Department of Health and Human Services
Center for Drug Evaluation and Research, HFD-550

Medical Officer Review

NDA	20-905, S-012 Extension Study Safety and Efficacy, Study HWA486/3504
Sponsor:	Aventis Pharmacetuicals, Inc. (Aventis)
Letter Date:	October 29, 2004
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Reviewer Received:	November 5, 2004
Review Completion Date:	May 20, 2005
Drug Name:	ARAVA (leflunomide) tablets
Pharmacologic Category:	Isoxazole immunomodulatory agent; pyrimidine synthesis inhibitor with antiproliferative effects
Dosage form and route:	10mg, 20mg and 100mg tablets, oral route
Materials reviewed:	NDA 20-905, Supplement -012, SE5, Polyarticular JRA Clinical Study Report for HWA486/3504 Extension Study
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Resume

This medical officer's review is of the **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, Leflunomide versus Methotrexate". This medical officer review summarizes the safety and durability results from the completed extension study which fulfills the sponsor's commitment to provide the Final Study Report, datasets and case report forms to the HFD-550 division upon completion of the study.

Background

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 about 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.

As of March 5, 2004, PDUFA date for the pediatric studies, the interim extension study HWA486/3504 results were reported through 8 weeks of the planned 8-month extension study. There were 33 JRA patients exposed to leflunomide and 37 JRA patients exposed to methotrexate; the interim data summary (IDS) was completed through week 8

(June 30, 2003) at the time of the NDA supplement review; 22 exposed to leflunomide; 27 exposed to methotrexate.

Executive Summary from NDA 20-905, S-012, SE5

See NDA 20-905, S-012, SE5 Medical Officer Review, March 5, 2004. 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 HWA486/3503. 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. As noted by the sponsor, both medications produced clinically important improvement in physical function as measured by the CHAQ.

This reviewer noted that 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 label insert explains that the recommended stating dose is 10mg/m2/week.

The smaller and younger patients were less responsive to selected doses of Leflunomide. It appeared that the smaller younger patients ≤ 40 kg were under-dosed compared to the patients > 40kg on the basis of 1) the M1 concentrations 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.

Completed Extension Study HWA486/3504

A. Dosing and Regimen

Each patient in extension study HWA486/3504 continued to receive double-blind treatment with either leflunomide and methotrexate placebo, or leflunomide placebo and methotrexate, according to their drug regimen at the completion of HWA486/3503. Each patient continued to received leflunomide or leflunomide placebo as a daily or every other day maintenance dose.

The initial maintenance dose in study HWA486/3503 was based on body weight as outlined in **Table 1**, Leflunomide maintenance dosing from study HWA486/3503. A decrease to a half dose was permitted for tolerability and was required in the case of LFT elevations of > 2 to 3 X ULN.

Table 1. Leflunomide maintenance dosing from HWA486/3503
(sponsor table 2, page 35 of 5923)

Weight	Initial leflunomide maintenance dose
< 20 Kg	5 mg/day (one 10 mg tablet ever other day)
20 – 40 Kg	10 mg/day (one 10 mg tablet every day)
> 40 Kg	20 mg/day (two 10 mg tablets once daily)

According to the sponsor, each patient also continued to receive methotrexate or methotrexate placebo once weekly on a fixed day of the week. The dose of methotrexate or methotrexate placebo in study HWA486/3503 was 0.5 mg/kg/week with a decrease of at least 2 tablets (5 mg) per week permitted for tolerability and required for LFT elevations > 2 to 3 X ULN. Patients taking 0.5 mg/kg/week at the end of study HWA486/3503 were allowed to increase dosage during the extension study (at the discretion of the investigator) up to 0.6 mg/kg/week (18 mg/m^2 week for a subject weighing 30 kg and having a body surface area of 1m^2. In cases where the calculated methotrexate dose was not a multiple of 2.5 mg, the patient was dosed at the closest whole number of methotrexate tablets.

B. Methods and Results, Safety

1. Disposition

Patient Exposure

All subjects who signed the informed consent for HWA486/3504 were included in the safety-evaluable population. JRA patients who completed 4 months of study HWA486/ 3503 and wanted to continue on their current study medication were eligible to enter the extension study HWA486/ 3504. There were 70 JRA patients, from 27 sites, enrolled and randomized in the safety population; 33 patients in the leflunomide group and 37 patients in the methotrexate group. See **Table 2**. Also see the **Appendix, Figure 1** for patient disposition information.

Table 2. Analysis Population (sponsor table 10, page 67 of 5923)

Populations **N**	**Leflunomide** **N**	**Methotrexate** **N**	**Total** **N**
Enrolled	33	37	70
Safety Evaluable	33	37	70
Efficacy Evaluable	33	35	68

In retrospect, there were 16 patients who completed Study HWA486/3503 but who did not enroll in the extension study HWA486/3504 (9 leflunomide and 7 methotrexate treated patients). Seven of these 16 patients were from investigator sites that elected not to participate in extension study 3504.

The leflunomide and the methotrexate groups were comparable for the total number of days of exposure to the study drug. The duration of study medication is summarized in **Table 3**, study medication duration (safety subjects).

Table 3. Study Medication Duration (Safety Patients) (sponsor table 8, page 64 of 5923)

Duration (days)				
		Treatment Group		
Characteristic	**Statistic**	**Leflunomide N=33**	**Methotrexate N=37**	**Probability**
Study Drug Duration				0.5620
	Mean (SD)	337.8 (84.4)	349.4 (78.4)	
	Median	350	345	
	Range	171-532	112-477	
	Number	33	37	

Drop-Outs

There were 55 JRA patients (24/33 patients in the leflunomide group and 31/37 patients in the methotrexate group) who completed the study; hence, there were 9 patients in the leflunomide group and 6 patients in the methotrexate group who did not complete the study to the week 48 endpoint. Five patients in the leflunomide group withdrew due to lack of efficacy and one withdrew due to progressive disease, whereas, no patients in the methotrexate group withdrew due to lack of efficacy.

Discontinuations due to TEAEs

One patient in the leflunomide group (3.0%) and 5 patients in the methotrexate group (13.5%) discontinued from the extension study due to TEAEs. See **Table 4,** second line, discontinuation of study medication due to AE.

Table 4. Other Significant Adverse Events (sponsor table 39, page 113 of 5923)

AE criteria	All TEAES N (%)		Possibly-related TEAES N (%)	
	Leflunomide N=33	**Methotrexate N=37**	**Leflunomide N=33**	**Methotrexate N=37**
Other significant TEAES: total subjects	23(69.7)	25(67.6)	7(21.2)	10(27.0)
Discontinuation of study medication due to AE	1(3.0)	5(13.5)	1(3.0)	3(8.1)
Therapy interrupted due to AE	2(6.1)	4(10.8)	0(0.0)	1(2.7)
Dose reduced due to AE	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Intervention other than change in study medication	9(27.3)	9(24.3)	3(9.1)	1(2.7)
AE Treated with counteractive medication	20(60.6)	22(59.5)	6(18.2)	8(21.6)
Medically important lab abnormalities (SAE)	0(0.0)	3(8.1)	0(0.0)	2(5.4)

Supporting data are provided in TableT96 (pg. 258) .

Discontinuations due to SAEs

One JRA patient in the leflunomide group (3.0%) with colitis and 5 patients in the methotrexate group (13.5%) [3 patients had elevated hepatic transaminases; 1 patient had

arthritis flare; 1 patient had a gastrointestinal disorder] were discontinued from the extension study due to treatment-emergent SAEs. Colitis, diagnosed by colonoscopy and biopsy, inflammatory bowel disease (ulcerative colitis), was diagnosed after 281 days of leflunomide treatment in patient 0205001 who had persistent diarrhea.

The ALT elevations in the 3 methotrexate patients were all alert terms (≥ 3 x ULN). JRA patients were required to have ALT and AST levels < 1.5 X ULN at baseline of Study 3503. All but 1 leflunomide subject were normal (defined as ≤ 1.2 X ULN) at baseline.

Each of the patients who discontinued due to an AE had an SAE that led to discontinuation. Two of the methotrexate patients had additional AEs leading to discontinuation that were not SAEs. Methotrexate patient 0601002 discontinued due to an SAE, gastro-intestinal disorder, and two associated symptoms reported as non-serious AEs, abdominal pain and fever, all assessed as possibly treatment-related. Methotrexate patient 0603005 discontinued due to 2 SAEs, ALT increased and AST increased, and one non-serious AE, Epstein-Barr virus infection, none of which were assessed as treatment related. See Table 5.

Table 5. Discontinuations of Study Medications
(sponsor table T-97, page 259 of 5923)

System Organ Class	Number ((%) of subjects All TEAEs			
	LEF (N=33)		MTX (N=37)	
Subjects with TEAEs	**1**	**3.0%**	**5**	**13.5%**
Gastrointestinal Disorders	**1**	**3.0%**	**1**	**3.0%**
Colitis	1	3.0%	0	0.0%
Abdominal Pain	0	0.0%	1	2.7%
Gastrointestinal disorder	0	0.0%	1	2.7%
General disorders and Administration Site Conditions	**0**	**0.0%**	**1**	**2.7%**
Pyrexia	0	0.0%	1	2.7%
Infections and Infestations	**0**	**0/0%**	**1**	**2.7%**
Epstein-Barr virus infection	0	0.0%	1	2.7%
Investigations	**0**	**0.0%**	**3**	**8.1%**
Alanine aminotransferase increased	0	0.0%	2	5.4%
Aspartate aminotransferase increased	0	0.0%	1	2.7%
Liver function test abnormal	0	0.0%	1	2.7%
Musculoskeletal and Connective Tissue	**0**	**0.0%**	**1**	**2.7%**

Disorders Arthritis	0	0.0%	1	2.7%
Note: The numbers in each column cannot be added because a patient may have more than 1 adverse event. (See **Tables 7 and 8** with patient identifier numbers)				

Withdrawals
There were 9 patients in the leflunomide group and 6 patients in the methotrexate group who did not complete the study to the week 48 endpoint. See above in Discontinuations of Study Medication section.

2. Compliance
In the leflunomide group, 78.8% of JRA patients were at least 80% complaint with leflunomide doses and 84.8% of JRA patients were at least 80% compliant with methotrexate placebo doses. In the methotrexate group, 91.7% of JRA patients were at least 80% complaint with methotrexate doses and 86.5% of the JRA patients were at least 80% compliant with the leflunomide placebo doses.

3. Demographics and Baseline Characteristics
Demographic characteristics are similar between treatment groups. The majority of patients in both treatment groups were white females < 12 years of age. The mean age of study patients was ~10 years old. In the leflunomide group, 45.5% of the JRA patients weighed > 40 kg, whereas in the methotrexate group, 59.5% of the patients weighed > 40 kg upon enrollment in the extension study. The majority in both treatment groups had JRA that was polyarticular at onset of the disease. Most were rheumatoid factor negative.

C. Findings of Safety Review for Extension Study HWA486/3504

Deaths
There were no deaths in any of the JRA patients (N=70) in study HWA486/3504.

Significant Overdose
There were no patients with significant overdose reported during this study.

Serious Adverse Events
There were no serious adverse events (SAEs) due to life-threatening illness, permanent or significant disability, or congenital anomaly/ birth defect. A total of 4 JRA patients (12.1%) experienced 5 treatment-emergent SAEs in the leflunomide group. A total of 9 JRA patients (24.3%) experienced 16 treatment-emergent SAEs (including 2 events of bursitis in 1 patient) in the methotrexate group. See **Table 6.**

Table 6. Serious Adverse Events, SAEs, by System Organ Class (sponsor table 38, page 109 of 5923)

Body system Preferred term	Leflunomide N=33		Methotrexate N=37	
	All N(%)	Possibly Related N(%)	All N(%)	Possibly Related N(%)
Subjects with TEAEs	**4(12.1)**	**1(3.0)**	**9(24.3)**	**4(10.8)**
Eye disorders	0(0.0)	0(0.0)	1(2.7)	1(2.7)
Iridocyclitis	0(0.0)	0(0.0)	1(2.7)	1(2.7)
Gastrointestinal disorders	3(9.1)	1(3.0)	2(5.4)	2(5.4)
Abdominal pain	1(3.0)	0(0.0)	0(0.0)	0(0.0)
Colitis	1(3.0) [a]	1(3.0) [a]	0(0.0)	0(0.0)
Intestinal infarction	1(3.0)	0(0.0)	0(0.0)	0(0.0)
Gastrointestinal disorder	0(0.0)	0(0.0)	1(2.7) [a]	1(2.7) [a]
Nausea	0(0.0)	0(0.0)	1(2.7)	1(2.7)
Vomiting	0(0.0)	0(0.0)	1(2.7)	1(2.7)
Infections, infestations	0(0.0)	0(0.0)	2(5.4)	0(0.0)
Ear infection	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Tonsillitis	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Viral infection	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Injury, poisoning, procedural complications	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Radius fracture	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Investigations	0(0.0)	0(0.0)	3(8.1)	2(5.4)
ALT increased	0(0.0)	0(0.0)	2(5.4) [a]	1(2.7) [a]
AST increased	0(0.0)	0(0.0)	1(2.7) [a]	0(0.0)
Liver function test abnormal	0(0.0)	0(0.0)	1(2.7) [a]	1(2.7) [a]
Musculoskeletal, connective tissue disorders	1(3.0)	0(0.0)	2(5.4)	0(0.0)
Juvenile arthritis	1(3.0)	0(0.0)	0(0.0)	0(0.0)
Arthritis	0(0.0)	0(0.0)	1(2.7) [a]	0(0.0)
Bursitis	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Joint effusion	0(0.0)	0(0.0)	1(2.7)	0(0.0)
Social circumstance	1(3.0)	0(0.0)	0(0.0)	0(0.0)
Social problem	1(3.0)	0(0.0)	0(0.0)	0(0.0)

[a] discontinued from study.

The SAEs in the leflunomide group were not different from previously reported serious adverse events in children and adults with leflunomide therapy. None of the leflunomide SAEs was hepatic**.** However, elevated hepatic transaminases were reported in 3 of the 9 methotrexate subjects with SAEs. According to the sponsor, the hepatic transaminase elevations were assessed as treatment-related in 2 of the 3 methotrexate patients; all 3 patients had alert term ALT elevations (ALT > 3 X ULN). See **Table 7 and 8.**

In 1 leflunomide patient (0205001), the SAE, colitis, was assessed as treatment-related. In 4 methotrexate patients, the SAE was assessed as treatment-related: iridocyclitis (0704001), gastrointestinal disorder (0601002); ALT increased, nausea, vomiting, (0901004) and LFT abnormal (0501001).

The incidence of all SAEs in the extension study patients decreased for the leflunomide group: (6 patients, 18.2% for HWA486/3503 versus 4 patients, 12.1% for study HWA486/3504). The incidence of all SAEs increased in the extension study for the methotrexate group (0 patients, 0.0% for study HWA486/3503 versus 9 patients, 24.3% for study HWA486/3504). See **Table 7 and 8.**

Table 7. Treatment Leflunomide, SAEs, HWA486/3504

Patient Number	**Hospitalized**	**Reason for d/c of Rx**		**SAE(study Rx not d/c)**	**Other Clinically important AEs**
		SAE	Non-SAE		
0134003					x, diarrhea, wt. loss,
0205001	x	x, colitis			
0606002	x			x, Epstein Barr infection	
0901005	x			x, diarrhea, epiploic infarction; JRA flare	Recovered w/o sequelae
1101003	x			x, Steroid inj. Rt. Knee, left wrist	Social problems at home

Table 8. Treatment with Methotrexate, SAEs, HWA486/3504

Patient Number	**Hospitalized**	**Reason for d/c of Rx**		**SAE (study rx not d/c)**	**Other clinically important AEs**
		SAE	Non-SAE		
0134002				x, fall/frx rt. radius	
0401002	x	x		x, flare of JRA	
0501001		X, ALT 5.3 xULN; AST 2.1 xULN; alk phos 3.6 xULN			
0601002	x	x, gastroenteritis, vasculitis of toes			
0603005		x, ALT 6.6x ULN; AST 4.1 xULN, norm alk phos and bili.			
0701001	x			x, eff. Rt./Lft. knee, Baker's Cyst	
0704001				x, iridocyclitis	
0802002	x			x, tonsillitis, otitis, recovered,	

				had tonsillectomy, myringotomy	
0901004		X, nausea, vomiting, ALT 4.47xULN, AST 1.1xULN		x	

Hospitalizations with SAEs
Four JRA patients in each group, leflunomide (12.1%) and methotrexate (10.8%), had SAEs for which hospitalization was the seriousness criterion. See **Tables 7 and 8.**

Treatment Emergent Adverse Events (See Table 10, TEAEs))
There were 29 patients in the leflunomide group and 31 patients in the methotrexate group with treatment-emergent adverse events (TEAEs), the onset during the 8-month extension study. Treatment-emergent AEs of the infections and infestations class were most frequently reported by both groups, followed by gastrointestinal disorders class, and then by the respiratory class, thoracic and mediastinal disorders class.

Infections/Infestations
The infections and infestations occurred in 13 leflunomide patients (39.4%) and 15 methotrexate patients (40.5%). The events were reported as upper respiratory tract infection, viral upper respiratory tract infection and nasopharyngitis. More patients in the leflunomide group than in the methotrexate group reported previous illnesses (45.5% versus 32.4%). The between group difference in the percent of patients reporting a past illness of varicella infection was: 15.2% of leflunomide patients versus 2.7% of methotrexate patients. However, the groups did not differ in terms of the proportion that had varicella antibody positive.

Gastrointestinal System
The gastrointestinal body system had the second highest incidence of adverse events in both treatment groups, occurring in 12 leflunomide patients (36.4%) and 14 methotrexate patients (37.8%). Gastrointestinal events considered by the investigator as possibly treatment-related occurred in 6 leflunomide patients (18.2%) and 10 methotrexate patients (27%). Most of the TEAEs were mild, 10 leflunomide patients (30.3%) and 10 methotrexate patients (27%) or moderate, 3 leflunomide patients (9.1%) and 5 metho-trexate patients (13.5%). One patient in each treatment group experienced an event that was assessed as severe in intensity and possibly related to study medication: patient 0205001 in the leflunomide group had her study medication discontinued due to the serious adverse event colitis, and patient 0601002 in the methotrexate group had her study medication discontinued due to a gastrointestinal disorder that was reported as a serious adverse event. Both subjects recovered without sequelae.

Abdominal pain, diarrhea, vomiting and nausea were the predominant gastrointestinal complaints in the leflunomide group. Abdominal pain, upper abdominal pain, vomiting, nausea, and gastrointestinal disorder were the predominant gastrointestinal complaints in the methotrexate group. Abdominal pain, or upper abdominal pain, occurred in 5 leflunomide patients (15.2%) and 4 methotrexate patients (10.8%). The incidence of

vomiting was greatest for the methotrexate group (6 patients (16.2%) versus 2 patients (6.1%). No patients in the leflunomide group, and 4 patients in the methotrexate group, had vomiting assessed as possibly related to study medication. In most of the patients with vomiting, it was assessed as mild, and in none was the vomiting assessed as severe.

The incidence of nausea was similar between the two groups (leflunomide versus methotrexate: 2 patients, 6.1% versus 2 patients, 5.4%), and all reports of nausea were assessed as possibility related to study medication. With the exception of one patient in the methotrexate group, in whom nausea was assessed as moderate in intensity, all reports of nausea were assessed as mild in intensity. A total of 4 leflunomide patients (12.1%) and 7 methotrexate patients (18.9%) had nausea and/or vomiting.

Respiratory, Thoracic and Mediastinal Disorders
The respiratory, thoracic, and mediastinal disorders body system had the third highest incidence of TEAEs in both treatment groups, occurring in 11 leflunomide patients (33.3%) and 9 methotrexate patients (24.3%). The events that were most common within this body system were as follows: pharyngolaryngeal pain, 5 patients (15.2%) treated with leflunomide and 2 patients (5.4%) treated with methotrexate; rhinitis, 3 patients (9.1%) treated with leflunomide and 2 patients (5.4%) treated with methotrexate; and cough, 1 patient (3.0%) treated with leflunomide and 5 patients treated with methotrexate.

These events were assessed as mild, with the exception of two patients in the methotrexate group who had rhinitis and cough that were assessed as moderate. Two of the patients in the leflunomide group who experienced pharyngolaryngeal pain had these events assessed as possibly related to study medication. In addition to the subjects with rhinitis, 2 leflunomide patients and 1 methotrexate patient had rhinorrhea, so the total with rhinitis and/or rhinorrhea was 5 leflunomide patient (15.2%) and 3 methotrexate patients (8.1%). The incidence of cough was greatest in the methotrexate group (5 patients, 13.5% versus 1 patient, 3.0%).

Nervous System
The most common event of this class was headache, occurring in 7 leflunomide patients (21.2%) and 5 methotrexate patients (13.5%). Headache was assessed as possibly related to study medication for 2 leflunomide patients (6.1%) and 1 methotrexate patient (2.7%). All patients had their headache assessed as mild, with the exception of one leflunomide patient who had a headache that was assessed as moderate in intensity. Dizziness and syncope were reported in 1 patient in the leflunomide group (0801002) and resolved without change in study medication. Mild peripheral neuropathy was reported in one leflunomide patient (0203002) after 286 days of treatment and was ongoing at the end of the study with no change in study medication (assessed as not treatment-related). One methotrexate patient (0702001) had vasovagal syncope on 2 occasions.

The two events that were ongoing at study completion were episodic headaches and peripheral neuropathy for leflunomide patient 0606002 and patient 0203002, respectively. The patient with peripheral neuropathy had primarily upper extremity tingling (hands) and, intermittently, lower extremity (feet) tingling; these symptoms were

not present at the final study visit, recurred at the post-study visit, off leflunomide treatment, and resolved one month after the post-study visit. The investigator assessed the event as mild, not related to study medication, and potentially related to the patient's mother and sister having similar symptoms. The opinion of the neurology consultant was that these symptoms were not peripheral neuropathy and the neurologic examination was normal. Electrophysiology studies were not performed.

Skin and Subcutaneous Tissue Disorders
The skin and subcutaneous tissue disorders occurred in 7 leflunomide patients (21.2%) and 6 methotrexate patients (16.2%). Events of this body system that were assessed by the investigator as possibly related to study medication occurred in 2 leflunomide patients (6.1%), both with alopecia, and 1 methotrexate patient (2.7%) with erythema of the toes and dry skin. Most patient in each group experienced TEAEs of this class that were assessed as mild (leflunomide: 6 patients, 18.2%; methotrexate: 5 patients, 13.5%) and only one patient in each group had an event of this class that was assessed as moderate. One methotrexate patient (0601002) had erythema of the toes that was assessed as severe in intensity and probable vasculitis.

The most common event of this class was alopecia, which was reported for 3 leflunomide patients (9.1%), 2 mild and 1 moderate, and no patients in the methotrexate group. The alopecia experienced by 2 of 3 leflunomide subjects was ongoing at study completion.

Methotrexate patient 0601002 had erythema of the toes (assessed as severe and not treatment-related) for which study medication was interrupted and which later resolved after study medication was discontinued due to a different adverse event. None of the other TEAEs in skin disorders led to a change in study medication.

Pruritus, experienced by 1 leflunomide and 1 methotrexate patient (who also had dry skin) were ongoing at study completion.

Musculoskeletal and Connective Tissue Disorders
One patient (0401002) in the methotrexate group had arthritis flare assessed as a SAE; this patient's medication was discontinued. It was the conclusion of the investigator that the child's arthritis flare was not study drug related. The subject recovered without sequelae. All other events of this body system were assessed as mild or moderate in intensity and resolved without changes in study medication, except for the SAEs Baker's cyst and synovial effusion that were reported for methotrexate patient (0701001), and were ongoing at study completion.

The most frequent TEAEs in the leflunomide group were: headache, abdominal pain, pharyngolaryngeal pain, and diarrhea. The most frequent TEAEs in the methotrexate group were upper respiratory tract infection, vomiting, pyrexia, headache and cough. See **Table 9.**

Table 9. TEAEs and Possibly-Related TEAEs occurring in more than 1 patient (>3%)
(sponsor table 37, page 98 of 5923)

Body system Preferred term	Leflunomide N=33		Methotrexate N=37	
	All N(%)	Possibly Related N(%)	All N(%)	Possibly Related N(%)
Subjects with TEAEs	**29(87.9)**	**12(36.4)**	**31(83.8)**	**15(40.5)**
Blood and lymphatic system disorders	2(6.1)	1(3.0)	0(0.0)	0(0.0)
Iron deficiency anemia	2(6.1)	1(3.0)	0(0.0)	0(0.0)
Eye disorders	1(3.0)	0(0.0)	4(10.8)	1(2.7)
Conjunctivitis	0(0.0)	0(0.0)	2(5.4)	0(0.0)
Gastrointestinal disorders	12(36.4)	6(18.2)	14(37.8)	10(27.0)
Abdominal pain	5(15.2)	3(9.1)	2(5.4)	2(5.4)
Diarrhea	4(12.1)	2(6.1)	1(2.7)	0(0.0)
Vomiting	2(6.1)	0(0.0)	6(16.2)	4(10.8)
Nausea	2(6.1)	2(6.1)	2(5.4)	2(5.4)
Abdominal pain upper	0(0.0)	0(0.0)	2(5.4)	0(0.0)
Gastrointestinal disorder	0(0.0)	0(0.0)	2(5.4)	2(5.4)

Note: **Table 9,** continues on the next page.

Table 9. TEAEs and Possibly-Related TEAEs occurring in more than 1 patient (>3%)
(sponsor table 37, page 98 of 5923)

General disorders	2(6.1)	0(0.0)	6(16.2)	2(5.4)
Pyrexia	1(3.0)	0(0.0)	6(16.2)	2(5.4)
Fatigue	1(3.0)	0(0.0)	3(8.1)	0(0.0)
Infections, infestations	13(39.4)	3(9.1)	15(40.5)	2(5.4)
Upper respiratory tract infection	3(9.1)	0(0.0)	6(16.2)	1(2.7)
Nasopharyngitis	3(9.1)	0(0.0)	1(2.7)	0(0.0)
Gastroenteritis	2(6.1)	1(3.0)	3(8.1)	1(2.7)
Viral infection	2(6.1)	0(0.0)	2(5.4)	0(0.0)
Bronchitis	2(6.1)	0(0.0)	1(2.7)	1(2.7)
Otitis media	2(6.1)	0(0.0)	1(2.7)	0(0.0)
Ear infection	1(3.0)	1(3.0)	2(5.4)	1(2.7)
Gastroenteritis viral	0(0.0)	0(0.0)	3(8.1)	0(0.0)
Viral upper respiratory tract infection	0(0.0)	0(0.0)	3(8.1)	0(0.0)
Gastritis viral	0(0.0)	0(0.0)	2(5.4)	0(0.0)
Pharyngitis	0(0.0)	0(0.0)	2(5.4)	0(0.0)
Pharyngitis streptococcal	0(0.0)	0(0.0)	2(5.4)	1(2.7)
Injury, poisoning, procedural complications	7(21.2)	0(0.0)	4(10.8)	0(0.0)
Arthropod bite	2(6.1)	0(0.0)	1(2.7)	0(0.0)
Joint sprain	2(6.1)	0(0.0)	0(0.0)	0(0.0)
Arthropod sting	1(3.0)	0(0.0)	3(8.1)	0(0.0)
Investigations	2(6.1)	2(6.1)	4(10.8)	3(8.1)
ALT increased	1(3.0)	1(3.0)	2(5.4)	1(2.7)
Musculoskeletal, connective tissue disorders	6(18.2)	0(0.0)	8(21.6)	2(5.4)
Arthraglia	3(9.1)	0(0.0)	3(8.1)	0(0.0)
Juvenile arthritis	2(6.1)	0(0.0)	1(2.7)	1(2.7)
Nervous system	8(24.2)	3(9.1)	6(16.2)	1(2.7)
Headache	7(21.2)	2(6.1)	5(13.5)	1(2.7)
Respiratory, thoracic and mediastinal disorders	11(33.3)	2(6.1)	9(24.3)	1(2.7)
Pharyngolaryngeal pain	5(15.2)	2(6.1)	2(5.4)	0(0.0)
Rhinitis	3(9.1)	0(0.0)	2(5.4)	0(0.0)
Rhinorrhea	2(6.1)	0(0.0)	1(2.7)	0(0.0)
Cough	1(3.0)	0(0.0)	5(13.5)	1(2.7)
Skin and subcutaneous tissue disorders	7(21.2)	2(6.1)	6(16.2)	1(2.7)
Alopecia	3(9.1)	2(6.1)	0(0.0)	0(0.0)
Rash	0(0.0)	0(0.0)	2(5.4)	0(0.0)

Laboratory Adverse Events

Hematology, blood chemistry, and urinalysis data were examined for changes that occurred during treatment and within the period of observation ending 42 days after last dose of study treatment.

Elevated Hepatic Enzymes
The AEs of most concern with both methotrexate and leflunomide treatment involve abnormal liver function tests, particularly increase in ALT, which is generally more sensitive to drug-induced elevation than AST. Elevated hepatic enzymes are a well documented potential adverse event with leflunomide and with methotrexate. Patients were required to have ALT and AST levels < 1.5 x ULN at baseline of Study 3503. All but 1 leflunomide patient were normal (defined as ≤ 1.2 x ULN) at baseline.

One leflunomide subject (0134003) and 4 methotrexate subjects (0901004, 0603005, 0501001, and 0303004) had elevated liver enzymes reported as AEs. All were assessed as possibly treatment-related except 0603005 assessed as related to Epstein-Barr virus infection. Liver enzyme elevations experienced by 3 of the 4 patients treated with methotrexate were SAE which led to treatment discontinuation after which the patients recovered without sequelae. See **Tables 10** and **11.**

ALT Elevations
All of the subjects in the leflunomide treatment group (5 subjects, 15.2%) who had elevated ALT values (>1.2 X ULN) at some point after week 16 during the extension study had values between 1.2 and 2 times the ULN (refer to **Table 11.**). All of the elevations had occurred by day 250 of the study. The patients in the methotrexate group (11 patients, 29.7%) who had elevated ALT values (>1.2 X ULN) during the study were as follows: 6 were between 1.2 and 2 times the ULN, 2 were between 2 and 3 times the ULN, 2 were between 3 and 8 times the ULN, and 1 was greater than 8 times the ULN. Four of the ALT elevations occurred from day 200 onward.

Three of the 5 subjects with ALT elevations in the leflunomide group and 3 of 11 with ALT elevations in the methotrexate group were taking concomitant corticosteroids. All subjects in the leflunomide group and 9 of 11 patients in the methotrexate group who had ALT elevations, were using concomitant NSAIDs; however, this was true of most of the study patients. Two of the methotrexate patients with ALT elevations were not taking NSAIDs. There were no significant clinically noteworthy changes in alkaline phosphatase or the total bilirubin. One patient 0401002 in the methotrexate group had a one-time clinically noteworthy abnormal laboratory value for GGTP (predefined change increase ≥ 29 u/L and > 2xULN).

AST Elevations
The patients with AST elevation are a subset of those with ALT elevations, with the exception of methotrexate patient (0113003) who had a maximum AST of 1.35 x ULN as an isolated value with normal ALT. There were 2 leflunomide patients and 5 methotrexate patients who had AST elevations after week 16. Both patients in the leflunomide group, and 2 patients in the methotrexate group, had AST values between 1.2 and 2 x ULN. In the methotrexate group, 2 patients had AST between 2 and 3 x ULN (0501001 and 0901004) and one had AST >3 x ULN (0603005). See **Tables 10** and **11.**

Table 10. Hepatic Enzyme Elevations as Special Investigations, HWA486/3504

Patient	**Treatment Group**	**Adverse Event (ALT ≥ 3xULN)**		**Comments**
0134003	Leflunomide	ALT 2.5xULN, GGT 2.9xULN, CRP increased; normal alk. phos and bilirubin	AE	+ Related to Study Med; labs became normal
0901004	Methotrexate	ALT increased	SAE; Rx d/c	+ Related to Study Med
0603005	Methotrexate	ALT, AST increased	SAE; Rx d/c	Not treatment related; Epstein Barr virus infection
0501001	Methotrexate	ALT, AST, alkaline phosphatase increased	SAE; Rx d/c	
0303004	Methotrexate	Hepatic Enzymes increased	AE	

Table 11. Study drug changes prior to normalization and reversal of ALT
(Sponsor table 40, page 119 of 5923)

	Leflunomide N = 33				Methotrexate N = 37			
Parameter	**>1.2-2 X ULN n(%)**	**>2-3 X ULN n(%)**	**> 3-8 X ULN n(%)**	**>8 X ULN n(%)**	**>1.2-2 X ULN n(%)**	**>2-3 X ULN n(%)**	**> 3-8 X ULN n(%)**	**>8 X ULN n(%)**
Number of subjects	**5(15.2)**	**0**	**0**	**0**	**6(16.2)**	**2(5.4)**	**2(5.4)**	**1(2.7)**
Number normal at baseline	**4**	**0**	**0**	**0**	**6**	**2**	**2**	**1**
Days from start of drug								
0-150	2	0	0	0	2	0	0	1
151-200	0	0	0	0	2	0	2	0
201-250	3	0	0	0	1	2	0	0
251-300	0	0	0	0	1	0	0	0
301-350	0	0	0	0	0	0	0	0
351-	0	0	0	0	0	0	0	0
Number normalized to ≤ 1.2 X ULN at end of treatment	5	0	0	0	6	2	0	1
Timing of normalization[a]								
0-14 days	1	0	0	0	0	0	0	0
15-28 days	2	0	0	0	1	2	0	0
29 or more days	2	0	0	0	5	0	0	1
Number reversed to ≤ 2 X ULN at end of treatment[b]	--	0	0	0	--	2	0	1
Timing of reversal[a]								
0-14 days	--	0	0	0	--	0	0	0
15-28 days	--	0	0	0	--	2	0	0
29 or more days	--	0	0	0	--	0	0	1
Discontinued due to liver enzyme abnormality	0	0	0	0	0	0	2	1
Concomitant meds								
Steroids	3	0	0	0	1	0	2	0
NSAIDs	5	0	0	0	5	2	2	0
No folate	1	0	0	0	1	0	0	1
Weight								
< 20 kg	0	0	0	0	2	0	0	1
20-40 kg	3	0	0	0	1	1	1	0
> 40 kg	2	0	0	0	3	1	1	0
Age less than 12 years	3	0	0	0	5	1	2	1

(Continued) Table 11. Study drug changes prior to normalization and reversal of ALT (Sponsor table 41, page 120 of 5923)

	Leflunomide N = 33				Methotrexate N = 37			
	>1.2-2 X ULN n(%)	>2-3 X ULN n(%)	>3-8 X ULN n(%)	>8 X ULN n(%)	>1.2-2 X ULN n(%)	>2-3 X ULN n(%)	> 3-8 X ULN n(%)	>8 X ULN n(%)
Number of subjects	5(15.2)	0(0.0)	0(0.0)	0(0.0)	6(16.2)	2(5.4)	2(5.4)	1(2.7)
Never normalized to ≤ 1.2 X ULN	0	0	0	0	0	0	2	0
Normalized to ≤ 1.2 X ULN	5	0	0	0	6	2	0	1
After discontinuation	0	0	0	0	0	0	0	1
After dose reduction	0	0	0	0	0	0	0	0
After dose interruption	1	0	0	0	0	0	0	0
After none of above	4	0	0	0	6	2	0	0
Never reversed to ≤ 2 X ULN	--	0	0	0	--	0	2	0
Reversed to ≤ 2 X ULN	--	0	0	0	--	2	0	1
After discontinuation	--	0	0	0	--	0	0	1
After dose reduction	--	0	0	0	--	0	0	0
After dose interruption	--	0	0	0	--	0	0	0
After none of above	--	0	0	0	--	2	0	0

Hematology Abnormalities

Neutrophil Count

Two subjects in the leflunomide group (0903001 and 0603001) and one in the methotrexate group (0501001) had an isolated neutrophil count ≥ 1.0 to < 1.5 G/L after week 16. No subject had a neutrophil count < 1.0 G/L.

Anemia

Two leflunomide patients had mild iron deficiency anemia, hemoglobin 6.45 mmol/L, reported as an AE. Patient 1201002 was a 15 year old female whose anemia was confounded by preexisting gastrointestinal symptoms on diclofenac, treated with omeprazole prior to and during the study; she was treated with iron supplements. The second patient 0302001 had a hemogloblin of 6.45 mmol/L which decreased to 5.28 mmol/L at week 32. Her treatment was confounded by chloramphenecol; iron supplements were started and the hemoglobin response reached 6.64 mmol/L by the end of the study.

Five subjects (15.2%) in the leflunomide group had hemoglobin <6.21 mmol/L (0302001, 0603003, 1101003, 1201002, and 0205001). All except subject 0205001 had low hemoglobin values at baseline (6.45, 5.71, 6.08, 7.01, and 7.45 mmol/L respectively). Subject 0205001 had a normal value at baseline and an isolated value <6.21 mmol/L at week 48 which normalized to 7.7 mmol/L at follow up after completing study treatment. One subject (0702001) in the methotrexate group (2.8%) had hemoglobin < 6.21 mmol/L during the extension.

WBC, Leukcocyte, Platelet Count

One patient (0702001) in the methotrexate group had a WBC count of 21.46 G/L, and a different patient (0401002) in the methotrexate group had a platelet count of 721.00 G/L.

There were no clinically noteworthy decreases in WBC count (< 2.0 G/L) or platelet count (< 100 G/L) in either treatment group. There were no leukocytes counts < 3.5 G/L or platelet counts < 120 G/L in either group.

Renal function
One patient (0802002) in the methotrexate group with tonsillitis and otitis media and no patients in the leflunomide group had an increase in BUN (increase ≥ 3.2 mmol/L) at week 24, week 40, and week 48. The elevated BUN normalized after treatment with antibiotics and surgery (tonsillectomy and myringotomy tubes). One patient (0113005) in the methotrexate group had an isolated increase in creatinine (increase ≥ 35 µmol/L) at week 32. No subject had creatinine or blood urea nitrogen elevation reported as an AE during the extension study. No pattern of urinalysis abnormality was found.

Other Safety Data

Tanner Staging
Tanner staging of secondary sex characteristics was consistent with the ages of the patients. One leflunomide and 3 methotrexate patients increased their Tanner stage score by more than 1 stage from screening to week 48 or their early exit visit.

Gynecomastia
Gynecomastia is reported as an infrequent adverse reaction for methotrexate. There was no evidence of gynecomastia in this study.

Vital signs
No hypertension was reported as an AE in either treatment group in extension study 3504. Clinically abnormal blood pressures were defined as systolic or diastolic blood pressure above the 95th percentile for age and height at baseline.

Clinically noteworthy systolic elevations occurred in 7 (21.2%) leflunomide patients and 12 (33.3%) of methotrexate patients. See **Table 12 and 13.** Diastolic elevation (> 95th percentile) was less common than systolic, occurring in 5 leflunomide patients (15.2%) and 2 methotrexate patients (5.6%). Patients who had persistent clinically noteworthy systolic or diastolic blood pressure elevations (> 95th percentile) one more than two occasions in the extension study are noted in Table 13.

Table 12. Percent of Patients w/ Clinically Noteworthy Abnormal BP (sponsor table T 124, p 390 of 3504)

		CNAVSV*			
Vital Signs	Criteria	LEF* N=33		MTX* N=37	
Systolic BP	> 95th percentile for age and height at baseline	7/33	21.2%	12/36	33.3%
Diastolic BP		5/33	15.2%	2/36	5.6%

* CNAVSV - Clinically Noteworthy Abnormal Vital Sign Value; LEF = leflunomide; MTX = methotrexate.

Table 13. Clinically Noteworthy Blood Pressure (BP)

Patient Number	Treatment	Comments *
# 0203002	Leflunomide	Elevations in systolic BP elevation at all extension study visits without diastolic BP elevation
# 0701002	Leflunomide	Elevations at wks 32, 56, and 62 (follow up)
# 0903001	Leflunomide	Elevations in diastolic BP at baseline and at all extension study visits except wk 48, but none were higher than her baseline. She also had a systolic BP elevation at baseline, but no elevations during the extension.
# 0134002	Methotrexate	Elevations in systolic and diastolic BP at screening and baseline; during extension study, pt. had intermittent elevations at wk 32 and wk 48 w/o clinically noteworthy diastolic elevation.
# 0502002	Methotrexate	Elevations in systolic BP at screening and baseline, and then during the extension study, the subject had clinically noteworthy systolic BP at all study visits.
# 501001	Methotrexate	Elevations in systolic BP at baseline and week 40.
* Clinically noteworthy comments		

Weight

No methotrexate patient had lost > 5% of their body weight at study end-point. One leflunomide extension patient (0302003) lost > 5% but < 10% of her body weight at the study endpoint. One leflunomide patient (0205001) lost >10% of her body weight at week 32 (colitis was diagnosed by colonoscopy and biopsy).

D. Adequacy of Safety Testing

The extension study HWA486/3504 was small as compared to adult studies with leflunomide as well as other DMARDS. The duration of patient exposure was acceptable.

E. Summary, Critical Safety Findings and Limitations of Data

The clinical safety data from 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, Leflunomide versus Methotrexate" demonstrates an overall safety profile consistent with the underlying disease, JRA, and the known adverse events of leflunomide and methotrexate.

Though the extension study was small (n = 70), the extension study includes one report of peripheral neuropathy, described as mild, in a patient taking leflunomide. This patient's medication was not changed or stopped. Peripheral neuropathy was reported as ongoing at study completion for this patient. Peripheral neuropathy is reported in the

current label post marketing safety data in adults. This finding was not seen in the safety data from the 16 week study HWA486/3503 and raises concern for longer term therapy with leflunomide in children and adolescents.

There were no deaths and no significant overdoses reported in the 8-month extension study. As reported in the 12-week efficacy and safety study HWA486/3503, the total number of JRA patients in the 8-month extension study was small. There were 70 JRA patients enrolled and randomized in the safety population; 33 patients in the leflunomide group and 37 patients in the methotrexate group. Lack of efficacy was the most common reason cited for the discontinuation of subjects in the leflunomide group contrasted with adverse events as the most common reason cited for the discontinuation of patients in the methotrexate group.

The serious adverse events (SAEs) in the leflunomide group were not different from previously reported serious adverse events in children and adults with leflunomide therapy. Of the known high risk hepatic adverse events, none of the leflunomide SAEs were alert level hepatic enzyme elevations, contrasted with results in the methotrexate treated group**.** Elevated hepatic transaminases were reported in 3 of the 9 methotrexate treated patients with SAEs.

One patient in the leflunomide group (3.0%) and 5 patients in the methotrexate group (13.5%) were discontinued from extension study HWA486/3504 due to treatment-emergent SAEs. The treatment emergent SAE that lead to discontinuation in the leflunomide group was colitis. The treatment-emergent SAEs leading to the discontinuation of methotrexate patients were hepatic transaminase elevations, arthritis flare and gastrointestinal disorder. Transaminase elevations were reported as AEs for 4 methotrexate subjects (10.8%) and 1 leflunomide subject (3.0%) during the extension. Three patients (8.1%) treated with methotrexate had protocol-defined alert term (ALT > 3 x ULN). There were no leflunomide treated patients who had alert-term hepatic function test elevations.

The incidence of treatment emergent adverse events was slightly higher in the leflunomide group, 29 patients (87.9%) versus 31 patients (83.8%) in the methotrexate group. The methotrexate treated patients had a slightly higher incidence of TEAEs, 15 patients (40.5%) versus 12 patients (36.4%).

Adverse events (AE) were highest in the class of infections and infestations (leflunomide: 13 patients, 39.4%; methotrexate 15 patients, 40.5%). However, there were more patients in the leflunomide group than in the methotrexate group who reported previous illnesses (45.5% versus 32.4%). Respiratory, thoracic and mediastinal disorders (leflunomide: 11 patients, 33.3%; methotrexate: 9 patients, 24.3%) was the second most frequent category followed by gastrointestinal signs and symptoms. Gastrointestinal signs and symptoms were noted as abdominal pain, diarrhea, vomiting and nausea as the most predominant GI complaints in the leflunomide group; abdominal pain, upper abdominal pain, vomiting, nausea and GI disorder were the most predominant GI complaints in the methotrexate group.

The nervous system demonstrated the third highest incidence of adverse events with headache, occurring in 7 leflunomide patients (21.2%) and 5 methotrexate patients (13.5%). Dizziness and syncope were reported in 1patient in the leflunomide group and resolved without change in study medication. Of note, peripheral neuropathy, described as mild, was reported in one leflunomide patient after 286 days of treatment and was ongoing at the end of the study with no change in study medication. The sponsor assessed this event as not treatment-related. One methotrexate patient treated with methotrexate had vasovagal syncope on two occasions. The two adverse events that were ongoing at the extension study completion were episodic headaches in one patient and peripheral neuropathy in a different patient, both treated with leflunomide. Mild peripheral neuropathy is the only reported adverse event in the extension study that is not reported in the current ARAVA (leflunomide) label for pediatrics. Peripheral neuropathy is reported in the current post marketing section of the ARAVA label for adults.

In the class of skin and subcutaneous tissue signs and symptoms, and musculoskeletal connective tissue disorders, there were no new adverse events noted in this pediatric extension study.

Among the laboratory tests monitored, there were no clinically meaningful changes in the alkaline phosphatase or total bilirubin in the patients with elevated hepatic enzymes and no significant differences between treatment groups in hematology, renal function (BUN and creatinine) or urinalysis. There were no patients with leukopenia < 3.5 G/L, neutropenia < 1.0 G/L or thrombocytopenia < 120 G/L. Anemia was noted in 5 patients in the leflunomide group, 4 of these 5 patients had low hemoglobin at baseline and one, whose hemoglobin decreased to 6.21mol/L, normalized at follow up. Two of the 5 patients had iron deficiency anemia which responded to iron therapy. One patient in the methotrexate group had hemoglobin <6.21mmol/L.

F. Conclusion, Critical Safety Findings

In the 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, Leflunomide versus Methotrexate”, leflunomide demonstrated an overall safety profile consistent with the underlying disease, JRA, and the known adverse events of leflunomide and methotrexate, active comparator. This extension study includes one new report of peripheral neuropathy in a patient treated with leflunomide, a previously unreported adverse event in pediatric patients treated with leflunomide. This finding resolved during post-study follow up.

G. Results - Efficacy (Durability of Response) of Study HWA486/3504

1. Patient Disposition

The efficacy evaluable population was 33 leflunomide-treated patients and 35 methotrexate-treated patients. Two patients in each treatment group had efficacy data after week 24 of treatment but none at week 24 (or between week 16 and week 24 that could be carried forward to week 24 analysis according to the LOCF algorithm defined in

the Statistical Analysis Plan. Therefore, the efficacy analyses, over time, reflect week 24 data based on 31 leflunomide patients and 33 methotrexate patients. See Appendix, Figure 1. Patient Accounting.

Note that two JRA patients (#0601002 and #0603005) in the methotrexate group took 3504 study medication but withdrew due to adverse events without having had an efficacy evaluation after entering the extension study. They were excluded from the efficacy evaluable population.

Discontinuations
There were 9 leflunomide patients and 6 methotrexate patients did not complete the study to the 48 week endpoint. Five patients (15.2%) in the leflunomide group withdrew due to lack of efficacy and one withdrew due to progressive disease (patient # 0801002); no subject in the methotrexate group withdrew due to lack of efficacy.

Duration
Total study duration was 8-months. [The largest proportion of extension study patients received study medication for 337 to 364 days in both treatment groups.]

Study Compliance
In the leflunomide group, 78.8% of subjects were at least 80% compliant with leflunomide doses, and 84.8% of subjects were at least 80% compliant with methotrexate placebo doses. In the methotrexate group, 91.7% of subjects were at least 80% compliant with methotrexate doses, and 86.5% of subjects were at least 80% compliant with the leflunomide placebo doses. See **Table 14.**

Table 14. Analysis Populations; Extension Study HWA486/3504

Populations N	Leflunomide N	Methotrexate N	Total N
Enrolled	33	37	70
Safety evaluable	33	37	70
Efficacy evaluable	33	35	68

N = number of subjects

2. Demographics and Baseline Characteristics:
The majority of the patients in both treatment groups were white females < 12 years-of age. The mean age of the study patients was approximately 10 years. In the leflunomide group, 45.5% of the patients weighed >40 kg, whereas in the methotrexate group, 59.5% of the patients weighed >40 kg upon enrollment in the extension study.

Treatment groups were similar in terms of measures of disease activity prior to study treatment with the exception of the physician global assessment of disease activity and CRP level. The mean baseline physician global assessment for the leflunomide group (53.4[18.39] mm) was higher than that of the methotrexate group (43.0[17.67] mm), indicating that the leflunomide patients were perceived at baseline to have more active disease than the methotrexate patients.

The mean CRP level for the leflunomide patients (18.88[22.548] mg/L) was greater at baseline than that of the methotrexate patients (8.66[17.895] mm), suggesting a higher level of inflammation for the leflunomide patients, relative to the methotrexate patients. The two treatment groups were similar with respect to all other JRA history and disease activity variables.

The patients' JRA clinical course was represented as:

Pauciarticular	Lef 9 (27.3%)	MTX 7 (20%);
Polyarticular	Lef 23 (69.7%)	MTX 28 (80%)
Systemic	Lef 1 (3.0%)	MTX 0 (0.0%)
TOTAL	33	35

Previous Illnesses
More patients in the leflunomide group than in the methotrexate group reported previous illnesses (45.5% vs. 32.4%). Fifteen patients in the leflunomide group reported 27 previous illnesses, and 12 patients in the methotrexate group reported 18 previous illnesses.

3. Concomitant Illnesses
The proportion of patients with at least one concurrent illness was comparable between treatment groups (42.2% vs. 43.2%). Patients in the leflunomide treatment group had a higher rate of blood or lymphatic disorders than did patients in the methotrexate group (12.1% vs 5.4%). For 2 of the 4 patients in the leflunomide group, anemia was the concurrent illness. In addition, the leflunomide patients had a higher rate of uveitis (6.1% vs 0%). There were more subjects in the methotrexate group with immune disorders (10.8% vs 3.0%); infections and infestations (8.1% vs. 3.0%), musculoskeletal and connective tissue disorders (8.1% vs 3.0%), disorders classified as back pain in 2 of the 3 methotrexate patients; and metabolism and nutrition disorders (5.4% vs 0.0%).

4. Previous medications
The patients in the extension study had early disease; only 6.1% of the leflunomide patients and 10.8% of the methotrexate patients had taken previous DMARDS prior to entry into Study 3503.

5. Protocol Deviations
Major protocol violations were not applicable to the 3504 extension study, since the primary efficacy analysis for randomized treatment group comparison was at the week 16 endpoint of the prerequisite Study 3503.

6. Primary Efficacy Outcome Measures
The primary efficacy outcome measures for the extension study were the same as in Study 3503:

(1) Percent (%) Improvement Index, and
(2) JRA DOI ≥ 30% responder rate [at the end of the 8-month extension study (week 48 of treatment)] compared to these measures at the end of Study 3503 to evaluate durability of efficacy.

Percent Improvement Index

The difference between weeks 16 and 48 in the mean % Improvement Index for the leflunomide treated patients was 0.70 (p=0.8774). Improvement at week 16 (-54.66%) was maintained at week 48 (-55.36%). Similarly, the difference between weeks 16 and 48 in the mean % Improvement Index for the methotrexate treated patients was 7.55 (p=0.0580). Improvement at week 16 (-57.96%) was maintained at week 48 (-65.51%). The durability of the leflunomide effect was demonstrated through to week 48 of the study. See **Table 15.**

Table 15. % Improvement Index Within-Group Comparison of Weeks 16 and 48
(sponsor table 17, page 77 of 5923)

Leflunomide							
16 weeks N=33		48 weeks N=33		Difference 16 weeks – 48 weeks			p-value[a]
Adj Mean	SE	Adj Mean	SE	Adj Mean	95%CI	SE	
-54.66	3.169	-55.36	3.169	0.70	-8.43; 9.83	4.482	0.8774

Methotrexate							
16 weeks N=35		48 weeks N=35		Difference 16 weeks – 48 weeks			p-value[a]
Adj Mean	SE	Adj Mean	SE	Adj Mean	95%CI	SE	
-57.96	2.723	-65.51	2.723	7.55	-0.27; 15.38	3.850	0.0580

JRA DOI ≥ 30% Responder Rate

In the leflunomide group, the DOI ≥ 30% responder rate at week 16 was 78.8% and it was the same at week 48. In the methotrexate group, the DOI ≥ 30% responder rate was also the same week 16 and week 48 (91.4%). These results demonstrate the durability of the leflunomide effect through to week 48 of the study. See **Table 16.** JRA DOI ≥ 30% Responder Rates within Treatment Groups at Weeks 16 and Weeks 48.

Table 16. JRA DOI ≥ 30% Responder Rates within Treatment Groups at Weeks 16 and Weeks 48
(sponsor table 18, page 78 of 5923)

Leflunomide		Methotrexate	
Week 16 N=33	Week 48 N=33	Week 16 N=35	Week 48 N=35
n (%)	n (%)	n (%)	n (%)
26 (78.)	26 (78.8)	32 (91.4)	32 (91.4)

7. Secondary Outcome Measures

Responder Rates, Over Time
DOI ≥ 50%
For the leflunomide group, DOI ≥ 50% responder rates were maintained from week 16 at each extension study time-point including the week 48 end-point. Nearly all of the DOI ≥ 30% responders at week 48 were also DOI ≥ 50% responders (25/26; 96.2%).

For the methotrexate group, the responder rates at weeks 24 and 32 were lower than week 16, while at weeks 40 and 48 they were maintained from week 16. As in the leflunomide group, nearly all of the DOI ≥ 30% responders at week 48 were also DOI ≥ 50% responders (30/32; 93.8%).

DOI ≥ 70%
For the leflunomide group, from week 16, the DOI ≥ 70% responder rate improved at each extension study time-point including the week 48 end-point. At week 32, the further improvement was statistically significant, using a McNemar test, in the leflunomide group. At week 48 the trend to more improvement was apparent ($p < 0.10$).

For the methotrexate group, DOI ≥ 70% responder rates compared to week 16 were lower at week 24 and higher at weeks 32, 40 and 48. At week 48 this trend to further improvement was apparent with p-value < 0.10. Most of the DOI ≥ 30% responders at week 48 were also DOI ≥ 70% responders (29/32; 90.6%). Of the 35 extension patients in the methotrexate group, 29 were DOI ≥ 70% responders at their last extension study visit (82.9%), representing 62% of the 47 patients initially randomized to methotrexate at the beginning of Study 3503.

Individual Core Set Variables, Mean Improvements from Baseline

Leflunomide
For the 6 individual core set variables, the mean improvements from baseline were similar at weeks 16 and 48 in the leflunomide group. Approximately half of the core set variables showed a small positive trend in improvement and half showed a small trend in effect but still improved from baseline. There was no statistical significance between week 16 and week 48. Improvement in physical function measured by CHAQ DI was maintained between week 16 (-0.48) and week 48 (-0.50) in the leflunomide group. Mean improvements in CRP and pain intensity score were also maintained between week 16 and week 48.

Methotrexate
For the 6 individual core set variables, the mean improvements from baseline were similar at weeks 16 and 48 in the methotrexate group. Similar to leflunomide, there was no statistical between week 16 and week 48. Improvement in physical function measured by CHAQ DI was maintained between week 16 (-0.42) and week 48 (-0.48) in the methotrexate group. Mean improvements in CRP and pain intensity score were not statistically significant.

H. Summary, Efficacy Results, Extension Study HWA486/3504

Leflunomide and methotrexate demonstrated durability of efficacy as measured by the Percent Improvement Index and the JRA DOI 30% by maintaining benefit and trending improvement from week 16 to week 48 of therapy. With both leflunomide and methotrexate, the durability of efficacy at week 48 was supported by the secondary outcome measures, the JRA DOI ≥ 50% and the JRA DOI ≥ 70% responder rates, with maintaining improvement from baseline in the 6 individual core set variables, CRP and pain score.

In the leflunomide patients, the mean percent improvement index showed -54.66 % at week 16 to -55.36% week 48 (p=0.8774). The JRA DOI ≥ 30% responder rate was 78.8% at week 48 (p=1.000). The JRA DOI ≥50 % responder rate was 72.7% at week 16 and 75.8% at week 48 (p=0.7389). Te JRA DOI ≥ 70% trended positively without statistical significance, 54.5% at week 16 and 69.7% at week 48.

In the methotrexate patients, the mean percent improvement index showed -57.6% at week 16 to -65.51% at week 48. The JRA DOI ≥ 30% responder rate was 91.4% at week 16 and 91.4% at week 48. The JRA DOI ≥50% responder rate was 85.7% at week 16 and 85.7% at week 48. The JRA DOI ≥ 70% trended positively at 65.7% for week 16 and 82.9% for week 48. (p=0.0578).

In the between group comparison, there were no statistically significant differences identified between the extension study leflunomide and methotrexate groups for the Percent Improvement Index or JRA DOI ≥ 30%, ≥50% or ≥ 70% at week 48 or at previous time points in the extension study.

Considering the safety profile of methotrexate versus leflunomide, methotrexate remains a preferable disease modifying anti-rheumatic drug (DMARD). Leflunomide, though studied in children and adolescents with JRA, does not have an approved indication in JRA. See the ARAVA (leflunomide label).

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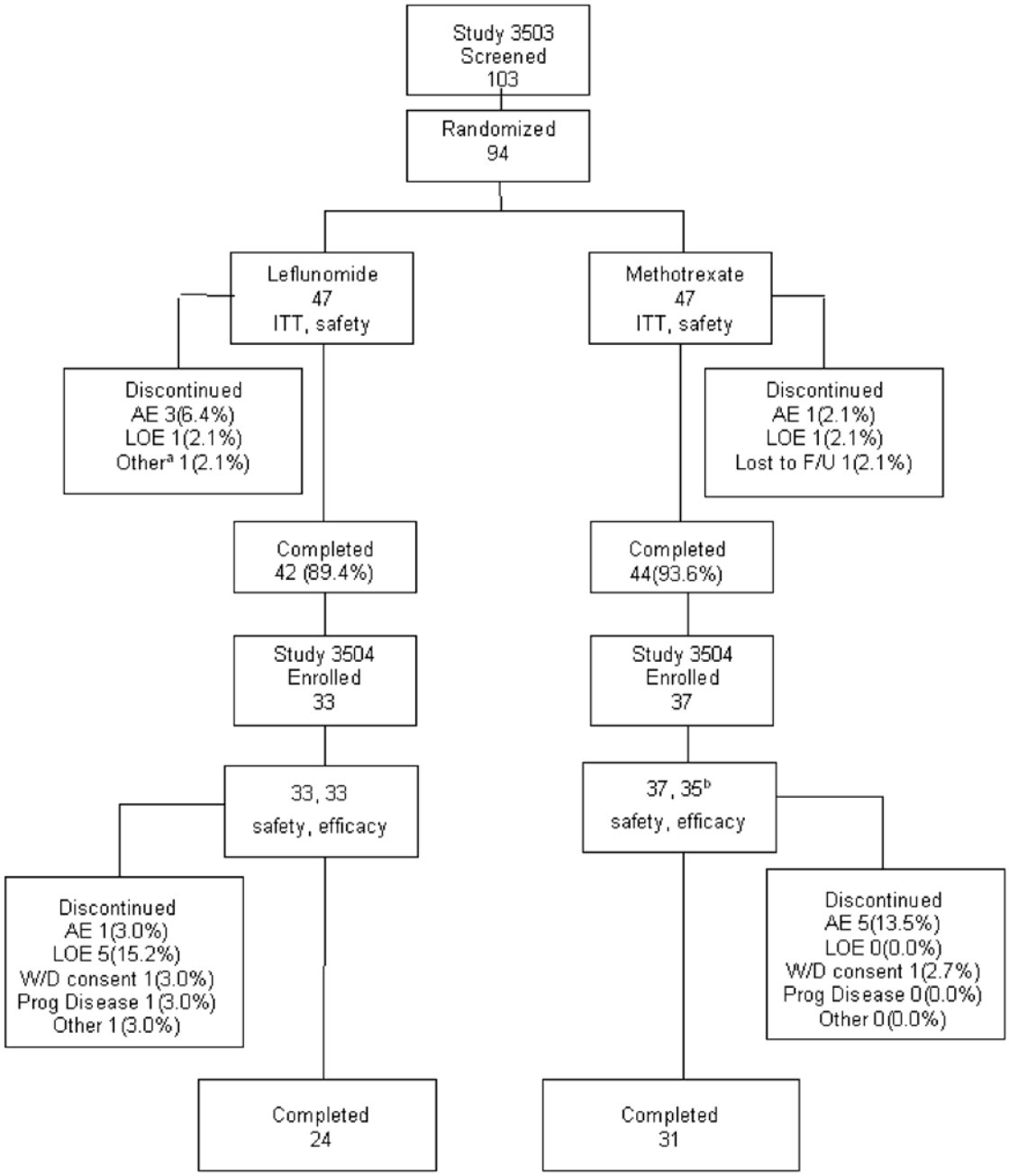
Medical Officer

APPENDIX

Figure 1. Subject Accounting, Extension Study HWA486/3504



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Carolyn L. Yancey
5/20/05 01:02:17 PM
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ARAVA pediatric extension safety and efficacy final review

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