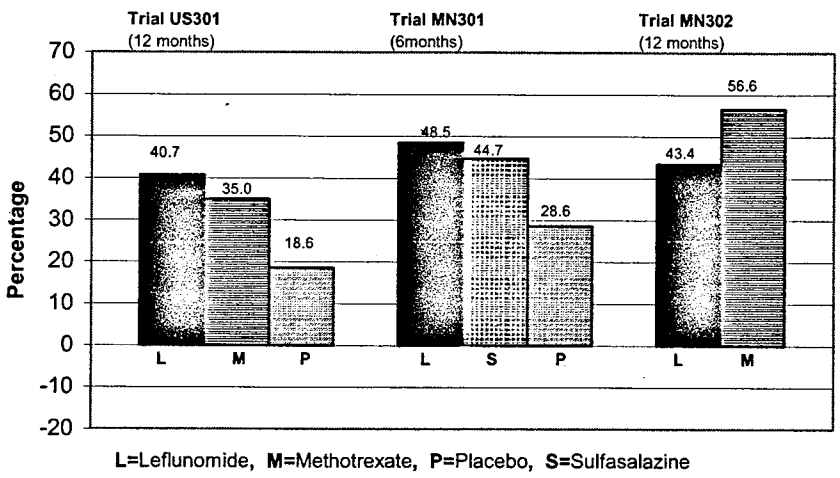
[1] Includes: lost to follow up, protocol violation, noncompliance, voluntary withdrawal, investigator discretion.

Clinical Trial Data

1. Signs and symptoms Rheumatoid Arthritis

The ACR20 Responder at Endpoint rates are shown in Figure 1. ARAVA was statistically significantly superior to placebo in reducing the signs and symptoms of RA by the primary efficacy analysis, ACR20 Responder at Endpoint, in study US301 (at the primary 12 months endpoint) and MN301 (at 6 month endpoint). ACR20 Responder at Endpoint rates with ARAVA treatment were consistent across the 6 and 12 month studies (41 - 49%). No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine. ARAVA treatment effect was evident by 1 month, stabilized by 3 - 6 months, and continued throughout the course of treatment as shown in Figure 2.

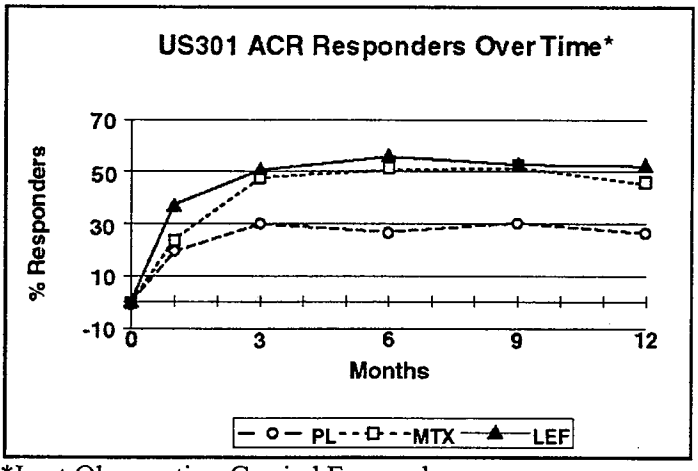
Figure 1



L=Leflunomide, M=Methotrexate, P=Placebo, S=Sulfasalazine

	Comparisons	95%Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(12, 32)	<0.0001
	Methotrexate vs. Placebo	(8, 30)	<0.0001
	Leflunomide vs. Methotrexate	(-4, 16)	NS
MN301	Leflunomide vs. Placebo	(7, 33)	0.0026
	Sulfasalazine vs. Placebo	(4, 29)	0.0121
	Leflunomide vs. Sulfasalazine	(-8, 16)	NS
MN302	Leflunomide vs. Methotrexate	(-19, -7)	<0.0001

Figure 2



*Last Observation Carried Forward.

ACR50 and ACR70 Responders are defined in an analogous manner to the ACR 20 Responder, but use improvements of 50% or 70%, respectively (Table 6). Mean change for the individual components of the ACR Responder Index are shown in Table 7.

Table 6. Summary of ACR Response Rates*

Study and Treatment Group	ACR20	ACR50	ACR70
Placebo-Controlled Studies			
US301 (12 months)			
Leflunomide (n=178)†	52.2‡	34.3‡	20.2‡
Placebo (n=118)†	26.3	7.6	4.2
Methotrexate (n=180)†	45.6	22.8	9.4
MN301(6 months)			
Leflunomide (n=130)†	54.6‡	33.1‡	10.0§
Placebo (n=91)†	28.6	14.3	2.2
Sulfasalazine (n=132)†	56.8	30.3	7.6
Non-Placebo Active-Controlled Studies			
MN302 (12 months)			
Leflunomide (n=495)†	51.1	31.1	9.9
Methotrexate (n=489)†	65.2	43.8	16.4

* Intent to treat (ITT) analysis using last observation carried forward (LOCF) technique for patients who discontinued early.
† N is the number of ITT patients for whom adequate data were available to calculate the indicated rates.
‡ $p<0.001$ leflunomide vs. placebo
§ $p<0.02$ leflunomide vs. placebo

Table 7 shows the results of the components of the ACR response criteria for US301, MN301, and MN302. ARAVA was significantly superior to placebo in all components of the ACR Response criteria in study US301 and MN301. In addition Arava was significantly superior to placebo in improving morning stiffness, a measure of RA disease activity, not included in the ACR Response criteria. No consistent differences were demonstrated between ARAVA and the active comparators.

Table 7. Mean Change in the Components of the ACR Responder Index*

Components	Placebo-Controlled Studies						Non-placebo Controlled Study	
	US301 (12 months)			MN301 Non-US (6 months)			MN302 Non-US (12 months)	
	Leflu-nomide	Metho-trexate	Placebo	Leflu-nomide	Sulfa-salazine	Placebo	Leflu-nomide	Metho-trexate
Tender joint count[1]	-7.7	-6.6	-3.0	-9.7	-8.1	-4.3	-8.3	-9.7
Swollen joint count[1]	-5.7	-5.4	-2.9	-7.2	-6.2	-3.4	-6.8	-9.0
Patient global assessment[2]	-2.1	-1.5	0.1	-2.8	-2.6	-0.9	-2.3	-3.0
Physician global assessment[2]	-2.8	-2.4	-1.0	-2.7	-2.5	-0.8	-2.3	-3.1
Physical function/disability (MHAQ/HAQ)	-0.29	-0.15	0.07	-0.50	-0.29	-0.04	-0.37	-0.44
Pain intensity[2]	-2.2	-1.7	-0.5	-2.7	-2.0	-0.9	-2.1	-2.9
Erythrocyte Sedimentation rate	-6.26	-6.48	2.56	-7.48	-16.56	3.44	-10.12	-22.18
C-reactive protein	-0.62	-0.50	0.47	-2.26	-1.19	0.16	-1.86	-2.45
Not included in the ACR Responder Index								
Morning Stiffness (min)	-101.4	-88.7	14.7	-93.0	-42.4	-6.8	-63.7	-86.6

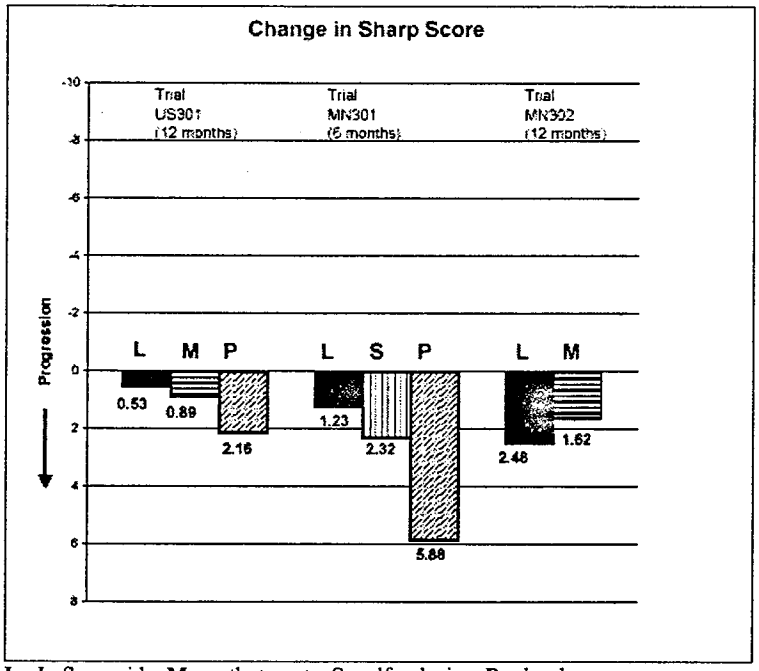
* Last Observation Carried Forward; Negative Change Indicates Improvement
1 Based on 28 joint count
2 Visual Analog Scale - 0=Best; 10=Worst

Maintenance of effect
After completing 12 months of treatment, patients continuing on study treatment were evaluated for an additional 12 months of double-blind treatment (total treatment period of 2 years) in studies US301, MN305, and MN304. ACR Responder rates at 12 months were maintained over 2 years in most patients continuing a second year of treatment.
Improvement from baseline in the individual components of the ACR responder criteria was also sustained in most patients during the second year of Arava treatment in all three trials.

2. Inhibition of structural damage

The change from baseline to endpoint in progression of structural disease, as measured by the Sharp X-ray score, is displayed in Figure 3. ARAVA was statistically significantly superior to placebo in inhibiting the progression of disease by the Sharp Score. No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine.

Figure 3



L= Leflunomide; M=methotrexate; S=sulfasalazine; P=placebo

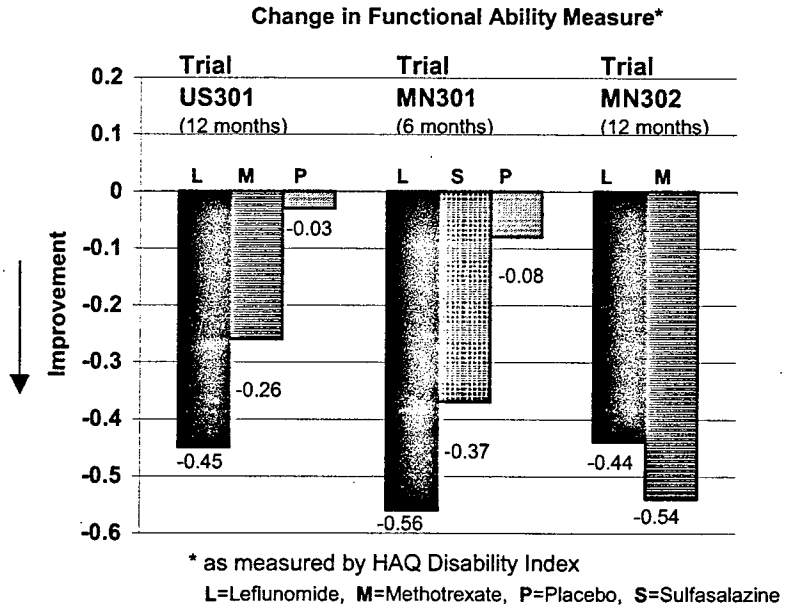
	Comparisons	95% Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(-4.0, -1.1)	0.0007
	Methotrexate vs. Placebo	(-2.6, -0.2)	0.0196
	Leflunomide vs. Methotrexate	(-2.3, 0.0)	0.0499
MN301	Leflunomide vs. Placebo	(-6.2, -1.8)	0.0004
	Sulfasalazine vs. Placebo	(-6.9, 0.0)	0.0484
	Leflunomide vs. Sulfasalazine	(-3.3, 1.2)	NS
MN302	Leflunomide vs. Methotrexate	(-2.2, 7.4)	NS

3. Improvement in physical function

The Health Assessment Questionnaire (HAQ) assesses a patient's physical function and degree of disability. The mean change from baseline in functional ability as measured by the HAQ Disability Index (HAQ DI) in the 6 and 12 month placebo and active controlled trials is shown in Figure 4. ARAVA was statistically significantly superior to placebo in improving physical function. Superiority to placebo was demonstrated consistently across all eight HAQ DI subscales (dressing, arising, eating, walking, hygiene, reach, grip and activities) in both placebo controlled studies.

The Medical Outcomes Survey Short Form 36 (SF-36), a generic health-related quality of life questionnaire, further addresses physical function. In US301, at 12 months, ARAVA provided statistically significant improvements compared to placebo in the Physical Component Summary (PCS) Score.

Figure 4



	Comparison	95% Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(-0.58, -0.29)	0.0001
	Leflunomide vs. Methotrexate	(-0.34, -0.07)	0.0026
MN301	Leflunomide vs. Placebo	(-0.67, -0.36)	<0.0001
	Leflunomide vs. Sulfasalazine	(-0.33, -0.03)	0.0163
MN302	Leflunomide vs. Methotrexate	(0.01, 0.16)	0.0221

Maintenance of effect

The improvement in physical function demonstrated at 6 and 12 months was maintained over two years. In those patients continuing therapy for a second year, this improvement in physical function as measured by HAQ and SF-36 (PCS) was maintained.

Clinical Trials in Pediatrics
ARAVA was studied in a single multicenter, double-blind, active-controlled trial in 94 patients (1:1 randomization) with polyarticular course juvenile rheumatoid arthritis (JRA) as defined by the American College of Rheumatology (ACR). Approximately 68% of pediatric patients receiving ARAVA, versus 89% of pediatric patients receiving the active comparator, improved by Week 16 (end-of-study) employing the JRA Definition of Improvement (DOI) ≥30 % responder endpoint. In this trial, the loading dose and maintenance dose of ARAVA was based on three weight categories: <20 kg, 20-40 kg, and >40 kg. The response rate to ARAVA in pediatric patients ≤40 kg was less robust than in pediatric patients >40 kg suggesting suboptimal dosing in smaller weight pediatric patients, as studied, resulting in less than efficacious plasma concentrations, despite reduced clearance of M1. (See Pharmacokinetics).

INDICATIONS AND USAGE
ARAVA is indicated in adults for the treatment of active rheumatoid arthritis (RA):
1. to reduce signs and symptoms
2. to inhibit structural damage as evidenced by X-ray erosions and joint space narrowing
3. to improve physical function.

(see CLINICAL STUDIES)

Aspirin, nonsteroidal anti-inflammatory agents and/or low dose corticosteroids may be continued during treatment with ARAVA (see PRECAUTIONS – Drug Interactions – NSAIDs). The combined use of ARAVA with antimalarials, intramuscular or oral gold, D penicillamine, azathioprine, or methotrexate has not been adequately studied (see WARNINGS - Immunosuppression Potential/Bone Marrow Suppression).

CONTRAINDICATIONS
ARAVA is contraindicated in patients with known hypersensitivity to leflunomide or any of the other components of ARAVA.
ARAVA can cause fetal harm when administered to a pregnant woman. Leflunomide, when administered orally to rats during organogenesis at a dose of 15 mg/kg, was teratogenic (most notably anophthalmia or microophthalmia and internal hydrocephalus). The systemic exposure of rats at this dose was approximately 1/10 the human exposure level based on AUC. Under these exposure conditions, leflunomide also caused a decrease in the maternal body weight and an increase in embryolethality with a decrease in fetal body weight for surviving fetuses. In rabbits, oral treatment with 10 mg/kg of leflunomide during organogenesis resulted in fused, dysplastic sternebrae. The exposure level at this dose was essentially equivalent to the maximum human exposure level based on AUC. At a 1 mg/kg dose, leflunomide was not teratogenic in rats and rabbits.
When female rats were treated with 1.25 mg/kg of leflunomide beginning 14 days before mating and continuing until the end of lactation, the offspring exhibited marked (greater than 90%) decreases in postnatal survival. The systemic exposure level at 1.25 mg/kg was approximately 1/100 the human exposure level based on AUC.
ARAVA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Immunosuppression Potential/Bone Marrow Suppression

ARAVA is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe, uncontrolled infections. In the event that a serious infection occurs, it may be necessary to interrupt therapy with ARAVA and administer cholestyramine or charcoal (see PRECAUTIONS – General – Need for Drug Elimination). Medications like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections. Rarely, severe infections including sepsis, which may be fatal, have been reported in patients receiving ARAVA. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection.

There have been rare reports of pancytopenia , agranulocytosis and thrombocytopenia in patients receiving ARAVA alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality.

Patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6- to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, chronic monitoring should be monthly. If evidence of bone marrow suppression occurs in a patient taking ARAVA, treatment with ARAVA should be stopped, and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide active metabolite (see PRECAUTIONS – General – Need for Drug Elimination).

In any situation in which the decision is made to switch from ARAVA to another anti-rheumatic agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. ARAVA washout with cholestyramine or charcoal may decrease this risk, but also may induce disease worsening if the patient had been responding to ARAVA treatment.

Hepatotoxicity

RARE CASES OF SEVERE LIVER INJURY, INCLUDING CASES WITH FATAL OUTCOME, HAVE BEEN REPORTED DURING TREATMENT WITH LEFLUNOMIDE. MOST CASES OF SEVERE LIVER INJURY OCCUR WITHIN 6 MONTHS OF THERAPY AND IN A SETTING OF MULTIPLE RISK FACTORS FOR HEPATOTOXICITY (liver disease, other hepatotoxins). (See PRECAUTIONS).

At minimum, ALT (SGPT) must be performed at baseline and monitored initially at monthly intervals during the first six months then, if stable, every 6 to 8 weeks thereafter. In addition, if ARAVA and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing monthly.

Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT elevation are recommended as follows: For confirmed ALT elevations between 2- and 3-fold ULN, dose reduction to 10 mg/day may allow continued administration of ARAVA under close monitoring. If elevations between 2- and 3-fold ULN persist despite dose reduction or if ALT elevations of >3-fold ULN are present, ARAVA should be discontinued and cholestyramine or charcoal should be administered (see PRECAUTIONS - General - Need for Drug Elimination) with close monitoring, including retreatment with cholestyramine or charcoal as indicated.

In clinical trials, ARAVA treatment as monotherapy or in combination with methotrexate was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients; these effects were generally reversible. Most transaminase elevations were mild (≤ 2-fold ULN) and usually resolved while continuing treatment. Marked elevations (>3-fold ULN) occurred infrequently and reversed with dose reduction or discontinuation of treatment. Table 8 shows liver enzyme elevations seen with monthly monitoring in clinical trials US301 and MN301. It was notable that the absence of folate use in MN302 was associated with a considerably greater incidence of liver enzyme elevation on methotrexate.

Table 8. Liver Enzyme Elevations >3-fold Upper Limits of Normal (ULN)

	US301			MN301			MN302*	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
ALT (SGPT)								
>3-fold ULN	8	3	5	2	1	2	13	83
(n %)	(4.4)	(2.5)	(2.7)	(1.5)	(1.1)	(1.5)	(2.6)	(16.7)
Reversed to ≤ 2-fold ULN:	8	3	5	2	1	2	12	82
Timing of Elevation								
0-3 Months	6	1	1	2	1	2	7	27
4-6 Months	1	1	3	-	-	-	1	34
7-9 Months	1	1	1	-	-	-	-	16
10-12 Months	-	-	-	-	-	-	5	6

*Only 10% of patients in MN302 received folate. All patients in US301 received folate.

In a 6 month study of 263 patients with persistent active rheumatoid arthritis despite methotrexate therapy, and with normal LFTs, leflunomide was added to a group of 133 patients starting at 10 mg per day and increased to 20 mg as needed. An increase in ALT greater than or equal to three times the ULN was observed in 3.8% of patients compared to 0.8% in 130 patients continued on methotrexate with placebo added.

Pre-existing Hepatic Disease

Given the possible risk of increased hepatotoxicity, and the role of the liver in drug activation, elimination and recycling, the use of ARAVA is not recommended in patients with significant hepatic impairment or evidence of infection with hepatitis B or C viruses. (See Warnings – Hepatotoxicity).

Skin Reactions

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving ARAVA. If a patient taking ARAVA develops any of these conditions, ARAVA therapy should be stopped, and a drug elimination procedure is recommended (see PRECAUTIONS - General - Need for Drug Elimination).

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppression with ARAVA. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of ARAVA, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with ARAVA.

Use in Women of Childbearing Potential

There are no adequate and well-controlled studies evaluating ARAVA in pregnant women. However, based on animal studies, leflunomide may increase the risk of fetal death or teratogenic effects when administered to a pregnant woman (see CONTRAINDICATIONS). Women of childbearing potential must not be started on ARAVA until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with ARAVA, patients must be fully counseled on the potential for serious risk to the fetus.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing and, if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of the active metabolite by instituting the drug elimination procedure described below at the first delay of menses may decrease the risk to the fetus from ARAVA.

Upon discontinuing ARAVA, it is recommended that all women of childbearing potential undergo the drug elimination procedure described below. Women receiving ARAVA treatment who wish to become pregnant must discontinue ARAVA and undergo the drug elimination procedure described below which includes verification of M1 metabolite plasma levels less than 0.02 mg/L (0.02 µg/mL). Human plasma levels of the active metabolite (M1) less than 0.02 mg/L (0.02 µg/mL) are expected to have minimal risk based on available animal data.

Drug Elimination Procedure

The following drug elimination procedure is recommended to achieve non-detectable plasma levels (less than 0.02 mg/L or 0.02 µg/mL) after stopping treatment with ARAVA:

1) Administer cholestyramine 8 grams 3 times daily for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly.)
2) Verify plasma levels less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.

Without the drug elimination procedure, it may take up to 2 years to reach plasma M1 metabolite levels less than 0.02 mg/L due to individual variation in drug clearance.

PRECAUTIONS

General

Need for Drug Elimination

The active metabolite of leflunomide is eliminated slowly from the plasma. In instances of any serious toxicity from ARAVA, including hypersensitivity, use of a drug elimination procedure as described in this section is highly recommended to reduce the drug concentration more rapidly after stopping ARAVA therapy. If hypersensitivity is the suspected clinical mechanism, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. The duration may be modified based on the clinical status of the patient.

Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of M1 by approximately 40% in 24 hours and by 49 to 65% in 48 hours.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite, M1, by 37% in 24 hours and by 48% in 48 hours.

These drug elimination procedures may be repeated if clinically necessary.

Renal Insufficiency
Single dose studies in dialysis patients show a doubling of the free fraction of M1 in plasma. There is no clinical experience in the use of ARAVA in patients with renal impairment. Caution should be used when administering this drug in this population.

Vaccinations
No clinical data are available on the efficacy and safety of vaccinations during ARAVA treatment. Vaccination with live vaccines is, however, not recommended. The long half-life of ARAVA should be considered when contemplating administration of a live vaccine after stopping ARAVA.

Information for Patients
The potential for increased risk of birth defects should be discussed with female patients of childbearing potential. It is recommended that physicians advise women that they may be at increased risk of having a child with birth defects if they are pregnant when taking ARAVA, become pregnant while taking ARAVA, or do not wait to become pregnant until they have stopped taking ARAVA and followed the drug elimination procedure (as described in WARNINGS – Use In Women of Childbearing Potential – Drug Elimination Procedure).
Patients should be advised of the possibility of rare, serious skin reactions. Patients should be instructed to inform their physicians promptly if they develop a skin rash or mucous membrane lesions.
Patients should be advised of the potential hepatotoxic effects of ARAVA and of the need for monitoring liver enzymes.
Patients should be instructed to notify their physicians if they develop symptoms such as unusual tiredness, abdominal pain or jaundice.
Patients should be advised that they may develop a lowering of their blood counts and should have frequent hematologic monitoring. This is particularly important for patients who are receiving other immunosuppressive therapy concurrently with ARAVA, who have recently discontinued such therapy before starting treatment with ARAVA, or who have had a history of a significant hematologic abnormality. Patients should be instructed to notify their physicians promptly if they notice symptoms of pancytopenia (such as easy bruising or bleeding, recurrent infections, fever, paleness or unusual tiredness).

Laboratory Tests
Hematologic Monitoring
At minimum, patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6 to 8 weeks thereafter.
Bone Marrow Suppression Monitoring
If used with concomitantly with immunosuppressants such as methotrexate, chronic monitoring should be monthly. (see WARNINGS - Immunosuppression Potential/Bone Marrow Suppression).
Liver Enzyme Monitoring
ALT (SGPT) must be performed at baseline and monitored at monthly intervals during the first six months then, if stable, every 6 to 8 weeks thereafter. In addition, if ARAVA and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing every month. (See WARNINGS – Hepatotoxicity.)
Due to a specific effect on the brush border of the renal proximal tubule, ARAVA has a uricosuric effect. A separate effect of hypophosphaturia is seen in some patients. These effects have not been seen together, nor have there been alterations in renal function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of leflunomide up to the maximally tolerated dose of 6 mg/kg (approximately 1/40 the maximum human M1 systemic exposure based on AUC). However, male mice in a 2-year bioassay exhibited an increased incidence in lymphoma at an oral dose of 15 mg/kg, the highest dose studied (1.7 times the human M1 exposure based on AUC). Female mice, in the same study, exhibited a dose-related increased incidence of bronchoalveolar adenomas and carcinomas combined beginning at 1.5 mg/kg (approximately 1/10 the human M1 exposure based on AUC). The significance of the findings in mice relative to the clinical use of ARAVA is not known.

Leflunomide was not mutagenic in the Ames Assay, the Unscheduled DNA Synthesis Assay, or in the HGPRT Gene Mutation Assay. In addition, leflunomide was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. However, 4-trifluoromethylaniline (TFMA), a minor metabolite of leflunomide, was mutagenic in the Ames Assay and in the HGPRT Gene Mutation Assay, and was clastogenic in the *in vitro* Assay for Chromosome Aberrations in the Chinese Hamster Cells. TFMA was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. Leflunomide had no effect on fertility in either male or female rats at oral doses up to 4.0 mg/kg (approximately 1/30 the human M1 exposure based on AUC).

Pregnancy

Pregnancy Category X. See CONTRAINDICATIONS section. Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to leflunomide, health care providers are encouraged to register such patients by calling 1-877-311-8972.

Nursing Mothers

ARAVA should not be used by nursing mothers. It is not known whether ARAVA is excreted in human milk. Many drugs are excreted in human milk, and there is a potential for serious adverse reactions in nursing infants from ARAVA. Therefore, a decision should be made whether to proceed with nursing or to initiate treatment with ARAVA, taking into account the importance of the drug to the mother.

Use in Males

Available information does not suggest that ARAVA would be associated with an increased risk of male-mediated fetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimize any possible risk, men wishing to father a child should consider discontinuing use of ARAVA and taking cholestyramine 8 grams 3 times daily for 11 days.

Drug Interactions

Cholestyramine and Charcoal

Administration of cholestyramine or activated charcoal in patients (n=13) and volunteers (n=96) resulted in a rapid and significant decrease in plasma M1 (the active metabolite of leflunomide) concentration (see PRECAUTIONS – General – Need for Drug Elimination).

Hepatotoxic Drugs

Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances. This is also to be considered when leflunomide treatment is followed by such drugs without a drug elimination procedure. In a small (n=30) combination study of ARAVA with methotrexate, a 2- to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. A >3-fold

increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Three patients met "ACR criteria" for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). No pharmacokinetic interaction was identified (see CLINICAL PHARMACOLOGY).

NSAIDs
In *in vitro* studies, M1 was shown to cause increases ranging from 13 - 50% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide
In *in vitro* studies, M1 was shown to cause increases ranging from 13 - 50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Rifampin
Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and rifampin.

Warfarin
Increased INR (International Normalized Ratio) when ARAVA and warfarin were co-administered has been rarely reported.

Pediatric Use
The safety and effectiveness of ARAVA in pediatric patients with polyarticular course juvenile rheumatoid arthritis have not been fully evaluated.. (See CLINICAL STUDIES). (See ADVERSE REACTIONS).

Geriatric Use
No dosage adjustment is needed in patients over 65.

ADVERSE REACTIONS

Adverse reactions associated with the use of leflunomide in RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash. In the controlled studies at one year, the following adverse events were reported, regardless of causality. (See Table 9.)

Table 9. Percentage Of Patients With Adverse Events ≥3% In Any Leflunomide Treated Group

	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301 and US 301				MN 302*	
	LEF (N=1339)[1]	LEF (N=315)	PBO (N=210)	SSZ (N=133)	MTX (N=182)	LEF (N=501)	MTX (N=498)
BODY AS A WHOLE							
Allergic Reaction	2%	5%	2%	0%	6%	1%	2%
Asthenia	3%	6%	4%	5%	6%	3%	3%
Flu Syndrome	2%	4%	2%	0%	7%	0%	0%

Infection, upper respiratory	4%	0%	0%	0%	0%	0%	0%
Injury Accident	5%	7%	5%	3%	11%	6%	7%
Pain	2%	4%	2%	2%	5%	1%	<1%
Abdominal Pain	6%	5%	4%	4%	8%	6%	4%
Back Pain	5%	6%	3%	4%	9%	8%	7%
CARDIOVASCULAR							
Hypertension[2]	10%	9%	4%	4%	3%	10%	4%
- New onset of hypertension		1%	<1%	0%	2%	2%	<1%
Chest Pain	2%	4%	2%	2%	4%	1%	2%
GASTROINTESTINAL							
Anorexia	3%	3%	2%	5%	2%	3%	3%
Diarrhea	17%	27%	12%	10%	20%	22%	10%
Dyspepsia	5%	10%	10%	9%	13%	6%	7%
Gastroenteritis	3%	1%	1%	0%	6%	3%	3%
Abnormal Liver Enzymes	5%	10%	2%	4%	10%	6%	17%
Nausea	9%	13%	11%	19%	18%	13%	18%
GI/Abdominal Pain	5%	6%	4%	7%	8%	8%	8%
Mouth Ulcer	3%	5%	4%	3%	10%	3%	6%
Vomiting	3%	5%	4%	4%	3%	3%	3%
METABOLIC AND NUTRITIONAL							
Hypokalemia	1%	3%	1%	1%	1%	1%	<1%
Weight Loss[3]	4%	2%	1%	2%	0%	2%	2%
MUSCULO-SKELETAL SYSTEM							
Arthralgia	1%	4%	3%	0%	9%	<1%	1%
Leg Cramps	1%	4%	2%	2%	6%	0%	0%
Joint Disorder	4%	2%	2%	2%	2%	8%	6%
Synovitis	2%	<1%	1%	0%	2%	4%	2%
Tenosynovitis	3%	2%	0%	1%	2%	5%	1%
NERVOUS SYSTEM							
Dizziness	4%	5%	3%	6%	5%	7%	6%
Headache	7%	13%	11%	12%	21%	10%	8%
Paresthesia	2%	3%	1%	1%	2%	4%	3%
RESPIRATORY SYSTEM							
Bronchitis	7%	5%	2%	4%	7%	8%	7%
Increased Cough	3%	4%	5%	3%	6%	5%	7%
Respiratory Infection	15%	21%	21%	20%	32%	27%	25%
Pharyngitis	3%	2%	1%	2%	1%	3%	3%
Pneumonia	2%	3%	0%	0%	1%	2%	2%
Rhinitis	2%	5%	2%	4%	3%	2%	2%
Sinusitis	2%	5%	5%	0%	10%	1%	1%
SKIN AND APPENDAGES							
Alopecia	10%	9%	1%	6%	6%	17%	10%
Eczema	2%	1%	1%	1%	1%	3%	2%
Pruritus	4%	5%	2%	3%	2%	6%	2%
Rash	10%	12%	7%	11%	9%	11%	10%
Dry Skin	2%	3%	2%	2%	0%	3%	1%
UROGENITAL SYSTEM							
Urinary Tract Infection	5%	5%	7%	4%	2%	5%	6%

* Only 10% of patients in MN302 received folate. All patients in US301 received folate; none in MN301 received folate.

1 Includes all controlled and uncontrolled trials with leflunomide (duration up to 12 months).
2 Hypertension as a preexisting condition was overrepresented in all leflunomide treatment groups in phase III trials
3 In a meta-analysis of all phase II and III studies, during the first 6 months in patients receiving leflunomide, 10% lost 10-19 lbs (24 cases per 100 patient years) and 2% lost at least 20 lbs (4 cases/100 patient years). Of patients receiving leflunomide 4% lost 10% of their baseline weight during the first 6 months of treatment.

Adverse events during a second year of treatment with leflunomide in clinical trials were consistent with those observed during the first year of treatment and occurred at a similar or lower incidence.

In addition, the following adverse events have been reported in 1% to <3% of the RA patients in the leflunomide treatment group in controlled clinical trials.
Body as a Whole: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain;
Cardiovascular: angina pectoris, migraine, palpitation, tachycardia, varicose vein, vasculitis, vasodilatation;
Gastrointestinal: cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder;
Endocrine: diabetes mellitus, hyperthyroidism;
Hemic and Lymphatic System: anemia (including iron deficiency anemia), ecchymosis;
Metabolic and Nutritional: creatine phosphokinase increased, hyperglycemia, hyperlipidemia, peripheral edema;
Musculo-Skeletal System: arthrosis, bone necrosis, bone pain, bursitis, muscle cramps, myalgia, tendon rupture;
Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo;
Respiratory System: asthma, dyspnea, epistaxis, lung disorder;
Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, maculopapular rash, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, ulcer skin;
Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion;
Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, prostate disorder, urinary frequency, vaginal moniliasis.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 WBC/mm^3 (rare).

Adverse events during a second year of treatment with leflunomide in clinical trials were consistent with those observed during the first year of treatment and occurred at a similar or lower incidence.

In post-marketing experience, the following have been reported rarely:
Body as a whole: opportunistic infections, severe infections including sepsis that may be fatal;
Gastrointestinal: pancreatitis;
Hematologic: agranulocytosis, leukopenia, neutropenia, pancytopenia, thrombocytopenia;
Hypersensitivity: angioedema;

Hepatic: hepatitis, jaundice/cholestasis, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal;
Respiratory: interstitial lung disease;
Nervous system: peripheral neuropathy
Skin and Appendages: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Adverse Reactions (Pediatric Patients)
The safety of ARAVA was studied in 74 patients with polyarticular course juvenile rheumatoid arthritis ranging in age from 3-17 years (47 patients from the active-controlled study and 27 from the open-label safety and pharmacokinetic study). The most common adverse events included abdominal pain, diarrhea, nausea, vomiting, oral ulcers, upper respiratory tract infections, alopecia, rash, headache, and dizziness. Less common adverse events included anemia, hypertension, and weight loss. Fourteen pediatric patients experienced ALT and/or AST elevations, nine between 1.2 and 3-fold the upper limit of normal and five between 3 and 8-fold the upper limit of normal.

DRUG ABUSE AND DEPENDENCE
ARAVA has no known potential for abuse or dependence.

OVERDOSAGE
In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200 - 500 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).
There have been reports of chronic overdose in patients taking ARAVA at daily does up to five times the recommended daily dose and reports of acute overdose in adults or children. There were no adverse events reported in the majority of case reports of overdose. Adverse events were consistent with the safety profile for ARAVA (see ADVERSE REACTIONS). The most frequent adverse events observed were diarrhea, abdominal pain, leukopenia, anemia and elevated liver function tests.
In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination (see PRECAUTIONS – General – Need for Drug Elimination).
Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that M1, the primary metabolite of leflunomide, is not dialyzable. (see CLINICAL PHARMACOLOGY – Elimination).

DOSAGE AND ADMINISTRATION
Loading Dose
Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.
Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past. (See WARNINGS — Hepatotoxicity).

Maintenance Therapy
Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104), treated with 25 mg/day, experienced a greater incidence of side effects;

alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes must be monitored and dose adjustments may be necessary (see WARNINGS – Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

ARAVA® (leflunomide) Tablets

Strength	Quantity	NDC Number	Description
10 mg	30 count bottle 100 count bottle	0088-2160-30 0088-2160-47	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle	0088-2161-30 0088-2161-47	Light yellow, triangular film-coated tablet embossed with "ZBO" on one side.
100 mg	3 count blister pack	0088-2162-03	White, round film-coated tablet embossed with "ZBP" on one side.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only.

Rev. xxx

Manufactured by
Usiphar, 60200 Compiegne, France
for
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137

Made in France

©2003 Aventis Pharmaceuticals Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

SUMMARY REVIEW

Clinical Team Leader's Memorandum:

Reviewer: James Witter MD, PhD (HFD-550)

Date: March 3, 2004

NDA: **20-905/S012**

Sponsor: Aventis Pharmaceuticals Inc.
ARAVA® (leflunomide) tablets-10, 20, and 100 mg

Summary:
NDA 20-905/S-012 is a pediatric efficacy supplement. It was submitted September 5, 2003 in response to a Pediatric Written Request (PWR) issued March 30, 1999 by this Division (HFD-550). The supplement included studies of ARAVA (leflunomide-LEF) tablets used in patients with polyarticular-course juvenile rheumatoid arthritis (JRA). ARAVA, the subject of a Citizen's Petition dated March 28, 2002 for its removal due to safety concerns, is currently approved (September 10, 1998) for use in adult rheumatoid arthritis (RA). Of note, the sponsor is not interested in an INDICATION in the labeling for JRA, but was granted 6-months of exclusivity based upon this NDA submission (November 10, 2003).

A total of 74 patients (aged 3-17 years) with JRA were evaluated in this NDA (27 patients-study 1307; 47 patient studies 3503 and 3504; see below). Three studies were submitted with the NDA that involved patients with JRA and are briefly summarized as follows:

-Study HWA 486/1307
This was the initial study of LEF in pediatric patients with JRA. This open-label study evaluated the pharmacokinetics (compared to adults in another study submitted in the NDA), safety and efficacy of LEF in patients who had previously failed methotrexate (MTX); methotrexate is approved for the treatment of JRA. There were 27 patients enrolled into the first portion of this study which lasted 26 weeks. An extension of this study out to 130 weeks enrolled 17 patients of the original cohort. Efficacy was assessed in this trial using the JRA-DOI (definition of improvement) ≥ 30%, 50%, and 70% which is a valid metric in this JRA population (*Giannini, et.al. Arth. Rheum. 1997; 40: 1202-1209*).

-Study HWA 468/3503
This *pivotal* study was originally designed as an equivalence trial (powered to include 120 patients per arm) to methotrexate. However, due to difficulties in enrolling patients, the PWR was amended (January 14, 2002) to a superiority-design trial against methotrexate (considered the current standard disease-modifying agent for JRA). A total of 47 patients with JRA were enrolled into each treatment arm (94 patients in total) in this double-blind, 16-week, multinational trial. Efficacy was again evaluated with the JRA-DOI endpoint, along with a second co-primary endpoint of Percent Improvement; the

latter essentially averages the mean responses of the six individual components that comprise the JRA-DOI responder index. In addition to safety, additional pharmacokinetic data were conducted in this trial.

-Study HWA 468/3504

This is an ongoing (at the time of NDA submission) trial that was designed as an 8-month extension to study 3503. A total of 70 patients with JRA (33 from the LEF arm, 37 from the methotrexate arm) from study 3503 were enrolled into this trial. The purpose of study 3504 was to evaluate the durability of efficacy and continued safety of LEF in this population. Efficacy was evaluated at the 8-week (see table below) time-point (this would be 24 weeks from the beginning of trial 3503) using the same endpoints as described above for study 3503.

Efficacy Summary:

The results for the three trials are summarized in the table below:

JRA DOI ≥ 30% (landmark analysis) for trials HWA 1307, 3503, and 3504

Study	Endpoint	Drug	Percent of Patients Improved at Endpoint (weeks)			
			8	16	26	130
1307	JRA 30	LEF	-	-	52	52
	JRA 50		-	-	44	41
	JRA 70		-	-	19	35
3503	JRA 30	LEF/MTX	-	68/89*	-	-
3504	JRA 30	LEF/MTX	82/81	-	-	-

* Based on ITT/LOCF, this 21% difference favoring methotrexate is statistically significant (p = 0.0156)

The difference in response rate in study 3503 between LEF and MTX may be the result of a combination of reasons including relative under-dosing of LEF in younger patients compared to the relatively aggressive MTX-dosing employed in this trial. In any event, the efficacy of LEF in these three studies as evidenced by the JRA-DOI responder index suggests that the response to LEF is both robust and sustainable. It should be noted that there was no advantage statistically in favor of either MTX or LEF at the week 16 endpoint using the other co-primary endpoint of Percent Improvement; there was also no apparent differences when the individual components of the JRA-DOI core set were evaluated.

Safety Summary:

In general, the adverse event profiles for LEF (and MTX) in these trials was similar to what has been observed in patients with adult RA. No deaths occurred in these studies and the adverse events listed as serious were limited to only a few patients and included events such as abdominal pain, cellulitis, anemia, petechia, hypertension, gastritis and elevated liver-associated enzymes (ALT, AST). Of note, elevations of these liver-associated enzymes were generally < 3 times the upper limit of normal (ULN) in the LEF group; of note two patients in the LEF group experienced increases < 8 ULN and one patient receiving MTX had elevations > 12 times the ULN. Of the adverse events listed

as mild to moderate in severity, abdominal pain, diarrhea, nausea, vomiting, headache, and dizziness were the most common.

Regulatory Action:
As noted above, the sponsor is not interested in the INDICATION for treatment of JRA although they did submit labeling in the NDA that included additions to the **Special Population-Pediatrics** and **Drug Interactions-Pediatric Use** sections. Owing to the fact that ARAVA has been (and will continue to be) used *off-label* in patients with polyarticular-course JRA because of the long-term nature of the disease and limited treatment options, the Division has concurred that more information needs to be included in the present labeling for ARAVA than proposed by the sponsor. This decision, which has been made after consultation with the Medical Policy and Pediatrics sections of CDER, also reflects the fact that the trials contained in this NDA represent the only available studies to date with LEF in this patient population.

Therefore, the proposed revisions to the ARAVA labeling will include additions to the **Special Population-Pediatrics** section (to describe pharmacokinetics), **Clinical Trials** section, **Precautions-Pediatric Use** section, and the **Adverse Reactions-Pediatric Patients** section. The proposed changes are included in the Appendix below. The action for the sponsor will be **APPROVABLE** pending agreement on the proposed labeling.

19 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Witter
3/3/04 06:06:01 PM
MEDICAL OFFICER
Team Leader Memo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

MEDICAL REVIEW(S)

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL OFFICER REVIEW
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS, HFD-550

NDA 20-905, Supplement Amendment 012, SE5
ARAVA®(Leflunomide) Tablets 10 mg, 20 mg and 100 mg
Polyarticular Juvenile Rheumatoid Arthritis

NDA:	20-905
IND:	41,533
Medical Officer:	Carolyn L. Yancey, MD
Submission Date:	September 5, 2003
Reviewer Received:	September 13, 2003
Review Completed:	March 5, 2004
PDUFA Date:	March 5, 2004
Applicant:	Aventis Pharmaceuticals, Inc.
Drug Name:	ARAVA® (Leflunomide) Tablets - 10 mg, 20 mg and 100 mg
Pharmacologic Category:	Isoxazole immunomodulatory agent; pyrimidine synthesis inhibitor with antiproliferative effects
Proposed Indication:	Anti-inflammatory and immunomodulation in children with polyarticular course JRA
Dosage Form and Route:	10 mg, 20 mg, 100 mg oral tablets
Materials reviewed:	- Original NDA 20-905 - IND 41,533 - NDA 20-905, Supplement 012 - HFD-550 Division file - HFD-550 Pediatric Exclusivity submission - Division of Surveillance, Research & Communications Support Report linked to the Office of Drug Safety Report

CLINICAL REVIEW

TABLE OF CONTENTS

CLINICAL REVIEW

CLINICAL REVIEW

Clinical Review Section

Clinical Review for NDA 20-905

EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) issued a Written Request (WR) on March 30, 1999, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to Aventis Pharmaceuticals, Inc. (Aventis) to obtain needed pediatric information on ARAVA (Leflunomide) tablets for the treatment of juvenile rheumatoid arthritis (JRA). Aventis responded to the Pediatric Written Request with Supplement-012 to NDA 20-905 consisting of the three studies.

I. RECOMMENDATIONS

A. RECOMMENDATION ON APPROVABILITY

This reviewer recommends approving NDA 20-905, Supplement-012 for labeling changes the Division has agreed to with the sponsor. The outcome of these trials does not support a pediatric indication but do provide useful clinical information about Arava (Leflunomide) in pediatric patients with polyarticular course JRA.

The Division recommends label changes in the following sections of the current approved Arava (Leflunomide) label: CLINICAL PHARMACOLOGY: Special Populations – Gender, Age and Pediatrics; CLINCIAL STUDIES, Clinical Trials in Pediatrics, Reduction of signs and symptoms in pediatric patients with polyarticular course JRA.;PRECAUTIONS, Pediatric Use and ADVERSE REACTIONS, Pediatrics. See Appendix IX., The Division's Proposed Label Changes for Arava (Leflunomide)

B. RECOMMENDATION ON PHASE 4 STUDIES AND/OR RISK MANAGEMENT STEPS

II. SUMMARY OF CLINICAL FINDINGS

A. BRIEF OVERVIEW OF CLINICAL PROGRAM

1. Product Name: ARAVA™(Leflunomide) is a pyrimidine synthesis inhibitor, available for oral administration as 10, 20 or 100 mg tablets.

2. Number of trials:

Study HWA486/1037, "Leflunomide in Pediatric Subjects with Polyarticular Course Juvenile Rheumatoid Arthritis", was designed to collect pharmacokinetic and safety data from which to determine whether therapy with leflunomide warrants further study in patients with polyarticular course JRA, the JRA subtype which most closely resembles adult RA.

Study HWA486/3503, "Efficacy and Safety of Leflunomide versus Methotrexate in the Treatment of Pediatric Patients with Juvenile Rheumatoid Arthritis" was a randomized, double-blind, active-controlled study. This design was used because of the ethical considerations of with-holding treatment for a progressive disease with risk of irreversible disability for which approved therapeutic drugs exist.

Extension Study HWA486/3504, "Double-Blind, 8-Month Extension of Study HWA 486/3503 to Collect Durability of Efficacy Data and Additional Safety Data in Subjects with Juvenile Rheumatoid Arthritis Completing the Double-Blind Comparison Study, HWA486/3503, of Leflunomide versus Methotrexate", was conducted over an eight month period to determine the durability of leflunomide versus the active comparator, methotrexate.

3. Number of patients enrolled:

Study HWA486/1037	Enrolled 27 patients, 17 patients completed trial.
Study HWA486/3503	Enrolled 94 patients (screened 103 patients), 86 patients completed trial.
Study HWA486/3504	Enrolled 70 patients, trial is ongoing.

4. Indications studied according to the pediatric written request:
Signs and symptoms of Juvenile Rheumatoid Arthritis

5. Overall number of patients exposed:

Study HWA486/1037	Enrolled 27 patients; exposed 27 to leflunomide; 17 patients completed 26 week protocol. (Enrolled patients had previously failed or were intolerant of methotrexate therapy.)
Study HWA486/3503	Screened 103 patients; enrolled, randomized and exposed 94 patients; 47/94 patients exposed to leflunomide; 47/94 patients exposed to methotrexate; 42 completed leflunomide therapy; 44 completed methotrexate therapy. (Enrolled patients were naïve to treatment with either leflunomide or methotrexate.)
Study HWA486/3504	Exposed 33 patients to leflunomide and 37 patients to methotrexate; interim data summary (IDS) completed

through week 8 (June 30, 2003); 22 exposed to leflunomide; 27 exposed to methotrexate.

B. EFFICACY

Arava (Leflunomide) did not perform as well as the active comparator, methotrexate, using one of the co-primary efficacy endpoints, Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30 % (JRA DOI ≥ 30 %), in the efficacy study submitted. The JRA DOI ≥ 30 % responder rate in the active comparator group was 89.4 % versus 68.1 % in the leflunomide group. Leflunomide did not perform statistically better than the active comparator using the adjusted mean improvement analysis, -52.87% versus -44.41 %, methotrexate versus leflunomide, respectively. Even though data did not support superiority of Leflunomide over the active comparator, the 68 % responder rate for the JRA DOI is comparable to results in adult clinical trials.

The difference in efficacy favoring the active comparator, methotrexate, was particularly strong from the smaller and younger patients who were especially responsive to the relatively high methotrexate dose used in the efficacy study. The dose used for methotrexate was 0.5 mg/kg/week, (15 mg/m^2/week), according to body weight in Study HWA486/3503 and Study HWA486/3504. The maximum allowable dose of methotrexate was 25 mg per week in both studies. The methotrexate dose described in the approved package insert explains that the recommended starting dose is 10 mg/m^2/week.
The smaller and younger patients were less responsive to selected doses of Leflunomide. It appears that the smaller patients ≤ 40 kg were under-dosed compared to the patients > 40 kg on the basis of 1) the M1 concentration being lower in the patients ≤ 40 kg, 2) efficacy was less in patients who were treated with the lower leflunomide doses and 3) adverse events were less frequent in patients < 40 kg.

Dosing was based on the initial PK Study HWA 486/1037 and assigned the adult loading and maintenance dose of one tablet (100 mg) per day x 3 consecutive days followed by 20 mg (two 10 mg tablets) for 16 weeks to patients > 40; for patients weighing 20 - 40 kg assigned one tablet (100 mg) per day for 2 consecutive days followed by 10 mg (one 10 mg tablet daily) for 16 weeks; and for patients weighing < 20 kg, assigned one tablet (100 mg) on one day followed by an average of 5 mg (one 10 mg tablet, every-other-day) for 16 weeks. However, the Population Pharmacokinetics (PPK) analysis that included data from Study HWA486/1037 and Study HWA486/3503 subsequently revealed that clearance in patients ≤ 40 kg is only reduced by a third compared to the adult dose.

The following summarizes results from the three studies submitted to support the requested label changes for Arava (Leflunomide):

Study HWA 486/1037
After 26 weeks of open-label study drug, leflunomide, administration, 51.9 % (14/27) of subjects were JRA DOI ≥ 30 % responders. Most of these subjects, 12 of 27 or 44.4 % of the total population achieved JRA DOI ≥ 50 % responses. Five of 27 subjects, 18.5 % attained a JRA DOI ≥ 70 % response. The body surface area (BSA)-rule for dosing leflunomide defined in the open-label study protocol was simplified in the subsequent double-blind protocol to dose adjustment based on body weight rather than BSA.

Study HWA 486/3503
Two co-primary endpoints were utilized in Study HWA486/3504 - the JRA DOI ≥ 30 % and the Percent Improvement Index.

Definitions of the two co-primary endpoints:

- **JRA DOI ≥ 30%** responder rate – is defined according to the patient's evaluation on 6 core set variables. Patients are classified as improved if they experienced ≥ 30 % improvement in at least three of the 6 core set variables, with no more than one of the 6 variables worsening by more than 30 %. The six variables used to calculate the 30 % improvement are: 1) disease severity, 2) overall well-being, 3) functional ability by the Childhood Health Assessment Questionnaire (CHAQ), 4) number of joints with active arthritis as defined by the ACR criteria, 5) number of joints with limited range of motion and the 6) erythrocyte sedimentation rate (ESR).
- **Percent Improvement Index** – is defined as the mean of the percent changes from baseline for all 6 DOI core set variables. This value is calculated for each subject as follows: (current value - baseline value) / baseline value x 100. Note: if the current value was negative, worse than baseline, the value was set to zero. The PPI is a continuous variable in which the JRA trial experience is limited. (The Division did not find the Percent Improvement Index sufficient as a single efficacy endpoint; hence, two co-primary endpoints in Study HWA486/3503 and Extension Study HWA486/3504.)

There was no statistically significant difference between leflunomide versus methotrexate treated polyarticular course JRA treatment groups in Percent Improvement Index at Week 16. The adjusted mean improvement was - 44.41 % and - 52.87 % for leflunomide versus methotrexate, respectively. Note: the larger the negative value, the more improved the clinical response. However, methotrexate performed statistically better than leflunomide, as measured by the JRA DOI ≥ 30 % responder rate. The JRA DOI ≥ 30 % responder rate was 89.4 % versus 68.1 %, methotrexate versus leflunomide, respectively. JRA DOI ≥ 50 % and ≥ 70 % responder rates were analyzed as secondary outcome variables and did not demonstrate statistically significant differences between the treatment groups at Week 16.

Extension Study HWA486/3504 collected ongoing blinded data from Week 16 through Week 24. There were no substantive changes in outcome measures; efficacy results were maintained through this 8 week period.

C. SAFETY

Safety information was collected from a total of 73 pediatric patients (27 patients from Study HWA486/1037 and 47 patients from Study HWA486/3503) who were treated with leflunomide. There were no deaths, malignancies, significant overdoses or pregnancies in these three clinical trials. There were a total of 21 serious adverse events across all three clinical trials. The overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of leflunomide. The most common adverse events included abdominal pain, diarrhea, nausea, vomiting, oral ulcers, upper respiratory tract infections, alopecia, rash, headache and dizziness. Less commonly seen adverse events included anemia, hypertension and weight loss. Hepatotoxicity is a well know risk factor of leflunomide treatment. There were 14 of 74 patients who experienced elevated ALT or AST elevations.

D. DOSING

No dosing regimen for pediatric patients with polyarticular course JRA can be recommended on the basis of the findings in NDA 20-905, Supplement-012. The dosing utilized during study HWA486/3503 was not associated with a finding of efficacy when compared with the results from methotrexate-treated patients. The dosing used for patients > 40 kg body weight was comparable to adult dosing of leflunomide based on PK data. In Study HWA486/3503 and Study HWA486/3504, leflunomide dosage was administered to pediatric patients based on body weight rather than body surface area, which was initially utilized in Study HWA486/1037.

As noted in **Table 1,** smallest and youngest patients received a loading dose that was approximately 25% less than the adult daily dosing. To efficiently prescribe available

manufactured tablet forms of Arava, the sponsor selected an alternate day dosing schedule for the very smallest and youngest patients (20 kg body weight) treated in the leflunomide group.

E. Special Populations

Juvenile Rheumatoid Arthritis (JRA) is one of the most common rheumatic diseases of childhood. The incidence of JRA varies from 2 to 22 per 100,000 population.[1,2,3] The American College of Rheumatology (ACR) criteria defines JRA as having three subtypes: pauci-articular, polyarticular and systemic type JRA.

Study HWA486/1037, Study HWA486/3503 and Study HWA486/3504 selected polyarticular course JRA for investigation of the Disease Modifying Anti-Rheumatic Drug (DMARD), Arava (Leflunomide). The reviewer notes that polyarticular course JRA reflects the JRA subtype most likely to be exposed to DMARD therapy and that most closely resembles adult rheumatoid arthritis, especially rheumatoid factor positive polyarticular JRA. The reviewer also concurs that individuals with systemic JRA are at greater risk for hepatotoxicity and/or hematologic sequelae, specifically, disseminated intravascular coagulation (DIC), and were, therefore, not included in these trials.

References

1. Laaksonen AL: A prognostic study of juvenile rheumatoid arthritis. Analysis of 544 Cases. Acta Paediatr Scand Suppl 1996, pp 1-163.

2. Oen KG, Cheang M: Epidemiology of chronic arthritis in childhood. Semin Arthritis Rheum 26: 575-591, 1996.

3. Gare BA: Juvenile Chronic Arthritis. A Population Based Study on Epidemiology, Natural History and Outcome. Goteborg Sweden, University of Goteborg, 1994.

CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

A. DRUG ESTABLISHED AND PROPOSED TRADE NAME, DRUG CLASS, SPONSOR'S PROPOSED INDICATION(S), DOSE, REGIMENS, AGE GROUPS

Arava™(Leflunomide) is a pyrimidine synthesis inhibitor with antiproliferative effects intended for use in the treatment of active rheumatoid arthritis (RA). Hoechst Marion Roussel, Inc. (HMR) developed leflunomide for the treatment of rheumatoid arthritis. Since May 30, 1999, Aventis Pharmaceuticals Inc. acquired HMR, owns the compound and holds the patent. The chemical structure is an isoxazole derivative with the chemical name N-(4'-trifluoromethylphenyl) -5-methylisoxazole-4-carboxamide.

The compound was originally developed as an anti-inflammatory agent but due to the significant immunomodulatory activity observed in animal models, the development and approval has been for the treatment of autoimmune diseases. The NDA was approved September 10, 1998 by the U.S. Food and Drug Administration. Arava ™(Leflunomide) is indicated in adults for the treatment of rheumatoid arthritis (RA):

1. To reduce the signs and symptoms
2. To inhibit structural damage as evidenced by X-ray erosions and joint space narrowing
3. To improve physical function

Adult dose, regimens and age groups (specific text in current package label):
Approved adult dosing regimen of Arava: Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that Arava therapy be initiated with a loading dose of one 100 mg tablet per day for three days. Maintenance therapy as daily dosing of 20 mg is recommended for treatment of patients with RA. Doses higher than
20 mg per day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily.

Pediatric dose, regimens and age groups:

No dosing regimen for pediatric patients with polyarticular JRA can be recommended on the basis of the findings in this supplement. The dosing utilized during study HWA486/3503 was not associated with a finding of efficacy when compared with the results from methotrexate-treated patients. The dosing used for patients of more than 40 kg body weight was comparable to adult dosing of leflunomide based on PK data.

Open-Label Study HWA486/1037 included children age 6 to 17 years with polyarticular course JRA. Leflunomide was administered as a loading dose for three days according to body surface area (BSA) measured in square meters (M^2) based on the adult loading dose of 100 mg/day for 3 days and an average adult BSA of 1.73 M^2. Leflunomide maintenance doses were calculated based on a low adult dose of 10 mg/day and an average adult BSA of 1.73 M^2. In pediatric patients without clinical response on or after 8 weeks, escalation to the equivalent of leflunomide 20 mg/day per 1.73 M^2 BSA was permitted by the investigator.

Study HWA486/3503 included children 3 to 17 years with polyarticular course JRA. Leflunomide was administered as a loading dose up to three days at 100 mg/day based on actual body weight. Leflunomide maintenance dose was 10 mg QOD, 10 mg daily or 20 mg daily based on actual body weight. MTX was a 2.5 mg tablet. MTX dose was 0.5 mg/kg/week (approximately 15 mg/m^2/week). MTX maximum dose was 25 mg/week.

Extension Study HWA486/3504 included children 3 to 17 years with polyarticular course JRA. Leflunomide was administered the same as in Study HWA486/3503. Methotrexate was a 2.5 mg tablet. MTX was administered as 0.5 mg/kg/week; maximum dose was 25 mg/week. MTX escalation was permitted up to 0.6 mg/kg/week, maximum 30 mg/kg/week.

B. STATE OF ARMAMENTARIUM FOR INDICATION(S)

Arava (leflunomide) is approved for adult use for the indications of signs and symptoms of rheumatoid arthritis, to inhibit structural damage as evidenced by X-ray erosions and joint space narrowing and to improve physical function.

C. IMPORTANT MILESTONES IN PRODUCT DEVELOPMENT

The three reviewed clinical trials are the first pediatric clinical trials submitted to the Arava (Leflunomide) NDA. See section Clinical Review, Introduction and Background section of this NDA review for history of the drug product submissions and adult approval. The sponsor is not requesting Arava (Leflunomide) be considered for an approved indication in pediatric patients with polyarticular course JRA.

D. OTHER RELEVANT INFORMATION

On March 28, 2002, Public Citizen Buyers Up, Congress Watch, Critical Mass, Global Trade Watch, Health Research Group, Litigation Group representing 135,000 consumers nationwide petitioned the Food and Drug Administration to immediately remove Arava (Leflunomide) from the market as an approved drug for the treatment of adult rheumatoid arthritis. This petition referenced hepatic reactions and t[illegible]

E. IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED AGENTS

There are no important issues to report with pharmacologically related agents.

II. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

See the Statistical review by Dr. Suktae Choi for a reanalysis of statistical comparisons and p-values.. No pharmatoxicology issues have been raised, see Pharmacology and Toxicology review by Dr. Asoke Mukherjee.

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

A. PHARMACOKINETICS

In humans, leflunomide is extensively converted to the active metabolite, M1, during the absorption process by pre-systemic and/or hepatic first-pass metabolism. Pediatric pharmacokinetics was investigated in Study HWA485/1037 and Study HWA486/3503 to establish a population pharmacokinetic (PPK) model that describes the pharmacokinetic characteristics of the active metabolite, M1 in the JRA polyarticular course population. See the Clinical Pharmacology and Biopharmaceutics review by Dr. Jenny Zheng.

Study HWA486/1037 demonstrated that the optimal PPK model obtained indicated that BSA-normalized CL in the pediatric patients with JRA was not different from adults with RA, which supported adjustment of the maintenance dose based on BSA. BSA normalized volume of distribution was approximately 22 % lower in the pediatric patients. The BSA-rule for dosing leflunomide defined in the study protocol was simplified to dose adjustment based on body weight using the following relationship:

$$f_{BSA} = (\text{weight} / 70)^{0.7} = \text{BSA} / 1.73$$

In **Study HWA 486/3503**, the patients in the heaviest weight group (> 40 kg) who received 20 mg leflunomide daily had an M1 exposure comparable to that in adult RA subjects. Subjects in the two lower weight groups (< 20 kg and 20- 40 kg) received 5 mg and 10 mg daily, respectively, tended to have lower M1 exposures than subjects in the heaviest (> 40 kg) weight group. Similarly, most of the difference in efficacy was observed in the smaller (< 40 kg) and younger subjects who were especially responsive to the higher end of dose range of methotrexate used in Study HWA486/3503. The smaller and younger patients were less responsive to the lower dose of leflunomide.

Comparison of PK between Pediatric and Adult Patients

The median values for CL/F, C_{ss}, and body weight in a total of 1171 adult patients with RA (Phase II and Phase III combined) is 0.024 L/h, 34 ug/ml and 70 kg, respectively. Based on the final PK model determined using the combined dataset of Study HWA 486/1037 and Study HWA 486/3503, a relationship between CL/F and WT was established. This model predicts a CL/F of 0.0254 L/h for a person weighing 70 kg, which is in agreement with prior findings from adult PPK analysis.

Therefore, in pediatric patients with polyarticular course JRA, as in adult RA patients, the pharmacokinetics of M1 following oral administration of leflunomide can be described by a one compartment model with first order input. In pediatric patients with polyarticular course JRA as in adult RA patients, there is a similarly wide inter-subject variability in CL/F. Body size is strongly correlated with V/F and weakly correlated with CL/F in pediatric patients with polyarticular course JRA.

the pharmacokinetics of the M1 metabolite, the efficacy for subjects weighing less than 20 kg might be improved with a dose > 5 mg/day and ≤ 10 mg/day . Dose adjustments might also be improved for patients weighing greater than or equal to 20 kg and less than 40 kg.

B. PHARMACODYNAMICS

Population pharmacokinetic (PPK) analysis was completed to investigate the steady state pharmacokinetics (PK) of leflunomide in pediatric patients with polyarticular JRA. Pediatric PK data was subsequently compared with PK results from adults and the sponsor then proposed

IV. DESCRIPTION OF CLINICAL DATA AND SOURCES

A. OVERALL DATA

Tables 2 A, 2 B and **2 C** summarize the three clinical trials submitted under NDA 20-905, S-012. This review focuses these three clinical trials used to support safety, efficacy and tolerability of administering Arava ™(Leflunomide) to pediatric patients with polyarticular course JRA. All data presented is derived from Aventis' submission NDA 20-905, S-012.

B. CLINICAL TRIALS

Table 2A. Study HWA486/1037 (This table is from the sponsor's submission)

Study No.; IND No.	Study objective and design	No. subjects; population type	Age range in [yrs]; Mean in (yrs)	Duration of study treatment	Medication, dosing regimen, route of administration
1307; IND 41,533	Open-label, multi-center, uncontrolled, pilot; population PK, safety, efficacy	27; JRA, MTX failure	6-17 yrs.; 12 years	Multi-dose, 26 wks primary endpoint. Extension to 30 mos.	LEF LD x 3 days @ 30-100 mg based on BSA divided by BSA category, then MD @ 10 mg QOD or 10 mg/day w/EscD allowed up to 20 mg/day based on BSA; oral; 10 mg or 100 mg tablets

Table 2B, Study HWA486/3503 (This table is from the sponsor's submission)

Study No.;	Study objective and design	No. subjects; population	Age range in [yrs];	Duration of study treatment	Medication, dosing regimen, route of administration

IND No.		type	Mean in (yrs)		
3503; IND 41,533	Comparative efficacy/safety; PK, population PK	94; JRA LEF and MTX naive	3-17 yrs; 10 yrs.	Multi-dose, 16 wks; extension study 3504 (8 mos. Ext.)	LEF: LD up to 3 days @ 100 mg/day based on wt. then MD 10 mg QOD, 10 mg daily, or 20 mg daily based on wt. MTX: 0.5 mg/kg/wk oral; LEF: 100 mg tabs for LD. LEF 10 mg tabs for MD or EscD. MTX: 2.5 mg tabs

Table 2C, Study HWA486/3504 (This table is from the sponsor's submission)

Study No.; IND No.	Study objective and design	No. subjects; population type	Age range in [yrs]; Mean in (yrs)	Duration of study treatment	Medication, dosing regimen, route of administration
3504; (Extension study of Study 3503) IND 41,533	Durability of efficacy; safety; active-control, double-dummy, double-blind, multi-center, parallel	70; 53 for IDS; JRA	3-17yrs.; 10 yrs.	Multi-dose, 8 months, treatment wk 16-48	LEF: MD 10 mg QOD, 10 mg daily, or 20 mg daily based on wt.; MTX: 0.5 mg/kg/wk with escalating allowed to 0.6 mg/kg/wk, max 30 kg/wk; oral; LEF: 10 mg tablets; MTX 2.5 mg tablets

BSA – Body Surface Area
EscD – Escalating dose

JRA – Juvenile Rheumatoid Arthritis
LEF – Leflunomide
MTX – Methotrexate

DOI – Definition of Improvement
IDS – Interim data summary, 2-month data time-points
LD – Loading Dose
MD – Maintenance Dose
PK – pharmacokinetic(s)

C. POSTMARKETING EXPERIENCE

There has been no post marketing information available for off-label use of Arava ** (Leflunomide) in pediatric patients with polyarticular course JRA.

D. LITERATURE REVIEW

None beyond articles referenced in NDA 20-905, S-012.

V. CLINICAL REVIEW METHODS

A. HOW THE REVIEW WAS CONDUCTED

The NDA 20-905, S-012 was submitted electronically in CTD format. All three clinical trials submitted to investigate safety; efficacy and tolerability were reviewed separately in NDA 20-905, S-012. All three trials were reviewed with the same level of intensity. Safety data from each trial was reviewed separately. The reviewer anticipates an integrated safety summary (ISS) at the completion Study HWA486/3504. Note the submitted Extension StudyHWA486/3504 is an interim data summary (IDS) through June 30, 2003.

B. OVERVIEW OF MATERIALS CONSULTED IN REVIEW

Studies submitted with NDA 20-905, Supplement 012 and IND 41,533, including past correspondences which led to amendments of the Pediatric Written Request, were the sole source of materials consulted for this review.

C. OVERVIEW OF METHODS USED TO EVALUATE DATA QUALITY AND INTEGRITY

According to the sponsor, appropriate steps were documented to ensure accurate, consistent and complete data has used in processing. All data / data-entry processing and quality control were performed by Aventis personnel. All data entry and data coordination were carried out using ClinTrial 4.2 run under HP-UNIX.

The sponsor noted the following steps:
Pre-entry review of data: CRFs were reviewed for missing pages, legibility, and consistency of subject identification on each page.
Data entry: independent double data-entry was performed with 100% comparison of first and second data entry to help ensure consistency between the CRF and the database.
Validation process: prior to the receipt of any data in-house, rules for validating the data were developed. These criteria, found in the Data Management Plan, document the computer checks that were performed, including both check on individual data points as well as logic checks across data points within and across panels, to confirm the accuracy of the data.

As data were entered, the computerized validation rules were executed against the database to identify data issues, termed discrepancies that needed to be addressed. Each was reviewed by the Data Coordinator with the Clinical Research Associate and the investigative site, if necessary, to determine the accuracy of the data value. An electronic audit log was maintained to document changes made to the database and included old value, new value, date and time of change, name of person making the change, and the reason for the change. All adverse events (diagnoses) were classified according to MedDRA Version 5.1. Classification of previous and concomitant

diseases was performed according to MedDRA. Previous and concomitant medications were coded using the World Health Organization Drug Reference List (WHO-DRL 88).
Quality control of the database was performed during the course of the study.
End of study audit: when all the CRF data were on-line and 90% of the exceptions resolved, CRFs for 4 subjects were randomly chosen and a 100% verification, comparing the CRF to the database, was performed on the 10,689 data fields in these CRFs. The calculated error rate resulting from the end of the study was 0.19% (2 errors / 10,689 fields). See **Table 3**. Because the calculated error rate was not greater than the Aventis standard of 0.1%, no further verifications were performed on the data.

Table 3. End of Clinical Study Audit Results (This table is from the sponsor's submission)

Subject number	Number of fields	Number of errors
0134002	2715	1
0603008	2695	1
0704002	2613	0
1103002	2666	0

Verification of mapping of external data (data not entered by Aventis data entry personnel): Cumulative routine laboratory data were received at monthly intervals throughout the trial. The data transfer program for transferring data from this external source into ClinTrial 4.2 was validated. In addition, consistency between subject number, age, sex, and sample data was checked.
Database finalization: disposition codes were assigned to each subject prior to database finalization following a pre-defined rule developed by Aventis statistics and clinical research departments. A 100% verification of the disposition codes was performed against the database to ensure accuracy of the data entry. On June 10, 2003, it was determined that all data were in-house, all discrepancies resolved, all coding reviewed for accuracy, and the above verifications had been performed. Following that confirmation, the database was considered finalized.

D. WERE TRIALS CONDUCTED IN ACCORDANCE WITH ACCEPTED ETHICAL STANDARDS

Yes, the clinical trials were conducted in accordance with accepted ethical standards.

E. EVALUATION OF FINANCIAL DISCLOSURE

Appropriate under FDA guidelines.

VI. Integrated Review of Efficacy

A. BRIEF STATEMENT OF CONCLUSIONS

STUDY HWA 486/1037

Study HWA 486/1037, an open-label trial design, supported further investigation of leflunomide in patients with polyarticular course JRA based on pharmacokinetic and safety data from 27 pediatric patients with JRA. In study HWA 486/1037, by week 12, 51.9 % of patients were responders, representing the maximum response, which was sustained through week 26 of this trial. In this study, the body surface area (BSA)-rule for dosing leflunomide, defined in the open-label study, was simplified in the double-blind protocol to dose adjustment based on body weight rather than BSA.

STUDY HWA 486/3504

Extension Study HWA 486/3504 reports data from the first 8 weeks, 24 weeks or 168 days, of Study HWA 486/3503. The Percent Improvement Index was unchanged in the leflunomide treatment group between week 16 and week 24, suggesting durability of the leflunomide effect over the 8 weeks, extension study. There was an increase in the responder rate relative to week 16 for the leflunomide group (69.6 % to 82.6 %) and a decrease in the responder rate relative to week 16 in the methotrexate group (88.5 % to 80.8 %). By week 24, there were no statistically significant differences between the leflunomide and methotrexate treatment groups with regard to Percent Improvement Index or responder rate JRA DOI ≥ 30 %, ≥ 50 % or ≥ 70 %.

Proposed Label Changes

Aventis Pharmaceuticals, Inc. submitted the following proposed changes in the current approved label for Arava (Leflunomide):

See Appendix IX. D. Arava Label, *for the Division's proposed label changes.*

B. General Approach to Review of the Efficacy of the Drug

Study HWA 486/1037 was an open-label non-controlled multi-center Phase IB study over 6 month treatment period with up to a 24-month extension phase in polyarticular course JRA patients who had previously failed or were intolerant to methotrexate

therapy. While not designed to support a finding of efficacy, the results were used to design the subsequent efficacy trials. The efficacy data base consists of two studies, Study HWA 486/3503 was intended as the primary support for efficacy and Study HWA 486/3504 was intended to provide evidence of durability and tolerance of effect and additional safety data. All three clinical studies are reviewed in detail in the following section. Questions generated by each study review are included in the specific review sections.

B. Detailed Review of Trials by Indication

STUDY HWA 486/1037
Title: Phase IB Trial of Leflunomide in Pediatrics Patients with Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Study Objectives:
Primary objective of this open-label phase IB trial was to determine whether therapy with leflunomide warrants further study in pediatric patients with polyarticular course JRA by obtaining PK and safety data from a small group of children and adolescents.

Secondary objective of Study HWA486/1037 was to collect data regarding preliminary efficacy and improvement (or no deterioration) in physical function

Study Design:
Open-label, multi-center, Phase IB study for 6 months (26 weeks) study. Optional continuation of the study drug was offered for up to an additional 24 months, 30 months or 130 weeks total, in patients who were tolerating treatment, as determined by the principal investigator, and wished to continue protocol participation. The primary endpoint for safety and exploratory efficacy was at 26 weeks.

Patients entering this study were to be between the ages of 3 to 17 years of age and were to have active, polyarticular course JRA, despite having been treated with an adequate trial of methotrexate. Patients were to be considered refractory to methotrexate, if after a three-month or longer trial of methotrexate at a dosage level at or above 15 mg/M^2/week, they continued to experience persistent articular disease activity including a minimum of five joints with active arthritis as defined by the American College of Rheumatology (ACR) criteria.

ACR Diagnostic Criteria for the Classification of Juvenile Rheumatoid Arthritis*:

1. Age at onset younger than 16 years
2. Arthritis in one or more joints, defined as swelling or effusion, or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat
3. Duration of disease ≥ 6 weeks
4. Type of onset of disease during the first 6 months classified as
    a. Polyarticular – 5 joints or more

b. Oligoarticular – 4 joints or fewer
c. Systemic disease with arthritis and intermittent fever

5. Exclusion of other forms of juvenile rheumatoid arthritis

* *Modified from Cassidy JT, Levinson JE, Bass JG et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis rheum 29:274, 1986.*

Study Medications:

Leflunomide was to be administered daily according to an algorithm:

- Loading dose for 3 days, to be calculated according to body surface area (BSA) measured in square meters (M^2) based on the labeled adult loading dose of 100 mg/day for 3 days and an average adult BSA of 1.73 M^2;
- Maintenance doses were to be calculated based on a low adult dose of 10 mg/day and average BSA of 1.73 M^2. Note the recommended adult maintenance dose is 20 mg/day and allows for a decrease to 10 mg/day for tolerability;
- In patients without clinical response on or after 8 weeks (based on Definition of Improvement [DOI] responder analysis for JRA patients published by Giannini et al 1997[1]) escalation was to be permitted to the equivalent of leflunomide 20 mg/day per 1.73 M^2 BSA at the discretion of the investigator.

Concomitant Treatments:

The following concomitant treatments were to be *permitted* during this study:

- Stable doses of background NSAIDs (no change in dose 2 weeks prior to the first dos of study medication or during the study);
- Stable doses of prednisone $\leq$ the equivalent of 10 mg/day in the 1.73 M^2 adult; no change in the dose 2 weeks prior to the first dose of study medication or during the study;
- Analgesic medicines including acetaminophen and/or propoxyphene, codeine or oxycodone for pain, as long as analgesics were not taken within 6 hours before a scheduled joint examination;
- No more than two intra-articular injections of corticosteroids during the first 26 weeks of leflunomide treatment
- Steroid eye drops
- During the extension phase, oral prednisone could be decreased or discontinued at the discretion of the investigator
- Other medication as clinically indicated at the principal investigator's discretion, except for medications expressly prohibited below:

The following concomitant treatments were not to be *permitted* during the study:

- Methotrexate
- Cholestyramine (except as indicated per protocol)
- Investigational drugs
- Any of the following DMARDs

- Plaquenil (Hydroxychloroquine)
- Azulfidine (Sulfasalazine)
- Ridaura (Auranofin)
- Myochrysine (gold Sodium thiomalate)
- Solganal (Aurothioglucose)
- Depen - Cuprimine (d-Penicillamine)
- Iveegam , Gammagard , Sandoglobulin , (Intravenous IgG)
- Minocin , Dynacin (Minocycline)

- Any of the following immunosuppressants:
  - Imuran (Azathioprine)
  - Cytoxan (Cyclophosphamide)
  - Sandimmune (Cyclosporine)

See IX Appendix, B. 1. a. Clinical Sites for Study HWA 486/1037

Study Population, Selection of Patients, Sample Size:
As described by the sponsor, a total of 25 patients were to be enrolled and treated with leflunomide. It was hoped that at least 20 would complete the 6-month trial. Patients were to be recruited from multiple sites in the US and Canada.

Inclusion Criteria:

- Diagnosis of polyarticular course JRA by ACR criteria for at least 6 months prior to enrollment (systemic disease could not have been active at time of study entry)
- Active disease on two different evaluations 7 to 21 days apart, including a minimum of 5 joints with active arthritis by ACR criteria
- Male or female, aged 3 to 17 years
- Minimum BSA of 0.45 M^2
- If female and of reproductive potential, neither pregnant nor nursing (a negative serum pregnancy test at screening was to have been required and pregnancy tests must have continued to be negative for the patient to remain in the trial)
- If sexually active, agreed to use adequate birth control throughout the treatment period (for females, oral contraceptives or intrauterine device [IUD] constituted adequate birth control; for males, condoms and a spermacide must have been used)
- Refractory to in intolerant of methotrexate, defined for the purpose of this study as EITHER continuing to experience persistent articular disease activity including a minimum of 5 joints with active arthritis by the ACR criteria after at least three months of methotrexate administration at a dose of $\geq$ 15 mg/M^2/week, OR exhibiting intolerance to methotrexate at any dosage after any length of trial
- Legal guardian read, understood, and signed written informed consent
- Informed consent/assent was to have been obtained from the patient in accordance with IRB/EC guidelines

- Second-line treatment DMARDs, including MTX was to have been discontinued at least 2 weeks prior to first dose of study medication
- Patients were not to have received intra-muscular, intra-articular or intravenous corticosteroids within 30 days prior to the first dose of study medication

Exclusion Criteria

- Current or past history of acute inflammatory disease of origin other than JRA, e.g., mixed connective tissue disease, seronegative spondyloarthropathy, rheumatic fever, or systemic lupus erythematosus
- History of any disease which, in the opinion of the investigator, would put the patient at risk if he or she were to participate in the study
- Clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease which would make implementation of the protocol or interpretation of the study results difficult
- Presence of persistent infection or severe infections within 3 months of enrolment, including (but not limited to) positive serology for hepatitis B or C, or HIV by seropositivity or clinical diagnosis Chronic use of cholestyramine
- History of hypersensitivity to drugs with similar chemical structures to leflunomide
- High likelihood of requiring treatment during the study period with drugs not permitted by the study protocol
- Treatment with any investigational drug in the last 90 days before study entry
- History of clinically significant drug or alcohol abuse
- Impaired hepatic function, as reflected in aspirate transaminase (AST) or alanine transaminase (ALT) levels > 1.5 x ULN
- Known hepatic disorder:

  Hematocrit (HCT) ≤ 24 % and / or
  Absolute white blood cells (WBCs) ≤ 4,000 and / or
  Platelet count ≤ 100,000 and / or
  Neutrophils < 1,000
- Legal guardian unable to understand the nature, scope and possible consequences of the study
- Patients unable to understand the nature, scope and possible consequences of the study to an extent deemed satisfactory for his / her age
- Legal guardian and/ or patient unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or other indicator of unlikelihood of completing the study
- Severe pulmonary disease

Primary outcome endpoint variable for Study HWA 486/1037 was at the end of the 6 month treatment period (26 weeks) defined as follows:

- Mean Percent Improvement Index Percent Improvement Index– defines the mean of the percent changes from baseline for all 6 DOI core set variables. This value is calculated for each subject as follows: (current value – baseline value)/ baseline value x 100. Note: if the current value was negative, worse than baseline, the value was set a t zero. The Percent Improvement Index is a continuous variable in which the JRA trial experience is limited. The Percent Improvement Index endpoint was not found to be sufficient as a single efficacy endpoint by the Division; hence, the sponsor was requested to use two co-primary endpoints in Study HWA486/3503 and Extension Study HWA486/3504.
- JRA DOI >30% Responder Rate - A responder analysis in which patients were classified as clinically improved or not improved using the *Giannini et al, 1997* Definition of Improvement (DOI) in patients with JRA.[1] Patients were classified as improved if they experienced ≥ 30 % improvement in at least three of the following 6 variables, with no more than one of the 6 variables worsening by more than 30 %. The 6 core set variables are as follows:
    1. Disease severity: physician's global assessment as measured on a 10 cm Visual Analogue Scale (VAS) anchored by the words "very severe" and "inactive";
    2. Overall well-being: parent or patient global assessment as measured on a 10 cm VAS anchored by the words "very poorly" and "very well";
    3. Functional ability: measured by the Childhood Health Assessment Questionnaire Disability Index (CHAQDI) (Singh et al, 1994)[2]
    4. Number of joints with active arthritis, as defined by the ACR criteria
    5. Number of joints with limited range of motion
    6. Erythrocyte sedimentation rate

Secondary outcome variables for efficacy analyses included number of joints with swelling, each of the 6 variables described and the severity score. Severity score was determined by the sum across all joints of the four clinical index ratings: 1) joint swelling, 2) pain on motion, 3) joint tenderness and 4) limitation of motion.

Statistical Analysis Plan

1. As described by the sponsor, "the primary objective of this study was to compare the efficacy and safety of leflunomide and methotrexate in the treatment of pediatric patients with polyarticular course of JRA. Clinical superiority of

---

[1] *Giannini EH: Ruperto N, Ravell A et al: Preliminary definition of improvement in juvenile arthritis, Arth Rheum 1997; 40: 1202-1209.*

[2] *Singh G, Athreya B, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arth Rheum. 1994; 37: 1761-9.*

leflunomide to methotrexate was to be demonstrated by comparing the mean % Improvement Index for the leflunomide and methotrexate treatment groups at the end of treatment. For purposes of this statistical analysis plan, the end of treatment or endpoint evaluation is the evaluation at week 16 (i.e. last on-treatment visit in this study) for patients completing Study HWA 486/3503, or at the last evaluation prior to week 16 for patients terminating study drug before planned end of study. At a power of 80 %, a sample size of 37 patients per group is necessary to observe a difference in the mean Percent Improvement Index of 15 % or greater, with a standard deviation of 23 %. In the event that superiority was not achieved with respect to the % Improvement Index, then non-inferiority was to be claimed as indicated in the original protocol, i.e. when the lower limit of the 95 % confidence interval of mean difference for the Percent Improvement Index is greater than or equal to –12.5%."

2. The sponsor explains that the study would have achieved its objective, i.e. demonstrating clinical superiority of leflunomide over methotrexate, when the difference in the mean Percent Improvement Indices favored leflunomide with an associated p-value less than 0.05 (two-sided), and there was a consistent finding for the JRA DOI ≥ 30 % responder rate at the end of treatment, but not necessarily statistically significant.

Analysis of Safety

As described by the sponsor, "the diagnosis term of the AE as reported by the investigator was analyzed by MedDRA preferred term. The number and frequencies of patients with Treatment Emergent Adverse Events (TEAEs) is given for each treatment group by body systems and coded terms within each body system. The number and frequencies of patients with possibly related TEAEs, serious TEAEs, and TEAEs leading to discontinuation of study medication was calculated for each treatment group by body systems and coded terms within each body system. Clinically significant differences, between treatment group event rates, were noted and, where appropriate, a Fisher Exact Test was performed to assess statistical significance.

All enrolled patients received at least one dose of study medication and were to be included in the safety analysis.

Protocol Amendments, Study HWA486/1037

This protocol was **amended 6 times**, the first amendment occurred on May 27, 1999. **Amendment 1** was written to include the addition of three study sites to achieve enrollment goals and the deletion of one study site due to lack of enrollment. The enrollment phase was extended from 6 to 9 months to 10 to 11 months. According to the sponsor, "Because several patients were experiencing a clinically significant response after 6 months, the study was extended for an additional year beyond the initial 6-month treatment period with extension renewable at the sponsor's discretion. Several changes were made to the protocol to accommodate the extension phase. For patients continuing

into the extension phase, single pharmacokinetic (PK) assessments were to be made. In order to ensure patients were receiving the most appropriate dose of leflunomide, assessment of body surface area (BSA) every 6 months was added to the protocol. The study schedule for the extension phase was added. In the extension phase, the investigators were allowed to decrease or discontinue non-steroidal anti-inflammatory drugs (NSAIDs) and prednisone administration and use intra-articular joint injections of corticosteroids at their own discretion. The erythrocyte sedimentation rate (ESR) assessment was changed from a screening procedure to a baseline procedure to more accurately reflect the real value just prior to the first dose of leflunomide. Early termination procedures were clarified. Physical exam requirements were changed to allow the investigator more flexibility in conducting such exams. The fact that height and weight were to be taken each time vital signs were taken was clarified. [redacted] was added due to a change in corporate name of the contract research organization and the drug packaging and shipping facility name wa[redacted]

The introduction section of the protocol was updated to reflect efficacy and safety data from Phase III clinical studies of leflunomide.

The packaging and labeling section was updated to reflect changes in company policy and to supply sites with sufficient quantity of 100 mg leflunomide. Also, the sites were instructed to return clinical trial material throughout the study in order to better facilitate storage, handling and distribution of study drug. Record retention requirements were updated when leflunomide was approved by the FDA for use in adults. Pharmacokinetic procedures were updated to specify the active metabolite of leflunomide as M1 rather than A77 1726 [redacted] egan to share monitoring responsibilities.

Inclusion criteria were changed to allow corticosteroids (intra-muscular, intra-articular, or intravenous) within 30 days prior to first dose of study medication

Due to a change in leflunomide product labeling, contraception was no longer required for 6 months after discontinuation of leflunomide. Also, upon discontinuation of leflunomide therapy, drug elimination procedures were added for females of childbearing potential and for males wishing to father a child. The first amendment corrected the pediatric dose of cholestyramine to be used if required.

Amendment 2, dated June 25, 1999, according to the sponsor, notes that the extension phase, being renewable yearly at the sponsor's discretion, were removed per the Health [redacted] egan to monitor all sites for the protocol.

Amendment 3 dated September 17, 1999, notes that two additional study sites were added to the protocol. Appropriate contact information was included in the additional sites' enrollment. In addition, the sponsor defined that for patients in the extension phase, the Week 74 visit and the final study visit are the same visit.

Amendment 4, dated April 3, 2000, noted the addition of a second 1-year extension phase to the study. Also of note was the name change of the sponsor to Aventis Pharma following a merger. (See NDA 20-905, S-012 Clinical Review, Introduction and Background section) According to the sponsor, to more accurately reflect timeframe, months were changed to weeks throughout the protocol. PK sampling was clarified for patients who discontinue leflunomide and are administered cholestyramine or who experience a leflunomide related adverse event. Statistical procedures were updated to allow for an interim analysis at the end of 26 weeks; however, no interim report was generated.

Amendment 5, dated October 23, 2000, notes that the name and contact information for the medical monitor was changed throughout the protocol.

Amendment 6, dated August 9, 2001, added severe pulmonary disease to the list of exclusion criteria and also changed the recommendation for discontinuation of leflunomide for persistent AST or ALT elevations > 3 x ULN to persistent ALT elevations > 3 x ULN or AST elevations > 2 x ULN.

Amendment to the Written Request for Pediatric Studies was made on **April 7, 2003** changing the study analysis from a **non-inferiority analysis to a superiority analysis.** The response to this request was received on July 9, 2003.

Schedule of Visits, Study HWA 486/1037: See **Table 4.**

Table 4, Study HWA486/1037, Schedule of Visits

Clinical Study Protocol June 2, 1998
Protocol Number HWA 486/1037

STUDY SCHEDULE

Procedure	Screening	Baseline	Day 3	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 26[1]	Week 30[2]	Week 42[2]	Floating[3]
Visit No.	0-1	000	001	002	004	006	008	012	016	020	026	030	042	
Informed Consent	X													
Medical Hx	X													
Medication Hx	X													
Physical Exam[4]	X							X			X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X		X
Rheum. Exam	X	X			X		X	X	X	X	X			
CHAQ	X	X			X		X	X	X	X	X			
Blood Chem.	X		X	X	X	X	X	X	X	X	X	X		X
Hematology	X		X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X		X	X	X	X	X	X	X	X	X	X		X
ESR	X				X		X	X	X	X	X			
Pregnancy Test[5]	X		X	X	X	X	X	X	X	X	X	X		
Adv. Exp Assmt.			X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispense		X	X	X	X	X	X	X	X	X	•6			
Concom. Meds	X	X	X	X	X	X	X	X	X	X	X			X
PK studies	X[7]		X[8]		X[8]			X[8]			X[8]		X[7]	

1 End of study. If patient terminates early, procedures specified for Week 26 should be performed at the patient's final visit.
2 Patients will be examined on Week 30 and Week 42 if they do not continue beyond Week 26. A new schedule will be provided in an amendment to this protocol for patients continuing.
3 Visit to be used subsequent to a dose increase or decrease
4 Except at screening, Week 12 and Week 26 or early termination, a complete physical exam is required only if there are any physical changes as a result of an adverse event or as clinically indicated.
5 In female patients of reproductive potential.
6 Patients may continue on leflunomide if indicated by a clinically important response.
7 Single sample.
8 Prior to dosing and 2, 4, 8, and 24 hours after dosing

Efficacy Results

Patient Disposition

Of the 27 patients enrolled who received at lease one dose of study medication, 17 completed the 26-week study period. Five patients withdrew due to lack of efficacy, four due to "other" reasons and one patient withdrew due to an adverse event. **Table 5,** Study HWA486/1037, patient disposition with leflunomide therapy describes the loading and maintenance dosing for patients in three weight categories.

Table 5, Study HWA 486/1037, Patient Disposition with Leflunomide Therapy (This table is from the sponsor's submission)

Patient	Adverse Event/ SAE	Withdrawal from study	Duration , Dose of LEF therapy prior to an AE,SAE
59001 15 year old Female	Serious Adverse Event, cellulitis of left foot; elevated LFT, hypertension	Yes (after the initial 26 week period)	Cellulitis (299dys); Elevated LFT (462 days) Petechial skin rash (462 days); Hypertension (863 days)
59003	Non-serious AE, alopecia, two episodes of abdominal pain, two episodes of urticaria	Yes, dose reduction followed by drug discontinuation	Abdominal pain (99 days), dose reduction from 15 mg/day to 10 mg/day; 9 days later patient discontinued LEF.

61001 13 year old Female	Non-serious AE, dizziness, headache, nausea	No, dose reduction from 15 mg/day to 10 mg/day.	Dizziness, headache, nausea, 15 mg/day (71 days), drug temporarily interrupted x 5 days, then restarted at 10 mg/day w/resolution of AE
62001 12 year old Female	Non-serious AE, ALT > 2 x ULN to 3 x ULN; Anemia	No, dose reduction	Elevated LFT (465 days) (10 mg/day x 8 wks, 20 mg/day until time of event, decreased dose to 10 mg/day, anemia (71 days)
59004 16 year old Female	Non-serious AE, Herpes Zoster	No, drug interrupted	Herpes Zoster (170 days)
59011 6 year old Female	Non-serious AE, diarrhea, GI disorder	No, drug interrupted (unspecified days)	Diarrhea (20 days), GI disorder (20 days)
59007 10 year old Female	Non-serious AE, Flu Syndrome	No, drug interrupted (unspecified days))	Flu Syndrome (513 days)

Baseline Characteristics and Demographics

Baseline data for the intent-to-treat population is summarized in **Table 6.** Patients with polyarticular course JRA defined by the ACR criteria, regardless of the onset type, aged 3 to 17 years, with active disease, refractory to or intolerant of methotrexate, were included in Study HWA 486/1037. It was planned that 25 patients would be enrolled in the study with at least 20 completing the 6 month trial.

Table 6, Study HWA486/1037, Baseline JRA Data for ITT Population (n=27)
(The following table is from the sponsor's submission)

Characteristic	N	%
Time Since JRA Diagnosis		
Mean years	6.95	NA
1 – 2 years	2	7.4
> 2 – 10 years	18	66.7
> 10 years	7	25.9
Type of JRA at Diagnosis		
Polyarticular	19	70.4
Pauciarticular	6	22.2
Systemic	2	7.4
Mean Duration of Previous Methotrexate Treatment (mos)	35.97	NA
Reason for Methotrexate Discontinuation		
Lack of efficacy	15	55.6
Intolerance	12	44.4
Positive Rheumatoid Factor (RF)	8	29.6
Positive Antinuclear Antibody (ANA)	6	22.2
Positive Varicella Zoster Antibody (n = 26*)	24	92.3

NA = not applicable

Protocol Deviations, Study HWA 486/1037

Protocol violations were noted in Study HWA486/1037 including violation of protocol procedures due to the use of concomitant medication dose changes, specifically prednisone or NSAID, to missed visits and PK labs not being drawn at the appropriate

time in the study schedule of visits. There were 7 patients who had a dose changes in medications other than the study drug.

- **Patient 62001**: Leflunomide dose was increased to 20 mg/day rather than 15 mg/day plus 10 mg every other day, based on body surface area; NSAIDS were temporally stopped and the patient was given IV pulse prednisolone secondary to low hematocrit, fatigue and ESR elevation; on two occasions, prednisone dose was increased; on one occasion, Leflunomide was stopped due to low hematocrit and hemoglobin, and then Leflunomide was restarted at 20 mg/day.
- **Patient 60001**: blood work was sent in expired tubes, had to be repeated and, hence, was not collected on screening day; study coordinator accidentally performed PK at week 6.
- **Patient 59001**: study medication not taken for 15 days.
- **Patient 59002**: Patient is being allowed to continue into the second year of study medication on the SAP program because approval was not granted by the IRB, Amendment 4.
- **Patient 59003**: missed a physical examination, one visit outside window and one PK not drawn.
- **Patient 59004**: Leflunomide was interrupted for 5 days, cholestyramine was given and the dose was miscalculated by BSA.
- **Patient 59005**: patient discontinued NSAIDs without notifying site for 4 days.
- **Patient 59006**: PK not done before or after dose increase; study medication dispensed without patient signing consent.
- **Patient 59007**: received methotrexate within 7 weeks of starting study drug.
- **Patient 59008**: patient had several inpatient admissions for physical therapy (the sponsor considered this a protocol deviation rather than a serious adverse event).
- **Patient 59009**: one low white count, PK done three days after the first study drug dose.
- **Patient 59010:** prescribed NSAIDs with a flare, unable to void at one visit, PK not done before or after dose increase.
- **Patient 59011:** physical examination and PK not done at final visit
- **Patient 59012:** not reconsented with most recent version.
- **Patient 59013:** visits not on schedule, not reconsented with most current version.
- **Patient 59014:** patient violated inclusion criteria as patient received joint injections; patient also had 3 unevaluable joints.
- **Patient 60002:** missed 11 days of medication; baseline labs clotted and were not repeated; one ESR was not drawn and a second ESR was missed.
- **Patient 61001:** four intra-articular injections were given on 01.25.00.
- **Patient 61002:** prednisone dose was increased, patient discontinued from the study; PK and PEX not done at study discontinuation.
- **Patient 61005:** NSAIDs were discontinued during the study.

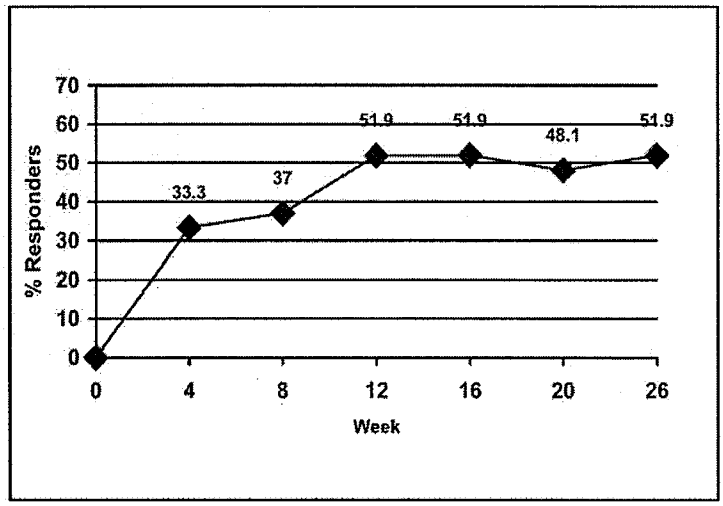
- **Patient 64001:** PK labs drawn at wrong time, discussed with study coordinator.
- **Patient 65001:** DMARD (Plaquenil) discontinued 2 days prior to first study drug dose, only 6 days between screening and baseline visit.
- **Patient 63001:** was not taking study medication between baseline visit and screening due to flu like symptoms.
- **Patient 63002:** study visit 034 was off schedule by 11 days.
- **Patient 63003:** patient refused PK studies at discontinuation visit; NSAIDs were increased due to joint pain.

Efficacy Analyses and Results of Primary Efficacy Variable:

Definition of Improvement

Responses using DOI were assessed at each study visit (Weeks 4, 8, 12, 16, 20 and 26). One-third of patients in the ITT efficacy analysis were responders at Weeks 4 (9/27 or 33.3 %) and 8 (10/27 or 37.0 %). Results increased to 14/27 or 51.9 % at Week 12 and were unchanged through Week 26. **Figure 1**, Study HWA 486/1037, summarizes JRA DOI ≥ 30 % over-time, ITT population, last observation carried forward.

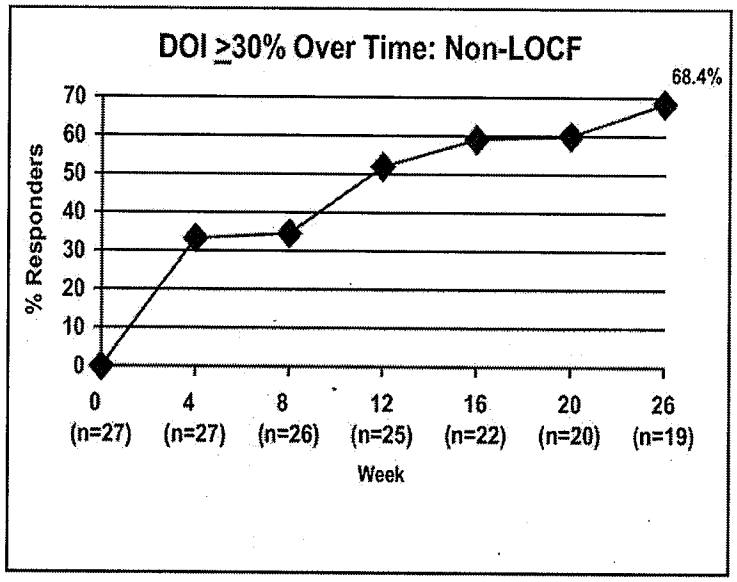
Figure 1. Study HWA 486/1037, DOI ≥ 30 % Over Time: ITT (n=27), LOCF
(The following figure is from the sponsor's submission)



In **figure 2**, Study HWA486/1037, using non-LOCF based on the same 6 variables, there is an increase in the JRA DOI ≥ 30 % responder rate to 68.4 %.

Figure 2. Study HWA486/1037 - DOI ≥ 30 % Over Time: Non-LOCF

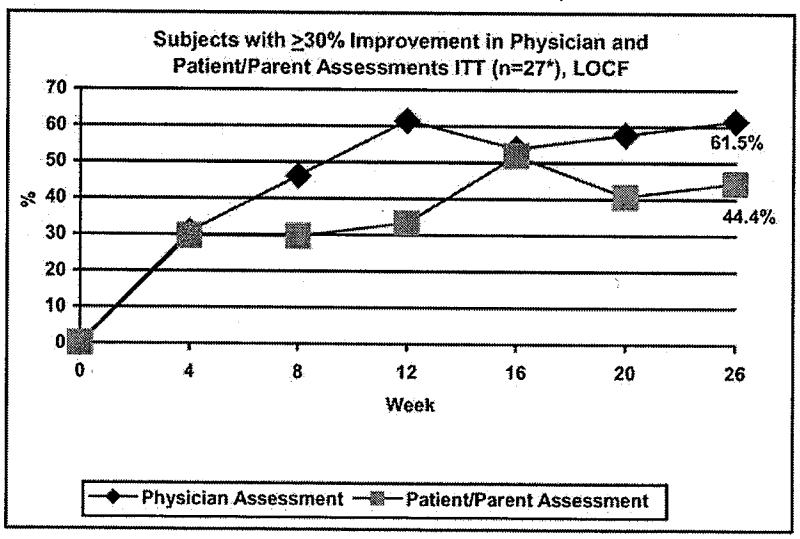
(The following figure is from the sponsor's submission)



Patients demonstrated improvement with leflunomide therapy by both the physician and patient/parent reported global assessments by Week 4 and maximal improvement in both the physician and the patient/parent assessment were sustained from Week 16 through Week 26 a shown in **figure 3.**

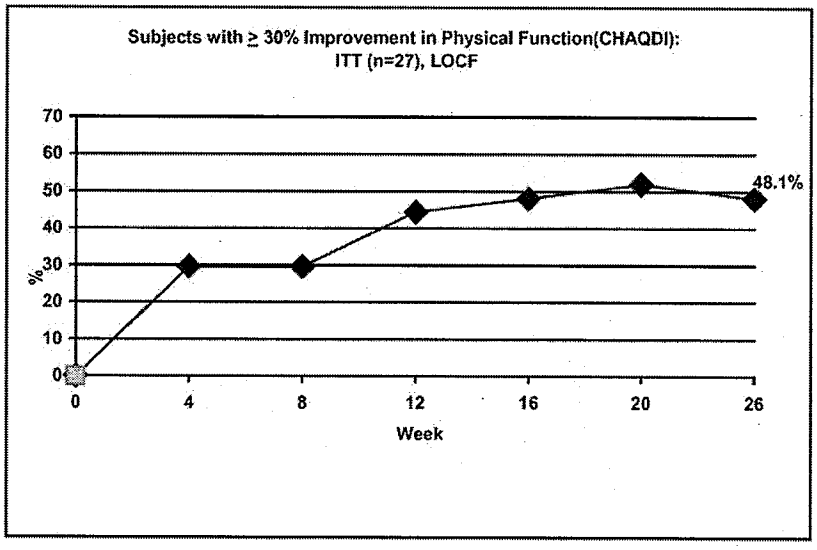
Figure 3. Study HWA486/1037, Patients with ≥ 30 % Improvement in Physician and Patient/Parent Assessments ITT, LOCF.

(The following figure is from the sponsor's submission)



The number of patients reporting ≥ 30 % improvement in the physical function CHAQ-DI increased from 8 patients (29.6 %) at Week 4 to 13 patients (48.2 %) at Week 26 as shown in **figure 4.**

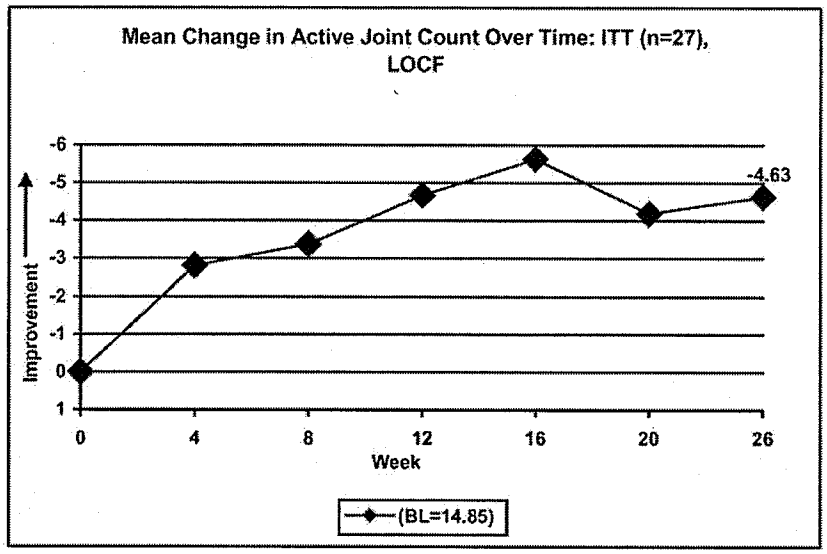
Figure 4, Study HWA486/1037, Patients with ≥ 30 Percent Improvement in Physical Function CHAQDI, Week 26 (The following figure is from the sponsor's submission)



Active joint count improvement was noted after Week 4 of therapy and continued to improve throughout Week 26. The mean change from baseline in joints with limited ROM did not show improvement at 26 Weeks.

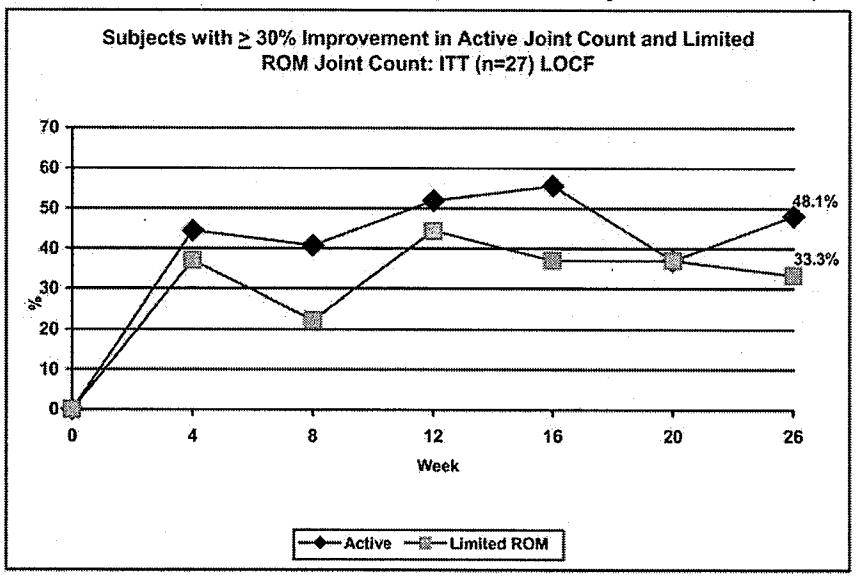
In the responder group (N=27), the mean changes from baseline in both active joints with limited ROM were evident after 4 Weeks of therapy and continued throughout 26 weeks. See **figure 5**, Study HWA486/1037.

Figure 5. Study HWA486/1037, Mean Change in Active Joints with limited ROM, LOCF. (The following figure is from the sponsor's submission)



Patient responders (N=27) with ≥ 30 % improvement were noted in both categories of active joint count and limited range of motion, see **figure 6.**

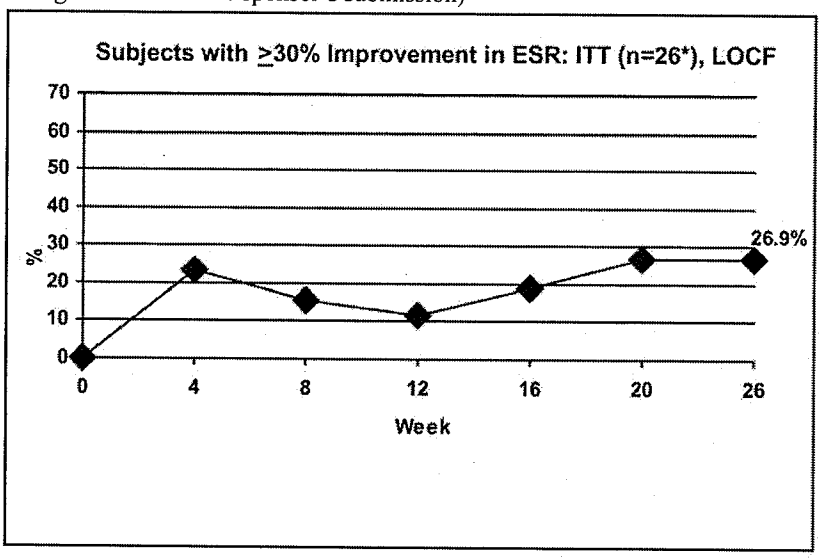
Figure 6. Study HWA 486/1037, ≥ 30 % Improvement in Active Joint Count and Limited ROM: ITT, LOCF. (The following figure is from the sponsor's submission)



By Week 26, only 7 of 26 (26.9 %) patients had ≥ 30 % improvement in ESR. The intent-to-treat population had only 26 patients rather than 27 patients because Patient 64001 had baseline ESR but no follow up ESR measurements. **Figure 7** demonstrates these ESR results.

Figure 7. Study HWA 486/1037, JRA DOI ≥ 30 % Improvement in ESR.

(The following table is from the sponsor's submission)



EXTENSION STUDY HWA 486/1037

Table 7 Summary: Baseline Data, Study HWA486/1037, Extension Phase, months 6-30, N=17. (This table is from the sponsor's submission)

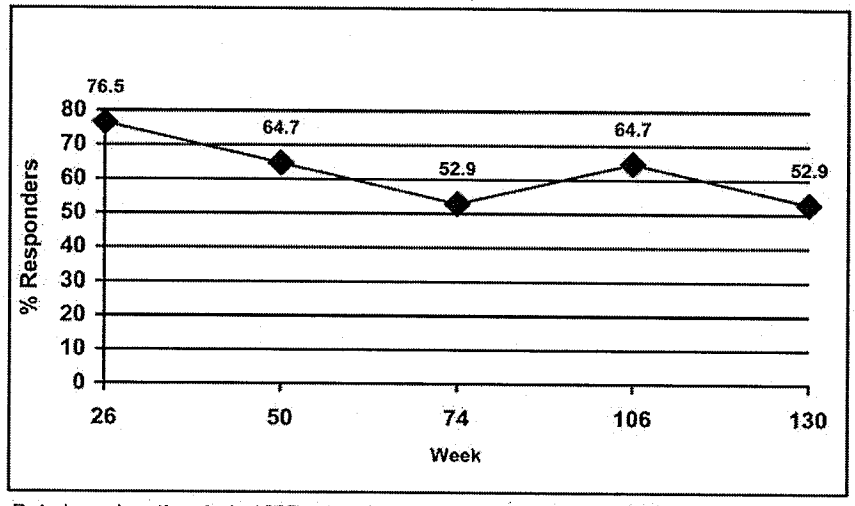
Characteristic	N	%
Time Since JRA Diagnosis		
Mean years	7.39	NA
1 – 2 years	2	11.8
> 2 – 10 years	10	58.8
> 10 years	5	29.4
Type of JRA at Diagnosis		
Polyarticular	12	70.6
Pauciarticular	5	29.4
Mean Duration of Previous Methotrexate Treatment (mos)	32.3	NA
Reason for Methotrexate Discontinuation		
Lack of efficacy	8	47.1
Intolerance	9	52.9
Positive Rheumatoid Factor (RF)	4	23.5
Positive Antinuclear Antibody (ANA)	3	17.6
Positive Varicella Zoster Antibody	16	94.1

NA = not applicable

In Extension Study HWA486/1037, improvement was calculated compared to baseline Week 0 and not Week 26. (Note 76.5 % at Week 26, see **figure 8**) Efficacy analysis for the extension cohort was conducted for Weeks 26, 50, 74, 106 and 130 visits. For patients discontinuing study participation prior to Week 130, the data from the last study visit was carried forward to Week 130.

At 26 weeks, Extension Study HWA 486/1037, 51.9 % (14/27) of patients were JRA DOI ≥ 30 % responders. Of these patients, 12 of 27 or 44.4 % of the total study population achieved DOI ≥ 50 % responses. Five of 27 patients, 18.5 % attained a DOI ≥ 70 % response. See **figure 8**, Extension Study HWA 486/1037 for JRA DOI ≥ 30 % Responder Rate.

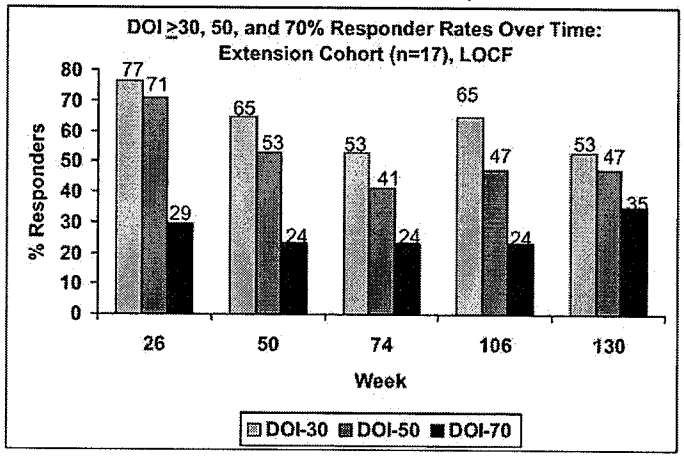
Figure 8. Study HWA 486/1037 JRA DOI ≥ 30 % Over Time: Extension Cohort (n=17), LOCF (The following figure is from the sponsor's submission)



Data based on the study 1037 extension ITT population (N=17) LOCF

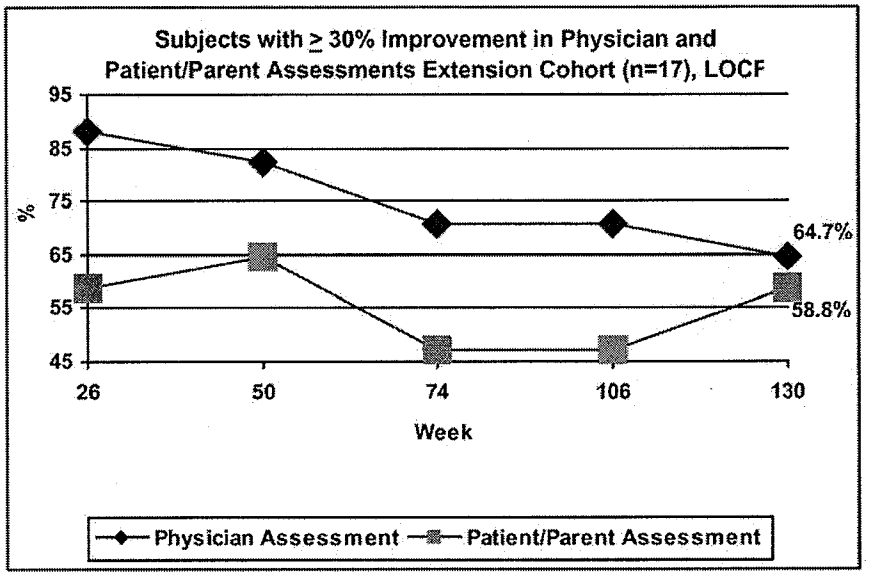
By week 130, only 9 patients (52.9%) in the Extension Study HWA 486/1037, extension cohort were JRA DOI ≥ 30 % responders and 8 (47.1 %) were non-responders. See **figure 9.**

Figure 9, Extension Study HWA486/1037, JRA DOI ≥ 30 % Responders
(The following figure is from the sponsor's submission)



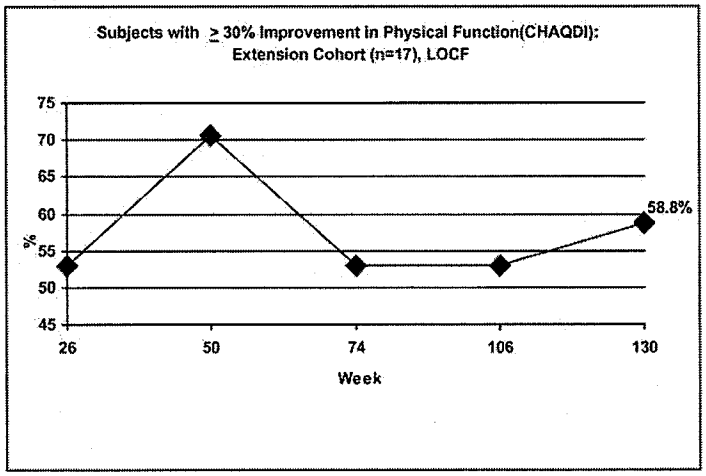
Study HWA 486/1037 patients demonstrated ≥ 30 % improvement in **physician** assessment (64.7%) and **patient/parent assessments** (58.8 %) extension cohort (n=17), LOCF. See **figure 10** for these results.

Figure 10, Study HWA486/1037, Patients with ≥ 30 % Improvement in Physician and Patient/Parent Assessments from the Extension Cohort.
(The following table is from the sponsor's submission)



The percentage of patients with ≥ 30 % improvement in **physical function**, the **CHAQ-DI,** was 58.8 % at Week 13 of the extension phase. See **figure 11**.

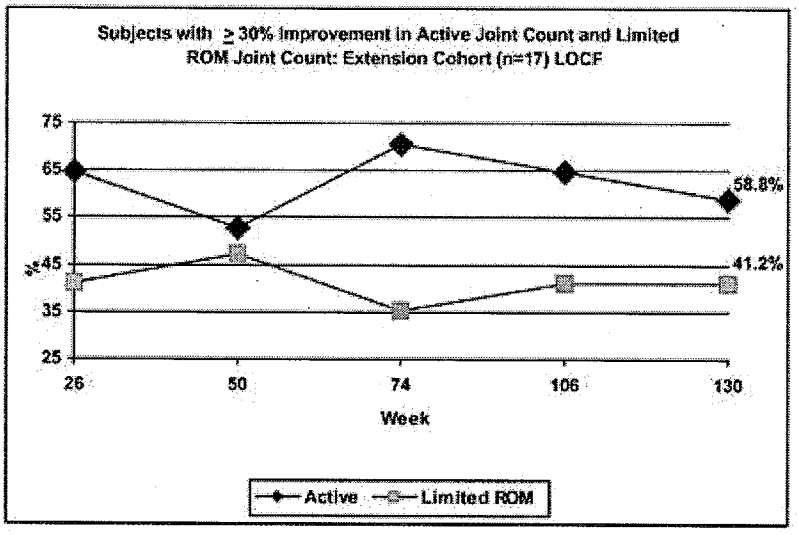
Figure 11. Study HWA 486/1037, ≥ 30 % Improvement in Physical Function
(The following table is from the sponsor's submission)



Ten patients (58.8 %) had ≥ 30 % improvement in **active joint count** at Week 130 which was similar to 11 patients (64.7 %) at Week 26. Seven patients (41.2 %) had ≥ 30 % improvement in **limited ROM** joint count at Week 130 which was the same percentage (41.1 %) at Week 26. Similarly, 6 to 8 patients (35.3 – 47.1 %) had ≥ 30 % improvement in the number of joints with **limited ROM.**

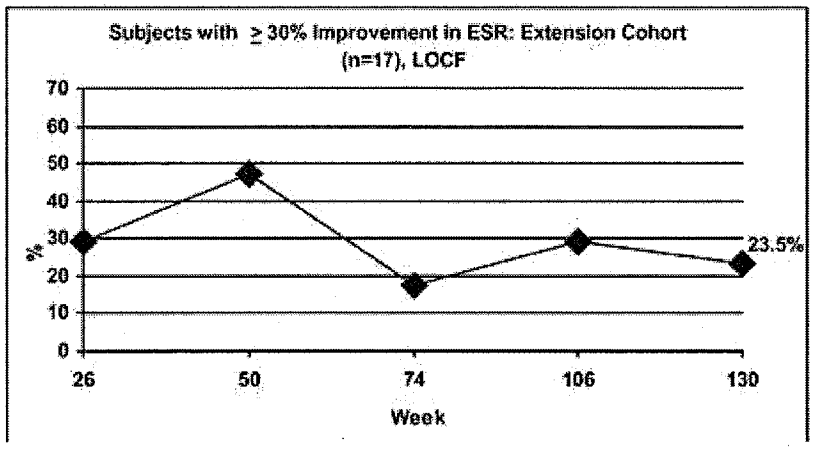
Ten patients (58.8 %) had ≥ 30 % improvement in active joint count at Week 130 which was similar to 11 patients (64.7 %) at Week 26. Seven patients (41.2 %) had ≥ 30 % improvement in limited ROM joint count at Week 130 which was the same percentage (41.1 %) at Week 26. Similarly, 6 to 8 patients (35.3 – 47.1 %) had ≥ 30 % improvement in the number of joints with limited ROM.

Figure 12, Study HWA486/1037, ≥ 30 % Improvement in Active Joint Count and Limited ROM Joint Count (The following figure is from the sponsor's submission)



In **figure 13,** Study HWA486/1037, the number of patients with JRA DOI ≥ 30 % improvement in ESR during the extension phase varied at the extension time points between 17.6 % and 47.1%. By Week 130, 4/17 (23.5 %) had JRA DOI ≥ 30 % improvement in ESR, similar to 5 of 17 (29.4 %) at Week 26. The 9 patients who were responders at Week 130 had further improvement in ESR at Week 130 (-11.33) compared to Week 26 (-10.56). Note: the larger the negative number the better the outcome.

Figure 13, Study HWA486/1037, ≥ 30 % Improvement in ESR
(The following figure is from the sponsor's submission)



Summary

Primary Efficacy, Study HWA486/1037

Efficacy was assessed using the Definition of Improvement (DOI), a responder analysis of JRA published by Giannini et al (1997), in the intent to treat population (ITT) using last observation carried forward (LOCF) analysis. Twenty-seven patients were enrolled and received at least one dose of study drug. In the study population of 27 patients: Preliminary efficacy was evident at Week 4 and increased until Week 12 when 51.9 % were responders. Responses were maintained thereafter until the Week 26 endpoint of the 6 month treatment period.

Fourteen patients (51.9 %) were DOI ≥ 30 % responders, 12 of these 14 or 44.4 % of the entire protocol population were 50% responders. Five of 14 (18.5% enrolled) achieved DOI ≥ 70 % responses after 26 Weeks of therapy. Improvement in physician global assessment, patient/parent global assessment was seen by Week 4 with maximal improvement seen after the 12 and 16 Weeks, respectively. These results were unchanged with leflunomide throughout the 6 month treatment phase. Improvement in physical function was evident after 4 weeks of leflunomide, plateaued after 12 Weeks and maintained over 26 Weeks.

Over the 6 month phase, a JRA DOI ≥ 30 % improvement in active joint counts and joints with limited range of motion were observed in 48.2 % and 33.0 % of patients. Leflunomide therapy was associated with an initial improvement in ESR at Week 4. ESR improvement decreased to almost baseline levels at Week 8 and below baseline levels by Week 12. After Week 16, improvement in ESR was again observed and was sustained to Week 26. A reduction in the swollen joint count was evident by Week 4 and increased until Week 16 and was then unchanged. Similarly, improvement in the severity score was evident at Week 4 and continued through Week 26.

Secondary Efficacy, Study HWA 486/1307 (Extension Phase, 6-30 months)

Extension phase results in the patients continuing beyond month 6 (N=17) support the primary efficacy observed in the 6 month treatment period and demonstrate that the

response was unchanged. At week 130 or last visit, 9/17 patients (52.9 %) were classified as JRA DOI ≥ 30 % responders. Forty-one percent (8/17) were also JRA DOI ≥ 50 % responders and 35.3 % (6/17) were JRA DOI ≥ 70 % responders. The reviewer agrees with the sponsor's conclusion that the results of Study HWA486/1037 warrant further study of leflunomide in a larger controlled pediatric clinical trial.

Study HWA486/3503
Title Phase IIIB: Efficacy and safety of leflunomide versus methotrexate in the treatment of pediatric patients with juvenile rheumatoid arthritis

Primary Objective
To assess efficacy and safety of leflunomide versus methotrexate in treatment of JRA as assessed by the Percent Improvement Index and JRA DOI ≥ 30 % Responder Rate at the endpoint or Week 16 visit. .

Secondary Objectives
To compare leflunomide and methotrexate with respect to the:
Percent Improvement Index and JRA DOI ≥ 30 % Responder Rate over time (Weeks 4, 8, and 12)
Time to achieve JRA DOI 30 % response
JRA DOI ≥ 50 % and ≥ 70 % responder rates
JRA DOI ≥ 30 %, ≥ 50 % and ≥ 70 % responders at endpoint (non-LOCF); patients must have a valid Week 16 visit
Global assessments by physician and patient/parent
Number of active joints
Number of joints with limitation of motion plus pain and / or tenderness
Functional assessment (CHAQ-DI)
Erythrocyte sedimentation rate (ESR) value
C-reactive protein (CRP) value
Pain assessment
To assess population pharmacokinetics of leflunomide based on plasma levels of the active metabolite, M1.

Study Design
This study was a multinational, multi-center, double-blind, double-dummy, randomized, parallel arm, active-controlled study. Methotrexate was to be the DMARD active control for the study drug, leflunomide.

Study Population, Selection of Patients, Sample Size
Two-hundred and forty patients (120 patients per treatment arm) were to be enrolled for a non-inferiority design. Upon amendment changing the study to a superiority design, enrollment was to result in 90 patients was planned (45 per treatment arm). . Patients were to be recruited from approximately 75 centers worldwide and were to enroll at least 3 to 5 pediatric patients per center.

The Intent-To-Treat (ITT) population was to include all randomized patients who took at least one dose of study drug and for whom there existed at least one on-treatment set of values for the six core set variables. All patients were to be analyzed according to the treatment group to which they were randomized. All efficacy analyses were to be based on the ITT population. Completer patients were to be defined as all ITT patients who completed the study, with values for the six core set variables measured on or after day 98 following the start of the study drug.

Inclusion criteria

- Male or female, ages 3-17 years
- Current with routine immunizations
- Methotrexate and leflunomide naïve
- Diagnosis of active polyarticular course JRA
- Exhibiting active disease at baseline as defined by at least 5 swollen joints (not secondary to deformity) and at least 3 joints with limitation of motion plus pain, tenderness, or both
- Have a minimum of 5 active joints
- Exclusion of other forms of juvenile arthritis
- Active disease on two different evaluations 7 to 21 days apart (between screening and baseline)
- Any previous DMARDs were to be discontinued at least 14 days prior to receipt of study medications (including etanercept, IV immunoglobulin, cyclosporin, infliximab, sulfasalazine, hydroxychloroquine, gold)
- If taking NSAIDs, patient was to agree to keep dose unchanged for at least 14 days prior to receipt of study medications and throughout the course of the study
- If taking corticosteroids, patient was to agree to keep dose unchanged ($\leq$ 0.2 mg/kg /day or the equivalent on an alternate day schedule, not exceeding 10 mg/day) for at least 14 days prior to receiving study medications and throughout the course of the study
- No intramuscular or intra-articular corticosteroids were to be permitted for at least 30 days prior to receiving study medications
- No intravenous corticosteroids were to be permitted for at least 14 days prior to receiving study medications
- Patients were required to be prepubescent or, if postpubertal and sexually active, practicing adequate contraception. For females, oral contraceptives or IUDs constituted adequate contraception. For males, condoms and spermacide constituted adequate contraception. Patients were required to use adequate contraception throughout the study.
- Patients were not to be pregnant or nursing. A negative serum pregnancy test was to be required at screening and negative tests were to be required for patients to remain in the study.
- Female patients were to agree not to get pregnant for 24 months after treatment with study medications or were to agree to a washout procedure with cholestyramine upon study exit because of the potential of being randomized to leflunomide. Because of the potential that the patient would be randomized to methotrexate, patients were to agree

to avoid pregnancy for at least 1 ovulatory cycle after discontinuation of study medication. Male patients were to agree to not father a child for 24 months after treatment with study medication or were to agree to a washout procedure with cholestyramine

- Written informed consent was to be obtained from all patients or their legal authorized representative in accordance with IRB/EC guidelines. Consent was obtained before any study procedures (including screening) were performed.

Exclusion Criteria

- Pregnant or breast-feeding
- Male patients who wished to father a child during the study
- Previous or current treatment with methotrexate or leflunomide
- Active systemic disease, including rash and/or fever, with the exception of uveitis, within four weeks of study entry
- Presence of persistent infection or severe infection within three months of enrollment, including (but not limited to) positive serology for hepatitis B or C, or HIV by seropositivity or clinical diagnosis
- Current or past history of acute inflammatory disease of origin other than JRA, e.g. mixed connective tissue disease, seronegative spondyloarthropathy (ACR criteria), rheumatic fever, systemic lupus erythematosus, definite psoriatic arthritis
- Functional Class IV by ACR criteria
- History of drug or alcohol abuse
- Consumption of alcoholic beverages (use was strictly prohibited during the course of the study)
- Impaired hepatic function as reflected in AST or ALT levels greater than 1.5 times ULN
- Impaired renal function as reflected in serum creatinine level greater than 1.2 times ULN
- Chronic use of cholestyramine
- History of hypertension requiring treatment
- Current psychiatric illness that would interfere with completion of the trial
- Treatment with any investigational drug within 30 days of enrollment
- Any concurrent medical condition (e.g. severe hypoproteinemia) that would, in the investigator's opinion, compromise the patient's ability to tolerate the study medication or to comply with the protocol (for patients in Spain, lactose intolerance is an exclusionary concurrent medical condition).
- Clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease that would make implementation of the protocol or interpretation of study results difficult
- History of hypersensitivity to drugs with similar chemical structures to methotrexate or leflunomide
- High likelihood of requiring treatment with drugs not permitted by the study protocol during the study period

- Known hematopoietic disorder: HCT ≤ 24% and/or absolute WBCs ≤ 4,000 cells/mm^3 and/or platelet count ≤ 150,000 cells/mm^3 (≤ 150 G/L) and /or neutrophils ≤ 1,000 cells/mm^3 (≤ 1.0 G/L)
- Patient/ parent/guardian unable to understand the nature, scope, and consequences of the study
- Patient /parent /guardian unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for follow-up visits, or other indicators).

Clinical Sites/ Investigators, Study HWA486/3503
See Appendix IX, B. 1. b. Clinical Sites/ Investigators, Study HWA486/3503

Schedule of Visits, Study HWA486/3503
See Appendix IX, B. 2. Schedule of Visits, Study HWA486/3503

Primary Efficacy Variables
Data collected at screening, baseline and weeks 4, 8, 12, 16:
There were to be two co-primary efficacy variables, Percent Improvement Index and JRA DOI ≥ 30 % responder status using the same 6 core set measures of the JRA Definition of Improvement.
The 6 core set measures are:

Physician's global assessment
Patient/parent global assessment
Number of active joints
Number of joints with limitation of motion plus pain and or tenderness
Functional assessment (CHAQ)
ESR

The **first** of the **co-primary efficacy variables** was to be the **Percent Improvement Index** at Week 16, e.g., end of treatment, after following the principle of last observation carried forward (LOCF).

Percent Improvement Index was to be calculated as follows:
For each patient, the Percent Improvement Index was to be the mean of the 6 core set percent changes from baseline. The percent change from baseline to end of treatment was to be calculated as follows:

(value at end of treatment – value at baseline) / value at baseline x 100)

In the event that the mean percent change was positive (worsened), then Percent Improvement Index for that patient was to be set to zero. As part of a sensitivity analysis to explore whether a bias had been introduced by setting positive values to zero, 2 additional Percent Improvement Indices were to be defined. The first, Percent Improvement Index – 30, set each positive Percent Improvement Index with a value greater than 30 equal to 30, and left any positive Percent Improvement Index with a value less than 30 "as is." The second index, Percent Improvement Index – 100, set each

positive Percent Improvement Index with a value greater than 100 equal to 100, and left any positive Percent Improvement Index with a value less than 100 "as is."
An active joint was to be defined as a joint with swelling not due to deformity or a joint with limitation of motion plus pain on motion and/or tenderness.
As described in the protocol, a patient with baseline and on treatment values for the local ESR less than 20 mm/hr was to be considered neither improved nor worsened. For the purposes of the Percent Improvement Index, the threshold value of 20 mm/hr was to be used for all values less than 20 mm/hr.

For patients with no baseline ESR, C-reactive protein was to be used instead of ESR as the measure of acute phase reactants.

Second co-primary efficacy variable was to be the JRA DOI ≥ 30 % responder rate at Week 16, e.g., end of treatment, after following the principle of LOCF.

JRA DOI ≥ 30% was to be defined as follows:
For each patient, the responder status was to be a binary variable which took a value of 1 (responder) when at least 3 of any core set measures had a percent change from baseline of no greater than –30 % (i.e. at least 3 improved by at least 30 %) with no more than 1 core set measure having a percent change from baseline greater than or equal to 30 % (i.e. not more than 1 worse by greater than or equal to 30 %), otherwise the JRA DOI 30 % took on the value of zero (non-responder). Patients entering the study with a local ESR value less than 20 mm/hr were to have a value greater than or equal to 26 mm/hr to be considered to be worsened for the ESR component of the JRA DOI ≥ 30 %. Patients with values less than the threshold value of 20 mm/hr that decreased by more than 30 % were to be considered to be unchanged. That is, the threshold value of 20 mm/hr was to be used for all values less than 20 mm/hr when calculating JRA DOI ≥ 30%.
In the event than an individual core set measurement was missing at a particular visit, then the value from the previous visit was to be used according to the principle of last observation carried forward (LOCF).

The secondary variables, JRA DOI 50 % and JRA DOI 70 % were to be similarly defined where the improvement for at least 3 of any core set measures must reach 50 % and 70 % respectively, with no more than 1 worse by greater than or equal to 30%.
The second co-primary efficacy variable was to be the JRA DOI 30% Responder Rate at week 16, i.e. end of treatment, following the principle of LOCF.

Secondary Efficacy Variables

- Percent Improvement Index at 4, 8, 12 Weeks
- JRA DOI 30 % at 4, 8, 12 weeks
- JRA DOI 50 % at 4, 8, 12 weeks. This was to be a binary variable that was assigned a value of 1 (responder) when 3 or more core set measures had an improvement from baseline of at least 50 % and no more than 1 core set measure worsened from baseline by 30 % or more. In all other cases, the JRA DOI 50 % was to be given a value of zero (non-responder).

- JRA DOI 70 % at 4, 8, 12 weeks. As described above. This was to require at least 70 % improvement for 3 or more core set measures and no more than 1 measure worsened by 30 % or more.
- JRA DOI 30 % responder-at-endpoint. If the patient reached week 16, then the JRA DOI 30 % responder-at-endpoint to be equal JRA DOI 30 % calculated for week 16. If the patient stopped study drug before the planned end of the study and there was to be no valid data to calculate a JRA DOI 30 % at week 16, then the JRA DOI 30 % responder-at-endpoint was to equal zero (non-responder). A similar definition was to be applied for JRA DOI 50 % responder-at-endpoint and JRA DOI 70 % responder-at-endpoint.
- JRA DOI 50 % responder-at-endpoint
- JRA DOI 70 % responder-at-endpoint
- AUC for JRA DOI 30 % based on LOCF
- JRA DOI 50 % responder-at-endpoint
- JRA DOI 70 % responder-at-endpoint
- Area-under-the-curve (AUC) for JRA DOI 30 % based on LOCF
- AUC for JRA DOI 30 % using actual response at each time point
- AUC for JRA DOI 50 % based on LOCF (method I)
- AUC for JRA DOI 70 % based on LOCF (method I)
- Time to reach JRA DOI 30 %: this was to be the day on which the first JRA DOI 30 % was achieved
- Change from baseline in physician global assessment at 4, 8, 12, 16 weeks
- Change from baseline in patient/parent global assessment at 4, 8, 12, 16 weeks
- Change from baseline in the number of active joints at 4, 8, 12, 16 weeks
- Change from baseline in the number of joints with limited range of motion (ROM) plus pain and/or tenderness at 4, 8, 12, 16 weeks
- Change from baseline in the CHAQ Disability Index at 4, 8, 12, 16 weeks
- Change from baseline in ESR at 4, 8, 12, 16 weeks
- Change from baseline in CRP at 4, 8, 12, 16 weeks.
- Change from baseline in the pain assessment at 4, 8, 12, 16 weeks

Safety Assessments

Data was to be collected at screening and/or at baseline, Weeks 2, 4, 8, 12 and 16 by incidence of adverse events, physical examination, vital signs, hematology, chemistry (including liver enzymes) and urinalysis. Hematology monitoring was to be assessed every two weeks, in addition to regular office visits at Weeks 6, 10 and 14.

Other safety variables:

Vital signs
Supine blood pressure (mmHg)
Pulse (beats/min)
Body Temperature (C)
Body weight (kg)
Height (cm)
Systolic BP: ≥ 20 point decrease or increase

Diastolic BP: ≥ 15 point decrease or increase
Pulse: lower limit of normal was 60 beats/min, upper limit of normal was 100 beats/min
≥ 15 beat decrease or increase

Pharmacokinetic variables were derived from the plasma concentration-time data as follows:
Population parameters
CL
Vd
Individual parameters and measures of exposure
CL
Vd
Css
t½

Study HWA486/3503, Schedule of Visits and Procedures, Visits 1-7. See **Table 8**
(The following table is from the sponsor's submission)

Table 8. Study HWA486/3503, Schedule of Visits and Procedures (Visits 1-7)

Assessment	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16
Informed Consent	x						
Demographic Data	x						
Relevant Medical /Surgical History	x						
Previous Medication	x						
Inclusion/Exclusion Criteria	x						
Joint Evaluation	x	x		x	x	x	x
Physician's Global Assessment		x		x	x	x	x
Childhood Health Assessment Questionnaire (CHAQ)		x		x	x	x	x
Vital Signs	x	x	x	x	x	x	x
Physical Examination	x	x	x	x	x	x	x
Tanner Staging	x						x
ANA	x						
Hepatitis B/C and Varicella Zoster Antibody	x						

Assessment	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16
Rheumatoid Antibody	x						x
Serum Pregnancy Test	x	x	x	x	x	x	x
Routine Heme	x	x	x	x	x	x	x
Erythrocyte Sedimentation Rate		x		x	x	x	x
C-Reactive Protein		x		x	x	x	x
Routine Biochemistry Data	x	x	x	x	x	x	x
Routine Urinalysis	x	x	x	x	x	x	x
Concomitant Medications		x	x	x	x	x	x
Pharmacokinetic Sample Collection			x			x	x
Study Medication		x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x
Termination Record							x

Study Medication

Table 9 summarizes the planned leflunomide and methotrexate maintenance doses for Study HWA 486/3503.

Randomized to leflunomide: each patient was to have received a leflunomide loading dose ranging from one-100 mg tablet /day for 1 day to one-100 mg tablet /day for 3 consecutive days, depending on body weight. Thereafter, patients were to have received a maintenance dose of 10 mg every other day, 10 mg daily, or two-10 mg tablets daily (20 mg daily), depending on weight. Patients also were to have received methotrexate placebo tablets weekly based on body weight.

Randomized to methotrexate: each patient was to have received methotrexate 2.5 mg tablets weekly, based on body weight, for a dose of 0.5 mg/kg/wk (approximately 15 mg/m2/wk) to a maximum of 25 mg/wk. Patients were to have received a leflunomide placebo loading dose followed by 1 or 2 leflunomide placebo tablets daily or, based on weight, 1 tablet every other day for 16 weeks. Due to the blinded methotrexate treatment arm, all patients in the study were to have received at least 5 mg folate per week, administered as 1 mg daily or as a 5 mg weekly dose.

Table 9. Study HWA486/3503, Maintenance Dose Description, Leflunomide and Methotrexate (The following table is from the sponsor's submission)

Weight (kg)	Study 3503 Maintenance Dose	
	Leflunomide	Methotrexate
< 20	1 x 10 mg tablet every other day Methotrexate placebo weekly	0.5 mg/kg/week Leflunomide placebo 1 x 10 mg every other day
20-40	1 x 10 tablet mg daily Methotrexate placebo weekly	0.5mg/kg/week Leflunomide placebo 1 x 10 mg daily
> 40	2 x 10 mg tablets once daily Methotrexate placebo weekly	0.5 mg/kg/week Leflunomide placebo 2 x 10 mg daily

Protocol Amendments, Study HWA486/3503
The original protocol was dated October 8, 2001 and the final protocol was dated December 14, 2001. There were **6 amendments** to the clinical study protocol.

Amendment 1 was written to address PK data being re-analyzed to reflect a more conservative dosing regimen being instituted (increased body weight upper limit to 20 kg for patients taking 5 mg of leflunomide/placebo as a daily maintenance dose). Standard immunization requirements were added to the inclusion criteria and individual standards of care for folate supplements were added.

Amendment 2 applied only i[redacted] was clarified that the study was only to be conducted in pediatric patients with *polyarticular* course JRA. Lactose intolerance was added to the exclusion criterion as lactose is contained in the leflunomide formulation.
Amendment 3 applied only i[redacted] where the [redacted] equested that ALT and AST be monitored at weeks 6, 10, 14 in addition to the study hematology monitoring.

Amendment 4, as explained by the sponsor, clarified the following: added JRA DOI 30% as a co-primary efficacy outcome parameter instead of a secondary efficacy parameter; added severe hypoproteinemia as a concomitant illness exclusion factor; clarified the methotrexate manufacturer; clarified course of action to be taken in cases of toxicity, significant toxicity, significant infection and serious treatment-related event; clarified duration of cholestyramine washout incase for females of child-bearing potential; clarified administration of leflunomide loading dose; clarified that influenza vaccine was allowed; added phenytoin, warfarin, tolbutamide, and Anakina as not allowed; at FDA request, a PK sample collection was added for immediately before and after cholestyramine washout in the event of a serious treatment-related adverse event; clarified that the post-study follow-up should include a laboratory assessment if a patient received one of the study medications in the post study follow-up period. Amendment 4 further defined in the study Appendix IX that the cholestyramine washout procedure for LFT elevations > 3 x ULN was clarified, the time window between screening and

randomization visits was clarified: ——— was approved and added to list of DMARDS not allowed and patients cannot be discontinued due to noncompliance on 2 consecutive visits.

Amendment 5, serum albumin determination was added to blood chemistry profile and corrected errors in tablet and bottle counts of methotrexate were included in some copies of protocols.

Amendment 6, adjusted the sample size from 240 pediatric patients to 90 patients and changes to statistical procedures as a result of changing the statistical analysis from one of equivalence to one of superiority.

Post-Hoc Analysis Plan

In the original study proposal, the analysis of the JRA DOI ≥ 30 % responder-at-Endpoint was to use the difference of responder rates of the treatment groups using normal approximation described in the statistical analysis plan. However, the sponsor utilized the Cochran Mantel Haenszel (CMH) procedure to calculate p-values in the NDA 20-905, S-012 final submission. See Statistical Review by Dr. Suktae Choi. All p-values were recalculated by Dr. Choi. The statistical review differs from the sponsor's analysis at the 8 Week and 12 Week efficacy results according to the JRA DOI ≥ 30 %: ITT patients. See **Table 10.**

Table 10. Study HWA486/3503, JRA DOI ≥ 30 %: ITT patients
(This table is from the sponsor's submission)

Table 25. JRA DOI 30%: ITT subjects

Visit Week	Leflunomide		Methotrexate		Difference LEF – MTX		p-value
	n/N	%	n/N	%	%	95% CI	
4	22/44	50.0	17/42	40.5	9.5	-11.4; 30.5	0.6296
8	29/47	61.7	32/47	68.1	-6.4	-25.7; 12.9	0.4571
12	32/47	68.1	40/47	85.1	-17.0	-33.8; -0.2	0.0930
16	32/47	68.1	42/47	89.4	-21.3	-37.3; -5.3	0.0156

n=number of subjects with a JRA DOI 30% response; N=number of subjects for whom data were available; 95% CI= 95% confidence interval for differences between percents; p-value based on Cochran Mantel Haenszel (CMH) procedure controlling for pooled site

Patient Disposition

Of the 103 patients screened, 94 were randomized in a 1:1 ratio into this study. Eighty six patients completed the study. As seen in **Table 11** there were a few more discontinuations due to AEs from the leflunomide group compared to the MTX group (3 vs. 1, respectively).

Table 11. Patient Disposition

	Leflunomide	Methotrexate
Randomized	47	47
Completed	42	44
Early discontinuations	5	3
Discontinue due to:		
AE	3 (4.6%)	1 (2.1%)
Lack of Efficacy	1 (2.1%)	1 (2.1%)
Other	1 (2.1%)	0
Lost to f/u	0	1 (2.1%)

Table12. Study HWA486/3503 Patient Completion Data, Discontinued Patients (Part the following table is from the sponsor's submission)

Site and Patient	Study Drug	Reason for discontinuation	Drug exposure (days)	Outcome
0205/003	LEF	Lack of Efficacy	73	N.A.
0501/002 10 year old Female	LEF	Serious Adverse Event, pityriasis lichenoides (coded as parasporiasis)	110	Ongoing
0706/001 14 year old Female	LEF	Serious Adverse Event, ALT 7.4 x ULN and AST 3.1 x ULN;	28	Recovered
1101/006	LEF	Refused to take medication	95	N.A.
1101/007 13 year old Male	LEF	Serious Adverse Event, diarrhea, abdominal pain, Crohn's disease	64	Ongoing
0131/004	MTX	Lost to Follow Up	115	N.A.
0205/006	MTX	Lack of Efficacy	82	N.A.
0401/001 10 year old F	MTX	Adverse Event, ALT elevations	35	Recovered

Baseline Characteristics and Demographics

The patients in Study HWA486/3503 had early disease, only 6% (3) in the leflunomide group and 9% (4) in the methotrexate group had previously taken DMARDS. As summarized in **Table 13,** over half (57 %) of the patients in both groups were younger than 12 years of age. Patients in the leflunomide group had a higher incidence of both previous and concurrent illnesses at baseline than did those in the methotrexate group. Nearly all patients were taking concomitant medications (98 % of leflunomide patients and 100 % of methotrexate patients). Most commonly, these concomitant medications were NSAIDs, gastrointestinal agents and analgesics, primarily acetaminophen, in

addition to the required folate. All patients were methotrexate naïve. The mean disease duration (from time of JRA diagnosis) was less than 2 years. Median disease duration was 0.33 years in both groups and 32 patients (68 %) in each group had duration < 12 months.

Table 13. Study HWA486/3503 Demographic and JRA Characteristics
(The following table is from the sponsor's submission)

Demographic or disease characteristic		Treatment group		
		Leflunomide N=47	Methotrexate N=47	p
Age (years)	mean (SD)	10.1 (4.0)	10.2 (3.8)	0.9310
< 12 years	n (%)	27 (57.4)	27 (57.4)	0.9495
≥ 12 years	n (%)	20 (42.6)	20 (42.6)	
Sex				
Male	n (%)	12 (25.5)	13 (27.7)	0.6930
Female	n (%)	35 (74.5)	34 (72.3)	
JRA duration (years)	mean (SD)	1.69 (3.2)	1.37 (1.97)	0.6923
Active joints	n (%)	14.4 (7.9)	14.0 (9.9)	0.9995
Limited ROM[a] joints	n (%)	7.7 (6.4)	8.0 (6.6)	0.3774
Physician global[b] (mm)	mean (SD)	55.1 (18.3)	47.3 (19.3)	0.1792
Patient global[bc] (mm)	mean (SD)	39.6 (28.1)	36.5 (23.8)	0.9533
CHAQ Disability Index[c]	mean (SD)	1.03 (0.71)	1.11 (0.74)	0.4687
ESR (mm/hr)	mean (SD)	30.8 (18.2)	34.5 (21.7)	0.2342
CRP (mg/L)	mean (SD)	19.57 (22.82)	13.81 (25.63)	0.3152
Pain[bc] (mm)	mean (SD)	41.1 (26.57)	41.6 (24.64)	0.4903

[a] ROM= Range of Motion
[b] Assessment using a 100 mm visual analogue scale
[c] Assessment by the subject or parent

Primary Efficacy Endpoints
The intent-to-treat (ITT) population was the primary population analyzed for efficacy.

JRA DOI ≥ 30 % Responder Rate
Methotrexate performed statistically significantly better than leflunomide as measured by the JRA DOI ≥ 30 % responder rate. The JRA DOI ≥ 30 % endpoint resulted in a responder rate of 89.4 % versus 68.1 %, methotrexate versus leflunomide, respectively. (p=0.009) (-37.3, -5.3 95% Confidence Interval of the difference)
See the Statistics Review by Dr. Suktae Choi.

Table 14. Post Hoc Analysis, Study HWA486/3503, JRA DOI ≥ 30% responder rate (ITT population). (The following table is from the sponsor's submission)

Visit Week	Leflunomide		Methotrexate		Difference LEF – MTX		p-value[a]
	n/N	%	n/N	%	%	95% CI	
4	22/44	50.0	17/42	40.5	9.5	-11.4; 30.5	0.6296
8	29/47	61.7	32/47	68.1	-6.4	-25.7; 12.9	0.4571
12	32/47	68.1	40/47	85.1	-17.0	-33.8; -0.2	0.0930
16	32/47	68.1	42/47	89.4	-21.3	-37.3; -5.3	0.0156

n=number of subjects with a DOI ≥ 30% response; N=number of subjects for whom data were available; 95% CI= 95% confidence interval for differences between percents [a]p-value based on Cochran Mantel Haenszel (CMH) procedure controlling for pooled site

Table 14, as noted in the Post Hoc Analysis section of this NDA Supplement review, demonstrates that the sponsor utilized a different statistical analysis for p-value results at visit Week 4, 8 and 12. Using the JRA DOI ≥ 30 % responder rate, by Week 16, patients treated with methotrexate demonstrate a statistically significant outcome as compared to patients treated with leflunomide.

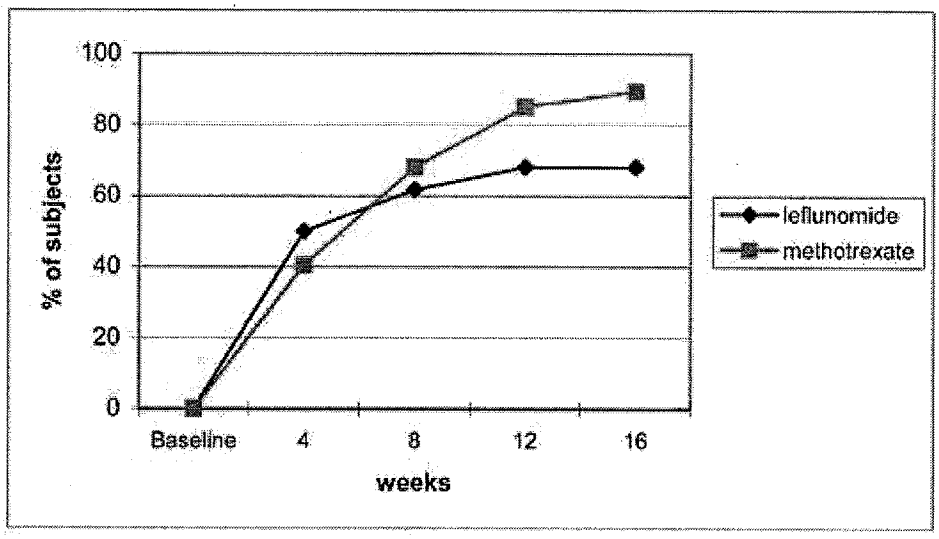
Additional analysis, as noted in **Table 15**, using the JRA DOI ≥ 30 % logistic regression results by subgroup (ITT population), demonstrates that patients weighing ≤ 40 kg and treated with leflunomide (16/27) had 59.3 % response rate versus patients weighing ≤ 40 kg and treated with methotrexate (19/21) 90.5 % response rate. In contrast, for patients in the weight category > 40 kg, leflunomide (16/20) response rate was 80.0 % versus methotrexate (23/26) response rate of 88.5 %. The reviewer believes this difference within the same category of patient weight is contributed to by the lower dose of leflunomide administered to the smaller. Lighter weight patients' dosage was based on conservative dosing from PK data. As also explained by the sponsor, patients in the two lower weight groups (, 20 kg and 20 to 40 kg) who received 5 mg and 10 mg daily, respectively, tended to have lower M1 exposures than patients in the heaviest weight group, > 40 kg.

Table 15, JRA DOI ≥ 30 %: logistic regression results by subgroup (ITT patients) (This table is from the sponsor's submission)

Subgroup	Leflunomide			Methotrexate			Odds ratio		Interaction p-value
	N	n	(%)	N	n	%	E[a]	95% CI	
Sex									
Male	12	8	(66.7)	13	12	(92.3)	0.57	0.04; 8.60	0.6876
Female	35	24	(68.6)	34	30	(88.2)			
Age									
< 12 years	27	18	(66.7)	27	25	(92.6)	0.37	0.04; 3.70	0.3989
≥12 years	20	14	(70.0)	20	17	(85.0)			
Race									
White	41	28	(68.3)	35	32	(91.4)	--	--	--
Not white	2	0	(0.0)	10	8	(80.0)			
JRA duration									
< 12 months	32	22	(68.8)	32	29	(90.6)	0.83	0.08; 8.61	0.8756
≥ 12 months	15	10	(66.7)	15	13	(86.7)			
Swollen joints									
< 10	24	16	(66.7)	27	24	(88.9)	1.26	0.12; 12.9	0.8469
≥ 10	23	16	(69.6)	20	18	(90.0)			
Weight									
≤ 40 kg[b]	27	16	(59.3)	21	19	(90.5)	0.24	0.02; 2.60	0.2387
> 40 kg	20	16	(80.0)	26	23	(88.5)			
Continent									
Australasia	4	2	(50.0)	4	3	(75.0)	1.97	0.06; 60.1	0.6964
North America	15	11	(73.3)	16	14	(87.5)	2.33	0.19; 28.1	0.5066
Europe	28	19	(67.9)	27	25	(92.6)			

Figure 14 demonstrates the JRA DOI ≥ 30 % responder rate for Study HWA486/3503.

Figure 14. JRA DOI ≥ 30 % responder rate over time for Study HWA486/3503 ITT population (The following figure is from the sponsor's submission)



*Cochran-Mantel-Haenszel statistic

Percent Improvement Index

At week 4 of treatment, the Percent Improvement Index score was essentially the same for both treatment groups. At week 16 the adjusted mean improvement was -44.41 % (SE 4.51) in the leflunomide group and -52.87 % (SE 4.39) in the methotrexate group, a difference of 8.46%. While, numerically favoring methotrexate, these results were not statistically significantly different. The largest incremental difference between treatment groups was observed between weeks 4 and 8 when it increased from 1.06 to 4.25. **Table 16** demonstrates that over the entire study, the change from baseline to week 16 was numerically, but not statistically greater for methotrexate.

Figure 15 demonstrates the Percent Improvement Index for Study HWA486/3503 as also summarized in Table 16.

Figure 15. Percent Improvement Index for (adjusted mean) for Study HWA486/3503 ITT population. (The following figure is from the sponsor's submission)

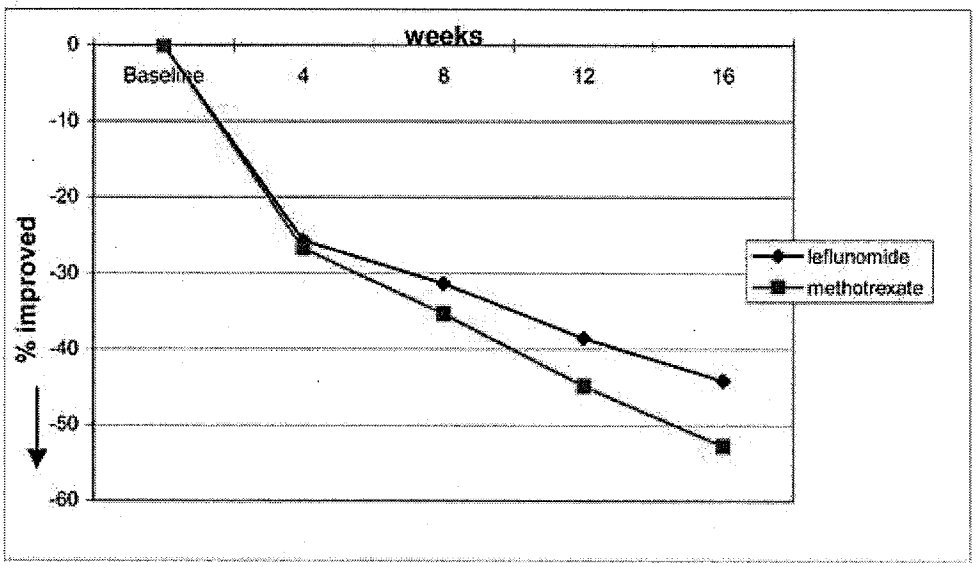


Table 16. Percent Improvement Index for Study HWA486/3503 ITT population. (The following table is from the sponsor's submission)

Visit Week	Leflunomide			Methotrexate			Difference LEF – MTX		p-value
	N	Adj mean	SE	N	Adj mean	SE	Adj mean	95% CI	
4	44	-25.56	3.817	42	-26.62	3.837	1.06	-9.27; 11.39	0.8388
8	47	-31.26	3.941	47	-35.51	3.843	4.25	-6.51; 15.01	0.4343
12	47	-38.63	4.311	47	-44.85	4.203	6.22	-5.55;17.98	0.2966
16	47	-44.41	4.513	47	-52.87	4.399	8.46	-3.86; 20.77	0.1758

[a] ANOVA = analysis of variance with treatment and site effects
N = number of subjects for whom data were available; adj mean=adjusted mean; SE=standard error; 95% CI = 95% confidence interval for differences of adjusted means

Subgroup analyses were predefined to investigate the consistency of effect across various subgroups. The analyses were performed with treatment, pooled center, background demographic variable and treatment by background variable interaction as fixed effects.

Among the leflunomide patients, sex, age, disease duration and the number of swollen joints, weight and site location (by continent) had no influence on the Percent Improvement Index data. As acknowledged by the sponsor, the data indicated that age and body weight had an effect on the response to methotrexate. Younger, lighter-weight patients showed a better response than older, heavier patients. The mean change from baseline for patients < 12 years of age was 57.5 % compared with 45.76 % for patients >

12 years, and the mean improvement in patients weighing < 20 kg was 66.9 % compared with 49.45 % in those weighing between 20 to 40 kg. These differences were not statistically significant but suggest a trend toward improved response in patients weighing < 20 kg that may be clinically significant.

Secondary Efficacy Variables

As demonstrated in **Table 17**, JRA DOI ≥ 50 % and DOI ≥ 70 % responder rates were analyzed as secondary variables and did not demonstrate statistical differences between the treatment groups at week 16 in the ITT group, LOCF. The differences become statistically significant in favor of methotrexate in the responder-at-endpoint analysis, which is an ITT, non-LOCF analysis defining a responder as a patient who completed the 16-week study as a responder.

Table 17, Study HWA486/3503, JRA DOI ≥ 30 %, ≥ 50 %, DOI ≥ 70 %
(The following table is from the sponsor's submission)

DOI ≥ 30%, 50%, 70% responder-at-endpoint rates

ITT WK 16	Leflunomide N=47			Methotrexate N=47			p-value		
DOI	≥ 30%	≥ 50%	≥ 70%	≥ 30%	≥ 50%	≥ 70%	≥30%	≥ 50%	≥ 70%
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)			
LOCF	32(68.1)	28(59.6)	20(42.6)	42(89.4)	36(76.6)	28(59.6)	.0156	.0989	.1431
Non-LOCF	30(63.8)	26(55.3)	18(38.3)	39(83.0)	35(74.5)	28(59.6)	.0303	.0385	.0436

There were no statistically significant between-group differences in area-under-the-curve (AUC) analysis of responder status over time. See **Table 18**.

Table 18, Study HWA486/3503, AUC Responder Status Over Time
(The following table is from the sponsor's submission)

AUC Analysis of Responder Status Over Time							
DOI	Leflunomide N=47		Methotrexate N=47		Difference LEF – MTX		p-value
	Adj mean	SE	Adj mean	SE	Adj mean	95% CI	
≥30%	1.86	0.171	2.12	0.167	-0.26	-0.73; 0.20	0.2670
≥50%	1.51	0.185	1.57	0.180	-0.06	-0.57; 0.44	0.8021
≥70%	0.88	0.169	0.92	0.165	-0.04	-0.50; 0.42	0.8665

There were no statistically significant differences between treatment groups in the changes from baseline for any of the 6 core set variables that are the components of the

Percent Improvement Index and JRA DOI ≥ 30 %. Changes in the core set variables from baseline to week 16 are described in **Table 19.**

Table 19. Study HWA486/3503, Changes in Core Set Variables from Baseline to Week 16. (The following table is from the sponsor's submission)

Changes in core set variables from baseline to week 16

Core set variables	Leflunomide			Methotrexate			P value
	N	Baseline mean(SE)	Change at wk 16 mean(SE)	N	Baseline mean(SE)	Change At wk 16 mean(SE)	
Number of active joints	47	14.2(1.45)	-8.1(0.99)	47	14.2(1.42)	-8.9(0.96)	.5671
Number of joints with limited ROM	47	7.6(0.97)	-5.2(0.81)	47	8.8(0.94)	-5.3(0.79)	.9157
Physician global assessment (mm)	47	52.4(2.82)	-31.5(2.98)	47	47.2(2.75)	-32.1(2.94)	.8884
Patient global assessment (mm)	47	36.5(4.09)	-15.9(2.97)	47	36.2(3.99)	-22.0(2.89)	.1359
CHAQ DI	47	1.00(0.114)	-0.44(0.075)	47	1.11(0.11)	-0.39(.073)	.6060
ESR (mm/hr)	43	29.5(3.26)	-6.5(1.28)	45	34.7(3.08)	-7.2(1.20)	.6588

The Childhood Health Assessment Questionnaire, CHAQ, which was derived from the adult, Health Assessment Questionnaire, HAQ[3] , was published in 1994.[2] It comprises two indices, Disability and Discomfort. The Disability Index assesses function in eight areas distributed among a total of 30 items. The Discomfort Index is determined by the presence of pain measured by a 100-mm visual analogue scale (VAS), extrapolated to a score of 0 to 3. In addition, a 100-mm VAS measures patient/parent global assessment of arthritis. The Childhood Health Assessment Questionnaire Disability Index (CHAQ DI) exceeded the minimum clinically important difference of 0.13 in both treatment groups.

Additional secondary variables were pain assessment and CRP level. Improvement in pain was not significantly different between the two treatment groups.

At baseline, adjusted mean CRP was 18.83 versus 13.58 mg/L for the leflunomide and methotrexate treatment groups, respectively. Mean improvement in CRP was apparent in both treatment groups, and the difference was statistically significantly better in the

[3] References

1. Scull SA, Dow MB, Athreya BH: Physical and occupational therapy for children with rheumatic diseases, Pediatr Clin North Am 33: 1053, 1986.2. Brewer EJ, McPherson M, Magrab P, et al: Family-centered, community-based, coordinated care for children with special healthcare needs. Pediatrics 83: 1055, 1989.

methotrexate group (-3.86 mg/L for leflunomide and -11.43 mg/L for methotrexate). The median CRP in the leflunomide group decreased from 10.4 to 3.4 mg/L, which was near the upper limit of normal (2.87 mg/L). In the methotrexate group, the median CRP decreased from a lower baseline of 3.7 mg/L to 1.49 mg/L.

Subgroup analyses by weight and age:
In **Table 20 and 21**, subgroup efficacy analyses of the co-primary outcome measures by pre-defined weight and age subgroups demonstrate that there were differences in efficacy outcomes between the treatment groups based on weight and age, in patients≤ 40 kg and patients < 12 years. The effect of body weight on the difference in response between the treatment groups was most apparent in the smallest patients (< 20 kg). In further analyses, the <20 kg and 20-40 kg weight groups were combined because 8/8 (100%) of the methotrexate patients < 20 kg were responders, creating a non-calculable odds ratio for that weight group. In the leflunomide group < 20 kg weight group, 5/8 (62.5%) were responders. The responder rate was 11/19 patients (57.9%) for the leflunomide 20-40 kg subgroup and 11/13 patients (84.6%) for the methotrexate 20-40 kg subgroup.

Therefore, the < 20 kg weight group treated with methotrexate had the highest JRA DOI ≥ 30% responder rate as was also seen with the Percent Improvement Index. There was a difference of 20% in responder rates between smaller (≤ 40 kg) and heavier (> 40 kg) leflunomide patients with more of the heavier patients achieving JRA DOI ≥ 30 %. The reviewer believes this result suggests the smaller patients were relatively under dosed in this study.

Table 20. Study HWA486/3503, Leflunomide and Methotrexate Doses by Subgroup (The following table is from the sponsor's submission)

Subgroup	Leflunomide N=47			Methotrexate N=47			Difference Leflunomide-methotrexate		Interaction p-value
	n	Adj Mean	SE	n	Adj Mean	SE	Adj Mean	95% CI	
Age									
< 12 years	27	-44.82	5.842	27	-57.50	5.637	12.68	-3.5; 28.9	0.4224
≥ 12 years	20	-42.96	6.877	20	-45.76	6.922	2.81	-15.7; 21.3	
Weight									
< 20 kg	8	-46.29	11.545	8	-66.92	10.590	20.63	-10.3; 51.5	0.6623
20-40 kg	19	-41.83	7.056	13	-49.45	8.323	7.63	-14.5; 29.8	
> 40 kg	20	-46.25	6.933	26	-50.86	6.102	4.61	-12.7; 22.0	

Table 21. JRA DOI ≥ 30 % responder rates, including age and weight subgroups (The following table is from the sponsor's submission) Note Table 21 is duplicated to facilitate the reader.

Subgroup	Leflunomide			Methotrexate			Odds ratio		Interaction p-value
	N	n	(%)	N	n	%	E[a]	95% CI	
Sex									
Male	12	8	(66.7)	13	12	(92.3)	0.57	0.04; 8.60	0.6876
Female	35	24	(68.6)	34	30	(88.2)			
Age									
< 12 years	27	18	(66.7)	27	25	(92.6)	0.37	0.04; 3.70	0.3989
≥12 years	20	14	(70.0)	20	17	(85.0)			
Race									
White	41	28	(68.3)	35	32	(91.4)	--	--	--
Not white	2	0	(0.0)	10	8	(80.0)			
JRA duration									
< 12 months	32	22	(68.8)	32	29	(90.6)	0.83	0.08; 8.61	0.8756
≥ 12 months	15	10	(66.7)	15	13	(86.7)			
Swollen joints									
< 10	24	16	(66.7)	27	24	(88.9)	1.26	0.12; 12.9	0.8469
≥ 10	23	16	(69.6)	20	18	(90.0)			
Weight									
≤ 40 kg[b]	27	16	(59.3)	21	19	(90.5)	0.24	0.02; 2.60	0.2387
> 40 kg	20	16	(80.0)	26	23	(88.5)			
Continent									
Australasia	4	2	(50.0)	4	3	(75.0)	1.97	0.06; 60.1	0.6964
North America	15	11	(73.3)	16	14	(87.5)	2.33	0.19; 28.1	0.5066
Europe	28	19	(67.9)	27	25	(92.6)			

[a]Odds ratio was not calculated when at least 1count was zero.
[b]In the logistic regression analysis, the < 20 kg and the 20-40 kg weight groups were combined because 8/8 (100%) of the methotrexate subjects <20 kg were DOI ≥ 30% responders, creating a non-calculable odds ratio for that weight subgroup. 5/8 (62.5%) of the leflunomide subjects < 20 kg were DOI ≥ 30% responders.

The effect on body weight and the safety profile trends similarly as did the responder rate data by JRA DOI ≥ 30 %. As noted by the sponsor, within the leflunomide group, the smallest patients (< 20 kg) had not ALT or AST elevations > 1.2 x ULN by laboratory analysis. Two subjects in the 20 to 40 kg weight group had ALT elevations 2to 3 x ULN. In addition, adverse events assessed by the investigator as possibly treatment-related occurred in fewer patients in the lower weight groups:

Table 21. Study HWA 486/3503, Adverse Events by Weight Group, Leflunomide

Weight Group	Percent of Patients with Adverse Events
< 20 kg	50 %
20 to 40 kg	57.9 %
> 40 kg	75 %

Summary
Study HWA 486/3503 demonstrated that efficacy of methotrexate 0.5 mg/kg/wk in early polyarticular JRA was superior to the efficacy of leflunomide dosed according to the study protocol. This study also demonstrated that the higher end of dose range selected for the methotrexate dose resulted in the smaller (≤ 40 kg) and younger (< 12 years of age) methotrexate patients having the greatest difference in efficacy compared to leflunomide.

Study HWA486/3504
Title: Double-blind, 8-month **extension study** to collect durability of efficacy data and additional safety data in patients with polyarticular course Juvenile Rheumatoid Arthritis completing the double-blind comparison Study HWA486/3503, of leflunomide versus methotrexate.

Objective: The objective of this extension study is to evaluate the continued safety, tolerability, and durability of efficacy of leflunomide versus methotrexate in patients who had previously completed the prerequisite pivotal study (HWA486/3503).

Study Design:
Multi-center, multi-national, double-blind, 8-month Extension Study of HWA486/3503.

Study Population, Selection of Patients and Sample Size:
Patients completing Study HWA486/3503 study were eligible for enrollment in the Extension Study. The estimated number of patients that would continue into Study HWA 486/3504 was 70-100.

Inclusion Criteria:
Inclusion criteria were the same as in Study HWA486/3503 as described in this review with the addition of the following:
- Patient completed Study HWA486/3503
- Patient was to be willing to continue on current study medication assignment at the time of the completion of Study HWA486/3503.
- Laboratory values obtained at Visit 6 (week 16, last visit) of Study HWA486/3503 were to be reviewed and found to be consistent with Study HWA486/3504 inclusion/exclusion criteria
- Informed consent was to be obtained, in accordance with IRB/EC guidelines, from the patient or the patient's legal authorized representative before any study procedures were to be performed.

Exclusion Criteria:
Patients who were excluded from Study HWA486/3503 were not included in Study HWA486/3504, along with the following additional criteria
- Patient did not complete Study HWA486/3503
- ALT and/or AST levels > 1.5 x ULN

- AST level > 1.2 x ULN at 2 or more visits in Study HWA486/3503
- Patient was taking a DMARD other than the assigned study medication
- Patient was likely to receive intramuscular, intravenous, or more than 2 intra-articular corticosteroid injections during the course of the study
- Patient was pregnant, breast feeding, not using adequate contraception, or, if male, wishing to father a child during the course of the study
- Patient has active systemic juvenile rheumatoid arthritis (JRA), including rash and/or fever, with the exception of uveitis
- Presence of persistent or severe infections including (but not limited to) positive serology for hepatitis B or C, or HIV
- Current or past history of acute inflammatory disease of origin other than JRA, e.g. mixed connective tissue disease, seronegative spondyloarthropathy (ACR criteria), rheumatic fever, systemic lupus erythematosus, definite psoriatic arthritis
- Functional Class IV by ACR criteria
- History of drug or alcohol abuse; likelihood of patient to consume alcoholic beverages during study (consumption of alcohol was strictly forbidden during the course of the \ study)
- Impaired renal function as reflected in a serum creatinine level > 1.2 x ULN
- Chronic use of cholestyramine
- History of hypertension requiring treatment
- Current psychiatric illness that would interfere with completion of the trial
- Any concurrent medical condition, e.g. severe hypoalbuminemia, or clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease that would, in the opinion of the investigator, compromise the patient's ability to tolerate study medication or comply with the protocol
- History of hypersensitivity to drugs with chemical structures similar to methotrexate or leflunomide
- High likelihood of requiring treatment during the study with drugs not permitted by the study protocol
- Known hematopoietic disorder (any or all of the following):
  - Hct ≤ 24%
  - Absolute WBC ≤ 4.000 cells/mm
  - Platelet count ≤ 150,000 cells/mm
  - Neutrophils ≤ 1,000 cells/mm
- Patient/parent/guardian unable to understand the nature, scope, or consequence of the extension study
- Patient/parent/guardian unlikely to comply with the protocol, e.g. uncooperative attitude,
inability to return for follow-up visits, or other indicator

Study Medications:
Patients entering the Extension Study HWA486/3504 were to remain on their study medication regimen, and continue to receive either leflunomide 10 mg every other day or 10 mg daily or 20 mg daily weekly, calculated according to body weight, or methotrexate

weekly, as noted in **Table 9**, Study HWA486/3503. In addition, all patients were to receive at least 5 mg folate per week, to be administered as 1 mg daily or as a 5 mg weekly dose. Dose escalation of leflunomide or methotrexate placebo was not to be allowed unless the patient's weight changed. Dose escalation of methotrexate or methotrexate placebo up to 6.0 mg/kg/week (maximum dose of 30 mg/week) was to be allowed at the discretion of the investigator.

Efficacy Outcomes
Co-primary efficacy outcome measures were to be the same as in Study HWA486/3503 Percent Improvement Index and the JRA DOI ≥ 30 % responder status

Secondary efficacy variables were to include:
JRA DOI ≥ 50 % and ≥ 70 % responder status
Mean change from baseline for the *individual core set variables* comprising the JRA DOI and the Percent Improvement Index
Number of active joints
Number of joints w/limitation of motion plus pain and/or tenderness
Physician's global assessment of disease activity
Patient/parent global assessment of disease activity
Physical function based on CHAQ-DI
ESR

Statistical procedures
The study was not expected to be complete at the time of submission. An interim data summary (IDS) was to be submitted for review. Baseline value for any instrument/assessment was to be the last assessment prior to the intake of the first dose of study medication in HWA486/3503. For efficacy and safety instruments, the end of treatment or endpoint was to be the last assessment made while the patient was on study medication. This was to be week 24 (day 168) of treatment (week 8 of the extension study) for patients who successfully completed the initial 24-week treatment period covered in the IDS.

The reviewer notes that the Division agreed for the sponsor to submit IDS data from the first 8 weeks of the extension Study HWA486/3504 available by June 30, 2003 for inclusion in the interim analysis.

Results
The sponsor has submitted the results from the *first 8 weeks* of the extension study containing data for a cohort of 53 safety patients and 49 efficacy patients. The reviewer notes that the sponsor has agreed to submit the remaining data at the end of the completed 8 months duration.

Patient Disposition

Of the 94 randomized patients in Study HWA486/3503, 86 patients completed the study and 70 enrolled in the extension study HWA486/3504. One patient in the leflunomide group subsequently withdrew consent, and three patients in the methotrexate group discontinued due to AEs. At the time of submission, efficacy data was available for 49 patients included in the intent-to-treat (ITT) population and safety information was available for 53 patients. See **Table 22.**

Table 22, Study HWA486/3504, Interim Data Summary Populations
(The following table is from the sponsor's submission)

Interim data summary populations

IDS Population	Leflunomide N	Methotrexate N	Total
Enrolled[a]	23	30	53
Safety	23	30	53
Efficacy (ITT)	23	26	49

There are 4 patients included in the IDS safety population who are not in the efficacy population: two of the patients (0103001; 0203001) are ongoing in the extension study but had only week 24 efficacy data available at the time of the data cutoff for the IDS.

Drug Exposure
Mean study medication duration in the respective safety populations were similar and are not statistically significant: leflunomide, 174.6 $\pm$ 9.7 days versus methotrexate, 169.0 $\pm$ 17.0 days. **Table 23** describes study drug exposure in Study HWA486/3504 demonstrating greater exposure in the leflunomide treated group than in the methotrexate treated group.

Table 23. Study HWA486/3504, Drug Exposure
(The following table is form the sponsor's submission)

Study drug exposure

Number of days	Leflunomide N=23		Methotrexate N=30	
	n	%	N	%
85-112	0	0.0	1	3.3
113-140	0	0.0	1	3.3
141-168	2	8.7	6	20.0
169-196	21	91.3	22	73.3

Baseline Characteristics and Demographics

Table 24 describes the demographic characteristics to be similar between the leflunomide and methotrexate treatment groups. Median age in both groups for the safety patients was 11 years and the mean age was 9.9 years, with more than half of the patients in each group 12 years of age or younger. The majority of patients were female.

Table 24. Demographic Characteristics, Study HWA486/3504.

Demographic	Treatment group		Probability
	Leflunomide N=23	Methotrexate N=30	
Age (years)			
Mean (SD)	9.9 (4.3)	9.9(3.8)	0.7883
Median	11	11	
Range	3 – 16	3 – 17	
Number	23	30	
Age group N(%)			
< 12 years	12(52.2)	18(60.0)	0.3741
≥ 12 years	11(47.8)	12(40.0)	
Sex N(%)			
Male	6(26.1)	10(33.3)	0.6259
Female	17(73.9)	20(66.7)	
Race N(%)			
White	20(87.0)	25(83.3)	0.3397
Other	0(0.0)	3(10.0)	
Not answered[a]	3(13.0)	2(6.7)	
Weight N(%)			
< 20 kg	5(21.7)	6(20.0)	0.9564
20–40 kg	7(30.4)	8(26.7)	
> 40 kg	11(47.8)	16(53.3)	

Efficacy Results

Study HWA486/3504

Primary Efficacy Variable: JRA DOI ≥ 30 % responder rate

Upon entering the Extension Study at Week 16, the methotrexate group had a higher response rate than did the leflunomide group, (23/26 patients) 88.5 % versus (16/23 patients) 69.6 %, respectively. (p = 0.3173). The leflunomide group had an increase in the responder rate relative to Week 16 (69.6 % at Week 16 up to 82.6 % at Week 24) while the methotrexate group had a decrease in the responder rate relative to Week 16 (88.5 % at Week 16 to 80.8 % at week 24). See **Table 25** for the within-group comparison by JRA DOI≥ 30 % responder rate.

Table 25. Study HWA486/3504, JRA DOI 30 % Responder Rate: Within-Group Comparison (This table is from the sponsor's submission)

Leflunomide			Methotrexate		
Week 16 N = 23	Week 24 N = 23	Difference 16 wks – 24 wks	Week 16 N = 26	Week 24 N = 26	Difference 16 wks – 24 wks
n(%)	N(%)	P-value[a]	n(%)	n(%)	P-value[a]
16(69.6)	19(82.6)	0.1797	23(88.5)	21(80.8)	0.3173

Of the 16 leflunomide responders at Week 16, 15/16 (93.8 %) continued to be responders at week 24, supporting the durability of response at Week 24 also supported by the JRA DOI ≥ 30 % responder rate and the Percent Improvement Index. See **Table 25.** There were 7 leflunomide non-responders at Week 16, 4/7 (57.1 %) who became responders at Week 24. Of the 23 patients in the leflunomide efficacy population, 65.2 % were responders at both Week 16 and Week 24. In addition, 17.4 % were non-responders at Week 16 but became responders at Week 24.

In the methotrexate group, 20/23 (87.0 %) Week 16 responders continued to be responders at Week 24, and 3 became non-responders at Week 24. See **Table 26.** Only 1 of the 3 non-responders at Week 16 (33.3 %) became a responder at Week 24. Of the 26 patients in the methotrexate efficacy population, 76.9% were responders at both Week 16 and Week 24, but only 3.8% changed from the non-responder to responder status at week 24.

Table 26. Study HWA486/3504, **JRA DOI ≥ 30 %**, Week 16 versus Week 24 (The table is from the sponsor's submission)

		Week 24	
		Responders n(% of total)	Non-responders n(% of total)
Week 16	Leflunomide N=23	N=19	N=4
	Responders N=16	15(65.2)	1(4.3)
	Nonresponders N=7	4(17.4)	3(13.0)
	Methotrexate N=26	N=21	N=5
	Responders N=23	20(76.9)	3(11.5)
	Nonresponders N=3	1(3.8)	2(7.7)

Secondary Efficacy Variables, DOI ≥ 50 % and ≥ 70 %

JRA DOI ≥ 50 % and ≥ 70 % responder rates were increased at Week 24 as described in **Tables 27** and **28.** In the leflunomide group, all of the 19 JRA DOI ≥ 30 % responders at Week 24 were also DOI ≥ 50 % responders and most were also DOI ≥ 70 % responders. The sponsor notes that, within group comparisons were not statistically significant by McNemar's test for either treatment group.

Table 27. Study HWA486/3504, **JRA DOI ≥ 50 %,** Within-Group Comparison
(The table is from the sponsor's submission)

Leflunomide			Methotrexate		
Week 16 N = 23	Week 24 N = 23	Difference 16 weeks – 24 weeks	Week 16 N = 26	Week 24 N = 26	Difference 16 weeks – 24 weeks
n(%)	n(%)	P-value[a]	n(%)	n(%)	P-value[a]
15(65.2)	19(82.6)	0.1025	22(84.6)	19(73.1)	0.1797

Table 28. Study HWA 486/3504, **JRA DOI ≥ 70 %,** Within-Group Comparison
(The table is from the sponsor's submission)

Leflunomide			Methotrexate		
Week 16 N = 23	Week 24 N = 23	Difference 16 weeks – 24 weeks	Week 16 N = 26	Week 24 N = 26	Difference 16 weeks – 24 weeks
n(%)	n(%)	P-value[a]	n(%)	n(%)	P-value[a]
12(52.2)	14(60.9)	0.4142	18(69.2)	16(61.5)	0.3173

Individual Core Set Variables
The sponsor notes there were no significant within-group differences for comparison of Week 16 versus Week 24 changes from baseline for any individual core set variable. Leflunomide patients demonstrated improvement in physical function between Weeks 16 and Weeks 24.

Between-Treatment Comparisons
Primary Efficacy Variable - Percent Improvement Index
Both treatment groups began the extension study at Week 16 with Percent Improvement Indexes showing more than 50 % improvement and no statistically significant difference between the groups. There was no significant difference between treatment groups for the comparison of the Percent Improvement Index at Week 24.

Primary Efficacy Variable - JRA DOI ≥ 30 % Responder Rate
Upon enrollment in the extension, the methotrexate group had a numerically higher proportion of responders and a numerically better mean Percent Improvement Index. However, the JRA DOI ≥ 30 % responder rate for the leflunomide patients was higher than that for the methotrexate patients at week 24, although this difference was not statistically significant.

Secondary Efficacy Variables – DOI ≥ 50 % and ≥ 70 %
More methotrexate than leflunomide patients began the extension as DOI ≥ 50 % and DOI ≥ 70 % responders at Week 16, although the difference between treatment groups was not statistically significant. By week 24, differences in DOI ≥ 50 % and ≥ 70 % were no longer present, although the leflunomide DOI ≥ 50 % responder rate numerically exceeded that of methotrexate.

- Leflunomide group DOI responder rates **increased** between Week 16 and Week 24:
  - DOI ≥ 50 %: 65.2 % to 82.6 %
  - DOI ≥ 70 %: 52.2 % to 60.9 %
- Methotrexate group DOI responder rates **decreased** between Week 16 and Week 24:
  - DOI ≥ 50 %: 84.6 % to 73.1 %
  - DOI ≥ 70 %: 69.2 % to 61.5 %

Individual core set variables
Upon enrolling in the extension study at Week 16 and Week 24, there were no significant or consistent differences between the treatment groups with regard to the 6 core set variables.

D. EFFICACY CONCLUSIONS

STUDY HWA486/3503

There were no substantial differences in the Percent Improvement Index between the treatment groups. The JRA DOI ≥ 30 % responder rate demonstrated a statistically significantly greater improvement in patients treated with methotrexate than with leflunomide. However, there was a notable response in leflunomide-treated patients, 68%. Efficacy results in favor of methotrexate may relate to several factors in this study. Of note, the drugs have been shown to have comparable efficacy in adults in a placebo controlled trial.

- The sponsor acknowledges that overall, the early disease of the population and very low number of previous failed DMARDs may explain the high level of responsiveness to both treatments in this study. Adult studies have shown methotrexate to have higher responder rates in adults with early disease rather than in adults with established disease.
- Leflunomide patients had more evidence of more inflammation at baseline. The leflunomide group had higher median and mean CRP levels and median and mean global assessments, although not statistically significantly different. More leflunomide patients had ≥ 10 swollen joints (leflunomide 23 patients, methotrexate 20 patients) and fewer leflunomide patients had < 10 swollen joints (leflunomide 24 patients, methotrexate 27 patients).

- The reviewer concurs with the sponsor's observation that pediatric patients with polyarticular course JRA appeared to be responsive to the higher start dose for methotrexate. The dose of methotrexate used in this study, 0.5 mg/kg/week (15 $mg/m^2/wk$), is the higher end of the methotrexate dose range The usual starting dose for methotrexate is 0.33 mg/kg/wk ($10mg/m^2/wk$). Pediatric patients may be gradually given a higher dose, depending on their clinical response and tolerance. The sponsor explains that 0.5 mg/kg/wk was selected for this study to assure adequate time on an aggressive enough dose of methotrexate for meaningful treatment comparison at the 4 month study endpoint.
- The smaller ($\leq$ 40 kg) and younger (< 12 years of age) patients receiving methotrexate had the greatest difference in efficacy compared to comparable patients receiving leflunomide. The difference in efficacy between the two treatment groups was most apparent in the smallest patients (< 20 kg) and youngest patients. The reviewer believes the decreased exposure, according to PK data analysis, of the smaller and younger patients to leflunomide, lower dosing in the smaller and younger patients, is the strongest reason for Study HWA486/3503 efficacy outcome difference.
- Retrospective subset analyses of efficacy by weight group and age, and pharmacokinetic data from this study analysis suggest that the smaller patients were relatively under dosed, having lower levels of the active metabolite (M1) compared to the larger patients who had levels comparable to those obtained adults.
- Despite evidence of relative under-dosing of the smaller weight patients treated with leflunomide compared to the larger weight patients, leflunomide demonstrated high responder rates and Percent Improvement Index as well as improvement in physical function measured by the CHAQ-DI which was not different between the treatment groups.
- Few patients discontinued study medication due to early due to an adverse event:
    - 3 in the leflunomide group (6.4 %)
    - 1 in the methotrexate group (2.1 %)

Efficacy Conclusions
Study HWA486/3504

- Leflunomide appeared to demonstrate durability between Week 16 and Week 24 according to the two co-primary efficacy measures: Percent Improvement Index and JRA DOI $\geq$ 30 % responder rate.
- The DOI $\geq$ 30 % responder rate improved for leflunomide treated patients between Week 16 and Week 24, although the change was not statistically significant.
- The leflunomide extension cohort demonstrated durability of efficacy at Week 24 by both primary efficacy analyses was also supported by increased JRA $\geq$ DOI 50 % and 70 % responder rates at Week 24 relative to Week 16.
- Methotrexate patients showed less improvement from baseline at Week 24 relative to Week 16. This difference (16 Weeks – 24 Weeks = -3.5) was not statistically significant.

VII. INTEGRATED REVIEW OF SAFETY

A. BRIEF STATEMENT OF CONCLUSIONS

Study HWA486/1037
No deaths, malignancies, significant overdoses or pregnancies were reported in study patients (n=27) during this 30 month study. There were 13 serious adverse events (SAEs) reported in 7 patients (26.0 % of study population). Six SAEs in three patients were considered possibly related to leflunomide treatment by the investigator. Two patients discontinued study drug; one patient discontinued secondary to the SAE of hypertension and the other patient discontinued secondary to non-serious adverse events (AE) of alopecia, abdominal pain and urticaria. The overall profile of adverse events was consistent with the underlying disease and known serious adverse events of leflunomide and methotrexate. There were 6 patients with elevated ALT and/or AST < 8 x ULN; 4 of 6 patients' elevated LFT were reported as adverse events. All these patients eventually had normalized ALT and AST values.

Study HWA486/3503
There were no deaths, malignancies, significant overdoses or pregnancies in this trial. Serious adverse events were reported in 3 leflunomide patients (6.4%) and no methotrexate patients. Four patients withdrew from this study, 3 leflunomide (6.4%) and one methotrexate (2.1%) due to an adverse event. Discontinuation due to a treatment-related adverse event was similar in the two treatment groups: 2 in the leflunomide group (4.3%) and 1 in the methotrexate group (2.1%). One subject in each treatment group discontinued early due to reversible and asymptomatic elevated hepatic transaminases, assess as treatment-related in both cases. The overall profile of adverse events was consistent with the underlying disease and known serious adverse events of leflunomide and methotrexate. Hepatotoxicity is a known risk of leflunomide treatment. As noted above, one patient in each treatment group discontinued early due to reversible and asymptomatic elevated hepatic transaminases, assessed as treatment-related in both case. ALT ≥ 3 x ULN was an alert term in this study and occurred in more methotrexate patients (3/47, 6.4%) than in leflunomide patients (1/47, 2.1%).

Study HWA486/3504
There were no deaths, malignancies, significant overdoses or pregnancies in this trial. There were a total of 5 SAEs in this study. No leflunomide patient discontinued study drug due to an AE. There was one patient with an SAE in the leflunomide group who was hospitalized due to an adverse event of abdominal pain which the investigator did not believe was secondary to study drug. There were 4 patients with SAE's in the methotrexate group. Only 2 of these 4 patients had SAEs (gastrointestinal disorder, one elevated ALT) assessed as possibly related to study drug. Hepatic transmainase

elevations were noted in one patient treated with leflunomide and 4 patients treated with methotrexate.

B. DESCRIPTION OF PATIENT EXPOSURE

The overall extent of exposure is presented in **Table 29** for Study HHWA 486/1037, Study HWA486/3503 and Study HWA486//3504. (This table is from the sponsor's submission)

Exposure variable	1037 Wk 0-130	3503 Wk 0-16		3504 IDS Wk 0-24	
	LEF N=27	LEF N=47	MTX N=47	LEF N=23	MTX N=30
Study drug exposure (days) [mean (SD)]	461.6 (313.9)	114.9 (19.8)	116.2 (19.4)	174.2 (9.7)	169.0 (17.0)
Median (days)	523	116	114	175	170
Range (days)	7-924	28-154	35-182	141-190	112-190
Study drug exposure [n (%)]					
1-28 days	1 (4)	1 (2)	0	-	-
29-84 days	2 (7)	-	-	-	-
29-56 days	-	0	1 (2)	-	-
57-84 days	-	2 (4)	1 (2)	-	-
85-182 days	6 (22)	-	-	-	-
85-112 days	-	13 (28)	14 (30)	0	1 (3)
113-140 days	-	28 (60)	28 (60)	0	1 (3)
141-168 days	-	3 (6)	2 (4)	2 (9)	7 (23)
169-182 days	-	0	1 (2)	-	-
169-196 days	-	-	-	21 (91)	21 (70)
183-350 days	2 (7)	-	-	-	-
351-518 days	2 (7)	-	-	-	-
519-742 days	8 (30)	-	-	-	-
>742 days	6 (22)	-	-	-	-

LEF = leflunomide
MTX = methotrexate

All enrolled patients (n = 27) received at least one dose of study medication, leflunomide, and were included in the safety analysis, including post treatment evaluations 16 weeks after receiving the last dose of study medication. Over the full 30 month study, mean treatment exposure for the ITT population was 461.56 days or 65.9 weeks and 18/27 (66.7 %) received leflunomide for > 182 days. See **Table 29**

Study HWA 486/3503

Table 29 demonstrates the study duration and drug exposure. There were no significant differences between the groups in the number of days of exposure to study drug 5 patients in the leflunomide group and 3 patients in the methotrexate group did not complete the study. One patient in each group was withdrawn due to lack of efficacy. Three patients in the leflunomide group and 1 patient in the methotrexate group discontinued due to adverse events. The exposure to study drug for the discontinued patients ranged from 28 days to 110 days in the leflunomide group and 35 days to 115 days in the methotrexate group.

Table 30, Study HWA 486/3503 and 3504, shows the dosage of each study medication based on patient weight.

Table 30. Study HWA486/3503 and HWA486/3504, Dosing Regimen
(This table is from the sponsor's submission)

Weight (kg)	Leflunomide/placebo loading dose	Leflunomide/placebo maintenance dose	Methotrexate/placebo
< 20	100 mg daily x 1 day	10 mg every other day	0.5 mg/kg weekly
20 – 40	100 mg daily x 2 days	10 mg every day	0.5 mg/kg weekly
> 40	100 mg daily x 3 days	20 mg every day	0.5 mg/kg weekly[a]

Study HWA 486/3504
There was no statistically significant difference between treatment groups for the mean study medication duration (leflunomide group, 174.6 ± 9.7 days, methotrexate group, 169.0 ± 17.0 days).

C. METHODS AND SPECIFIC FINDINGS OF SAFETY REVIEW

The studies reviewed under the efficacy section of this NDA review are the same studies reviewed under the safety section of this NDA.

Deaths
No deaths occurred in any of the subjects (N=121) in **Study HWA486/1037, Study HWA486/3503 or Study HWA486/3504 Extension.**

Serious Adverse Events (SAEs)
(See Appendix IX. A.1. Serious Adverse Events in Study HWA486/1037, Study HWA 486/3503 and Study HWA 486//3504).

Study HWA486/1037
A total of 13 SAEs were reported in 7 patients (26 % this study population) No SAE was reported in more than one patient. Six of 13 SAEs noted in 3 patients were considered possibly related to leflunomide treatment by the investigator. Similarly, of these 13

SAEs, 12 were treatment emergent, two SAEs occurred in two patients during the first 26 weeks of therapy. Ten SAEs were reported in 5 patients in the Extension Phase of Study HWA 486/1037.

Six SAEs in three patients were considered to be related to the study drug during administration: cellulitis, elevated liver enzymes, petechiae, hypertension, stress fracture right leg (investigator believed this case may not be study drug related, rather secondary to prolonged corticosteroid use and low intake of calcium and Vitamin D) and possible gastritis. Hospitalization occurred in 6 patients secondary to 8 SAEs. See **Table 31**

TABLE 31, STUDY HWA486/1037 (THIS TABLE IS FROM THE SPONSOR'S SUBMISSION)

Serious Adverse Events Reported in the Safety Population (n=27)

Subject No	Age/Sex	Adverse Event	Duration of leflunomide Prior to Event	Serious Criteria	Resolved	Related	Action Taken with Study Drug
59001	15/F	Cellulitis	299 days	Hospitalization, Medically important	Yes	Yes	Temporarily interrupted for 16 days
		Elevated liver enzymes	462 days	Medically important	Yes	Yes	Temporarily interrupted for 18 days
		Petechiae skin rash	462 days	Medically important	Yes	Yes	Temporarily interrupted for 18 days
		Hypertension	863 days	Medically important	Yes	Yes	Treatment withdrawal
59002	16/F	Valgus deformity right lower extremity	528 days	Hospitalization	Yes	No	None, study drug continued
59004	16/F	Stress fracture right femur	277 days	Hospitalization, Medically important	Yes	Yes	Temporarily interrupted for 23 days
		Adjustment disorder with depression	596 days	Hospitalization	Yes	No	None, study drug continued
59005	9/F	JRA flare	- 44 days*	Hospitalization, Medically important	Yes	No	Not applicable

Study HWA 486/3503

Eleven serious adverse events occurred in 10 patients (21.3%). All of these patients were treated with leflunomide; 7/10 were assessed as mild to moderate by the investigator. SAEs included gastrointestinal events, pityriasis lichenoides rash and elevated hepatic enzymes. One subject had 2 serious adverse events reported: ALT elevation and AST

There was 1 patient with an SAE in the leflunomide group who was hospitalized due to an AE abdominal pain which the investigator did not believe was study drug related. Four patients in the methotrexate group had SAEs. One patient had gastrointestinal disorder and the other patient had elevated ALT. The investigator assessed both these patients SAE as possibly related to study drug. See **Table 32.**

Table 32. Summary, Safety Results from Study HWA486/3503.
(The following table is from the sponsor's submission)

Event	Leflunomide N=47	Methotrexate N=47
Death	0 (0.0)	0 (0.0)
Serious adverse event	10 (21.3)	0 (0.0)
Discontinued[a]	3 (6.4)	----
Possibly related	3 (6.4)	---
Discontinued[a]	2 (4.3)	---
Adverse event	43 (91.5)	38 (80.9)
Discontinued[a]	3 (6.4)	1 (2.1)
Possibly related	30 (63.8)	21 (44.7)
Discontinued[a]	2 (4.3)	1 (2.1)

[a]discontinued prior to the week 16 study visit due to the adverse event

Study HWA468/3504
Serious adverse events occurred in 4 subjects (13.3 %) in the methotrexate group and 1 subject (4.3%) in the leflunomide group. One subject (0606002) in the leflunomide treatment group experienced an SAE: The subject was a 12-year-old male who experienced abdominal pain and was hospitalized. The event was assessed as being of moderate intensity and not related to study drug. The duration of the event was 8 days and the subject recovered without sequela. Study medication was continued and no countermeasures were required. Four methotrexate patients had SAEs,
See Appendix IX, A.1. Serious Adverse Events

Withdrawals

Study HWA486/1037

One patient had study drug withdrawn due to non-serious AEs alopecia, abdominal pain and urticaria. Alopecia was noted in 29.6 % of patients. One treatment emergent SAE, hypertension, led to discontinuation of study drug in one child.

Study HWA486/3503

Three patients in the leflunomide group (6.4%) and one in the methotrexate group (2.1%) discontinued study medication. AS described by the sponsor, discontinuation due to a treatment-related adverse event was similar in the two treatment groups: 2 in the leflunomide group (4.3%) and one in the methotrexate group (2.1%). One patient in each treatment group discontinued early due to reversible and asymptomatic elevated hepatic transmainases, assessed as treatment-related in both cases.

Table 33, Study HWA 486/3503, Discontinuations due to TEAEs
(The following table information is from the sponsor's submission)

Patient Age/Sex, Wt. Kg	**Drug**	**Dose**	**Adverse Event**	**AE or SAE**	**Possibly Related**	**Intensity**	**SAE Criteria**	**Outcome**
0501002 10 yrs./F; 48 kg	LEF	300/20	Pityriasis lichenoides; (para-psoriasis)	SAE	Yes	Severe	Medically important	Ongoing
0706001 14 yrs/F; 53 kg	LEF	300/20	ALT elevated; AST elevated	SAE SAE	Yes Yes	Severe Severe	Hospitalized Hospitalized	Recover-Ed; Recovered
1101007 13 yrs/M; 39 kg	LEF	200/10	Crohn's Disease	SAE	No	Moderate	Hospitalized	Ongoing
0401001 10yrs/F 39 kg	MTX	20 QW	ALT increased	AE	Yes	Mild	None	Recover-ed

Study HWA486/3504

No leflunomide patients discontinued study drug due to an adverse event; 3 methotrexate patients discontinued due to an adverse event; in 2 of these patients the events were assessed as possibly related to study drug.

Non-Serious Adverse Events

See Appendix IX, A.2. Adverse Events

Study HWA486/1037

The overall profile of adverse events was consistent with the underlying disease and the known adverse events of leflunomide. Non-serious adverse events included alopecia, abdominal pain, urticaria, dizziness, headache, liver function abnormality, nausea, rash, Herpes Zoster, flu syndrome, diarrhea, gastrointestinal disorder and two reports of anemia. There were 18 reports of anemia, decreased hemoglobin and decreased red blood cell count reported in 4 patients (14.8%). Anemia resolved on leflunomide treatment in 2 patients and continued from the 6 month treatment period through the extension phase in another patient. There were no adverse events specifically of allergic reaction, pruritus or maculopapular rash were reported. One patient had a non-serious and a serious episode of *hypertension* reported during the extension phase of the Study HWA 486/1037. SE, hypertension, occurred post study drug treatment for 28 months, resulting in withdrawal of study medication. There were no significant changes in creatine phosphokinase (CPK), creatinine, total bilirubin or neutrophil count. The sponsor notes that decreased hematocrit, increased platelet counts, elevated white blood cells and increased blood urea nitrogen (BUN) were reported. All resolved without changes to study drug administration with the exception of 1 patient with decreased hematocrit. Elevated alkaline phosphatase occurred in 3 patients; however, two were not reported as AE by the investigator. Significantly elevated alkaline phosphatase occurred in a third patient and one serious AE was reported. One patient had elevated alkaline phosphatase at baseline and all study visits and another patient had a one-time elevation observed after 42 weeks of therapy. No adjustment in leflunomide administration was made and these two patients completed 130 weeks of the study.

In summary, per the sponsor, 26 patients experienced a total of 307 adverse events (all serious and non-serious TEAEs) over the entire 30 months. The most common events were: headache (17 patients; 63.0%; respiratory infection (17 patients; 63.0%; abdominal pain (11 patients; 40.7%; nausea (10 patients; 37.0%); diarrhea (10 patients; 37.0%); and rheumatoid arthritis (10 patients; 37.0%).

The safety analysis of Study HWA486/1307, Phase IB clinical data notes that the AEs are consistent with, and, those most frequently reported with, leflunomide therapy in the treatment of adults with rheumatoid arthritis in Phase III placebo-controlled studies (US 301 and MN301). In Study HWA486/1037, the highest incidence of AEs is described in **Table 34**.

Table 34. Study HWA486/1037, Most Frequently Reported AEs.

Body system		**Incidence (%)**	
General and digestive system		***81.5 %***	
	Abdominal pain	48.1 %	
	Diarrhea	37.0 %	

	Nausea and/or vomiting	44.4 %	
	Oral ulcers		
	Weight loss	7.4 %	
Nervous system		77.8 %	
	Headache	63.0 %	
	Dizziness	25.9 %	
Respiratory system		74.1 %	
	Respiratory infections	63.0 %	
Skin and Appendages		63.0 %	

Non-Serious Adverse Events (continued)
See Appendix IX, A.2. Adverse Events for Study HWA486/1037, 3503 and 3504

Study HWA486/3503
The overall profile of adverse events was consistent with the underlying disease and the known adverse effects of leflunomide and methotrexate. The most commonly reported AE in ≥ 15 % of patient treatment groups were headache, nasopharyngitis or pharyngitis and gastrointestinal symptoms (unspecified or upper abdominal pain, nausea and diarrhea). Additional AE were headache, nasopharyngitis, alopecia and diarrhea. The types of adverse events most commonly reported were similar in both treatment groups: *headache, nasopharyngitis or pharyngitis,* and *gastrointestinal symptoms* (*predominantly unspecified or upper abdominal pain, nausea, and diarrhea*). Of these, *headache, nasopharyngitis,* and *abdominal pain* were reported more often with leflunomide. Gastrointestinal symptoms, headache, and alopecia tended to occur early in the course of leflunomide treatment, with the majority of these AE occurring within the first 2-4 weeks. *Alopecia* was also common in the leflunomide patients and occurred more often with leflunomide than with methotrexate. The reviewer finds the incidence of headaches higher than expected in these pediatric studies. In the adult studies, the incidence of headache

Study HWA486/3504
Six of 23 patients who received leflunomide included in the analysis (26.1 %) and 11 of 30 patients who received methotrexate included in the analysis (36.7 %) experienced TEAEs after enrolling in the Extension Study HWA486/3504. Of these, only 2 (8.7 %) leflunomide patients and 3 (10.0 %) methotrexate patients had TEAEs that were assessed by the investigator as possibly related to study medication. Arthralgias occurred in two patients in each treatment group and were assessed as not related to study medication. No other TEAEs occurred in more than one patient in either treatment group. One patient, a 12 year male in the leflunomide group, experienced a decrease in neutrophil count on day 163 from 3.31 G/L at baseline to 1.61 G/L 6 weeks after entering the Extension Study that fulfilled the criteria for a PCA (predefined change abnormal) and was reported as an adverse event. The investigator assessed the event as possible related to study treatment

and of mild intensity. One patient in the methotrexate group, a 4 year old female experienced hepatomegaly on day 116 along with a viral upper respiratory infection and gastroenteritis. Investigator assessed the event as not related to study medication and of mild intensity. Liver enzymes were not elevated.

There were 4 patients in the leflunomide group with *hemoglobin* < 6.21 mmol/L. Each of these patients baseline values were below normal range and remained below normal range from the point of baseline testing through week 24. The *neutrophil count* was low, ≥ 1 .0 to < 1.5 g/L, in one patient taking leflunomide; the count was within a normal range at baseline and by week 16; however, at week 18 the neutrophil count was 1.00 g/L. The patient's neutrophil count normalized by Week 22 testing. There were no abnormal values for *leukocyte counts* or *platelet counts* in the LEF or MTX groups. *Blood pressure* changes were considered noteworthy if they were above the 95th percentile for the patient's age and height at baseline. No hypertension adverse events were reported despite the following elevations in BP as described in **Table 35.**

Table 35. Study HWA486/3504, Blood Pressure Results, Leflunomide versus Methotrexate Treated Patients

Leflunomide Treated Patients	**Clinically noteworthy elevation of BP**	**Methotrexate Treated Patients**	**Clinically noteworthy elevation of BP**
3/23 (13 %)	Systolic BP	4/30 (13.3 %)	Systolic BP
4/23 (17.4%)	Diastolic BP	1/30 (3.3 %)	Diastolic BP

Weight changes in these pediatric patients were minimal with the exception of one patient taking methotrexate at week 24 where there was a greater than 5 % weight loss from baseline. No leflunomide patients had a weight loss greater than 5 % or 10 % at week 24 of the extension study.

Hepatotoxicity

Study HWA486/1037

Clinically significant elevations in ALT and/or AST, were noted in 6 patients treated with leflunomide; 4/6 patient's liver function test elevations were noted as AE; one of the four was a SAE. Duration of study drug administration prior to elevated LFT ranged from 3 to 462 days. All elevations normalized within 10 to 71 days with no change in study drug administration in three patients, one dose reduction, one temporary interruption for 18 days and one elevation occurring in a patient off study drug due to lack of efficacy at the time of event.

The sponsor describes this patient , as a 6 year old female, with > 3 x ULN to 8 x ULN elevations in AST and ALT reported at a follow up visit 5 days after discontinuing study drug due to lack of efficacy. She had received leflunomide for over 28 weeks with normal AST and ALT values. Methotrexate therapy was initiated upon the discontinuation of leflunomide. Following the marked AST and ALT elevations found at the follow up visit,

methotrexate was discontinued and a full course of cholestyramine was given to the subject for the first time. Nine days after the follow up visit, ALT and AST levels had normalized.

Study HWA486/3503
The adverse events of most concern with both methotrexate and leflunomide involve *abnormalities in liver function, particularly increase in ALT, which is generally more sensitive than elevation of AST.* Patients were required to have ALT and AST levels < 1.5 x ULN at baseline.

All but 1 leflunomide patient were normal at baseline. By laboratory data analysis, ALT elevation >1.2 x ULN, with or without AST elevation, occurred in more methotrexate patients than patients treated with leflunomide. ALT elevations > 3 x ULN in methotrexate patients clustered to patients weighing < 40 kg and patients < 12 years of age. One patient in each treatment group discontinued due to an adverse event of elevated hepatic transaminases (ALT, AST); both had ALT ≥ 3 x ULN and were symptomatic. ALT elevations > 1.2 x ULN detected by laboratory data analysis, with or without AST elevation, occurred in more methotrexate patients (15/47) 32 % than leflunomide treated patients (7/47) 15 %.

Within the leflunomide group, adverse events assessed by the investigator as possibly treatment-related occurred less often in the < 20 kg and the 20 - 40 kg weight groups than in the > 40 kg weight group. Moreover, the smallest weight leflunomide patients (<20 kg) had no ALT elevations > 1.2 x ULN. All of the ALT elevations in the leflunomide patients occurred in the weight group greater than 20 kg: 4 patients weighed between 20 to 40 kg and 3 patients were heavier than 40 kg. No leflunomide patient < 20 kg had an ALT elevation > 1.2 x ULN.

Overall, most of the methotrexate ALT elevations were also in the heavier weight groups: 9 patients were heavier than 40 kg and 4 patients weighed between 20 and 40 kg. However, 2 methotrexate patients with significant ALT elevations (>2 x ULN) weighed less than 20 kg and the 3 methotrexate patients with ALT > 3 x ULN weighed < 40 Kg. The data showed clustering of the higher ALT elevations to the smaller and younger methotrexate patients.

Only one patient had elevated alkaline phosphatase reported as an AE.

The safety profile was generally more favorable with methotrexate in this pediatric population with the exception of ALT elevations. The younger and smaller of the methotrexate patients, who had the highest efficacy, also had the highest incidence of ALT elevations >3 x ULN.

Study HWA486/3504
As per the sponsor, in the methotrexate group, 2 subjects (6.7%) had laboratory abnormalities assessed by the investigator as medically important, and therefore, as

serious adverse events. In one subject (0501001), the laboratory abnormality (ALT ε 3 x ULN; alert term) was assessed by the investigator as possibly related to study drug. This event was reported as "liver function test abnormal". The other subject (0603005) had elevated ALT ε 3 x ULN; alert term) and elevated AST adverse events that were assessed as unrelated to methotrexate, but rather to an Epstein-Barr virus infection reported as an adverse event in study 3503. None of the leflunomide subjects had ALT or AST values assessed by the investigator as medically important. Two patients taking methotrexate had medically important laboratory abnormalities. Both had alert term ALT elevations. See **Table 36.**

Table 36, Study HWA486/3504, Alert Term Elevations in ALT

Patient age and sex	**Liver function Tests**	**Outcome Description**
5 year old Female	ALT 6.6 x ULN AST 4.1 x ULN	Discovered in the final visit for Study HWA486/3503 and worsened after enrolling into Extension Study HWA486/3504. Abnormal LFT was reported as non-serious AE in study HWA 468/3503 with ALT elevation 12.6 x ULN and AST elevation 5.0 x ULN. These LFT elevations were interpreted as not related to the study medication rather related to an Epstein-Barr virus infection. The patient was discontinued from the extension study and recovered.
9 year old Female	ALT ≥ 3 x ULN	Assessed as moderate

See **Table 37** for a summary of the highest *liver enzyme elevations* in Study HWA486/3504.

Table 37 Extension Study HWA486/3504 - Highest Liver Enzyme Elevations

Study Drug	**Patient**	**> 1.2 to 2 x ULN**		**> 2 to 3 x ULN**		**> 3 x ULN**	
LEF	0704003	1.86 x ULN	1.40 x ULN				
MTX	0501001 discontinued MTX.					3.41 x ULN	

	0502002	1.26 x ULN					
	0603005, highest reported ALT and AST elevations; MTX discontinued; Epstein Barr infection					12.56 x ULN	5.02 x ULN
	1101005	1.29 x ULN					

LEF = leflunomide; MTX = Methotrexate

D. ADEQUACY OF SAFETY TESTING

The total number of patients was small as noted in the three clinical trials submitted. The duration of patient exposure is acceptable. The reviewer requests review of the complete Extension Study HWA486/3504 data from the sponsor, though the IDS data, (first 30 days), is part of this NDA 20-905, S-012 submission and review. The clinical efficacy, safety and PK study data raise significant concern as to whether the smaller and younger patients (≤ 40 Kg) treated with leflunomide were under dosed as compared to the larger patients > 40 Kg.

E. SUMMARY OF CRITICAL SAFETY FINDINGS AND LIMITATIONS OF DATA

These three clinical studies raise concern about limited data in that there may have been under dosing of the smaller and younger patients treated with leflunomide. The sponsor and reviewer concur in that the difference in the number of serious adverse events between the leflunomide and methotrexate treatment groups in this study does not appear to be explained by treatment-related toxicity.

The proportion of serious adverse events occurring in patients < 12 years of age (60 % of the serious adverse events) were consistent with their representation in the treatment group (57 %). The reviewer concurs with the sponsor that there was no evidence that serious adverse events occurred more frequently in the smallest patients. The lowest weight group had one serious adverse event, which was disproportionately low compared to the intermediate and higher weight groups. As also noted by the sponsor, the linear decrease in incidence of possibly treatment-related adverse events with decreased body weight and the absence of liver enzyme elevations in the lowest weight group, suggests

that the younger, smaller children may be able to tolerate a higher daily maintenance dose than was used in Study HWA486/3503.

The incidence of total TEAEs was higher in the methotrexate group (36.7%, 11 patients) than in the leflunomide group (26.1%, 6 patients). The only TEAE assessed as severe was in the methotrexate group (gastrointestinal disturbance). No leflunomide patients and 1 methotrexate patient had the study drug interrupted (due to a non-serious adverse event of viral gastroenteritis). **Table 38** shows all and possibly related TEAEs classified by "other significant AEs" with the number of patients who had interventions/countermeasures due to a serious or non-serious adverse event.

Table 38. All and Possibly Related TEAEs Classified by "Other significant" Criteria
(The following table is from the sponsor's submission)

Criteria	Leflunomide N = 23		Methotrexate N = 30	
	All N (%)	Possibly Related N (%)	All N (%)	Possibly Related N (%)
Total Number	5 (21.7)	0	9 (30.0)	3 (10.0)
Discontinuation of study medication	0	0	3 (10.0)	2 (6.7)
Therapy interrupted	0	0	1 (3.3)	0
Intervention other than change in study medication	0	0	1 (3.3)	1 (3.3)
Treated with corrective medication	5 (21.7)	0	6 (20.0)	1 (3.3)
Medically important lab abnormality	0	0	2 (6.7)	1 (3.3)

VIII. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

For the treatment of polyarticular course JRA, the three submitted clinical studies under NDA 20-905, S-012 review included the administration of two different drugs, **leflunomide** and **methotrexate.** Leflunomide is manufactured as 10mg, 20 mg and 100 mg immediate release tablets and is combined with inactive ingredients. Methotrexate is manufactured as a 2.5 mg tablet.

Open-label study HWA486/1037 in patients aged 6 to 17 years, polyarticular course JRA, included the administration of an oral leflunomide loading dose for three days, according to body surface area (BSA) measured in square meters (M^2), based on the adult loading dose of 100 mg/day for 3 days and an average adult BSA of 1.73 M^2. Leflunomide maintenance doses were calculated based on a low adult dose of 10 mg/day and an average adult BSA of 1.73 M^2. In pediatric patients without clinical response on or after 8 weeks, escalation to the equivalent of leflunomide 20 mg/day per 1.73 M^2 BSA was permitted by the investigator.

From the open-label study results, the sponsor adjusted the leflunomide dosing regimen to be based on actual body weight of the pediatric study patients rather than BSA of 1.73 M^2 in Study HWA486/3503 and the Extension Study HWA4686/3504. In Study HWA 468/3503 in patients 3 to 17 years, polyarticular course JRA, were administered oral leflunomide or methotrexate. The leflunomide loading dose (multiple of 100 mg tablets) up to 3 days was 100 mg/day based on actual body weight. Leflunomide maintenance dose 10 mg QOD, 10 mg daily, or 20 mg daily was based on actual body weight. In Study HWA486/3503, the JRA DOI ≥ 30 % responder rate in children weighing less than or equal to 40 kg (n=27) and treated with leflunomide was 59.3 % (16/27) versus children treated with methotrexate was 90.0 % (19/21).

Reviewer comments:
This observation may be dose related. Study HWA486/3503 administered methotrexate at a higher starting dose of 0.5 mg/kg/week, maximum dose of 25 mg per week. The community standard effective dose for methotrexate in children with polyarticular JRA is in the range of 10 to 15 mg/ m^2/week or 0.3 to 0.6 mg/kg/week.

Methotrexate dose was 0.5 mg/kg/week (approximately 15 mg/m^2/week) with a maximum dose was 25 mg/week in Study HWA486/3503 and Study HWA486/3504. Methotrexate is customarily started at 0.3 mg/kg/week in pediatric patients with JRA rather than the higher end of dose range, 0.5 mg/kg/week, in Study HWA 486/3503 and, consequently, Extension Study HWA 486/3504. The methotrexate dose was 0.5 mg/kg/week, maximum 25 mg /week. Methotrexate dose escalation was allowed up to 0.6 mg/kg/week, maximum 30 mg/kg/week by the treating investigator. "The standard effective doses of methotrexate in children with JRA are in the range of 10 to 15 mg/m^2/week or 0.3 to 0.6 mg/kg/week. However, some children seem to tolerate much higher doses than adults, and some series have described using up to 20 to 25 mg/m^2/week or up to 1.1 mg/kg/week in children with resistant disease with relative safety in short term." [1,2,3] The longest term safety of methotrexate therapy at these doses is not known." [3]

Reviewer comments:
The sponsor did not adequately explain why a higher than customary starting dose of methotrexate was administered in these protocols. The reviewer recommends further

IX. Use in Special Populations

A. *Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation*

There does not appear to be any differences in efficacy or safety between genders across the three studies under review. In polyarticular course JRA, the sex ratio of females to males is reported as 3:1. [3] Studies HWA486/1037, Study HWA486/3503 and Study HWA486/3504 include a larger number of females to males as expected from the polyarticular course JRA disease incidence and prevalence. The studies are acceptable in regard to patient's gender and efficacy analyses.

B. *Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy*

Observations by Hanson and colleagues, suggest that in North America there are proportionately fewer black than white children with JRA. Some reports suggest that JRA and RA are less frequent in African than in European populations. [4] The proportions of white versus minority children in the study are consistent with the limited information regarding the racial incidence of JRA.

C. *Evaluation of Pediatric Program*

The studies conducted were specifically targeted for pediatric patients with polyarticular course JRA. The clinical trials studied the subset of polyarticular course JRA patients. Note that none of these trials included children with active pauci-articular or systemic course JRA.

D. *Comments on Data Available or Needed in Other Populations*

medication, such as methotrexate, used in Study HWA486/3503 and Extension Study HWA486/3504.

REFERENCES

1. Reiff A, Shaham B, Wood BP, et al: High dose methotrexate in treatment of refractory juvenile rheumatoid arthritis. Clin Exp Rheumatol 13: 113-118, 1995.

2. Wallace C, Sherry DD: Preliminary report of higher dose methotrexate treatment in juvenile rheumatoid arthritis. J Rheumatol 19: 1604-1607, 1992.

3. Cassidy JT, Petty RE. Textbook of Pediatric Rheumatology, 4 Ed, WB Saunders. 2001, Chapter-Pharmacology and Drug Therapy by Laxer RM, Garzarin M. pp90-146.

4. Hanson V, Korneich HK, Bernstein B, et al: Three subtypes of juvenile rheumatoid arthritis (correlations of age at onset, sex and serologic factors). Arthritis Rheum Suppl 20: 184, 1977. Cassidy J, Petty RE. Textbook of Pediatric Rheumatology, Ed 4, Chapter 12 – Juvenile Rheumatoid Arthritis

X. CONCLUSIONS AND RECOMMENDATIONS

A. CONCLUSIONS

In conclusion, the reviewer concurs that a placebo controlled trial in polyarticular course JRA is not ethically feasible; hence, the study design comparing Arava**(Leflunomide) to an active comparator, methotrexate. In Study HWA 486/3503, Arava **(Leflunomide) did not demonstrate statistical significance against the active comparator, methotrexate, using the co-primary efficacy endpoint, Juvenile Rheumatoid Arthritis Definition of Improvement ≥ 30 % (JRA DOI ≥ 30 %), a responder analysis of JRA published by Giannini et al (1997)[1], in pediatric patients with polyarticular course JRA. In addition, Leflunomide did not perform statistically better than the active comparator, methotrexate, using the adjusted mean Percent Improvement Index analysis. Even though the data did not support the efficacy of leflunomide, compared to methotrexate, the reviewer believes there is important clinical information to be included in the Arava **(Leflunomide) label regarding the outcome of the three studies submitted in NDA 20-905, Supplement-012.

Open label pilot Study HWA 486/1307, based on pharmacokinetic and safety data, demonstrated efficacy according to the JRA DOI ≥ 30 % after 26 Weeks of leflunomide administration. LFT, ALT and/or AST were clinically significant in 6 patients (22.2%); four were reported as AE, one serious. All 6 patients' ALT and AST values normalized over time. The AE profile in Study HWA486/1037 was consistent with AEs most

frequently related to leflunomide therapy in the treatment of adults with rheumatoid arthritis in Phase III placebo-controlled studies (US 301 and MN301).

In Study HWA486/3503, the active comparator, methotrexate, performed statistically better than leflunomide, using the JRA DOI ≥ 30 %, 89.4 % versus 68.1 %, methotrexate versus leflunomide, respectively. Methotrexate was administered at a high dose level, 0.5 mg/kg/wk which is usually not prescribed at the initiation of methotrexate therapy in pediatric patients with polyarticular course JRA. This study results suggest that the high methotrexate dose selected may have resulted in the smaller (≤ 40 kg) and younger (< 12 years of age) methotrexate patients having the greatest difference in efficacy compared to leflunomide while also having the highest incidence of ALT elevations > 3 x ULN. Younger, lighter-weight patients showed a better response than older, heavier patients to methotrexate treatment. These differences in mean change from baseline were not statistically significant but suggest a trend toward improved response in children

Similarly, in the same Study HWA486/3503, using the other co-primary endpoint, Percent Improvement Index, results were essentially the same for both treatment groups at Week 4 of treatment. At Week 16 the difference was 8.46 %, numerically favoring methotrexate but not statistically significant. There were not statistically significant differences between treatment groups in the changes from baseline of the 6 core set variables that are the components of the Percent Improvement Index and JRA DOI ≥ 30 %. Improvement in physical function, Childhood Health Assessment Questionnaire Disability Index (CHAQ DI), well exceeded the minimum clinically important difference of 0.13 in both treatment groups. Among the leflunomide patients, sex, age, disease duration and the number of swollen joints, weight and site location (by continent) had no apparent influence on the Percent Improvement Index data.

In further analysis, the <20 kg and 20-40 kg weight groups were combined because 8/8 (100 %) of the methotrexate patients < 20 kg were responders, creating a non-calculable odds ratio for that weight group. In the leflunomide group < 20 kg weight group, 5/8 (62.5 %) were responders. The responder rate was 11/19 patients (57.9 %) for the leflunomide 20-40 kg subgroup and 11/13 patients (84.6 %) for the methotrexate 20-40 kg subgroup. Therefore, the < 20 kg weight group had the highest JRA DOI ≥ 30 % responder rate to methotrexate, as was also seen in the Percent Improvement Index and the difference in response to leflunomide and methotrexate treatment was most apparent in the smallest weight group. There was a difference of 20 % in responder rates between smaller (≤ 40 kg) and heavier (> 40 kg) leflunomide patients with [illegible] patients achieving JRA DOI ≥ 30 %. T

Both drugs had clinically important improvement in physical function as measured by the CHAQ DI with no difference between treatment groups even though the smaller of the leflunomide patients were dosed conservatively relative to the larger patients.

Upon entering the extension Study HWA486/3504 at week 16, according the to JRA DOI ≥ 30 %, the methotrexate group had a higher response rate than the leflunomide group, 88.5 % versus 69.6%, respectively. The JRA DOI ≥ 30 % responder rate for the leflunomide patients was higher than that for the methotrexate patients at week 24, although this difference was not statistically significant. By week 24, differences in DOI ≥ 50 % and DOI ≥ 70 % were no longer present, although the leflunomide DOI ≥ 50 % responder rate numerically exceeded that of methotrexate.

Furthermore, in the extension phase of Study HWA486/3504, the Percent Improvement Index was unchanged in the leflunomide treatment group between week 16 and 24 time points, hence durability over the 8 weeks. Methotrexate patients showed less improvement from baseline at week 24 relative to week 16, without statistical significance. No leflunomide patients discontinued study drug due to an AE; 3 methotrexate patients discontinued due to an AE. In 2 of these patients the events were assessed as possibly related to study drug. The incidence of total TEAEs was higher in the methotrexate group (36.7 %, 11 patients) than in the leflunomide group (26.1%, 6 patients).

The safety profile was generally more favorable with methotrexate in this pediatric population with the exception of ALT elevations. Hepatotoxicity is a well known risk factor for both of these drugs. The younger and smaller of the methotrexate patients, who had the highest efficacy, also had the highest incidence of ALT elevations >3 x ULN. No leflunomide patients were discontinued from the extension due to an adverse event; 3 methotrexate patients were discontinued due to an adverse event occurring within the time frame of the IDS analysis.

C. RECOMMENDATIONS

XI. APPENDIX

A. Other Relevant Materials

A.1. Serious Adverse Events (SAE) for Study HWA 486/1037, Study HWA486/3503 and Study HWA486/3504.

Subject age (yrs) sex wt (kg) country drug (mg)[a] plasma conc[b]	Serious adverse event	AE On-set day no.	Related/ intensity[9]/ SAE criteria/ drug action/ resolved	Description
Study 1037 (n=7)				
59001 15 F 29.6	Cellulitis	299	Yes/-/hosp; medical imp/inter/ yes	Subject developed cellulitis left foot after 42 wks treatment (10 mg/day x 8 wks, increased to 15 mg/day due to lack of efficacy. Drug interrupted, cholestyramine washout done, subject hospitalized for aspiration, antibiotic therapy. Event resolved in 7 days.. Drug restarted No recurrence of event
	Elevated liver enzymes	462	Yes/-/ medical imp/inter/ yes	The subject had elevated liver enzymes on Day 462 (02May00) for 10 days. Local laboratory data revealed ALT (5.8xULN), AST (6.7xULN), and alkaline phosphatase (4.5xULN) levels that precipitated study drug (LEF) interruption 3 days later; washout followed. Concomitant naproxyn was disc. Central laboratory data (05May00) also revealed elevated ALT (8.2xULN). Alcohol ingestion occurred 4-6 days before 1st event. Epstein-Barr titers were positive, but no clinical symptoms other than pruritic rash with excoriations and petechiae. The event was assessed as possibly related by the investigator. The event resolved in 13 days with normal ALT and AST and decreased alkaline phosphatase to 1.8xULN. Study drug was re-loaded 18 days after event.
	Petechiae skin rash	462	Yes/-/ medical imp/inter/ yes	Coincident with elevated ALT, AST. Treated with loratidine and resolved. Investigator questioned whether petechiae secondary to scratching rash.
	Hypertension	863	Yes/-/ medical imp/discon/yes	After 28 months, developed hypertension (173-178/ 100-111. Drug discontinued, methotrexate begun. Hypertension resolved with amlodipine.
59002 16 F 49.9	Valgus deformity right lower extremity	528	No/-/hosp/no change/yes	Valgus deformity present on enrollment into study. After 75 weeks treatment with study drug, hospitalized for osteotomy of right tibia and fibula. Investigator assessed event as not related to study drug.
59004 16 F 38.4	Stress fracture right femur	277	Yes/-/hosp; medical imp/inter/ yes	Developed stress fracture after 9 months treatment with study drug. Hospitalized for joint aspiration Rt. knee, drug interrupted. Event resolved in 21 days, drug restarted. Event associated with prolonged corticosteroid use, increased activity, low dietary intake.
	Adjustment disorder with depression	596	No/-/hosp/no change/yes	Suicide attempt resulting in hospitalization for 24 hours. Evidence of several psychosocial stressors plus history of dysfunctional behavior and depression.
59005 9 F not app	JRA flare	-44[f]	No/-/hosp; medical imp/NA/yes	Hospitalized for flare before beginning treatment with leflunomide and after discontinuing methotrexate. Event resolved within 14 days. Prior history of multiple flares.

Study 1037 (n=7)				
61001 13 F [illegible] 41.4	Possible gastritis	58	Yes/-/hosp/inter/yes	Developed worsening of GERD symptoms, possible gastritis 1 day after dose increased from 10 to 15 mg/day due to lack of efficacy. Drug interrupted x 7 days events resolved after treatment with triamcinolone and domperidone. Previous history of GERD, gastrointestinal upset.
	Appendicitis	401	No/-/medical imp inter/yes	Presented with acute appendicitis after 401 days on drug. Drug temporarily interrupted; subject hospitalized for appendectomy. Study drug restarted at 10 mg/day 5 days after resolution of event.
62001 12 F [illegible] 127.6	Anemia	113	No/-/ medical imp/inter/ yes	Developed moderate anemia after 29 days of drug at 10 mg/day. Resolved without countermeasures in 16 days. Serious anemia (HCT 20%, HGB 64%) developed 68 days later after increase to 20 mg/day 56 days before. Steroid pulse given 1 month before for HCT 23.5%, HGB 69 g/L. Steroid pulse given again; event resolved after 31 days and did not recur.
63001 14 F [illegible] 49.6	Worsening degenerative left hip disease	352	No/-/hosp/ inter/yes	Received study drug x 1 year before developing worsening degenerative disease left hip. Study drug interrupted x 3 days, subject hospitalized for hip arthroplasty, total hip replacement. Event not related to study drug.
	Worsening degenerative right hip disease	461	No/-/hosp/ inter/yes	After 15 months of study treatment, she developed worsening right hip degenerative disease, hospitalized for right hip replacement. Study drug interrupted while subject in hospital. Event not related to study drug

Study 3503 (n=10)				
0103003 6 F 23.8 200;10 98.9	Facial cellulitis	19	No/mild/ hosp/inter/ yes	The subject had facial cellulitis on study Day 19, [redacted] due to a tooth abscess. Because of the cellulitis, she was hospitalized for i.v. clindamycin. The facial cellulitis and the underlying tooth abscess resolved after 5 days, on [redacted] Study drug (LEF) was interrupted for 3 days during the hospitalization. Oral Augmentin was given 28Jan to 03Feb03. The event was assessed as not related to study drug. The subject completed the study and entered the extension.
0303003 11 F 34.2 [redacted] 200;10 18.5	Worsening of JRA	78	No/mod/ hosp/no change/yes	The subject had worsening of arthritis on Day 78 [redacted] She completed the study with no change in study drug (LEF). At the week 16 final study visit, 16Jan03, she had further worsening in the knee and wrists and was hospitalized for i.v. methylprednisolone and i.a. corticosteroids. She did not enter the extension study. The event resolved 4 months post-study, and the investigator assessed it as not related to study drug but to very aggressive arthritis.
0501002 10 F 47.5 300;20 83.0	Pityriasis lichenoides (parapsoriasis)	91	Yes/severe /important/ discon/no	The subject had a pruritic, papular, excoriated, ulcerative rash on Day 91, 03Apr03, diagnosed initially as urticarial vasculitis then changed to pityriasis lichenoides based on dermatology consultation (parapsoriasis). Study drug (LEF) was discontinued on Day 110 due to the event, assessed as possibly related by the investigator but not drug-related by the dermatologist report. The event was ongoing but improved. Biopsy results available later showed nonspecific findings.
0603001 4 M 12.8 100;10 QOD 17.1	Fever of viral origin	60	No/mild/hosp/inter/yes	The subject was hospitalized for mild fever on [redacted] diagnosed as fever of viral origin not related to study drug (LEF). Hospital lab reported elevated CRP, platelet count, and WBC count (13.2 G/L with 2% hyperbasophilic lymphocytes). For 3 days, study drug was interrupted, and i.v gentamicin and amoxicillin were given as prophylaxis for bacteremia. He recovered in 3 days with normal WBC count and decreased CRP. He completed the study and entered the extension.
0606002 12 M 61.2 300;20 24.5	Fractured tibia	35	No/mod/ important/ no change/ yes	The subject suffered trauma during volleyball on [redacted] and tibial fracture was diagnosed in the emergency room. He was released to recover at home with prn paracetamol in addition to his background naproxen 550mg daily. He recovered after [redacted] He completed the study with no change in study drug (LEF) and entered the extension. The investigator assessed the event as medically important and not related to study drug.
0701002 10 F 44.7 300;20 40.9	Worsening of JRA (right wrist)	45	No/mild/ hosp/ no change/ yes	The subject had progressive swelling and effusion of the wrist recorded as mild on [redacted] She was hospitalized that day for intensified physiotherapy and i.a. corticosteroid injection. The subject recovered and was discharged 10 days later on d[redacted] he subject completed the study without change in study drug (LEF) and entered the extension study. The investigator assessed the event as not related to study drug.

Study 3503 (n=10)				
0706001 14 F 53.4 300;20 37.0	ALT elevated AST elevated	22	Yes/severe/hosp; important/ discon/yes	On Day 22, 02Aug02, ALT was 7.4xULN, AST 3.1xULN, alkaline phosphatase and bilirubin normal. On 06Aug02, ALT was 4.6xULN; AST was 1.3xULN. Study drug (LEF) was discontinued day 28, 08Aug. Assessment was treatment related. Due to distance, she was hospitali[illegible] cholestyramine. ALT was 2xULN by 13Aug. ALT and AST were normal after 48 days, on18Sep. Voltaren was taken 10,12,17July. Paracetamol ± codeine taken 19-25 July was co-suspect.
0901006 5 F 21.7 200;10 30.3	Viral resp. infection	114	No/mod/ important/ inter/yes	The subject had a viral respiratory infection with fever and cough on Day 114, 11Apr03, treated with amoxicillin-clavulanate. On 15Apr03, she completed the study and entered the extension. Lab from 15Apr03 revealed ALT 2.9x and AST 3.5xULN, WBC 2.32 G/L, neutrophils 0.74 G/L, and CRP 3.54 reported as secondary to the infection, which was assessed as medically important and not related to study drug (LEF). On 23Apr03, ALT was 1.5xULN and the other labs normal. Study drug was interrupted from 23Apr to 13May03, at which time the event was resolved and ALT normal.
1101007 13 M 38.8 200;10 26.2	Crohn's disease	50	No/mod/ hosp; important/ discon/no	The subject had moderate abdominal pain and slightly bloody diarrhea onset [illegible] with increased WBC/platelet counts and CRP. Hospitalization for colonoscopy/biopsy revealed Crohn's disease. Study drug (LEF) was discontinued on day 64, [illegible]e event was ongoing at follow-up on prednisone treatment. The mother also has Crohn's disease. It was assessed as not related to study drug but due to evolution of Crohn's disease as the etiology of his arthritis.
1201002 15 F 70.0 300;20 33.8	Suspected salmonellosis	40-44	Yes/mild/ hosp/ no change/ yes	The subject had mild nausea, diarrhea, abdominal pain, fever on Days 40-44, 15-19Sep02, diagnosed as suspected salmonellosis possibly related to study drug (LEF). Omeprazole was initiated 18Sep02. [illegible]e was hospitalized for evaluation. Stool/ blood cultures were negative. There was serologic evidence of past salmonellosis but not acute infection. She was given prophylactic ciprofloxacin. She completed the study and enrolled in the extension study.

Study 3504 (n=5)				
0606002 12 M [redacted] LEF: 20 not app	Abdominal pain NOS	148	No/mod/hosp/ no change /yes	This subject with serious adverse event of fractured tibia fracture during Study 3503 also had a serious adverse event in extension Study 3504. On Day 148 (04Feb03), he had abdominal pain and was hospitalized; slight hepatomegaly was noted. No abnormal liver tests found. Abdominal X-ray evidenced stercorous stasis (fecal impaction); a rectal irrigating enema was performed. On [redacted] the subject was discharged with the event resolved. The event was assessed as not related by the investigator. Study drug (LEF) was not interrupted.
0501001 9 F 23.6 [redacted] MTX: 12.5 QW not app	Liver function test abnormal	183	Yes/mod/ medical imp/ disc/yes	The subject had ALT 3.4xULN on Day 183 (02Jan03), with no other physical signs or symptoms and study drug (MTX) was not interrupted. Several months later, on 24Apr03, ALT was 5.4xULN and AST 1.4xULN. Alkaline phosphatase on 29Apr03 was 1.2xULN. Study drug was discontinued (28Apr03); there was no washout. 22May03 laboratory data show ALT, AST within normal range; alkaline phosphatase 1.1xULN. The event was assessed as possibly related by the investigator.
0601002 8 F 24.0 [redacted] MTX: 12.5 QW not app	Gastrointestinal disturbance (codes to Gastrointestinal disorder NOS)	112	Yes/severe/ hosp/ disc/yes	On Day [redacted] the subject had malaise, abdominal pain, vomiting, fever, and a purple toenail. This subject had cutaneous lesions on the toes that suggested vasculitis during Study 3503 reported as erythema of the toes. She was hospitalized for they symptoms and study drug (MTX) was discontinued followed by cholestyramine, I.V. fluids, and domperidone. The gastrointestinal event was assessed as possibly related by the investigator. The event was resolved on [redacted] Dermatologist's exam suspected the cutaneous lesions beginning in 3503 may have been vasculitis (dated: 27Feb03) although the investigator did not change the previous diagnosis.
0603005 5 F 15.4 [redacted] MTX: 7.5 QW not app	ALT increased AST increased	120	No/mild/ medically imp/ disc/yes	This subject with an alert term AE of increased LFTs during Study 3503 had worsening of ALT and AST reported as serious adverse events in extension Study 3504. On 11Apr 03, elevated ALT (6.6xULN) and AST (4.1xULN) revealed no clinical manifestations and no elevated alkaline phosphatase or bilirubin. Study drug (MTX) was continued. On 17Apr03, elevated ALT (12.6xULN) and AST (5.0xULN) lead to a discontinuation of study drug (MTX) on 19Apr03. On 29Apr03, the ALT was 3.5xULN; the AST was 3.5xULN. Epstein-Barr viral serology was IgM positive. The event was assessed as not related to drug by the investigator but related to EBV infection reported as a 3503 AE. The event was resolved.
0701001 13 F 60.5 [redacted] MTX: 25 QW not app	Joint effusion (Baker's cyst) coding to Bursitis	171	No/mod/ hosp/ no change/yes	The subject had a history of resection of Baker's cyst on the left knee. During the extension study, on Day 171, she developed effusion and Baker's cyst of right knee occurring [redacted] She was hospitalized and arthrocentesis with IA injection (triamcinolone) was performed with recove[redacted]The event was assessed as not related by the investigator. On 28Oct03 she had the same occur in the left knee but was not hospitalized. Study drug (MTX) was not interrupted. The event was resolved.

A. 2. Adverse Events for Study HWA486/1037, Study HWA486/3503 and Study HWA486/3504

Table 4 – TEAEs reported in ≥2 subjects in Studies 1037, 3503 and 3504

Adverse event [n (%)]	Study 1037 (N=27)		Study 3503				Study 3504	
			LEF (N=47)		MTX (N=47)		LEF (N=23)	MTX (N=30)
	All	Poss related	All	Poss related	All	Poss related	All	All
Total no. subjects [n (%)]	**26 (96.3)**	**26 (96.3)**	**43 (91.5)**	**30 (63.8)**	**38 (80.9)**	**21 (44.7)**	**6 (26.1)**	**11 (36.7)**
Headache	17 (63.0)	13 (48.1)	18 (38.3)	8 (17.0)	11 (23.4)	5 (10.6)	0 (0.0)	1 (3.3)
Abdominal pain[a]	11 (40.7)	8 (29.6)	12 (25.5)	5 (10.6)	5 (10.6)	4 (8.5)	1 (4.3)	1 (3.3)
Nasopharyngitis	0 (0.0)	0 (0.0)	12 (25.5)	4 (8.5)	3 (6.4)	1 (2.1)	1 (4.3)	0 (0.0)
Nausea	10 (37.0)	8 (29.6)	10 (21.3)	9 (19.1)	12 (25.5)	7 (14.9)	0 (0.0)	0 (0.0)
Alopecia	8 (29.6)	8 (29.6)	7 (14.9)	7 (14.9)	3 (6.4)	2 (4.3)	1 (4.3)	0 (0.0)
Diarrhea	10 (37.0)	7 (25.9)	7 (14.9)	3 (6.4)	8 (17.0)	3 (6.4)	0 (0.0)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	6 (12.8)	0 (0.0)	2 (4.3)	1 (2.1)	1 (4.3)	0 (0.0)
Cough	7 (25.9)	5 (18.5)	5 (10.6)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	4 (14.8)	1 (3.7)	5 (10.6)	2 (4.3)	5 (10.6)	2 (4.3)	0 (0.0)	1 (3.3)
Pharyngolaryngeal pain	-	-	4 (8.5)	2 (4.3)	4 (8.5)	1 (2.1)	1 (4.3)	0 (0.0)
Pyrexia or fever	3 (11.1)	2 (7.4)	4 (8.5)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	1 (3.3)
Arthralgia	4 (14.8)	4 (14.8)	3 (6.4)	1 (2.1)	2 (4.3)	0 (0.0)	2 (8.7)	2 (6.7)
Conjunctivitis	3 (11.1)	2 (7.4)	3 (6.4)	0 (0.0)	2 (4.3)	0(0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	6 (22.2)	0 (0.0)	3 (6.4)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	7 (25.9)	6 (22.2)	3 (6.4)	1 (2.1)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)
JRA worsening[b]	10 (37.0)	2 (7.4)	3 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Overdose	-	-	3 (6.4)	3 (6.4)	3 (6.4)	1 (2.1)	0 (0.0)	0 (0.0)
Rash	9 (33.3)	5 (18.5)	3 (6.4)	1 (2.1)	3 (6.4)	0 (0.0)	0 (0.0)	1 (3.3)
Rhinitis	7 (25.9)	5 (18.5)	3 (6.4)	1 (2.1)	1 (2.1)	0 (0.0)	1 (4.3)	0 (0.0)
Respiratory infection[c]	17 (63.0)	8 (29.6)	3 (6.4)	1 (2.1)	6 (12.8)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain, upper[d]	5 (18.5)	4 (14.8)	2 (4.3)	1 (2.1)	6 (12.8)	1 (2.1)	0 (0.0)	0 (0.0)
Acute tonsillitis	-	-	2 (4.3)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased	1 (3.7)	1 (3.7)	2 (4.3)	1 (2.1)	2 (4.3)	2 (4.3)	0 (0.0)	0 (0.0)
Arthritis	1 (3.7)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	1 (3.7)	1 (3.7)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine increased	-	-	2 (4.3)	2 (4.3)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)
Dyspepsia	4 (14.8)	4 (14.8)	2 (4.3)	2 (4.3)	1 (2.1)	0 (0.0)	1 (4.3)	0 (0.0)
Fatigue	-	-	2 (4.3)	1 (2.1)	4 (8.5)	2 (4.3)	1 (4.3)	1 (3.3)
Impetigo	-	-	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver function test abnormal	3 (11.1)	3 (11.1)	2 (4.3)	2 (4.3)	2 (4.3)	1 (2.1)	0 (0.0)	1 (3.3)
Platelet count increased	-	-	2 (4.3)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	2 (7.4)	1 (3.7)	1 (2.1)	0 (0.0)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)
Contusion	-	-	0 (0.0)	0 (0.0)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)
Excoriation	-	-	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	1 (3/3)
Herpes simplex	1 (3.7)	1 (3.7)	1 (2.1)	1 (2.1)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Joint sprain	-	-	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis media	3 (11.1)	2 (7.4)	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	1 (3.3)
Infection, unspecified	3 (11.1)	2 (7.4)	-	-	-	-	-	-
Pharyngitis[e]	7 (25.9)	4(14.8)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flu syndrome[f]	6 (22.2)	4 (14.8)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	6 (22.2)	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Mouth ulcerations	6 (22.2)	4 (14.8)	1 (2.1)	1 (2.1)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)
Pain NOS	6 (22.2)	3 (11.1)	-	-	-	-	-	-
Accidental injury[g]	4 (14.8)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	4 (14.8)	4 (14.8)	1 (2.1)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ecchymosis	4 (14.8)	3 (11.1)	-	-	-	-	-	-
Myalgia	4 (14.8)	2 (7.4)	-	-	-	-	-	-
Contact dermatitis	3 (11.1)	1 (3.7)	-	-	-	-	-	-
Insomnia	3 (11.1)	2 (7.4)	-	-	-	-	-	-
Lymphadenopathy	3 (11.1)	1 (3.7)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	3 (11.1)	0 (0.0)	-	-	-	-	-	-

Table 4 TEAEs reported in ≥2 subjects in extension Studies 1037, 3503 and 3504 –(cont'd)

Adverse event [n (%)]	Study 1037 (N=27)		Study 3503				Study 3504	
			LEF (N=47)		MTX (N=47)		LEF (N=23)	MTX (N=30)
	All	Poss related	All	Poss related	All	Poss related	All	All
Total no. subjects [n (%)]	26 (96.3)	26 (96.3)	43 (91.5)	30 (63.8)	38 (80.9)	21 (44.7)	2 (8.7)	3 (10.1)
Nail disorder[h]	3 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vesicular bullous rash	3 (11.1)	1 (3.7)	-	-	-	-	-	-
Anorexia	2 (7.4)	2 (7.4)	1 (2.1)	1 (2.1)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)
Asthenia	2 (7.4)	2 (7.4)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	2 (7.4)	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	1 (4.3)	0 (0.0)
Cramps (leg)	2 (7.4)	1 (3.7)	-	-	-	-	-	-
Flatulence	2 (7.4)	1 (3.7)	-	-	-	-	-	-
Hypercholesteremia	2 (7.4)	1 (3.7)	-	-	-	-	-	-
Hyperlipemia	2 (7.4)	2 (7.4)	-	-	-	-	-	-
Hypesthesia	2 (7.4)	1 (3.7)	-	-	-	-	-	-
Migraine	2 (7.4)	2 (7.4)	-	-	-	-	-	-
Pain (back)	2 (7.4)	2 (7.4)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain (chest)	1 (3.7)	1 (3.7)	-	-	-	-	-	-
Pain (eye)	2 (7.4)	1 (3.7)	-	-	-	-	-	-
Pharyngitis'	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)	4 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)
Synovitis	2 (7.4)	0 (0.0)	-	-	-	-	-	-
Urticaria	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Uveitis	2 (7.4)	1 (3.7)	-	-	-	-	-	-
Weight decreased	2 (7.4)	1 (3.7)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhea	-	-	0 (0.0)	0 (0.0)	4 (8.5)	0 (0.0)	0 (0.0)	1 (3.3)
Papular rash	-	-	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)

B. Clinical Sites/Investigators and Study Visits/Schedules

B.1. a. Study HWA486/1037, Clinical Sites and Investigators

(The following table is from the sponsor's submission)

5 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

Screening visit (weeks –3 to 0)	Informed consent Evaluation for inclusion/exclusion criteria History and physical exam Joint examination Screening laboratory tests: antinuclear antibodies (ANA), varicella, hepatitis B and C, rheumatoid factor, chemistry, hematology, serum pregnancy, urinalysis
Baseline visit (Visit 1) Randomization visit	History and physical, including medications, global assessment Joint examination Laboratory tests: chemistry, hematology, serum pregnancy, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urinalysis Administer CHAQ Perform physician's global assessment Evaluate for adverse events (AEs) Dispense medications, instruct in use Provide subject logs
Visit 2 (week 2 ± 5 days)	Physical examination Laboratory tests: chemistry, hematology, serum pregnancy, PK, urinalysis Evaluate for AEs
Visits 3 (week 4), 4 (week 8), 5 (week 12), 6 (week 16)	Physical examination Joint examination Physician's global assessment Administer CHAQ Laboratory tests: chemistry, hematology, serum pregnancy, PK, CRP, ESR, urinalysis Evaluate for adverse events Evaluate concomitant medication usage Dispense medications (weeks 6, 10, 14 in Finland, CBC and ALT/AST values obtained)

B. 3. INDIVIDUAL MORE DETAILED STUDY REVIEWS (IF PERFORMED)

No additional detailed study reviews were performed.

B. 4. a. Study HWA486/3504, Clinical Sites/Investigators are from the same list of Clinical Sites/Investigators for Study HWA 486/3503. See B. 1. b.

B. 4. b. Study HWA 486/3503, Study Visits/Schedule
(The following table is from the sponsor's submission.)

Screening visit (weeks –3 to 0)	Informed consent Evaluation for inclusion/exclusion criteria History and physical exam Joint examination Screening laboratory tests: antinuclear antibodies (ANA), varicella, hepatitis B and C, rheumatoid factor, chemistry, hematology, serum pregnancy, urinalysis
Baseline visit (Visit 1) Randomization visit	History and physical, including medications, global assessment Joint examination Laboratory tests: chemistry, hematology, serum pregnancy, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urinalysis Administer CHAQ Perform physician's global assessment Evaluate for adverse events (AEs) Dispense medications, instruct in use Provide subject logs
Visit 2 (week 2 ± 5 days)	Physical examination Laboratory tests: chemistry, hematology, serum pregnancy, PK, urinalysis Evaluate for AEs
Visits 3 (week 4), 4 (week 8), 5 (week 12), 6 (week 16)	Physical examination Joint examination Physician's global assessment Administer CHAQ Laboratory tests: chemistry, hematology, serum pregnancy, PK, CRP, ESR, urinalysis Evaluate for adverse events Evaluate concomitant medication usage Dispense medications (weeks 6, 10, 14 in Finland, CBC and ALT/AST values obtained)

At every visit patient diaries were evaluated for incidence of adverse events, medication compliance, recording of dates and times of medication administration, use of concomitant medications. At the completion of the study all patients were given the option of continuing on their double-blind regimen for an additional eight months in extension protocol HWA 486/3504

For patients not continuing in the extension protocol, the study site contacted each patient by telephone for a safety follow-up four weeks after the patient completed the study or terminated early. Any serious or non-serious adverse events were reported using the form located in the CRF and with a visit to the study site, if indicated, and with follow-up laboratory evaluation for any abnormal values at the final study visit or, if clinically indicated.

C. 4. c. Study HWA486/3504 Study Visits/Schedule is unchanged from Study HWA486/3503.

D. Arava®(Leflunomide) label with proposed changes

See Addendum to the Review for the package insert.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carolyn L. Yancey
3/5/04 04:47:07 PM
MEDICAL OFFICER

James Witter
3/5/04 05:07:05 PM
MEDICAL OFFICER
Congrats on first NDA-concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	N20-905/SE012
Drug Name:	AVARA™ (leflunomide 20 mg)
Indication(s):	Rheumatoid Arthritis
Applicant:	Aventis Pharmaceuticals, Inc.
Date(s):	Received: October 1, 2003
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Suktae Choi, Ph.D.
Concurring Reviewers:	Stan Lin, Ph.D.
Medical Division:	Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)
Clinical Team:	Carolyn Yancey, M.D.
Project Manager:	Jane Dean

Keywords: Active Control/Superiority, Clinical Studies, Confidence Interval

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This NDA supplement failed to establish the efficacy of leflunomide comparing to methotrexate in treatment of JRA. The efficacy results demonstrated statistical superiority of methodtrexate for DOI 30% responder rate which is one of two co-primary efficacy variables. The other co-primary efficacy variable, % Improvement Index, showed in favor of methotrexate but the difference was not statistically significant.

1.2 Brief Overview of Clinical Studies

This submission is being made to supplement the current approved NDA with pediatric data pertaining to the clinical utility of leflunomide in juvenile reheumatiod arthritis. The sponsor submitted three studies (1037, 3503, and 3504) under the pediatric program. Study 1037 was an open-label, non-controlled, five-centers, Phase IB study over a 6 month treatment period with up to a 24-month extension phase. Study 3503 was a randomized, double blind, parallel group 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve. This study was originally planned 240 subjects (120 per treatment group) for a non-inferiority design, but amended to 94 (47 per group) because of the difficulty of recruitment. Study 3504 was an eight month extension of study 3503 and still ongoing. This review will focus only on study 3503.

In study 3503, following efficacy variables were observed at screening, baseline, week 4, 8, 12, and 16: Percent Improvement Index and JRA DOI $\geq$ 30% responder status using the 6 core set measures of the JRA Definition of Improvement. Additional response assessments were time to response, DOI $\geq$ 30%, $\geq$ 50%, and $\geq$ 70% responder-at-endpoint rates, AUC, physician's global assessment, subject/parent global assessment, number of active joints, number of joints with limitation of motion plus pain and/or tenderness, functional assessment (CHAQ), ESR, CRP, and pain score.

1.3 Statistical Issues and Findings

- Methotrexate performed statistically better than leflunomide as measured by the JRA DOI $\geq$ 30% responder rate. The rate in the methotrexate group was 89.4% vs. 68.1 % in the leflunomide group. P-value is 0.0091 and 95% Confidence Interval of the difference is (-37.3%, -5.3%).

- The percent Improvement Index demonstrated no significant difference between treatment groups at week 16, LS Mean improvement was –44.41% (SE4.51) in the leflunomide group and –52.87% (SE4.39) in the methotrexate group.

- JRA DOI ≥ 30% responder rate was requested to add as a primary efficacy variable by agency, because this variable is one of the most commonly used efficacy variable. In fact, percent Improvement Index is rarely used as a primary efficacy variable.

- Secondary analyses showed similar results with primary analyses. All the secondary efficacy variables at week 16 showed in favor of methotrexate compared with leflunomide except CHAQ, and some of them showed significant differences. At week 4, 8, 12, and 16, majority of them showed in favor of methotrexate.

- Since both primary efficacy variables showed in favor of methotrexate, and one of them showed significant difference, we cannot conclude that the efficacy of leflunomide is as good as the efficacy of methotrexate in this study.

2. INTRODUCTION

2.1 Overview

This submission is being made to supplement the current approved NDA with pediatric data pertaining to the clinical utility of leflunomide in juvenile reheumatiod arthritis. The sponsor submitted three studies (1037, 3503, and 3504) under the pediatric program. Study 1037 was an open-label, non-controlled, five-centers, Phase IB study over a 6 month treatment period with up to a 24-month extension phase. Study 3503 was a randomized, double blind, parallel group 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve. This study was originally planned 240 subjects (120 per treatment group) for a non-inferiority design, but amended to 94 (47 per group) because of the difficulty of recruitment. Study 3504 was an eight month extension of study 3503 and still ongoing. This review will focus only on study 3503.

2.2 Data Sources

Hard Copies: Volume 1 through 7 submitted 10/1/2003

Electric files: \\CDSESUB1\N20905\S_012\2003-09-30

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The study was a multinational, multicenter, two arms, double-blind, double-dummy, randomized, parallel, and active controlled study. Duration was 16 weeks. Among 103 patients screened, 94 were randomized (47 per each group). Patients were between the ages of 3-17 years. Visits were at week 4, 8, 12 and 16.

Dosage schedule

Randomized to leflunomide: each subject received a leflunomide loading dose ranging from one 100 mg tablet /day for 1 day to one 100 mg tablet /day for 3 consecutive days, depending on body weight. Thereafter, subjects received a maintenance dose of 10 mg every other day, 10 mg daily, or two-10 mg tablets daily (20 mg daily), depending on weight. Detail of dosage schedule is summarized in Table 1 of appendix. Subjects also received methotrexate placebo tablets weekly based on body weight.
Randomized to methotrexate: each subject received methotrexate 2.5 mg tablets weekly, based on body weight, for a dose of 0.5 mg/kg/wk to a maximum of 25 mg/wk. If the calculated methotrexate dose was not a multiple of 2.5 mg, the subject was dosed at the closest whole number of methotrexate tablets. Subjects also received leflunomide placebo.

For those children who were unable to swallow a tablet, tablets were permitted to be crushed and mixed in applesauce or jam.

Efficacy data

Primary efficacy variables:
1. JRA DOI $\geq$ 30% responder rate at week 16
2. Percent Improvement Index at week 16

Percent Improvement Index is defined as follow:
- This variable is based on the JRA DOI's 6 core set measures.
- For each subject, the % Improvement Index was the mean of the 6 core set percent changes from baseline.
  The percent change from baseline to end of treatment was calculated as follows:

(value at end of treatment – value at baseline)/value at baseline x 100

- In the event that the mean percent change was positive (worsened), then the % Improvement Index for that subject was set to zero.

Secondary efficacy variables:

1. JRA DOI $\geq$ 50% and $\geq$ 70% responder rates
2. JRA DOI $\geq$ 30%, $\geq$ 50%, and $\geq$ 70% responder-at-endpoint rates (this variable considers non-completers as not responders)
3. AUC of DOI $\geq$ 30%, $\geq$ 50%, and $\geq$ 70% responses: Months of response
4. Time to JRA DOI 30% response
5. Physician global assessment of disease activity
6. Patient/parent global assessment of disease activity
7. Number of active joints
8. Joints with limited range of motion
9. CHAQ disability index
10. Erythrocyte sedimentation rate (ESR)
11. Pain score
12. C-reactive protein (CRP)

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 2 and Table 3 of appendix, two treatment groups are similar in disposition and in key demographic characteristics. Primary disease were compared between two treatment groups at baseline by sponsor, and the variables were JRA type at onset, JRA duration, Active joint count, Limited ROM joint count, MD global assessment score, Patient global assessment, Disability index, ESR, CRP, and Pain score, but none of them showed significant difference.

3.1.3 Statistical Methodologies

The following inferential null hypothesis was tested:

H_0: no treatment difference between leflunomide and methotrexate for JRA DOI 30% Responder rate at endpoint (or mean % Improvement Index).

H_1: treatment difference between leflunomide and methotrexate for JRA DOI 30% Responder rate at endpoint (or mean % Improvement Index).

The null hypothesis H_0 will be tested against the alternative H_1 two-sided with α=0.05. Since both comparisons have to show significant difference, multiple comparison adjustment is not necessary.

For the analysis for JRA DOI 30% Responder at Endpoint, the difference of responder rates of treatment groups was supposed to be compared using the normal approximation in

statistical analysis plan (Appendix B of sponsor's NDA submission). However, in the sponsor's NDA final report, CMH method was used to calculate p-values, which was not specified in the statistical analysis plan. The p-values using the protocol specified method were calculated by this reviewer and replaced with CMH p-values in this review, because the primary analysis must be the one specified in the protocol.

For the analysis of % Improvement Index, ANOVA was used on the mean % Improvement Index with treatment and country as fixed effects. This was specified in the statistical analysis plan.

For secondary analyses, 95% CI of responder rate difference between treatment groups using normal approximation was used for binary variables (p-values are correspondent to this CI), and ANCOVA with factors of treatment and baseline was used for changes from baseline continuous variables.

ITT was used in efficacy analyses for primary population, and LOCF was used as an imputation method for early dropout for all the efficacy analysis as specified in the protocol.

3.1.4 Results and Conclusions

- Methotrexate performed statistically better than leflunomide as measured by the JRA DOI $\geq$ 30% responder rate. The rate in the methotrexate group was 89.4% vs. 68.1 % in the leflunomide group. P-value is 0.0091 and 95% Confidence Interval of the difference is (-37.3%, -5.3%). The comparison results during the study period are summarized in Table 4 and Figure 1.

- The percent Improvement Index demonstrated no significant difference between treatment groups at week 16, LS Mean improvement was –44.41% (SE4.51) in the leflunomide group and –52.87% (SE4.39) in the methotrexate group. The comparison results during the study period are summarized in Table 5 and Figure 2.

- JRA DOI $\geq$ 30% responder rate was requested to add as a primary efficacy variable by agency, because this variable is one of the most commonly used efficacy variable. In fact, percent Improvement Index is rarely used as a primary efficacy variable.

- Secondary analyses showed similar with primary analysis results. All the secondary efficacy variables at week 16 showed in favor of methotrexate compared with leflunomide except CHAQ, and some of them showed significant differences. At week 4, 8, 12, and 16, majority of them showed in favor of methotrexate. Details of secondary analysis results are summarized in Table 6 to Table 17 of appendix.

- Since both primary efficacy variables showed in favor of methotrexate, and one of them showed significant difference, we cannot conclude that the efficacy of leflunomide is as good as the efficacy of methotrexate in this study.

3.2 Evaluation of Safety

Safety data were not reviewed.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup analysis results for gender and age are summarized in Table 18 and Table 19 for JRA DOI 30% and percent Improvement Index, respectively. Race was not included because most of RA patients are white. Since these subgroup analyses were not planned in the protocol, CMH method is acceptable for analysis of DOI 30%. As shown, there is no significant interaction between subgroup and treatment group.

4.2 Other Special/Subgroup Populations

Subgroup analysis result for Body weight is summarized in . As shown, there is no significant interaction between subgroup and treatment group.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- Methotrexate performed statistically better than leflunomide as measured by the JRA DOI ≥ 30% responder rate. The rate in the methotrexate group was 89.4% vs. 68.1 % in the leflunomide group. P-value is 0.0091 and 95% Confidence Interval of the difference is (-37.3%, -5.3%).

- The percent Improvement Index demonstrated no significant difference between treatment groups at week 16, LS Mean improvement was –44.41% (SE4.51) in the leflunomide group and –52.87% (SE4.39) in the methotrexate group.

- JRA DOI ≥ 30% responder rate was requested to add as a primary efficacy variable by agency, because this variable is one of the most commonly used efficacy variable. In fact, percent Improvement Index is rarely used as a primary efficacy variable.

- Secondary analyses showed similar results with primary analyses. All the secondary efficacy variables at week 16 showed in favor of methotrexate compared with leflunomide except CHAQ, and some of them showed significant differences. At week 4, 8, 12, and 16, majority of them showed in favor of methotrexate.

- Since both primary efficacy variables showed in favor of methotrexate, and one of them showed significant difference, we cannot conclude that the efficacy of leflunomide is as good as the efficacy of methotrexate in this study.

5.2 Conclusions and Recommendations

This NDA supplement failed to establish the efficacy of leflunomide comparing to methotrexate in treatment of JRA. The efficacy results demonstrated statistical superiority of methotrexate for DOI 30% responder rate which is one of two co-primary efficacy variables. The other co-primary efficacy variable, % Improvement Index, showed in favor of methotrexate but the difference was not statistically significant.

7 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suktae Choi
3/5/04 02:21:17 PM
BIOMETRICS

Stan Lin
3/5/04 03:58:34 PM
UNKNOWN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA Number	20-905 (SE5-012)
Submission Date(s)	September 4th, 2003
Brand Name	Arava®
Generic Name	Leflunomide
Reviewer	Abimbola Adebowale Ph.D.
PM Reviewer	Jenny J. Zheng Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DPE-III
OND division	HFD-550
Sponsor	Aventis Pharmaceuticals Inc., Bridgewater, NJ 08807-0890
Relevant IND(s)	41, 533
Submission Type; Code	Labeling Supplement with Pediatric Clinical Data, Submission of Pediatric Study Reports, Pediatric Exclusivity Determination Requested
Formulation; Strength(s)	Tablets; 10 mg, 20 mg, 100 mg
Indication	Juvenile Rheumatoid Arthritis

1. Executive Summary

This application consists of pediatric study reports for Arava®, to fulfill the requirements of a Written Request issued on March 30, 1999. The request was for pediatric information on the use of Arava® in the treatment of active polyarticular-course Juvenile Rheumatoid Arthritis (JRA). Several amendments were made to the original written request between December 6th, 2000 and July 9th, 2003. The final correspondence from the Agency approving the changes to the Written Request that was proposed by Aventis ® was dated July 9th 2003. The original NDA for Arava ® was approved on September 10th, 1998 with an indication in adults for active rheumatoid arthritis (RA). In this submission the applicant is asking for pediatric exclusivity and, labeling changes that includes pertinent pediatric data in two sections of the current approved package insert for Arava ® tablets. The FDA granted the pediatric exclusivity on November 10th, 2003.

The PK study proposed in the Written Request was to characterize steady state pharmacokinetics of leflunomide in children and adolescent (aged 3 to 17 years old) patients with a clinical diagnosis of polyarticular course JRA. Justification of the dose should be provided based on pharmacokinetic data. In addition to the primary analysis, a comparison to pharmacokinetic parameters in adult patients should be performed and, covariate analysis performed across gender, age and body weight in the target population.

The pharmacokinetics (PK) of leflunomide was investigated in two clinical efficacy and safety studies (Study 1037 and 3503). The pooled data was then evaluated using the

pharmacokinetics of the active metabolite (M1) of leflunomide in pediatric polyarticular JRA patients. In addition the individual PK parameters and exposure measures at steady-state in the pediatric JRA patients were compared to those of adult RA patients and the appropriate dose recommendations for use of leflunomide in pediatric patients were calculated to match the adult exposure data.

1.1 Recommendation:

The applicant has conducted an adequate population pharmacokinetic analysis (POPK) on the pooled data from two clinical studies, to characterize the pharmacokinetics of M1 (the active metabolite of leflunomide) in pediatric patients with polyarticular-course JRA ranging in age from 3 to 17 years old. The results of the population pharmacokinetic analysis demonstrated that children with body weights < 40 kg have a reduced clearance of M1 relative to children with body weights > 40 kg and, adult rheumatoid arthritis patients.

In the pivotal efficacy and safety study (# 3503), the mean systemic exposure for patients who weighed > 40 kg was comparable to that of adult RA patients. However, the mean steady state concentration (Css average) obtained in children with body weights < 20 kg was about 63 % lower than that of children who weighed > 40 kg. In addition the mean Css average for responders was about 31 % less than that obtained in non-responders, suggesting that a certain exposure may be required to obtain a response to treatment. [*The clinical division also observed that the response rate of leflunomide in children < 40 kg was less robust than in children with body weights greater than 40 kg*]. Therefore the exposure/response data suggests that the doses administered to the children who weighed < 20 kg may have been sub-optimal in spite of their reduced clearance which, normally would have resulted in increased plasma levels with matched doses.

[ ] However, they have not requested for this proposed regimen to be included in the label. The clinical division has decided that due to the inadequacy of the efficacy and safety information provided by the applicant, this indication is not recommended in the pediatric population, therefore no dosing recommendations are proposed at this time.

The clinical division has, however, decided to include the limited efficacy and safety data obtained from the pediatric JRA clinical studies in the label. Consequently, from a clinical pharmacology and biopharmaceutics perspective the information provided is acceptable to meet the requirements of the pediatric written request. Provided that satisfactory agreement is reached between the applicant and the Agency, limited changes to the language in the package insert should be included to incorporate some of the pediatric pharmacokinetics information without allowing the indication at this time.

1.2 Phase IV Commitments: None were identified.

Abimbola Adebowale, Ph.D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Dennis Bashaw, Pharm.D.
Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

2 Table of Contents

3. Summary of CPB Findings

Based on the pediatric written request and agreements between the FDA and Aventis, three studies were conducted and submitted in this NDA as follows:

- Study 1037 was an open-label, non-controlled, multi-center, Phase IB study over a 6-month treatment period with up to a 24-month extension phase.
- Study 3503 was a randomized, double blind, parallel group 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve.
- Study 3504 was an eight month extension of study 3503

Pharmacokinetics (PK) was investigated in pooled data from studies 1037 and 3503 and evaluated using the population (POPPK) approach. The objectives of the POPPK analysis were:

A. to establish a model that describes the pharmacokinetic characteristics of the active metabolite (M1) of leflunomide in the JRA population
B. to examine the influence of demographic covariates (i.e., sex, age, body weight, BSA) on the pharmacokinetics of M1 in the JRA population
C. to compare the POSTHOC estimates of individual PK parameters and exposure measures at steady-state in the pediatric JRA patients to those of adult RA patients
D. to determine appropriate dose recommendations for leflunomide use in the JRA population

The review of the data obtained from the POPPK analysis is summarized below:

Pharmacokinetics of M1 in JRA patients

In pediatric subjects with polyarticular course JRA, the pharmacokinetics of M1 (active metabolite of leflunomide) was well described by a one-compartment model with first order input similar to adult RA patients. There was also a wide inter-subject variability in CL/F observed in the pediatric patients similar to adult RA patients. However, results of a CL/F by weight evaluation of the POPPK data demonstrated that pediatric patients with polyarticular course JRA with body weights < 40 kg have a reduced clearance of M1 relative those with body weights > 40 kg (see table below) and, to adult RA patients (estimated clearance in current label = 31 ml/h)

Table 1 : Population Pharmacokinetic estimate of M1 for Clearance in pediatric patients with polyarticular course JRA Mean ±SD [Range]

N	Body Weight (kg)	CL (mL/h)
10	13-20	18 ± 9.8 [6.8-37]
30	20-40	18 ± 9.5 [4.2-43]
33	40-75	26 ± 16.0 [9.7-93.6]

In study 3503, the mean systemic exposure for patients who weighed > 40 kg was comparable to that of adult RA patients (mean Css = 34 mcg/mL). However, the dosage regimen studied produced lower mean systemic exposures in the pediatric patients who weighed < 20 kg relative to the patients who weighed > 20 kg. The mean Css average in patients with body weights < 20 kg was about 63 % lower than that obtained in patients with body weights > 40 kg (see table below).

Table 2: Average Steady State Concentration (Css) Mean ± SD in pediatric patients with polyarticular course JRA in Study 3503

N	Body Weight (kg)	Studied Daily Dose in Study 3503	Css in Study 3503 (mcg/mL)
8	13-20	5	14.5 ± 7.2
19	20–40	10	30.0 ± 19.3
20	40-75	20	38.9 ± 20.4

The results of the comparison between exposure and response (employing the JRA 30 % definition of improvement (DOI) responder endpoint) demonstrated that there was a trend for lower exposures in the group of patients who failed to respond to leflunomide. The mean average steady state concentration obtained was 35.0 ± 22.4 and 24.2 ± 10.1 mcg/mL, for

responder (n=32) and non-responder (n=15), respectively. This suggests that a certain exposure may be required to obtain a response to treatment. The mean exposure obtained in the responders was about 59 % greater than what was achieved in the children with body weights < 20 kg suggesting that the doses administered to the patients who weighed < 20 kg may have resulted in less efficacious plasma concentrations despite the reduced apparent oral clearance. In addition, the medical reviewer (Dr. C. Yancey) informed this reviewer that the response rate to leflunomide in children who weighed < 40 kg was less (59% response rate) than those who weighed > 40 kg (80 % response rate). The doses administered to the patients who weighed < 40 and <20 kg was ½ and ¼ that of the adult dose, respectively. Since the CL in the patients who weighed < 20 kg was decreased by about one-third, the ¼ dose was probably too low for a response to treatment in spite of the reduced clearance.

Dosing Recommendation

Although the doses used in the pivotal efficacy and safety study (# 3503) were based on the pharmacokinetic data obtained from the pilot study (# 1037), the exposure and response data suggests that the doses administered to the children who weighed < 20 kg may have been sub-optimal, in spite of their reduced clearance. The sub-optimal doses predicted based on the model obtained in study # 1037 were probably because the relationship between CL and body weight was overestimated, so that the changes in CL with body weight was actually less than what was predicted. Thus, the reduction in doses predicted based on a linear relationship between CL and body weight was lower.

A refined leflunomide treatment regimen was proposed by the applicant to optimally target the desired median steady-state M1 concentration in the pediatric JRA population, considering the wide inter-subject variability and the formulation strengths available:

[ ]

ıe limited safety data (confirmed with the medical reviewer, Dr. C. Yancey) in the pediatric population do not support the inclusion of these increased doses in the label.

4. QBR

4.1 General Attributes

Physical-Chemical Properties: Chemically, leflunomide is an isoxazole derivative with the chemical name N- (4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. It has a molecular weight of 270.2.

Mechanism of Action and Therapeutic Indication: Leflunomide is an isoxazole immunomodulatory agent. It inhibits dihydroorotate dehydrogenase (an enzyme involved in de

novo pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti- inflammatory effect. Juvenile rheumatoid arthritis (JRA) is a chronic inflammatory disease of childhood characterized by arthritis and, in some subjects, by extra-articular features. JRA may occur in both males and females but is more predominant in females. It is classified into three types–polyarticular, pauciarticular, and systemic – distinguished either by symptoms at onset or, because the initial presentation does not necessarily predict subsequent disease manifestations, by disease course. Polyarticular JRA is the only subset that is similar to adult RA. Polyarticular JRA (≥ 5 joints involved) affects approximately 30% of children with JRA.

Proposed Dosage (s) and Route(s) of Administration

The applicant did not propose any labeling changes to the dosage regimen for adult patients in the currently approved package insert. As noted above, based on their POPPK analysis, the applicant did include a refined proposed leflunomide treatment regimen for the pediatric population:

[ ]

4.2 General Clinical Pharmacology

What is the steady state pharmacokinetics of the active metabolite of leflunomide (M1) in pediatric patients with JRA?

The population pharmacokinetic (POPPK) analysis demonstrated that in the pediatric polyarticular course JRA patients as in adult RA patients, the pharmacokinetics of M1 was well described by a one-compartment model with first order input.

The PK population consisted of 73 subjects (27 subjects in Study 1037 and 46 subjects in Study 3503). Among them, 57 subjects were female and 16 subjects were male. The ages ranged from 3 to 17years. Their weight ranged from 13 to 75 kg and their BSA ranged from 0.56 to 1.83 m^2. There was a total of 10 subjects who weighed < 20 kg, 30 subjects weighed 20-40 kg and 33 subjects weighed > 40 kg. A total of 674 [M1] observations were included in the POPPK database. Of those, 493 observations were collected from Study 1037 and, 181 were collected from Study 3503. Descriptive summary of the PK parameter estimates from the final POPOPK model are reproduced in the table below:

Descriptive Summary of the individual Bayesian POSTHOC PK Parameter Estimates and Demographic Variables Based on the Final "Optimal" PPK Model

	WT (kg)	CL/F (L/h)	V/F (L)	T1/2 (days)	AGE (years)	BSA (m^2)	HT (cm)
N	73	73	73	73	73	73	73
Min	13	0.00422	2.44	1.92	3.1	0.56	88
Max	75	0.09358	9.98	26.50	17.4	1.83	176
Median	37.4	0.01867	5.46	8.75	12.0	1.22	144
Mean	38.8	0.02184	5.58	9.13	11.2	1.22	140
SD	16.2	0.01347	1.92	4.85	3.9	0.34	21
%CV	41.6	61.7	34.5	53.1	35.1	27.8	15

Based on the POPPK analysis, the remaining inter-subject variability in CL/F and V/F in the pediatric population is approximately 50 % and 19% respectively, expressed as %CV. The inter-subject variability in CL/F and V/F was estimated to be 61% and 25%, respectively in the adult RA subjects. Therefore, in pediatric patients with polyarticular course JRA, there is a wide variability in CL/F similar to that observed in adult RA patients.

What are the characteristics of the exposure-response relationships in pediatric patients with polyarticular course JRA?

Among the 47 subjects treated with leflunomide in Study 3503, thirty-two were categorized as responders and 15 as non-responders as measured by JRA DOI ≥ 30% when assessed after 16 weeks of treatment. To examine whether the non-responders had lower exposures to M1 the model-predicted average Css were plotted against response status (i.e. responder or nonresponder) as shown in the figure below. It appears that there is a trend for lower exposures in the subjects who were non- responders to leflunomide. The applicant stated that the majority of subjects (80 %) in the non-responder group had exposures to M1 that were less than the median exposure in the responder group.

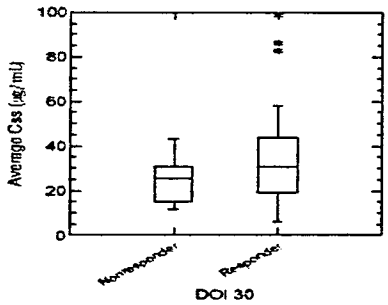
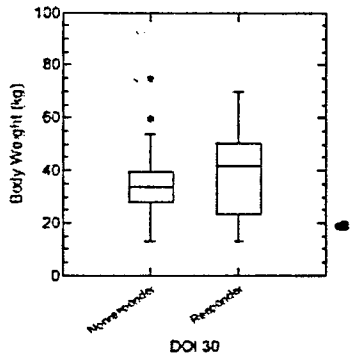


Table: Descriptive Statistics for Css and WT by DOI ≥ 30 % Response

	Responder		Nonresponder	
	Css (µg/mL)	WT (kg)	Css (µg/mL)	WT (kg)
N	32	32	15	15
Min	6.1	12.8	11.3	13.8
Max	98.9	70.0	43.4	76.1
Median	30.9	41.3	24.5	34.2
Mean	35.0	38.4	24.2	36.9
SD	22.4	17.8	10.1	16.4
C.V.	0.64	0.46	0.42	0.44

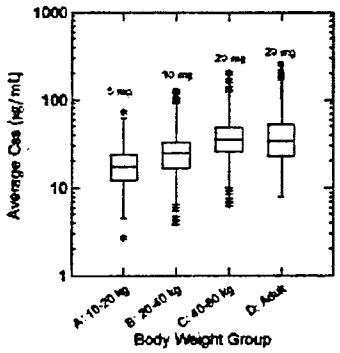
The table above shows that the mean average steady state concentration is 35.0 and 24.2 mcg/mL, for responder (n=32) and non-responder (n=15), respectively. This suggests that a certain exposure may be required to obtain a response to treatment. The graph below shows there was also a trend for the non-responders to be those in the lower weight groups. This



suggests that non-responders had lower exposures and possibly were also in the lower weight group. The medical reviewer (Dr. C. Yancey) informed me that in the clinical study # 3503 subgroup analysis, the number of responders by weight group was as follows:

Weight	N	Number of responders (%)
≤40 kg	27	16 (59.3)
> 40 kg	20	16 (80.0)

The data in the table above indicates that there were more non-responders that weighed ≤40 kg. This was consistent with the exposure data obtained in Study 3503. The leflunomide regimens investigated in study 3503 showed a difference in exposure to M1 across the three weight groups (see graph below). Only the 20 mg daily maintenance dose administered to pediatric subjects weighing > 40 kg achieved systemic exposures comparable to those observed in adults. The



graph below indicates that the dosage regimen studied produced lower exposures in the two lower weight groups relative to the adult RA patients. The mean Css in patients with body weights below 20 kg was about 63 % lower than that obtained in patients with body weights > 40 kg as shown in the table below:

Table Descriptive Statistics of the Css Achieved in Study 3503

	Weight (kg) Group		
	<20	20-40	>40
		Css (µg/mL)	
N	8	19	20
Minimum			
Maximum			
Median	12.6	26.2	36.7
Mean	**14.5**	**30.0**	**38.9**
SD	7.2	19.3	20.4
C.V.	0.50	0.64	0.52

Therefore, it appears that the leflunomide doses prescribed for pediatric patients with body weights < 20 kg and between 20 and 40 kg were low relative to those > 40 kg. Thus suggesting that the doses used in 3503, predicted based on the model obtained in study # 1037 were suboptimal for children with body weights < 40 kg. This was probably because the relationship between CL and body weight was overestimated, such that the changes in CL with body weight was less than what was predicted. Therefore the reduction in doses predicted based on a linear relationship between CL and body weight was lower.

4.3 Intrinsic Factors

Age

Are the pharmacokinetic parameters in children comparable to that in the adult patients?

The clearance (CL/F) of M1 in pediatric subjects with polyarticular course JRA, who weigh > 40 kg is comparable to those in adult RA patients. However, those who weigh < 40 kg do not have a comparable CL/F of M1 relative to adults.

The applicant stated that in a previous POPPK analysis of Phase III adult M1 concentration-time data, the CL/F and V/F was estimated to be 0.025 L/h (25 mL/h) and 12.1 L, respectively, in a typical RA patient with a body weight of 70 kg. Based on the final PK model determined using the combined dataset (Study 1037 and Study 3503), the predicted CL/F for a person weighing 70 kg was 0.0254 L/h, which agrees with the previous adult PPK analysis. Based on the final POPPK model, the mean CL/F is similar to that obtained in a pediatric JRA patient (0.022 L/h) with a mean body weight of ~ 40 kg.

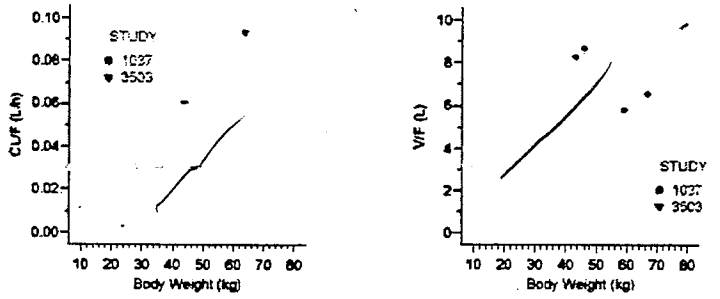
However, results of a CL/F by weight evaluation of the POPPK data demonstrated that pediatric subjects with polyarticular course JRA with body weights < 40 kg have a reduced clearance of M1 relative to adult RA patients as shown in the table below (see Pharmacometrics Review in Appendix by Dr. J. Zheng for details):

Table : Population Pharmacokinetic Estimate of M1 for Clearance in Pediatric Patients with Polyarticular Course JRA Mean ±SD [Range]		
N	Body Weight (kg)	CL (mL/h)
10	<20	18 ± 9.8 [6.8-37]
30	20-40	18 ± 9.5 [4.2-43]
33	>40	26 ± 16 [9.7-93.6]

Weight

The NONMEM stepwise regression showed that clearance (CL/F) was weakly correlated with body weight (WT), and V/F was strongly correlated with body weight. The figures below show the relationship between CL and WT and V/F and weight:

Relationships Between Clearance and Body Weight (left panel) and Volume of Distribution and Body Weight (right panel)



What is the dosing recommendation for the pediatric population based on the PK data?

[redacted]

4.4 Extrinsic Factors:

None that were pertinent to the pediatric population were identified.

4.5 Biopharmaceutics:

Leflunomide was developed as 10, 20, and 100 mg film coated immediate release tablets. Biopharmaceutics information was presented in details in the original approved NDA submission. The applicant stated that no further formulation development has been conducted with leflunomide.

4.6 Analytical Methods:

Were the analytical methods used to determine M1 in biological fluids adequately validated?
Yes, insert details of assay method.

Analytical Method Validation: Report No. 98.376 for Study No.HWA/1037

Assay Method	[redacted]
Analytical Site	
Compound	
Internal Standard	
Matrix	
Accuracy *Between-day*	
Imprecision (CV%) *Between-day*	
Standard curve range	
Sensitivity (LOQ)	
Selectivity	
Stability	

5. Detailed labeling recommendations:

Applicant's Proposed Recommended Label:

[redacted]

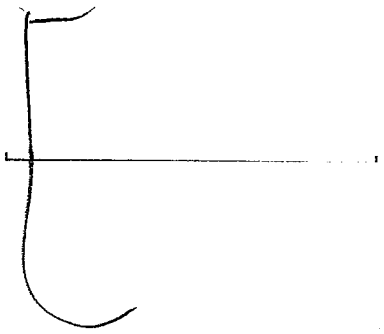
Reviewer's Labeling Recommendations:
Strikethrough indicates deletion and bolded Italics text indicates addition

Special Populations

Gender: Gender has not been shown to cause a consistent change in the in vivo pharmacokinetics of M1.
Age: Age has been shown to cause a change in the in vivo pharmacokinetics of M1. (See PEDIATRICS).

Pediatrics
The pharmacokinetics of M1 following oral administration of leflunomide have been investigated ***in 73 pediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) ranging in age from 3 to 17 years.***

[redacted]



6 Appendices

6.1 PM review

See Next Page

PHARMACOMETRIC REVIEW

NDA number:	20-905/SE5
Submission date:	09-04-2003
Product:	10 mg, 20 mg, and 100 mg tablet
Brand name:	ARAVA
Generic name:	leflunomide
Sponsor:	Aventis Pharmaceuticals Inc.
Type of submission:	PM consult/Population Pharmacokinetic Analysis
Primary Reviewer:	Adebowale Abimbola, Ph.D.
PM reviewer:	Jenny J Zheng, Ph.D.

This submission contains the pediatric study reports for leflunomide to fulfill the required information as described in the written request and the applicable amendments. A population pharmacokinetic (PPK) analysis was conducted to characterize the steady state pharmacokinetic (PK) of leflunomide in pediatric subjects. In addition, the PK in pediatric subjects was compared with PK in adults and the doses in pediatric subjects were proposed.

The findings of PPK analysis are as the follows:

1. In pediatric patients with polyarticular course juvenile rheumatoid arthritis (JRA) as in adult rheumatoid arthritis (RA) patients, the pharmacokinetics of M1, the metabolite of leflunomide, following oral administration of leflunomide can be well described by a one-compartment model with first order input.
2. In pediatric patients with polyarticular course JRA as in adult RA patients, there is similarly wide inter-subject variability in CL/F.
3. Body size is strongly correlated with V/F and weakly correlated with CL/F in pediatric patients with polyarticular course JRA.
4. To optimally target the desired median steady-state M1 concentration considering the large intersubject variability and the formulation strengths available, a refined leflunomide treatment

[redacted]

COMMENTS:

1. The mean steady state concentration (Css) in the efficacy trial (Study 3503) are 14.5, 30.0, and 38.9 µg/mL at the daily dose of 5 mg, 10 mg, and 20 mg in subjects with body weight below 20 kg, 20 to 40 and >40 kg, respectively. The results suggested that the Css at studied doses is about 63% lower in subjects with body weight <20 kg than the Css in the subjects with bodyweight above 20 kg. To reach comparable exposure across population, the increased doses from 5 mg daily to 10 mg daily were proposed in subjects with body weight below 20 kg and from 10 mg daily to 15 mg daily for the subjects with body weight between 20 to 40 kg. However, even at these increased doses, the mean Css in subjects with body weight below 20 kg are still expected to be 26% lower than Css in subjects with body weight above 40 kg.

[redacted]

pediatric subjects. The [redacted] would be acceptable if safety profile is expected to be similar when the exposures are similar between adults and pediatric subjects.

3. The mean average steady state concentration is 35.0 and 24.2 μg/mL, for responder (n=32) and non-responder (n=15), respectively, which may suggest that a certain exposure may be required to respond to the treatment.

4. Even though the doses used in study 3503 was based on the pharmacokinetic data obtained from study 1037, it appeared that the subjects with body weight below 20 kg were still under dosed because the Css in the subjects with body weight below 20 kg was about 63% lower than Css in the subjects with body weight above 40 kg. The reasons could be that 1) A relationship between clearance (CL) and body weight was over estimated so that the changes in CL with body weight was less than what the model predicted; 2) No subject with body weight below 20 kg was included in Study 1037, which may attribute the over estimated relationship between CL and body weight.

RECOMMENDATION:

The sponsor has conducted adequate population pharmacokinetic analysis (PPK) on the pooled data from two studies to characterize pharmacokinetic of leflunomide in pediatric subjects aged from 3 to 17 years old. The proposed doses would be acceptable if the safety profile is expected to be similar when exposures are similar between adults and pediatric subjects. The above COMMENTS should be conveyed to the medical reviewer.

Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

Title: Population pharmacokinetics of A77 1726 (M1) after oral administration of leflunomide in pediatric subjects with polyarticular course juvenile rheumatoid arthritis.

Objectives:

1. To establish a PPK model that describes the pharmacokinetic characteristics of the active metabolite (M1) of leflunomide in the JRA population.
2. To examine the influence of demographic covariates (i.e., sex, age, body weight, BSA) on the pharmacokinetics of M1 in the JRA population.
3. To compare the POSTHOC estimates of individual PK parameters and exposure measures at steady-state in the pediatric JRA patients to those of adult RA patients.
4. To determine appropriate dose recommendations for leflunomide use in the JRA population.

Study design: The data from two studies, Study 1037 and 3503, were pooled for the PPK analysis.

Study 1037 was an open-label, non-controlled, multicenter, Phase IB study over a 6-month treatment period with up to a 24-month extension phase. Leflunomide was administered orally according to the following algorithm: a loading dose for 3 days according to body surface area (BSA) measured in square meters (m2) based on the labeled adult loading dose of 100 mg/day for 3 days and an average adult BSA of 1.73 m^2; maintenance doses were calculated based on a low adult dose of 10 mg/day and an average adult BSA of 1.73 m^2. In subjects without clinical response on or after 8 weeks (based on *Definition of Improvement* [DOI] responder analysis for JRA subjects published by Giannini et al) escalation to the equivalent of leflunomide 20 mg/day per 1.73 m^2 BSA was allowed, at the discretion of the investigator.

Study 3503 was a randomized, double blind, parallel group, 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve.

A more simplified treatment regimen was developed for study 3503 based on the results of study 1037. Loading doses (some multiple of 100 mg tablets) and maintenance doses (some multiple of 10 mg tablets) were assigned based on actual body weight as described below.

[redacted]

Pharmacokinetic Data:

Study 1037: Blood samples were collected from each subject at baseline (prior to beginning study treatment), Day 3 (last day of the loading dose), Weeks 4, 12, and 26 during the initial 6-month treatment phase. On Day 3, Weeks 4, 12, and 26, serial assessments (5 samples) were made at each visit. In addition, single samples were to be collected on several pre-specified occasions.

Study 3503: Two blood samples were obtained for determination of leflunomide, M1, and 4-trifluoromethylaniline, a minor metabolite of leflunomide (TFMA) concentrations in plasma at each of the study visits for weeks 2, 4, 8, 12, and 16. An effort was made to collect absorption and elimination phase samples from each subject during the study. Fixed sampling times were not specified. Plasma was separated from whole blood and analyzed using validated methodologies to determine the concentrations of leflunomide, M1, and TFMA.

Assay:
Study 1037: Plasma samples were analyzed for M1 using a validated high-performance liquid chromatography (HPLC) method with UV detection and a limit of quantification of 100 ng/mL (0.1 μg/mL).

Study 3503: Plasma samples were analyzed for M1, leflunomide, and TFMA. M1 concentrations in plasma were quantified using the same HPLC/UV method that had been used for study 1037. A validated gas chromatography (GC) method with a nitrogen selective detector and a validated GC method with mass selective detection were used to determine leflunomide and TFMA concentration in plasma, respectively.

Data analysis:

The data were analyzed by a nonlinear mixed-effect model using the NONMEM system (NONMEM version V Level 1.1, NONMEM Project Group, UCSF/GloboMax). The first-order conditional estimation (FOCE) method with interaction was used. SYSTAT Version 10 (SPSS, Chicago) and S-PLUS Professional 6.1 (Insightful Corporation, Seattle) were used for data handling and for numerical and graphical analyses of the relevant NONMEM output.

Model development:
Base model:
The M1 concentration-time data from adult subjects were well-described by a one-compartment model with first order input as the base model. The same structural PK model was used to describe the PK of M1 in the pediatric population following oral administration of leflunomide. The three basic parameters, CL/F, V/F, and Ka were used to describe the model. The random effects (between subject variability on the parameters) were described as follows:

$$p_j = \theta * \exp(\eta_j)$$

where P is the parameter of interest, j is the jth subject, θ is the estimate of the population mean and η_j is the deviation from the population mean for the jth subject under the assumption that
For a one-compartment model, random effects were modeled on CL/F, V/F and ka. A diagonal covariance matrix for the random effects was used. Residual error was modeled as a combination of additive and proportional error model (APEM) as follows:

$$y_{ij} = c_{ij} * (1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

Once the base model was identified, individual patient pharmacokinetic parameters for which random effects were included in the model were calculated by the posterior conditional estimation technique (POSTHOC) of NONMEM using first order conditional estimation (FOCE) with interaction. A scatter plot correlation matrix was made for the pharmacokinetic parameters. If any clear correlation trend was identified between two PK parameters, a covariance term between the random effects (pharmacokinetic parameters) showing significant correlation was added to the base model covariance matrix. The significance of the additional covariance terms was then evaluated using the nested model selection criteria.

Covariate screening:
For covariates that were continuous in nature (e.g., WT, BSA), a scatter plot correlation matrix was created to examine the dependency of the PK parameters on individual covariates. Scatter plots of pharmacokinetic parameter estimates versus each possible covariate overlaid with a nonparametric locally weighted scatter plot smoother (LOESS) was used to help identify functional relationships.
For covariates that were categorical in nature (e.g., SEX), box and whisker plots of pharmacokinetic parameters for each of the groups were used to identify differences between groups.

The potential covariates were examined by NONMEM stepwise regressions. Once significant covariates were identified by trends in the scatter matrix plot, they were added to the base model incrementally and tested by NONMEM to determine if they were indeed statistically significant. The covariate with the strongest apparent correlation was entered first into the model. If a covariate was continuous in nature, a nonlinear covariate model was tested by adding one covariate at a time to the model in a median normalized manner:

$$CL_j = \theta_1 * (WT_j / WT_{median})^{\theta 2}$$

Final Model:

Upon selection of the final population pharmacokinetic-covariate model, the population PK parameter estimates, both fixed and random effect parameters, were tabulated. The individual pharmacokinetic parameters (i.e., CL/F, V/F, ka and t1/2) were calculated using the POSTHOC technique (FOCE).

Results:

The results of the initial PK modeling indicated that a one-compartment model with first order input fit the M1 concentration-time data obtained from studies 1037 and 3503 well. A combined model of additive plus proportional did not produce a better fit than that produced using only a proportional error model. Therefore, proportional model was selected as the base model for subsequent comparisons ($p<0.05$).

The scatter plot matrices revealed a clear trend for correlation between V/F and WT or BSA, and a much less evident and weaker correlation between these covariates and CL/F. A box whisker plot was also generated to depict any apparent effect of SEX on CL/F and V/F in the pediatric population. It indicated that females had slightly lower CL/F and V/F.

The population PK parameter estimates of the final "optimal" model (Model 11) are summarized in Table 1. The individual Bayesian POSTHOC pharmacokinetic parameter estimates of the final model are summarized in Table 2.

Table 1. The Final PPK Model and Its Parameter Estimates

Parameter	Regression Model and Parameter Estimates (SE)[a]	Inter-Subject Variability (SE)[a], %[b]
CL/F (L/h)	$CL/F = \theta 1 * (WT/40)^{\theta_4}$	50.4 (22.0)
	$\theta 1 = 0.02$ (0.00127)	
	$\theta 4 = 0.43$ (0.192)	
V/F (L)	$V/F = \theta 2 * (WT/40)^{\theta_5}$	18.6 (10.0)
	$\theta 2 = 5.8$ (0.23)	
	$\theta 5 = 0.769$ (0.0989)	
ka (h^{-1})	$\theta 3 = 1.13$ (0.455)	171.5 (101.5)
Residual Variability (SE)[c], %	18.2 (6.3)	

WT is the actual body weight in kg. θs are the regression parameters estimated by NONMEM

a SE = Standard error of the estimate

b Estimate expressed as percent coefficient of variation (%CV)

c Residual variation in the M1 plasma concentration, C (μg/mL), expressed as percent coefficient of variation (%CV)

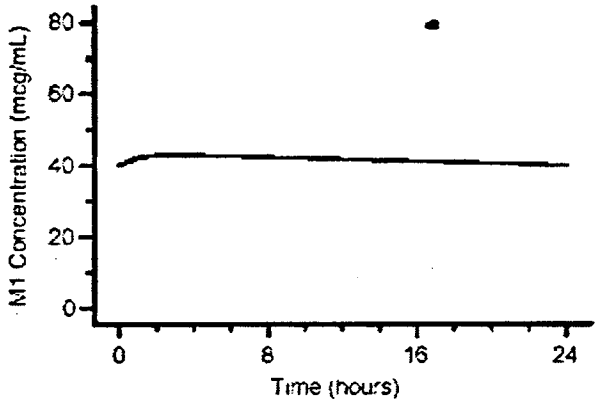
Table 2. Descriptive Summary of the Individual Bayesian POSTHOC PK Parameter Estimates and Demographic Variables Based on the Final PPK Model

	WT	CL/F	V/F	$T_{1/2}$	AGE	BSA	HT
	(kg)	(L/h)	(L)	(Days)	(years)	(m^2)	(cm)
N	73	73	73	73	73	73	73
Min	13	0.00422	2.44	1.92	3.1	0.56	88
Max	75	0.09358	9.98	26.50	17.4	1.83	176

Median	37.4	0.01867	5.46	8.75	12.0	1.22	144
Mean	38.8	0.02184	5.58	9.13	11.2	1.22	140
SD	16.2	0.01347	1.92	4.85	3.9	0.34	21
%CV	41.6	61.7	34.5	53.1	35.1	27.8	15

According to the final model with WT as the sole covariate, the CL/F and V/F were estimated to be 0.020 L/h and 5.8 L, respectively, in a typical pediatric patient with a body weight of 40 kg. The steady state M1 concentration time profile in a typical 40 kg pediatric patient after administration of 20 mg leflunomide daily is shown in Figure 1.

Figure 1. Steady-State M1 Concentration-Time Profile in a Typical 40 kg Pediatric Patient Administered 20 mg Daily



The V/F of M1 was strongly correlated with WT:

$$V_j = 5.8 * (WT_j / 40)^{0.769}$$

while the CL/F of M1 was weakly correlated with WT:

$$CL_j = 0.020 * (WT_j / 40)^{0.43}$$

The goodness-of-fit of the final model was assessed from the population point of view using identity plots and residual/weighted residual plots (Figure 2 and 3). These plots indicated that the data of both studies were fitted equally well with no apparent difference between studies.

Figure 2. Plots of the Observed Concentrations versus the Population Predictions (Left) or Individual Bayesian POSTHOC Predictions (Right) Based on the Final Model

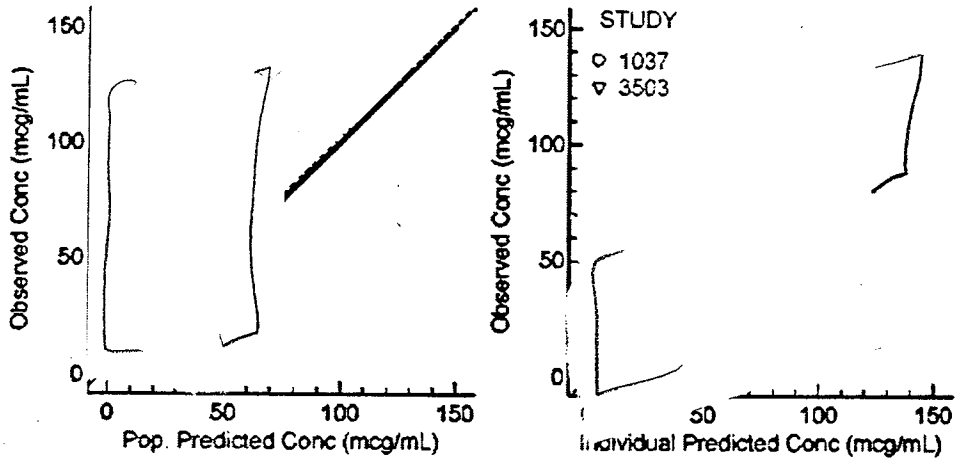
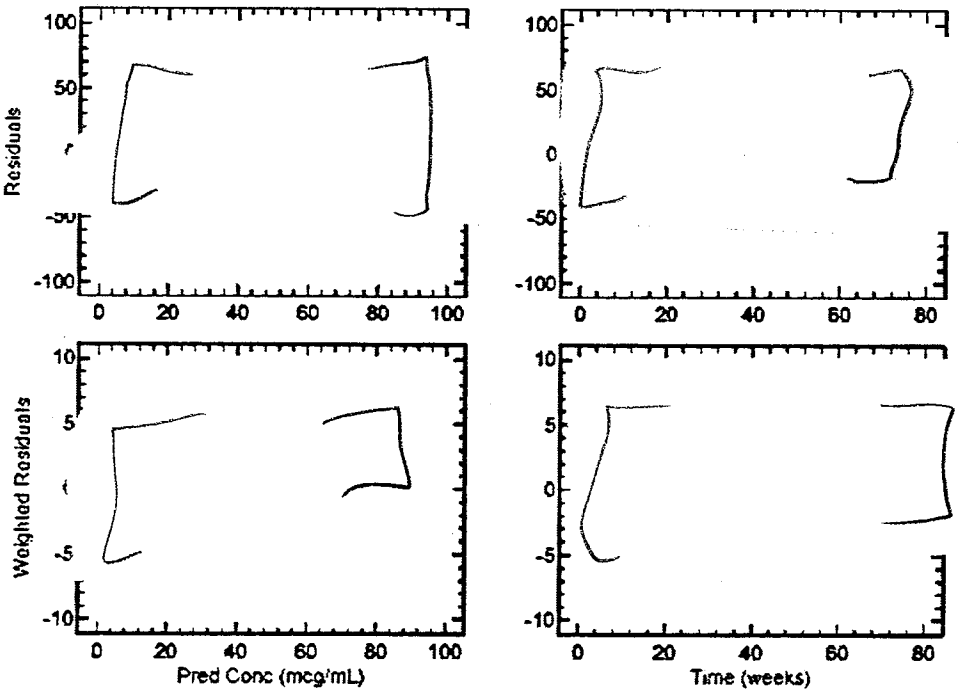


Figure 3. Residuals or Weighted Residuals Versus the Population (Fixed-Effects) Predicted Concentrations (Left) or Time (Right)



Model Validation:

Evaluations of the model were conducted by two approaches: cross study evaluation and predictive check.

- Cross-Study Evaluation:

The same set of models was tested with the data from each of the two studies separately. The population PK parameter estimates obtained from each of the data sets were quite similar (Table 3), indicating that the model was robust for the data from the two studies.

Table 3. Cross-Study Evaluation of the Final PPK Model

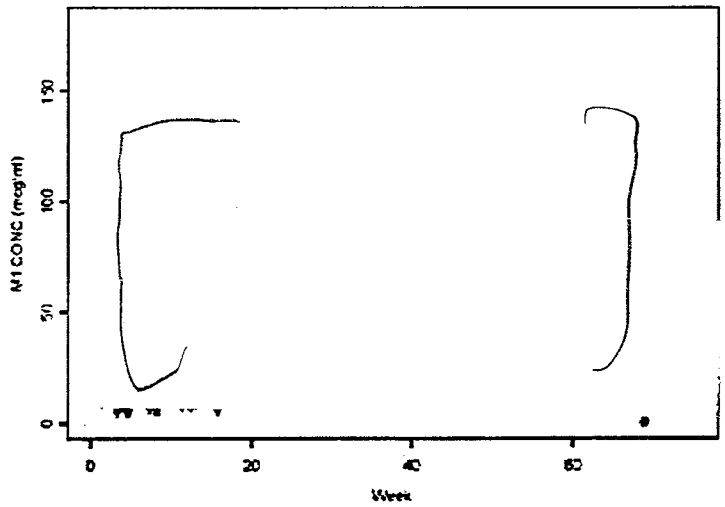
Study	CL/F	V/F	Ka	Exponent[b] For V/F	Exponent[b] for CL/F	ηCL	ηV	ηka	ε
	(L/h)	(L)	(h-1)			(%)	(%)	(%)	(%)
1037	0.0191	5.67	1.07	0.811	0.377	46.7	18.4	170.7	17.7
3503	0.0206	6.37	1a	0.719	0.452	52.7	19.3	0a	19.5
1037+3503	0.020	5.80	1.13	0.769	0.43	50.4	18.6	171.5	18.2

a: Due to lack of data obtained from the rising phase, k_a and its variance were fixed to 1 and 0, respectively.
b: The format of the covariate model was: $P_j = P_{typical} * (WT/40)^{exponent}$

- Predictive Check:

Monte Carlo simulations using the final PPK model, including final fixed effect and random effect parameters (inter-subject and residual variances), were conducted using NONMEM to create 100 replicates of the observed dataset with identical sample collection time points and body weights. The resulting simulated observations were sorted by approximate target observation times. The 50th (median), 97.5th and 2.5th percentiles of the simulated data were calculated at each sample collection time point. The results of the predictive check are displayed in Figure 4. The observed M1 data are plotted as individual points, indicated by circles for Study 1037 and triangles for Study 3503. The solid line represents the median values of the 100 simulated data sets, while the upper and lower bounds of the shaded area represent the 97.5th and 2.5th percentiles of the simulated data, respectively. The predictive check revealed that the population PK model adequately described both the central tendency and variability of the observed plasma M1 concentration data.

Figure 4. Predictive Check Using Final PPK Model



- Sensitivity test:

The time of first dose administration was unknown in Study 3503 and was arbitrarily set to 0:00. Using this time as the nominal dosing time throughout the study made the M1 concentration observations appear to be later in the dosing interval than they actually were.

To test the impact of dosing times on the PPK parameter estimates from the final model, 23 additional runs of the final model were performed with 23 different times of first dose administration using increments of 1:00 for an entire 24 hour period. The key PPK parameter estimates from each model run are listed in Table 4, sorted by objective function value.

Table 4. Sensitivity Tests of the Final Model Using Different Dosing Times

Dosing Time	OFV	CL	V	ka	Exponent for V/F	Exponent for CL/F	η^{CL}	η^{V}	η^{ka}	ε
		(L/h)	(L)	(h^{-1})			(%)	(%)	(%)	(%)
17:00	3157.585	0.0197	5.70	1.09	0.807	0.419	49.6	18.4	170.9	18.0
18:00	3157.669	0.0198	5.70	1.09	0.807	0.419	49.7	18.3	171.2	18.0
19:00	3157.759	0.0198	5.71	1.09	0.807	0.418	49.9	18.3	171.2	18.0
14:00	3157.821	0.0198	5.71	1.04	0.813	0.416	49.7	18.4	168.2	18.0
20:00	3157.857	0.0199	5.71	1.10	0.806	0.417	50.0	18.3	171.2	18.0
21:00	3157.962	0.0199	5.71	1.10	0.805	0.416	50.1	18.3	171.2	18.0
22:00	3158.076	0.0200	5.71	1.10	0.804	0.414	50.3	18.3	171.5	18.0
23:00	3158.194	0.0200	5.72	1.10	0.805	0.414	50.4	18.3	171.2	18.0
13:00	3158.349	0.0198	5.72	1.01	0.818	0.420	49.7	18.5	168.5	18.0
16:00	3158.354	0.0197	5.70	1.03	0.815	0.418	49.7	19.6	167.6	18.0
15:00	3159.559	0.0197	5.70	0.98	0.810	0.420	49.8	18.4	166.7	18.0
12:00	3159.596	0.0198	5.72	0.94	0.822	0.422	49.6	18.5	167.9	18.0
11:00	3161.017	0.0199	5.73	0.83	0.821	0.418	49.9	18.5	162.2	18.0
10:00	3165.475	0.0200	5.74	0.71	0.814	0.417	50.1	18.5	168.8	18.0
9:00	3166.198	0.0201	5.75	0.79	0.812	0.419	50.4	18.4	181.1	18.0
8:00	3167.526	0.0202	5.75	0.73	0.815	0.423	50.6	18.4	189.2	18.0
7:00	3169.569	0.0202	5.75	0.68	0.811	0.421	50.8	18.4	188.4	18.0
6:00	3170.881	0.0202	5.76	0.67	0.809	0.421	50.8	18.4	191.6	18.0
0:00	**3171.152**	**0.0200**	**5.80**	**1.13**	**0.769**	**0.430**	**50.4**	**18.6**	**171.5**	**18.2**
1:00	3171.401	0.0200	5.81	1.13	0.768	0.429	50.5	18.6	171.5	18.2
2:00	3171.662	0.0201	5.81	1.14	0.766	0.428	50.7	18.4	171.8	18.2
5:00	3171.76	0.0202	5.76	0.71	0.807	0.420	50.9	18.4	195.4	18.0
3:00	3171.924	0.0201	5.81	1.13	0.765	0.427	50.8	18.6	171.5	18.2
4:00	3172.191	0.0202	5.82	1.13	0.765	0.427	51.0	18.7	171.5	18.2

These tests indicated that the PPK analyses were insensitive to the dosing times. This is likely due to the long half-life of M1 (9.14 days, on average) relative to the dosing interval. With such a long half-life and daily dose administration, the fluctuation in M1 plasma concentration at steady-state is minimal.

Comparison of PK between pediatric and adult patients:

In a previous PPK analysis of Phase 3 adult M1 concentration-time data, the CL/F and V/F was estimated to be 0.025 L/h and 12.1 L, respectively, in a typical RA patient with a body weight of 70 kg. The same analysis approach in Phase 2 yielded a CL/F of 0.019 L/h and a V/F of 15.4 L for a typical RA patient with a body weight of 70 kg. The unexplainable inter-subject variability in CL/F and V/F was estimated to be 61% and 25%, respectively.

Based on the final PK model determined using the combined dataset (Study 1037 and Study 3503), the predicted CL/F for a subject with body weight of 70 kg was 0.0254 L/h, which agrees with the previous adult PPK analysis. The remaining unexplainable inter-subject variability in CL/F in the pediatric population is approximately 50%, expressed as %CV.

Dose recommendation for pediatric subjects:

Figure 5. Simulations of 2000 Pediatric "Patients" Using the Refined Leflunomide Dose Recommendations (left panel) and the Leflunomide Dose Regimens From Study 3503 (right panel): Comparison to Observed Adult Css

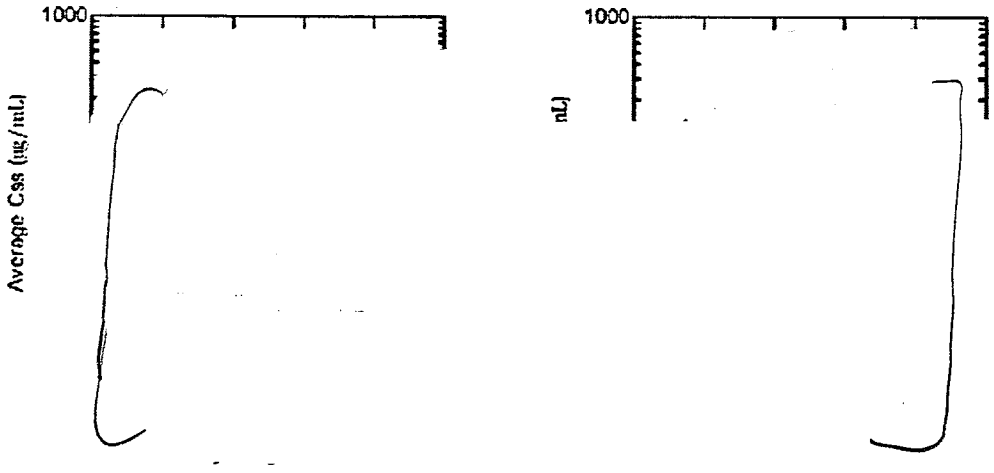


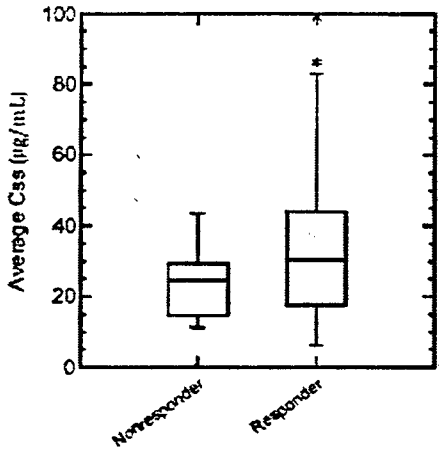
Table 5. Descriptive Statistics for the Css Achieved with Study 3503

	Body weight
N	
Min	
Max	
Median	
Mean	
SD	
C.V.	

Comparison of PK between responders and non-responders:

Among the 47 subjects treated with leflunomide in study 3503, 32 were categorized as responders and 15 were categorized as non-responders when assessed following 16 weeks of treatment. The model estimated Css for the responders and non-responders are shown in Figure 5.

Figure 5. Estimated Css between responder and non-responder in Study 3503



A clear trend for lower exposures in the group of subjects who failed to respond to leflunomide was observed. The majority of subjects (80%) in the non-responder group had exposures to M1 that were less than the median exposure in the responder group.

Conclusion:

- In pediatric patients with polyarticular course JRA as in adult RA patients, the pharmacokinetics of M1 following oral administration of leflunomide can be well described by a one-compartment model with first order input.
- In pediatric patients with polyarticular course JRA as in adult RA patients, there is similarly wide inter-subject variability in CL/F. Body size is strongly correlated with V/F and weakly correlated with CL/F in pediatric patients with polyarticular course JRA.
- To optimally target the desired median steady-state M1 concentration considering the large intersubject variability and the formulation strengths available, a refined leflunomide treatment

[ ]

Comments:

1. The studied doses in Study 3503, the mean steady state concentration (Css) at the studied doses, and the proposed doses for approval are shown in the following table. The Css in Study 3503 are 14.5, 30.0, and 38.9 µg/mL in subjects with body weight below 20 kg, 20 to 40 and >40 kg, respectively. The results suggested that the Css at studied doses is lower in subjects with body weight <20 kg than Css in the subjects with bodyweight above 20 kg. Therefore,

[ ]

Css (µg/mL)=Dose (mg)/CL/F (L/h)/24 (h)
sd= standard deviation
n: the number of subjects

2. The impact of lower exposure in the subjects with body weight below 20 kg on efficacy of the drug may not be able to be evaluated due to the limited sample size (n=8) in the population.
3. The proposed dose is about 100% and 50% higher than the studied doses for the subjects with body weight below 20 kg and between 20 to 40 kg, respectively. Even though the increased doses were supported by the pharmacokinetic analysis, no safety data exists at the increased dose in the pediatric subjects. The increased doses would be acceptable if safety profile is expected to be similar when the exposures are similar between adults and pediatric subjects.
4. Even though the doses used in study 3503 was based on the pharmacokinetic data obtained from study 1037, it appears that the subjects with body weight below 20 kg maybe under dosed because the Css in the subjects with body weight below 20 kg was about 63% lower than Css in the subjects with body weight above 40 kg.
5. The mean average steady state concentration in this study is 35.0 and 24.2 µg/mL, for responder (n=32) and non-responder (n=15), respectively, which may suggest that a certain exposure may be required to respond to the treatment.

Study #: 1037
Title: Phase IB Trial of Leflunomide in Pediatric Subjects with Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Objectives:

- To determine whether therapy with leflunomide warrants further study in patients with polyarticular course juvenile rheumatoid arthritis by obtaining PK and safety data from a small group of patients.
- To collect data regarding preliminary efficacy and improvement (or no deterioration) in physical function and to determine whether therapy with leflunomide warranted further study in subjects with polyarticular course JRA.

Design: It is an open label, multi-center, Phase IB study, 6-months treatment with voluntarily continued study drug administration for up to an additional 24 months provided therapy was well tolerated. Subjects with polyarticular course JRA by [redacted] criteria, regardless of onset type, aged 3 to 17 years, with active disease who were refractory to or intolerant of methotrexate.

Dose: Leflunomide was administered daily according to the following algorithm: a loading dose for 3 days according to body surface area (BSA) measured in square meters (M_2) based on the labeled adult loading dose of 100 mg/day for 3 days and an average adult BSA of 1.73 M^2; maintenance doses were calculated based on a low adult dose of 10 mg/day and an average adult BSA of 1.73 M^2. In subjects without clinical response on or after 8 weeks (based on *Definition of Improvement* [DOI] responder analysis for JRA subjects published by Giannini et al) escalation to the equivalent of leflunomide 20 mg/day per 1.73 M^2 BSA was allowed, at the discretion of the investigator. The final dose algorism is the followings:

BSA m^2	Loading dose for 3 days mg/day	Maintenance dose mg/day	Max maintenance dose mg/day
0.45-0.50	30	5	5
0.51-0.60			10
0.61-0.75	40		
0.76-0.90	50		
0.91-1.00	60		
1.01-1.05		10	15
1.06-1.20	70		
1.21-1.35	80		
1.36-1.50	90		20
1.51-1.73 & up	100		

Data collection: Whole blood samples were collected from each subject at baseline (prior to beginning study treatment), Day 3 (last day of the loading dose), Weeks 4, 12, and 26 during the initial 6-month treatment phase. On Day 3, Weeks 4, 12, and 26, serial samples (prior to dosing, 2, 4, 8 and 24 hours following administration) were collected at each visit. In addition, single samples were to be collected on the following occasions:

- 16 weeks following completion of the initial 6-month treatment phase for subjects not entering the extension
- At Weeks 50 and 74 for subjects continuing treatment in the extension portion of the study
- 16 weeks following treatment discontinuation for any subject withdrawn from the study prior to Week 74

Data analysis: Plasma M1 concentration-time data were pooled with the adult data from Phases I, II, and III and analyzed using a population approach implemented in NONMEM. A one compartment model with first order input previously established in adults was used to describe the pharmacokinetic behavior of M1 with a proportional correction factor for the influence of BSA on clearance and volume in the pediatric population.

Results:

The final number of concentration observations included in the analysis was 494 with an average of 18 (range 5 to 23) plasma M1 concentrations per subject.

The final population pharmacokinetic model was an adaptation of previously developed one compartment model with first order input for M1 using a proportional correction factor for the influence of BSA on CL and V in the pediatric population. BSA was calculated by Du Bois equation as: $BSA = WT^{0.425} HT^{0.725} 0.007184$. Population pharmacokinetic analysis was conducted on the pooled data from Study 1037 and other phase 1/2/3 studies in adults. The relationship between clearance and body surface area, sex, and study population is described as

$$CL = \theta_{Cl}(\frac{BSA}{1.73})^{\theta_{bsa,cl}}(1+f_{sex,cl})(1+f_{ph,cl}) \bullet \exp(\eta_{cl})$$

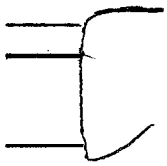
with $f_{sex,cl}$=0 for male and $f_{sex,cl}$= θ_{sex} for female
and $f_{ph,cl}$=0 for phase 3 study, $f_{ph,cl}$= $\theta_{ph1,cl}$ for phase 1 study, $f_{ph,cl}$= $\theta_{ph2,cl}$ for phase 2 study, $f_{ph,cl}$= $\theta_{ph3,cl}$ for study 1037.

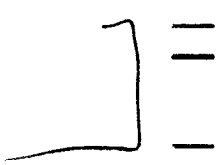
The relationship between volume and body surface area, sex, and study population is described as

$$V = \theta_{v}(\frac{BSA}{1.73})^{\theta_{bsa,v}}(1+f_{sex,v})(1+f_{ph,v}) \bullet \exp(\eta_{v})$$

with $f_{sex,v}$=0 for male and $f_{sex,v}$= θ_{sex} for female
and $f_{ph,v}$=0 for phase 3 study, $f_{ph,v}$= $\theta_{ph1,v}$ for phase 1 study, $f_{ph,v}$= $\theta_{ph2,v}$ for phase 2 study, $f_{ph,v}$= $\theta_{ph3,v}$ for study 1037.

The final model showed that the clearance (CL) of drug is linearly related with body surface area, indicating that dose might be needed to be adjusted according to the body surface area. However, it is more practical to adjust the dose by body weight, another measure of body size. Therefore, the sponsor used the relationship of BSA=(body weight/70)^0.7 to calculate the body weight at which the dose should be adjusted to ½ and ¼. The corresponding body weight was 26 kg and 10 kg. The midpoint of 1-1/2 and ½-1/4 are ¾ and 3/8 which corresponds to the body weight of 46 kg and 17 kg. A simplified dose recommendation based on the body weight was made and presented in the following table:





The population pharmacokinetic parameters estimated from the final model are presented in the table below:

	Median	seau	CV%	sd_e	95%	
					lower	upper
Structural model						
$\theta_{CL/F}$ (L/h)	0.025	0.00114	4.56		0.0228	0.0272
$\theta_{V/F}$ (L)	12.1	0.222	1.83		11.7	12.5
Inter-individual Var.						
ω^2_{CL}	0.375	0.016	4.27	61.2	58.6	63.7
ω^2_V	0.0642	0.00619	9.64	25.3	22.8	27.6
Fixed effects						
$\theta_{bw=70}$	1					
$\theta_{bw=V}$	1					
$\theta_{formula=2}$	−0.151	0.0392	25.5		−0.231	−0.0772
$\theta_{formula=3}$	−0.148	0.0221	14.9		−0.191	−0.105
$\theta_{pk=II2}$	0.383	0.122	31.9		0.141	0.622
$\theta_{pk=III}$	0					
$\theta_{pk=II3}$	−0.258	0.0349	13.5		−0.328	−0.19
$\theta_{pk=III}$	0.27	0.0352	13		0.201	0.339
$\theta_{bw=70}$	0					
$\theta_{bw=V}$	−0.222	0.0503	22.7		−0.321	−0.123
Residual error						
$\theta_{pk=I}$	0.286	0.0631	21.4		0.172	0.42
$\theta_{pk=II}$	0					
$\theta_{pk=III}$	13.2	2.68	20.3		7.95	18.5
θ_{bw}	10.8	12.7	118		−14.1	35.7
$\sigma^2_{pk=I}$	0.011	0.00135	12.3	10.5	9.11	11.7
$\sigma^2_{pk=II}$	0.039	0.00315	8.08	19.7	18.1	21.3
$\sigma^2_{pk=III}$	0.0201	0.00176	8.76	14.2	12.9	15.3
σ^2_{bw}	0.0281	0.0122	43.4	16.8	6.47	22.8

Table 3: NONMEM result of the final model. The data from study BWA1867037 were fitted together with the data from phase I, II, and III

Conclusion:

- The final population pharmacokinetic model obtained indicated that BSA-normalized CL in the pediatric subjects with JRA was not different from adults with RA, which supported adjustment of the maintenance dose based on BSA.
- For practical reason, dose adjustment was proposed by body weight instead of BSA. The relationship between BSA and body weight, BSA=(body weight/70)^0.7, was used.

Comment: The source of the relationship between BSA and body weight used for proposed dose adjustment was not provided.

6.2 Proposed labeling:

Not included because only change to current label proposed by applicant was under PK and Precautions (pediatric use).

6.3 Individual Study reviews

Please note that the PM review above included a lot of information on the design, objective and analysis of the studies, so they will not be repeated here. Only those areas that were not covered will be inserted here.

Study No. HWA 486/1037

Title: Phase IB Trial of Leflunomide in Pediatric Subjects with Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Population: Twenty-seven subjects (4 M, 23F) were enrolled ranging in age from 6 to 17 years. Weights ranged from 17.8 –66.7 kg. All had failed methotrexate therapy: 15 due to lack of efficacy and 12 as a result of intolerance.

Analytical methods

Plasma was separated from the whole blood samples and analyzed to determine the concentration of the active metabolite of leflunomide (M1). All plasma samples were analyzed for M1 concentration using a validated HPLC method with UV detection. The limit of quantification was 0.1 mcg/mL.

Analytical Method Validation: Report No. 98.376 for Study No.HWA/1037

Assay Method	HPLC using UV detection @ 292 nm
Analytical Site	
Compound	M1 (A771726) the main metabolite of leflunomide
Internal Standard	
Matrix	Plasma
Accuracy *Between-day*	94.8 % - 109.5 %
Imprecision (CV%) *Between-day*	1.7%-6.5%
Standard curve range	0.1-100 mcg/mL
Sensitivity (LOQ)	0.1 mcg/mL (CV% = 4.4 % and Accuracy = 102.3%)
Selectivity	No interfering peaks were observed at the retention time for M1 and its IS.
Stability	Stable in human plasma for at least 53 weeks at –10°C to –30 °C

Data Analysis and Statistical Procedures:

A population PK model was developed using adult and pediatric data (see PM review for details).

Results-Pharmacokinetics

Final POPPK Model: The population pharmacokinetic parameters estimated from the final model are presented in the table below:

Table 11. Estimates of Typical Values at BSA=1.73 M^2 and Inter-Individual Variability for CL and V

Parameter	Population Typical Value	CV%
CL (mL/h)	25.0	61.2
V (L)	12.1	25.3

Individual POSTHOC estimates:

Bayesian estimates for pharmacokinetic parameters were calculated for each subject using the POSTHOC option in NONMEM®. The mean estimates of CL, V, and a calculated elimination half-life ($t_{1/2}$) are presented in the table below (N = 27):

Subject	**WT (kg)**	**Age (years)**	**CL (mL/hr)**	**CL/BSA (mL/hr per M^2)**	**V (L)**	**V/BSA (L per M^2)**	**$T_{1/2}$ (days)**
Mean	40.46	12.3	20.31	16.86	5.79	4.62	9.98
SD	14.29	3.34	9.02	8.54	1.79	0.91	5.72
CV%	35.3	27.2	44.4	50.7	30.9	19.8	57.4
Median	37.4	13	18.78	14.53	5.64	4.46	9.21
Minimum							
Maximum							

Conclusions

Final population PK model obtained indicated that BSA-normalized CL in pediatric subjects (aged 6-17 years old) with polyarticular course JRA was similar to that obtained in adult RA patients. Therefore adjusting the pediatric

maintenance dose to achieve systemic exposure measures comparable to adults using body surface area was supported by this data. An adjusted dosing scheme based on this data was then used for the pivotal efficacy study 3503 in pediatric JRA patients. The dosing recommendation was based on weight for practical reasons no references were provided on how the equation between dose and body weight used for the proposed dose adjustment was derived.

HWA 486/3503

Title: Efficacy and Safety of Leflunomide versus methotrexate in the treatment of Pediatric Patients with Juvenile Rheumatoid Arthritis

Objectives:

Primary objective:

To assess efficacy and safety of leflunomide versus methotrexate in treatment of JRA as assessed by the Percent Improvement Index and JRA DOI 30% Responder Rate at the endpoint or week 16 visit. For subjects terminating early, the endpoint will be the last evaluation prior to week 16 (LOCF). Safety was assessed by adverse events, laboratory tests, vital signs, physical examination.

Secondary objective:

To assess population pharmacokinetics of leflunomide based on plasma levels of the active metabolite

Study design

The study was a multinational, multicenter, double-blind, double-dummy, randomized, parallel, and active controlled study.

Population

Demographic or disease characteristic		Treatment group		
		Leflunomide N=47	Methotrexate N=47	p
Age (years)	mean (SD)	10.1 (4.0)	10.2 (3.8)	0.9310
< 12 years	n (%)	27 (57.4)	27 (57.4)	0.9495
≥ 12 years	n (%)	20 (42.6)	20 (42.6)	
Sex				
Male	n (%)	12 (25.5)	13 (27.7)	0.6930
Female	n (%)	35 (74.5)	34 (72.3)	
JRA duration (years)	mean (SD)	1.69 (3.2)	1.37 (1.97)	0.6923

Analytical Methods:

Analytical Method Validation for Study No. HWA 486/3503

Assay Method	HPLC using UV detection @ 292 nm
Analytical Site	
Compound	M1 (A771726) the main metabolite of leflunomide
Internal Standard	
Matrix	Plasma
Accuracy *Between-day*	101 % - 104.5 %
Imprecision (CV%) *Between-day*	1.6%-12.1%
Standard curve range	0.1-100 mcg/mL
Sensitivity (LOQ)	0.1 mcg/mL (CV% = 2 % and Accuracy = 101. %)
Selectivity	No interfering peaks were observed at the retention time for M1 and its IS.
Stability	Stable in human plasma for at least 53 weeks at –10°C to –30 °C

Assay Method	GC/MS
Analytical Site	
Compound	TFMA [(trifluoromethyl)-aniline]
Internal Standard	
Matrix	Plasma
Accuracy *Between-day*	98 % - 101.7 %

Imprecision (CV%) *Between-day*	4.0 %-8.6 %
Standard curve range	0.5-50 ng/mL
Sensitivity (LOQ)	0.5 ng/mL (CV% = 3.7 % and Accuracy = 100%)
Selectivity	No interfering peaks were observed at the retention time TFMA
Stability	Stable in human plasma for at least 55 weeks at –10°C to –30 °C

Assay Method	GC with Nitrogen Selective Detection
Analytical Site	
Compound	Leflunomide
Internal Standard	
Matrix	Plasma
Accuracy *Between-day*	107.5 % - 111.3 %
Imprecision (CV%) *Between-day*	5.0 %-5.8%
Standard curve range	5-1000 ng/mL
Sensitivity (LOQ)	5 ng/mL (CV % = 2.2 % and Accuracy = 99 %)
Selectivity	No interfering peaks were observed at the retention time for Leflunomide
Stability	Stable in human plasma for at least 61 weeks at –10°C to –30 °C

Statistical procedures

The focus of the pharmacokinetic analysis was the plasma M1 concentrations. Plasma M1 concentration-time data were pooled with the M1 concentration-time data from study HWA486/1037 and analyzed using a population approach implemented in NONMEM ® (see PM review for details)

Results – Pharmacokinetics

Bayesian estimates of the pharmacokinetic parameters were calculated for each subject using the POSTHOC option in NONMEM. The individual estimates of CL/F, V, and a calculated elimination half-life ($t_{1/2}$) for the 46 subjects who received leflunomide and had at least 1 measurable M1 level are descriptively summarized in the table below:

Table - Statistical summary of the individual PK parameter estimates using POSTHOC Bayesian estimation in Study 3503

Parameter	CL/F L/h	V/F L	$T_{½}$ days
N	46	46	46
Min			
Max			
Median	0.0186	5.39	7.6
Mean	0.0225	5.51	8.9
SD	0.0155	2.04	5.0
%CV	68.7	36.9	55.8

- Although mean CL is similar to adult RA patients, POPPK analysis of the pooled data from both studies indicated pediatric subjects weighing < 20 kg had a reduced clearance compared to the adult RA patients.

Table Descriptive Statistics of the Css Achieved in Study 3503

	Weight (kg) Group		
	<20	20-40	>40
		Css (□g/mL)	
N	8	19	20
Minimum			
Maximum			
Median	12.6	26.2	36.7
Mean	14.5	30.0	38.9
SD	7.2	19.3	20.4
C.V.	0.50	0.64	0.52

As shown in the table above, the mean Css in patients with body weights below 20 kg was about 52 % and 63 % lower than that obtained in patients with body weights ranging from 20-40 kg and > 40 kg respectively. There is an imbalance in the sample size of the different weight groups which limits the data interpretation. The actual impact of lower exposure in the subjects with body weights < 20kg on the efficacy of the drug may be difficult to evaluate due to the small sample size of these patients (n=8). With the dosage regimens studied, the systemic exposures to M1 in JRA subjects weighing > 40 kg was comparable to that in adult RA subjects (~34 mcg/mL). However, the M1 exposure was lower in the subjects in the 2 lower weight categories (< 20 kg, 20 – 40 kg). Based on an anlysis between responder and non-responder the mean Css was 35 and 34.2 mcg/mL, for responder (n=32) and non-responder (n=15) respectively. This suggests that a certain exposure may be required for response to treatment.

Any potential effect of crushing the leflunomide tablet and mixing it in applesauce or jam on exposure to M1 could not be determined for study 3503. Only 7 subjects had crushed and mixed some of their doses of leflunomide during the study. Because those subjects who did crush and mix some of their doses tended to be the younger subjects, a meaningful comparison of the M1 concentrations observed for those subjects who crushed some of their doses and those who reported swallowing every dose whole could not be performed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Abi Adebowale
3/4/04 03:44:48 PM
BIOPHARMACEUTICS

Dennis Bashaw
3/5/04 10:05:16 AM
BIOPHARMACEUTICS
Since this review was finalized, additional labeling discussions were held with the sponsor on 3/4/04. The labeling as of this date, while not identical to that in this review is consistent with the reveiw and is acceptable.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CONFIDENTIAL

Hoechst Marion Roussel

Hoechst Marion Roussel, Inc.
Patent Department

2110 East Galbraith Road
MAIL: P. O. Box 156300
Cincinnati, Ohio 45215-6300
Telephone: 513/948-7960
Telefax: 513/948-7961/-4681
Telex: 214320

25 February 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

PATENT NUMBER(S):	United States Patent No. 4,284,786
EXPIRATION DATE(S):	December 13, 1999, under the provisions of Uruguay Pact of the General Agreement on Tarrifs and Trade ("GATT")
PATENT OWNER:	Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany
TYPE OF PATENT:	Drug Substance

The undersigned declares that United States Patent No. 4,284,786 covers leflunomide, the drug substance of the drug product for which the above-referenced NDA is being submitted for approval for use in treating rheumatoid arthritis, and also covers both the drug product (formulation) containing the drug substance and methods of using said drug substance in treating rheumatoid arthritis. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:

Gary D. Street
Vice President
Hoechst Marion Roussel, Inc.
Patent Department

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

Hoechst Marion Roussel

Hoechst Marion Roussel, Inc.
Patent Department

2110 East Galbraith Road
MAIL: P. O. Box 156300
Cincinnati, Ohio 45215-6300
Telephone: 513/948-7960
Telefax: 513/948-7961/-4651
Telex: 214320

26 February 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

PATENT NUMBER(S):	United States Patent No. 4,351,841
EXPIRATION DATE(S):	December 13, 1999, under the provisions of Uruguay Pact of the General Agreement on Tariffs and Trade ("GATT")
PATENT OWNER:	Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany
TYPE OF PATENT:	Drug Product (formulation) and Method of Use

The undersigned declares that United States Patent No. 4,351,841 covers the drug product (formulation) containing the drug substance leflunomide and a method of using said drug substance and said drug product in treating rheumatoid arthritis. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:

Gary D. Street
Vice President
Hoechst Marion Roussel, Inc.
Patent Department
2110 E. Galbraith Rd.
Cincinnati, OH 45215-6300

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

Hoechst Marion Roussel

Hoechst Marion Roussel, Inc.
Patent Department

2110 East Galbraith Road
MAIL: P. O. Box 156300
Cincinnati, Ohio 45215-6300
Telephone 513/948-7960
Telefax 513/948-7961/-4681
Telex 214320

26 February 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

PATENT NUMBER(S):	United States Patent No. 5,679,709
EXPIRATION DATE(S):	October 21, 2014
PATENT OWNER:	Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany
TYPE OF PATENT:	Method of Use

The undersigned declares that United States Patent No. 5,679,809 covers a metabolite of leflunomide and a method of using drug substance (leflunomide) and drug product (formulation) containing said drug substance in treating rheumatoid arthritis. United States Patent 5,679,709 has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:

Gary D. Street
Vice President
Hoechst Marion Roussel, Inc.
Patent Department
2110 E. Galbraith Rd.
Cincinnati, OH 45215-6300

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA _3/30/99. Application Written Request was made to: NDA/IND#_20-905____
Timeframe Noted in Written Request for Submission of Studies _9/9/03
NDA# _20-905____ Supplement # 012____ Choose one: SE5
Sponsor _Aventis_Pharmaceuticals_____
Generic Name _leflunomide_____ Trade Name _Arava_____
Strength _10 mg, 20 mg, 100 mg_____ Dosage Form/Route__tablets, oral_____
Date of Submission of Reports of Studies _9/5/03
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 12/6/03.

Was a formal Written Request made for the pediatric studies submitted?	Y _X_	N ___
Were the studies submitted after the Written Request?	Y _X	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y _X	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y _X	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y _X_	N ___
Did the studies fairly respond to the Written Request?	Y _X_	N ___

SIGNED Carolyn L Yancey (for) DATE 11/04/03

DES FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ___ Granted Denied

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-905	NCE	9/10/03
"	I-395	6/13/03

SIGNED _____ DATE 11/10/03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Grace Carmouze
11/12/03 11:05:09 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-905 Supplement Type (e.g. SE5): SE5 Supplement Number: 012

Stamp Date: September 5, 2003 Action Date: March 5, 2004

HFD 550 Trade and generic names/dosage form: Arava® (leflunomide) tablets 10 mg, 20 mg, 100 mg

Applicant: Aventis Pharmaceuticals Inc. Therapeutic Class: DMARD

Indication(s) previously approved: Treatment of active rheumatoid arthritis in adults to reduce signs and symptoms and to retard structural damage as evidenced by X-ray erosions and joint space narrowing.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: rheumatoid arthritis in adults

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred __X__Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

tudies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr.__3__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17__ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 20-905
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jane Dean
4/2/04 05:58:21 PM

16. DEBARMENT CERTIFICATION

Aventis Pharmaceuticals Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 (a) or (b) in connection with this application.

22 August 2003

Joseph Scheeren, PharmD
Head, Global Regulatory Coordination
Aventis Pharmaceuticals Inc.

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-905/S-012

Aventis Pharmaceuticals, Inc.
Attention: Joseph Scheeren, PharmD
Head Global, Regulatory Coordination
200 Crossing Boulevard
PO Box 6890
Bridgewater, NJ 08870-0890

Dear Dr. Scheeren:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Arava® (leflunomide) tablets, 10 mg, 20 mg and 100 mg
NDA Number:	20-905
Supplement number:	S-012
Review Priority Classification:	Priority (P)
Date of supplement:	September 4, 2003
Date of receipt:	September 5, 2003

This supplemental application proposes changes in labeling to include information about clinical studies conducted in the pediatric population of patients with Juvenile Rheumatoid Arthritis.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 4, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 4, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane

Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any question, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, RPh
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carmen DeBellas
11/10/03 09:17:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-905/S-012

Aventis Pharmaceuticals, Inc.
Attention: Joseph Scheeren, PharmD
Head Global, Regulatory Coordination
200 Crossing Boulevard
PO Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Scheeren:

Please refer to your September 4, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arava® (leflunomide) tablets, 10 mg, 20 mg and 100 mg.

We also refer to your submission dated September 30, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 4, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, MD
Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lee Simon
11/7/03 02:06:23 PM

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301)827-2040

MEMORANDUM

DATE: March 5, 2004

TO: File, NDA 20-905

THROUGH: Brian Harvey, M.D. Ph.D., Acting Director, DAAODP, CDER (HFD-550), Deputy Office Director, ODE V

FROM: Sharon Hertz, M.D., Deputy Director, DAAODP

RE: Supervisory Review of Pediatric Supplement SLR-012, NDA 20-905

BACKGROUND

ARAVA (leflunomide) is an isoxazole derivative that acts as a pyrimidine synthesis inhibitor. Although initially under development as an anti-inflammatory agent, leflunomide was found to have immunomodulating activity and the clinical activity relevant to the indication is an antiproliferative effect.

Leflunomide was approved as 10, 20, and 100 mg film coated tablets by the Agency on September 10, 1998 for the following indication:
Arava is indicated in adults for the treatment of rheumatoid arthritis (RA):
1) To reduce the signs and symptoms
2) To inhibit structural damage as evidenced by X-ray erosions and point space narrowing
3) To improve physical function

The sponsor has submitted labeling supplement SLR-012, dated September 5, 2003, to NDA 20-905 in response to a Pediatric Written Request issued March 30, 1999 and amended on January 14, 2002 and again on July 8, 2003. The Pediatric Written Request specified that the pharmacokinetics (PK), safety and efficacy of leflunomide must be evaluated in the treatment of juvenile rheumatoid arthritis (JRA) in pediatric patients ages 3-17 years. The results of three clinical trials were submitted to fulfill the objectives of the Written Request. Pediatric exclusivity was granted on November 10, 2003.

The sponsor has requested labeling changes to the Pediatrics section of CLINICAL PHARMACOLOGY and Pediatric Use section of PRECAUTIONS. No pediatric indication is being sought with this submission.

Studies in adults with rheumatoid arthritis revealed that leflunomide is rapidly metabolized to a primary metabolite, M1, by the liver and during passage through the wall of the gut. Both leflunomide and the M1 metabolite have been shown to have the antiproliferative effects on lymphocytes. The elimination half-life was found to be approximately 15 days and the pharmacokinetics were linear for doses from 5 to 25 mg per day. Elimination of the M1 metabolite could be enhanced by oral administration of activated charcoal or cholestyramine. The recommended adult dose of leflunomide is a 100 mg loading dose for three days followed by a maintenance dose of 20 mg per day. If the 20 mg maintenance dose is not well tolerated, a daily dose of 10 mg is recommended. Monitoring of liver enzymes is necessary.

CONCLUSIONS

I concur with recommendation of Dr. Carolyn L. Yancey, Medical Officer, to approve this supplement with the labeling changes as proposed by the Division and agreed to by the sponsor. (See action letter for package insert.) Based on the review of the results of the three studies provided in this supplement, a pediatric indication cannot be supported nor can a pediatric dosing regimen be recommended at this time. The primary outcome measure from the efficacy trial, the Juvenile Rheumatoid Arthritis Definition of Improvement (JRA DOI) $\geq$30% Responder Analysis, was statistically significantly better for methotrexate than leflunomide (89% vs. 68%, respectively, =0.016) in the treatment of patients with polyarticular juvenile rheumatoid arthritis. The second primary outcome, Percent Improvement Index (PII), was similar for both treatment groups. Although these results failed to meet the study criteria for success of leflunomide, the 68% responder rate for the JRA DOI $\geq$30% responder analysis was comparable to the response rate for patients with rheumatoid arthritis reaching the American College of Rheumatology (ACR) 20 efficacy criteria in the adult studies. The results from the pediatric studies were sustained for an additional eight weeks during the extension study. There were no unexpected adverse events and the adverse events were comparable to those observed during adult clinical trials, including 14 patients with liver enzyme elevations.

Features of the study design may have contributed to this outcome in which, despite a notable responder rate, the study was considered a failure with respect to demonstrating the efficacy of leflunomide according to the prespecified criteria for success. The JRA DOI $\geq$30% responder rate for patients in the methotrexate group was notably high, 89%, and the dose of methotrexate in the study, 15 mg/kg, was a relatively high dose for JRA patients, often reserved for patients who have had inadequate responses to lower doses. This created a relatively high bar to beat for a superiority claim. Ethical concerns preclude the use of a placebo-control in a 16-week trial in JRA due to the risk of irreversible damage from progression of disease. Due to the risk of unacceptable toxicity

from use of leflunomide in addition to methotrexate, a placebo-controlled, add-on trial was considered unsafe.

The data also indicate that the dosing model created as a result of PK data from the first study, Study 1037, resulted in patients 40 kg and less being under dosed. This conclusion is based on the following information:

- The serum M1 concentrations in patients less than 20 kg and 20-40 kg in weight were less than the concentrations from patients over 40 kg.
- Fewer patients 40 kg and less in weight met the efficacy criteria for the JRA DOI $\geq$ 30% than patients over 40 kg.

SUMMARY OF FINDINGS

Pharmacokinetics

A population PK analysis was performed based on data from 73 patients from Studies 1037 and 3503. As described below, the dosing for these two studies differed. Dosing in Study 1037 was calculated using body surface area and the adult dosing regimen. A model was created based on the findings of Study 1037 and using this information, a decision was made to dose Study 3503 based by weight. Three weight categories were used: <20 kg, 20-40 kg, and >40 kg. The patients over 40 kg in weight were dosed comparably to adults with 20 mg per day. The 20-40 kg group received half the adult dose (10 mg per day) and the <20 kg received one quarter the adult dose (5 mg per day). The resulting average steady-state concentration was 14.5, 30 and 38.9 ug/mL for the <20 kg, 20-40 kg , and >40 kg weight groups, respectively. Of note, the clearance of M1 in patients over 40 kg was comparable to adult values, but was 1/3 less for patients 40 kg and less in weight.

Efficacy

The JRA DOI ≥30% responder rate, the first of two co-primary endpoints, was 68% for the leflunomide-treated patients and 89% for the methotrexate-treated patients, a difference that was statistically significantly different and favored methotrexate. There were effects based on weight for both the leflunomide and methotrexate groups. While the methotrexate-treated patients weighing less than 20 kg had a greater response than the heavier patients, the leflunomide-treated patients weighing less than < 20 kg and 20-40 kg had fewer responders than patients weighing more than 40 kg. There was little difference for patients more than 40 kg in weight (80% vs. 89%, leflunomide and methotrexate, respectively). Leflunomide-treated patients less than 20 kg had a lower responder rate of 63% compared with 100% for methotrexate patients less than 20 kg in weight. For patients 20-40 kg in weight, there was also a notable difference in response (58% vs. 85%, leflunomide and methotrexate, respectively).

The Percent Improvement Index, the second of two co-primary endpoints, demonstrated no statistically significantly difference for the two treatment groups, although there was a trend in favor of methotrexate (-44.4% vs. -52.9% for leflunomide and methotrexate, respectively).

Safety

The safety profile from the three pediatric studies demonstrated an adverse event profile for leflunomide in patients with JRA that was qualitatively similar to that seen in adult patients with rheumatoid arthritis. The most common adverse events were headache, abdominal pain, nasopharyngitis/pharyngitis, nausea, alopecia, diarrhea, viral infection, cough, vomiting, gastroenteritis, dizziness, JRA worsening, respiratory infection, abdominal pain and dyspepsia. Hypertension was a less common adverse event. Fourteen patients had liver enzyme abnormalities, four of whom had levels within 3-fold to 8-fold the upper limit of normal.

INDIVIDUAL STUDIES

Pharmacokinetics and Safety

Study 1037 was a 6-month, open-label, clinical trial without a control group, with an optional 24-month extension phase. Study 3053 was a 16-week, double-blind, active-control, efficacy study with an optional 8-month extension. Efficacy was evaluated primarily in Study 3503 with additional information on durability of effect from Study 3504. The medical officer review by Dr. Carolyn Yancey provides a detailed review of the protocol and results of these trials which are summarized below.

Study 1037 enrolled 27 patients with active polyarticular JRA who had failed or were intolerant of methotrexate (MTX) therapy. The patients ranged from 6 to 17 years of age with a mean age of 12.3 years. Three patients weighed less than 20 kg, 12 weighed between 20 and 40 kg, and eleven weighed 40 kg or more. Pediatric doses were calculated to be proportional to adult doses based on body surface area (BSA) and the recommended loading dose of 100 mg/day for 3 days followed by the lowest adult

maintenance dose of 10 mg/day. If there was no clinical response evidenced by the JRA Definition of Improvement (DOI) responder analysis by 8 weeks, dosing was escalated to the equivalent of an adult dose of 20 mg/day. Patients continued treatment with leflunomide for an average of 22 weeks, ranging from 1 to 30 weeks. Twenty patients (74%) had a dose increase, ranging from 5 to 20 mg/day according to the protocol which permitted adjustment of dose based on efficacy and tolerability. Two subjects required subsequent dose reduction. Seventeen patients completed the 26-week initial treatment phase and entered the extension phase. Five patients withdrew due to lack of efficacy and one due to an adverse event. Four patients were identified as withdrawing for other reasons. Three of the 17 patients entering the extension phase completed a total of 30 months, with an additional six patients continuing until the study was discontinued, but prior to reaching 30 months.

The PK model created by the sponsor with the data from this study suggested that the BSA-normalized clearance in pediatric patients with JRA was not different from adults with rheumatoid arthritis. The results further suggested that dosing could be based on body weight and a simplified dosing regimen was created for Study 3503 as described in Table 1. Please refer to the Biopharmaceutics Review by Dr. Abi Adebowale for details of the PK analysis.

Table 1. Loading and Maintenance Dose Recommendations for Further Study of

The sponsor noted in the submission that, "The above treatment regimens remain empirical and may be too conservative (i.e., inadequate therapy) for younger and/or smaller children. Additional PK data obtained from a larger number of subjects in a subsequent clinical trial, particularly those less than 6 years of age and/or less than 20 kg, will allow appropriate refinement of these dose recommendations for leflunomide in the pediatric population."(p. 83, Clin Study Report No. B2001CLN).

The efficacy information from Study 1037, an open-label clinical trial, can only be considered preliminary at best. The sponsor used the JRA DOI ≥30% responder analysis and imputed missing data by carrying forward the last observation (LOCF). (Note, this resulted in imputing results for 10 of the 27 patients enrolled.)

The JRA DOI ≥30% responder analysis classifies subjects as responders if they have a ≥30% improvement in at least three of the following six variables, provided there was no more than one of the variables worsening by >30%.
1. Physician's global assessment of disease severity, as measured on a 10 cm visual analogue scale (VAS), anchored by the words "very severe" and "inactive"
2. Patient's or parent's global assessment of overall well-being, as measured on a 10 cm VAS, anchored by the words "very poorly" and "very well"

3. Physical function, as measured by Child Health Assessment Questionnaire Disability Index (CHAQDI)
4. Number of joints with active arthritis, as defined by the American College of Rheumatology (ACR) criteria (a joint with swelling not due to deformity or a joint with limited range of motion plus pain and/or tenderness)
5. Number of joints with limited range of motion (ROM) plus pain and/or tenderness
6. Erythrocyte Sedimentation Rate (ESR)

The JRA DOI ≥30% responder rate with imputed data for missing values was 34% of patients at Week 4 and increased to 52% at Week 12 where it remained through Week 26. For the 19 patients able to remain in the trial with adequate data, the JRA DOI ≥30% responder rate was 68% (N=13). Using a JRA DOI of ≥ 50%, 12 patients (63%) in the completer group met these criteria. The results from the physician and patient/parent global assessments, number of active joints, and physical function mirrored the composite result. The mean change in number of joints with limited ROM did not improve. The ESR initially improved, worsened to below baseline at Week 12 and then improved through Week 26. Overall, these results were considered promising given that one of the inclusion criteria was for patients to be intolerant or resistant to treatment with methotrexate.

Efficacy, Safety, and Pharmacokinetics.
Study 3503 enrolled 94 patients with polyarticular JRA, ages 3 to 17 years, 47 of whom were randomized to treatment with leflunomide and 47 to methotrexate. Patients were, in contrast to patients entering study 1037, not required to have failed prior therapy with methotrexate. Dosing with leflunomide was based on the results of Study 1037 as noted in Table 1. The methotrexate dose was 0.5 mg/kg (15 mg/m^2) weekly up to a maximum of 25 mg per week. All patients received folate supplementation. Completion rates for this 16 week trial were high, 89% and 94% for leflunomide- and methotrexate-treated patients, respectively. Three patients discontinued leflunomide therapy due to adverse events, one of which was an elevation in liver enzymes. One patient discontinued methotrexate due to an adverse event. One subject discontinued from each treatment group due to lack of efficacy. One subject discontinued leflunomide therapy due to refusal to take study drug and one subject from methotrexate therapy who was lost to follow-up. Patients in both treatment groups were generally similar with respect to baseline characteristics and demographics. Mean C-reactive protein was higher in the leflunomide group at baseline, although there were no differences in mean ESR.

The efficacy analysis was based on two primary efficacy outcome measures, the JRA Definition of Improvement (DOI) ≥30% responder analysis as described above and the Percent Improvement Index (PII). The study was initially designed as a non-inferiority trial. Slow patient enrollment resulted in the sponsor amending the outcome to a superiority trial.

The PII was based on the same 6 core set measures as the JRA DOI noted above. The PII was calculated as the mean of the percent change from baseline of each of the 6 core set variables for each subject. A negative score represents improvement. Positive scores

representing worsening were set to zero for that subject. Numerous secondary efficacy outcomes were planned and analyzed.

The JRA DOI ≥30% responder analysis using the LOCF to impute missing data favored leflunomide at Week 4, but all subsequent comparisons favored methotrexate. The difference reached statistical significance at Week 16 (68.1% and 89.4%, leflunomide and methotrexate, respectively, p=0.016). There were effects based on weight for both the leflunomide and methotrexate groups as demonstrated in Table 2. The methotrexate-treated patients weighing less than 20 kg had a greater response than the heavier patients. The leflunomide-treated patients weighing less than < 20 kg and 20-40 kg had fewer responders than patients weighing more than 40 kg. The results from the completer analysis were similar.

Table 2. JRA DOI ≥30% Responder Rates by weight group (LOCF)

Weight group	Leflunomide	Methotrexate
<20 kg	5/8 (62.5%)	8/8 (100%)
20-40 kg	11/19 (57.9%)	11/13 (84.6%)
>40 kg	16/20 (80.0%)	23/27 (88.5%)

Secondary analyses of the JRA DOI ≥50% responder rate produced results similar to the JRA DOI ≥30% responder analysis, although the differences between treatment groups did not reach statistical significance at any of the time points assessed.

The following table, modified from the sponsor's Table 29, displays the results of an analysis of responder rates for patients with data at the Week 16 timepoint. Methotrexate was statistically significantly better than leflunomide for all JRA DOI responder rates.

Table 3. JRA DOI Responder- at- Endpoint Rate: ITT Subjects

Responder %	Leflunomide	Methotrexate	p-value[a]
30%	30/47 (63.8 %)	39/47 (83.0 %)	0.0303
50%	26/47 (55.3 %)	35/47 (74.5 %)	0.0385
70%	18/47 (38.3%)	28/47 (59.6%)	0.0436

a. p-value based on Cochran Mantel Hansel (CMH) procedure controlling for pooled site

Area under the curve analyses of the number of months patients were responders were performed by the sponsor using LOCF and for completers. There were no notable differences between the two treatment groups for these analyses.

The PII at the end of the 16-week trial the primary analysis, using LOCF to impute missing values, demonstrated no statistically significant difference for the two treatment groups, although after Week 4, there was a trend in favor of methotrexate (-44.4% vs. -52.9% for leflunomide and methotrexate, respectively). Unlike the JRA DOI ≥30% responder analysis, the response to leflunomide did not vary by patient weight ranging from -46.3% for patients weighing less than 20 kg to -45.3% for patients over 40 kg. The response to methotrexate did vary by weight with the greatest effect for patients less than 20 kg (-66.9%) compared to patients weighing 20-40 kg and over 40 kg (-49.5% and -50.9%, respectively).

Analyses of the six core variables did not reveal any between-group differences for physician global assessment, number of active joints, joints with limited ROM, CHAQ Disability Index, or ESR.

Patient/parent global assessment was better for methotrexate than leflunomide, but only by a relatively small amount that did not reach statistical significance.

The PK data from this study found the range of CL/F values for the M1 metabolite observed in the pediatric patients was generally within the range of values estimated in the adult RA population. When broken down by weight group, the clearance for patients weighing more than 40 kg was comparable to that seen in adults; for patients weighing 40 kg and less, the clearance was approximately one third less.

Based on the range of doses studied, the systemic exposures to M1 in JRA subjects weighing more than 40 kg was comparable to that in adult RA subjects. However, even with the reduced clearance of M1 in patients weighing less than 40 kg, the M1 exposure was lower in these patients, suggesting they were under-dosed. The results of a simulation performed by the sponsor suggests that a higher daily maintenance dose for patients weighing under 40 kg could result in M1 steady-state concentrations comparable to pediatric patients weighing over 40 kg and adult patients.

Efficacy and Safety

Study 3504 was ongoing at the time of the supplement submission. Data from the first 8 weeks of the study were analyzed in an interim data summary and submitted with the supplement according to a prior agreement between the Agency and the sponsor. This extension study for Study 3503 offered ongoing double-blind treatment with study drug for up to an additional 8 months. Seventy patients opted to continue study drug. Twenty three patients in the leflunomide group and 30 in the methotrexate group had safety and/or efficacy data available at the time of the interim data summary. One leflunomide-treated patient discontinued study participation after withdrawing consent and three methotrexate-treated subjects discontinued study participation due to a new onset adverse event within the initial 8-week reporting period. Total drug exposure was 21 leflunomide-treated patients with 169-196 days, two with 141-168 days. For methotrexate-treated patients, 21 had 169-196 days of exposure, seven had 141-168 days exposure, and 2 had 85-140 days exposure.

The efficacy data demonstrated overall durability for much of the efficacy resulting from treatment with leflunomide and methotrexate. For the 23 leflunomide-treated patients with efficacy data at Week 24, 19 met the JRA DOI $\geq$30% responder criteria at Week 24, 4 of whom had been nonresponders at Week 16. One prior responder converted to a nonresponder at Week 24. As a result, 83% of the 23 patients were responders at Week 24 compared with 68% of the 47 patients at Week 16. For the methotrexate-treated patients with efficacy data at Week 24, 21 met the JRA DOI $\geq$30% criteria at Week 24, one of whom had previously been a nonresponder, and three converted to nonresponders at Week 24. There was no substantial change in the PII for either treatment group at 24

weeks compared to 16 weeks. The six core set variables were each relatively stable during the eight additional weeks of study.

INTEGRATED ASSESSMENT OF SAFETY

The safety of leflunomide has not been fully evaluated, particularly for patients under 40 kg of weight who appear to have been under dosed as evidenced by relatively lower M1 values and less efficacy than patients over 40 kg. There were no unexpected events and the adverse event profile was similar to the adverse event profile in adults.

There were no deaths during any of the three studies.

Serious adverse events (SAEs) are detailed in Table 4. There were 13 SAEs in seven patients in Study 1037. The worsening of joint disease and deformity and appendicitis are unlikely related to study drug. The relationship of study drug to the remainder is possible. In Study 3503, there were 10 leflunomide-treated patients (21.3%) with 11 SAEs. While the Crohn's Disease and fracture had no apparent relationship to study drug, it is possible that the infections were related. The liver enzyme elevations were likely related. There were five SAEs during Study 3504, one in a leflunomide-treated patient, four in methotrexate-treated patients. The relationship of these to study drug is possible for all, although less likely for the fecal impaction and joint effusion.

Table 4. SAEs

	Number of Patients	
SAE	Leflunomide	Methotrexate
Study 1037		
Cellulitis, elevated liver enzymes, petechiae, hypertension	1	
Valgus deformity of right lower extremity	1	
JRA flare	1	
Gastritis/appendicitis	1	
Anemia	1	
Worsened left and right hip disease	1	
Stress fracture of right femur, depression	1	
Study 3503		
Crohn's Disease	1	
Infections (facial cellulitis, viral infection, salmonellosis)	4	
Tibia fracture (fall during volleyball)	1	
JRA worsened	2	
Pityriasis lichenoides	1	
Elevated LFTs (ALT 7.4xULN and AST 3.1xULN)	1	
Study 3504		
Abdominal pain requiring hospitalization (impaction)	1	
Elevated LFTs, ≥ 3X ULN		2
Abdominal pain, fever, vomiting		1
Joint effusion		1

Six patients withdrew from Study 1037 due to adverse events, although in the disposition table, two of these patients are counted in the "other" category. The adverse events responsible for early discontinuation were one case each of hypertension (also considered an SAE), headache, and mouth ulcer, and two cases each of abdominal pain and urticaria.

During study 3503, four patients discontinued due to adverse events, three from the leflunomide group, all of which were described as SAEs, and one from the methotrexate group which was due to an elevation in ALT.

No leflunomide-treated patients in Study 3504 discontinued due to an adverse event. Three methotrexate-treated patients discontinued due to an adverse event, either elevated liver enzymes or gastrointestinal symptoms. All were previously reported as SAEs.

Adverse events were common, occurring in more than 90% of leflunomide-treated patients and 81% of methotrexate-treated patients. The most common adverse events were headache, abdominal pain, nasopharyngitis/pharyngitis, nausea, alopecia, diarrhea, viral infection, cough, vomiting, gastroenteritis, dizziness, JRA worsening, respiratory infection, abdominal pain and dyspepsia. Table 5, modified from the sponsor's table of adverse events, provides additional detail on the adverse events.

Table 5. Adverse Events Occurring In 4 Or More Patients

	Study 1037	Study 3503		Study 3504	
	(N=27)	LEF (N=47)	MTX (N=47)	LEF (N=23)	MTX (N=30)
Total no. subjects [n (%)	**] 26 (96.3)**	**43 (91.5)**	**38 (80.9)**	**6 (26.1)**	**11 (36.7)**
Headache	17 (63.0)	13 (48.1)	8 (17.0)	5 (10.6)	1 (3.3)
Abdominal pain	11 (40.7)	8 (29.6)	5 (10.6)	4 (8.5)	1 (3.3)
Nasopharyngitis	0 (0.0)	0 (0.0)	4 (8.5)	1 (2.1)	0 (0.0)
Nausea	10 (37.0)	8 (29.6)	9 (19.1)	7 (14.9)	0 (0.0)
Alopecia	8 (29.6)	8 (29.6)	7 (14.9)	2 (4.3)	0 (0.0)
Diarrhea	10 (37.0)	7 (25.9)	3 (6.4)	3 (6.4)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
Cough	7 (25.9)	5 (18.5)	2 (4.3)	0 (0.0)	0 (0.0)
Vomiting	4 (14.8)	1 (3.7)	2 (4.3)	2 (4.3)	1 (3.3)
Pharyngolaryngeal pain	-	4 (8.5)	2 (4.3)	1 (2.1)	0 (0.0)
Pyrexia or fever	3 (11.1)	2 (7.4)	1 (2.1)	0 (0.0)	1 (3.3)
Arthralgia	4 (14.8)	4 (14.8)	1 (2.1)	0 (0.0)	2 (6.7)
Conjunctivitis	3 (11.1)	2 (7.4)	0 (0.0)	0(0.0)	0 (0.0)
Gastroenteritis	6 (22.2)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Dizziness	7 (25.9)	6 (22.2)	1 (2.1)	1 (2.1)	0 (0.0)
JRA worsening	10 (37.0)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)
Overdose	-	3 (6.4)	3 (6.4)	1 (2.1)	0 (0.0)
Rash	9 (33.3)	5 (18.5)	1 (2.1)	0 (0.0)	1 (3.3)
Rhinitis	7 (25.9)	5 (18.5)	1 (2.1)	0 (0.0)	0 (0.0)
Respiratory infection	17 (63.0)	8 (29.6)	1 (2.1)	0 (0.0)	0 (0.0)
Abdominal pain, upper	5 (18.5)	4 (14.8)	1 (2.1)	1 (2.1)	1 (3.3)
Acute tonsillitis	-	2 (4.3)	2 (4.3)	0 (0.0)	0 (0.0)
ALT increased	1 (3.7)	1 (3.7)	1 (2.1)	2 (4.3)	0 (0.0)
Arthritis	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	1 (3.7)	1 (3.7)	1 (2.1)	0 (0.0)	0 (0.0)
Creatinine increased	-	2 (4.3)	2 (4.3)	1 (2.1)	0 (0.0)
Dyspepsia	4 (14.8)	4 (14.8)	2 (4.3)	0 (0.0)	0 (0.0)
Fatigue	-	2 (4.3)	1 (2.1)	2 (4.3)	1 (3.3)
Impetigo	-	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
LFT abnormal	3 (11.1)	3 (11.1)	2 (4.3)	1 (2.1)	1 (3.3)
Platelet count increased	-	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	2 (7.4)	1 (3.7)	0 (0.0)	1 (2.1)	0 (0.0)
Contusion	-	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)
Excoriation	-	1 (2.1)	0 (0.0)	0 (0.0)	1 (3/3)
Herpes simplex	1 (3.7)	1 (3.7)	1 (2.1)	0 (0.0)	0 (0.0)
Joint sprain	-	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis media	3 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	1 (3.3)
Infection, unspecified	3 (11.1)	2 (7.4)	-	-	-
Pharyngitis	7 (25.9)	4(14.8)	0 (0.0)	0 (0.0)	0 (0.0)
Flu syndrome	6 (22.2)	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	6 (22.2)	4 (14.8)	0 (0.0)	0 (0.0)	1 (3.3)
Mouth ulcerations	6 (22.2)	4 (14.8)	1 (2.1)	1 (2.1)	0 (0.0)
Pain NOS	6 (22.2)	3 (11.1)			
Accidental injury	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	4 (14.8)	4 (14.8)	1 (2.1)	0 (0.0)	0 (0.0)

Study 1037 was coded using COSTART, Studies 3503 and 3504 using MEDRA

Leflunomide and methotrexate are both known to have a risk of hepatotoxicity based on experience with use in adults. A total of 14 of 74 pediatric patients treated with leflunomide had elevated liver enzymes. Twelve of these were elevated to up to 3-fold the upper limit of normal. Two patients had elevations in liver enzymes between 3- and 8-fold the upper limit of normal. Elevén of these abnormalities resolved within the follow-up period for the study following dose reduction or drug discontinuation. Two returned to levels less than 2-fold the upper limit of normal and one did not reverse. None of the elevated liver enzymes occurred in patients weighting less than 20 kg, although as noted in the efficacy review, these patients appear to have been under dosed.

Fifteen methotrexate-treated patients had elevated liver enzymes, 12 in the 1.2 to 3-fold the upper limit of normal range, and three with levels over 3-fold the upper limit of normal. Two patients under 20 kg and three less than 40 kg had elevated liver enzymes. Eleven of these patients had normal liver enzymes at study completion, three reverse to a value of two or less times the upper limit of normal and one did not reach a level of 2-fold the upper limit of normal.

The one patient with liver enzyme elevation while treated with leflunomide during Study 3504 had resolution of the abnormality after discontinuation of study drug.

Infections occurred in 78% of patients in Study 1037, most of which (63%) were upper respiratory infections that resolved without intervention. One infection, a case of cellulitis, was considered serous and required hospitalization. One patient developed herpes zoster that did not disseminate. Leflunomide was temporarily interrupted. In Study 3503, the occurrence of infections was similar between the two treatment groups, approximately 54%. Most of these were nonspecific viral infections and upper respiratory tract infections, followed by nonspecific gastroenteritis. There were single cases of herpes simplex and cellulitis in leflunomide-treated patients and a single case of Epstein-Barr virus in methotrexate-treated patients.

Rashes were infrequent, occurring in three leflunomide-treated patients and three methotrexate-treated patients. None were considered serious except one case of pityriasis lichenoides (parapsoriasis) in a leflunomide-treated patients. This is not generally considered a drug-induced rash, and is more likely idiopathic or triggered by infection. The rash continued following drug discontinuation. One methotrexate-treated patient discontinued due to erythema of the toes that resolved after treatment was interrupted.

Renal function assessed by serum creatinine was not notably altered by either study drug during these clinical trials.

There were sporadic elevations in blood pressure during Study 1037 with six patients demonstrating more persistent elevations in systolic and /or diastolic blood pressure. One patient discontinued study participation early due to an episode of hypertension after 28 months of treatment with leflunomide (178/111) which resolved following treatment with amlodipine. Sporadic elevations were also noted during treatment with leflunomide in Study 3503 and Study 3504. See Dr. Yancey's review for further details.

Headache occurred in 63% of leflunomide-treated patients in Study 1037 and 38% in Study 3503 compared to 17% of methotrexate-treated patients in Study 3503. This is more frequent than the occurrence in adult clinical trials of leflunomide in rheumatoid arthritis as described in Dr. Yancey's review. The clinical significance of this finding is unknown.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Hertz
3/5/04 03:20:48 PM
MEDICAL OFFICER

Brian Harvey
3/5/04 03:32:59 PM
MEDICAL OFFICER

September 4, 2003

SUBMISSION OF PEDIATRIC STUDY REPORTS
PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic & Ophthalmologic Drug Products (HFD-550)
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

NDA 20-905: ARAVA® (leflunomide) Tablets S012
Labeling Supplement with Clinical Data
Submission of Pediatric Study Reports
Pediatric Exclusivity Determination Requested

Dear Dr. Simon:

Reference is made to our NDA for 20-905 for Arava and to the correspondence from the Agency dated March 30, 1999, requesting pediatric information on Arava ®(leflunomide tablets) for the treatment of juvenile rheumatoid arthritis (Attachment 1). Additional reference is made to the continuing correspondence between Aventis and the Agency from December 6, 2000 until April 09, 2003, wherein several amendments were made to the original written request for pediatric studies (details captured in regulatory history Appendix 1). Reference is also made to the correspondence dated July 9, 2003 approving the changes requested by Aventis (Attachment 2). The correspondence required that Aventis submit all pediatric study reports on or before September 9, 2003.

This submission contains the pediatric study reports for leflunomide as requested in the above captioned written request and the applicable amendments. As requested by the Agency these reports are being provided for review consideration prior to November 9, 2003. An assessment of the clinical study reports included in this submission will demonstrate that each element of required information as specified in the written request has been fulfilled by Aventis. For the convenience of the reviewers, a detailed checklist (Attachment 3) is attached identifying each element of required information contained in the final correspondence dated July 9, 2003.

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

This supplement also provides for annotated draft labeling reflecting inclusion of pertinent pediatric data in the current approved package insert for Arava®.

In submitting these pediatric studies, Aventis is entitled to a temporary stay of FDA acceptance or approval of any abbreviated or §505(b)(2) applications citing Arava® (leflunomide) as a reference listed drug. Aventis currently has five year new chemical entity (NCE) exclusivity for Arava pursuant to §505(c)(3)(D)(ii) of the FDCA. This exclusivity is set to expire on **September 10, 2003.** It is possible that FDA may not determine that the submitted studies meet the requirements for pediatric exclusivity until after Aventis' NCE exclusivity expires. In such cases, §505A(e) of the FDCA requires that the Agency grant a temporary stay against acceptance or approval of any application under sections 505(b)(2) or 505(j) of the Act. The statute requires that the stay remain in place until (a) FDA grants or denies pediatric exclusivity based on the submitted studies, or (b) 90 days, whichever comes first.

meeting in place

Based on this submission, Aventis has met the statutory and regulatory requirements for pediatric exclusivity for leflunomide. It is our understanding that the granting of pediatric exclusivity is not connected, or dependent upon approval of the attached revised labeling. We request that six months exclusivity be granted to Aventis for leflunomide.

Aventis certifies that all electronic media are free from computer virus. Virus scan, for the entire submission, was performed using Symantec's Norton Antivirus Corporate Edition Version 7.0, Scan Engine Version 1.1.11 and the Virus Definition File is Version 50819C. The electronic archival copy, of this application, consists of 1 DLT 35/70 Digital Tape. The approximate size of the data is 1 gigabyte.

Should you require any additional information, or have any further questions, please contact me at 908-231-3848, or in my absence Steve Caffé, M.D., at 908-231-5863.

Sincerely,

Joseph Scheeren, Pharm.D.
Head Global Regulatory Coordination

Cc: Ms. Jane Dean
Cc: Office of Generic Drugs, FDA (HFD-600) (cover letter only)

September 30, 2003

Food and Drug Administration
Attention: Lee Simon, M.D.
Director, Division of Anti-Inflammatory, Analgesic &
Ophthalmologic Drug Products, HFD-550
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA 20-905: ARAVA® (leflunomide) Tablets
Supplement 012-amendment
Juvenile Rheumatoid Arthritis

Dear Dr. Simon,

Reference is made to our Supplement 012 submission received by FDA on September 5, 2003 and subsequent discussions with Ms Jane Dean.

We have informed the FDA on September 10, 2003 that we had discovered a small number of errors in hyperlinks and several erroneous references in the modules and study reports of Supplement 012. These findings have been corrected.

We found in addition errors pertaining to the text mainly of the clinical study report 3503 and also a few ones in the clinical study report 3504. We have corrected the error findings and amended the report 3503 and 3504.

Please note that all end of text tables are identical to the ones submitted September 5, 2003. Only two end of text tables of the clinical study report 3503 have a footnote text that needed correction.

Finally, Post It notes were found on some pages of the CRF's of all three studies 1037, 3503 and 3504 partially obscuring the CRF's pages. We have replaced these CRF pages with ones without the Post It notes.

The summary modules 2.5, 2.7.3, 2.7.4, 2.7.6 and 5.2 have been reconciled with the corrected study reports.

Please find enclosed a partial electronic replacement file as an amendment to Supplement 012 addressing all error findings in the original submission for:

- Module 2.5

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

- Module 2.7.3
- Module 2.7.4
- Module 2.7.6
- Module 5.2
- Study report 1037 and the corresponding CRF's
- Study report 3503 and the corresponding CRF's
- Study report 3504 and the corresponding CRF's

This electronic partial replacement file is on one 1 CD (approximately 350 MB) labeled "partial replacement" and the electronic full replacement file is on one CD (approximately 700 MB) labeled "full replacement":

Norton Antivirus	
7.50.846	Program
4.1.0.6	Scan Engine
50924h	Definition File
9/24/03	Update Date

As requested by the agency on September 10, 2003, we have enclosed a paper review aid. This paper review aid consists of three copies of 7 volumes including the summary modules and text and tables of the study reports.

We consider the information included in this submission to be confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis Pharmaceuticals Inc.

Should you have any further questions, or require any additional information, please feel to contact me at 908-231-3848, or Steve Caffé, M.D., at 908-231-5863.

Sincerely,

Joseph Scheeren, Pharm.D.
Head Global Regulatory Coordination

Cc: Ms. Jane Dean, RN, MSN
Regulatory Health project Manager

Attachments:

- Delivered to the Central Document Room:

-CD electronic partial replacement
-CD electronic full replacement

- Delivered to Ms Jane Dean:

-Paper review aid 7 volumes (3 copies)