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

Table of Contents 2

Executive Summary 5

I. Recommendations 5

A. Recommendation on Approvability 5

B. Recommendation on Phase 4 Studies and/or Risk Management Steps 5

II. Summary of Clinical Findings 5

A. Brief Overview of Clinical Program 5

B. Efficacy 7

C. Safety 9

D. Dosing 9

E. Special Populations 10

Clinical Review 10

I. Introduction and Background 10

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups 10

B. State of Armamentarium for Indication(s) 12

C. Important Milestones in Product Development 12

D. Other Relevant Information 12

E. Important Issues with Pharmacologically Related Agents 12

CLINICAL REVIEW

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews 12

III. Human Pharmacokinetics and Pharmacodynamics 12

A. Pharmacokinetics 13

B. Pharmacodynamics 14

IV. Description of Clinical Data and Sources 14

A. Overall Data 14

B. Tables Listing the Clinical Trials 14

C. Postmarketing Experience 15

D. Literature Review 15

V. Clinical Review Methods 16

A. How the Review was Conducted 16

B. Overview of Materials Consulted in Review 16

C. Overview of Methods Used to Evaluate Data Quality and Integrity 16

D. Were Trials Conducted in Accordance with Accepted Ethical Standards. 17

E. Evaluation of Financial Disclosure 17

VI. Integrated Review of Efficacy 17

A. Brief Statement of Conclusions 17

B. General Approach to Review of the Efficacy of the Drug 18

C. Detailed Review of Trials by Indication 27

D. Efficacy Conclusions 66

VII. Integrated Review of Safety 68

A. Brief Statement of Conclusions 68

B. Description of Patient Exposure 69

C. Methods and Specific Findings of Safety Review 70

D. Adequacy of Safety Testing....79

E. Summary of Critical Safety Findings and Limitations of Data....79

VIII. Dosing, Regimen, and Administration Issues....80

IX. Use in Special Populations....81

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation....82

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy....82

C. Evaluation of Pediatric Program....82

D. Comments on Data Available or Needed in Other Populations....82

X. Conclusions and Recommendations....83

A. Conclusions....83

B. Recommendations....85

XI. Appendix....85

A. Other Relevant Materials....89

Arava ••(Leflunomide) label with proposed label changes, marked copy....TBD

B. 1. Clinical Sties and Investigators, Study HWA 468/1307....90

2. Clinical Sites and Investigators, Study HWA 468/3503....91-93

3. Individual More Detailed Study Reviews (If performed)....97

4. Schedule of Visits, Study HWA 468/3505....94

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)

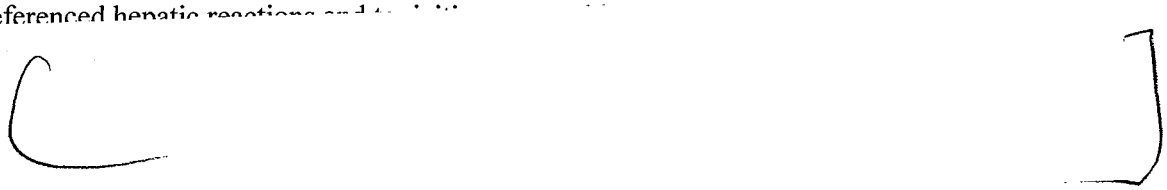
Arava (leflunomide) is approved for adult use for the indications of signs and symptoms of rheumatoid arthritis, to inhibit structural damage as evidenced by X-ray erosions and joint space narrowing and to improve physical function.

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 [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

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[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. ——— was added due to a change in corporate name of the contract research organization and the drug packaging and shipping facility name wa ———

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 ——— 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 ——— 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.

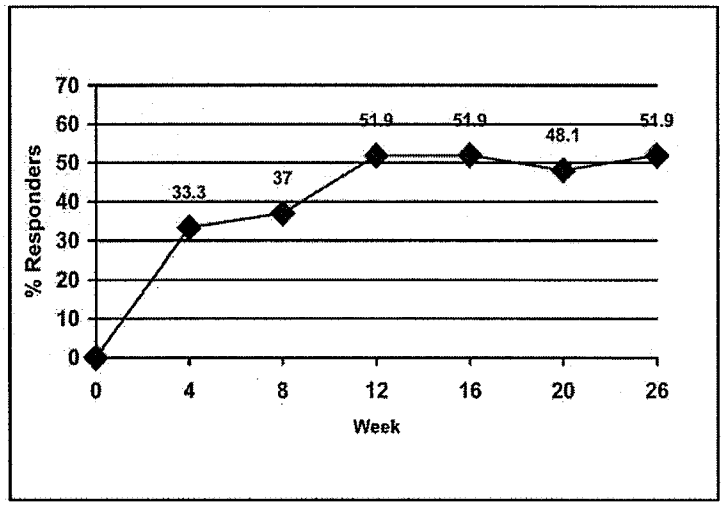
- **Patient 64001:** PK labs drawn at wrong time, discussed with study coordinator.
- **Patient 65001:** DMARD (Plaquenil) discontinued 2 days prior to first study drug dose, only 6 days between screening and baseline visit.
- **Patient 63001:** was not taking study medication between baseline visit 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.

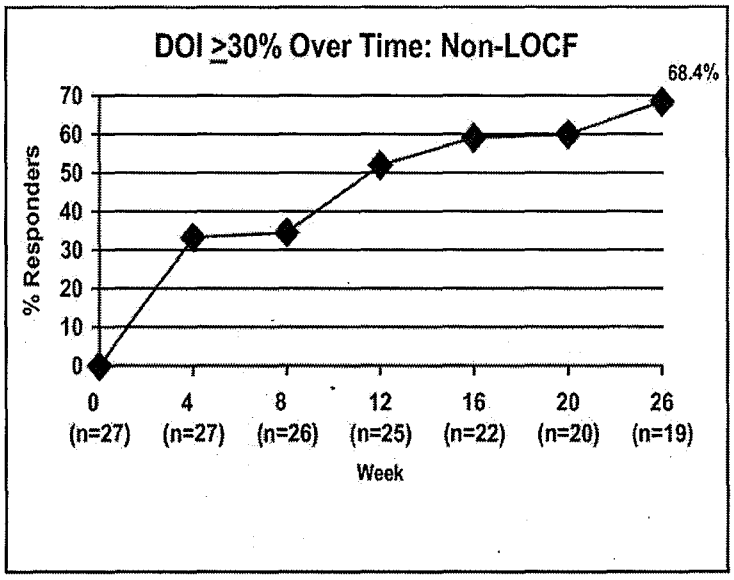
Figure 1. Study HWA 486/1037, DOI ≥ 30 % Over Time: ITT (n=27), LOCF
(The following figure is from the sponsor's submission)



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

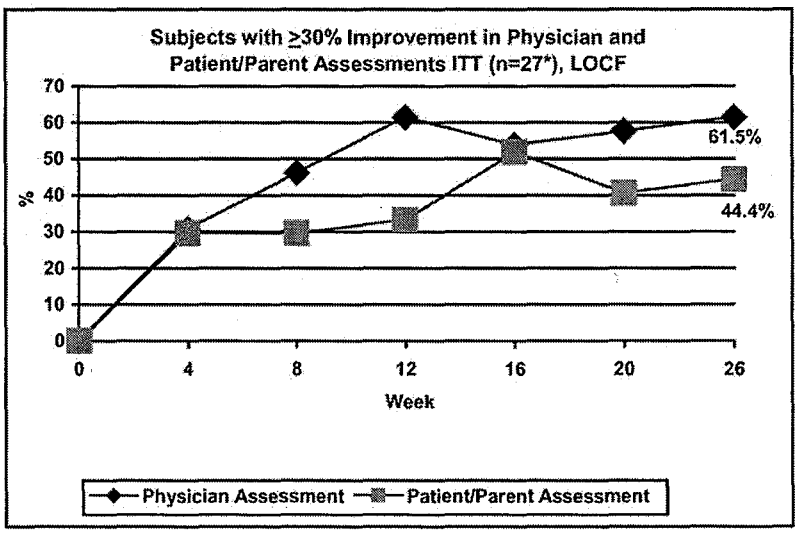
(The following figure is from the sponsor's submission)



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.**

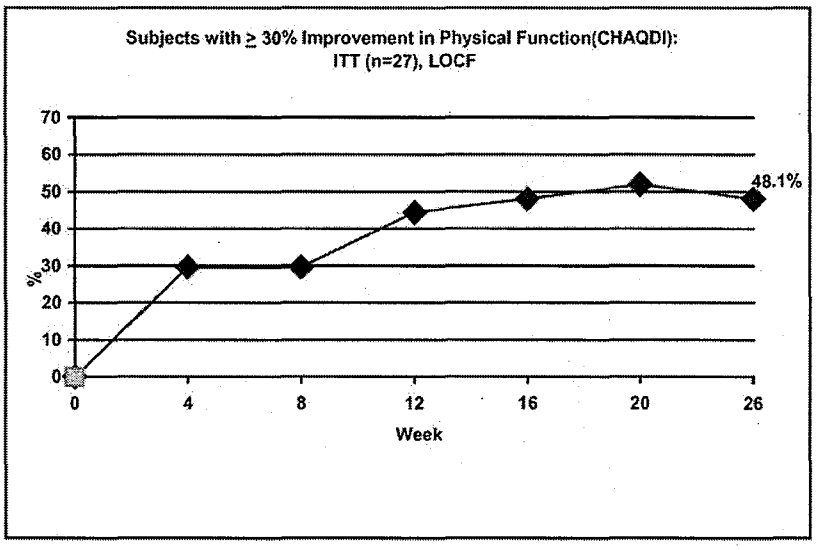
Figure 3. Study HWA486/1037, Patients with ≥ 30 % Improvement in Physician and Patient/Parent Assessments ITT, LOCF.

(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.**

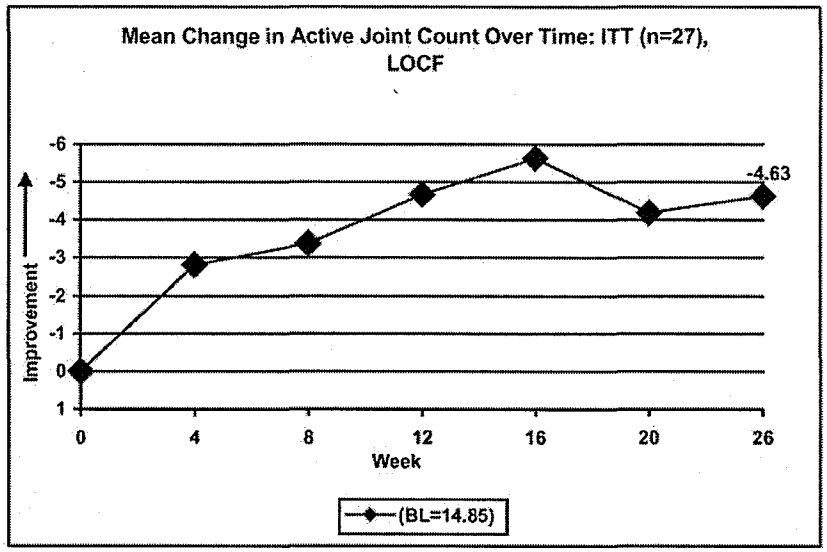
Figure 4, Study HWA486/1037, Patients with ≥ 30 Percent Improvement in Physical Function CHAQDI, Week 26 (The following figure is from the sponsor's submission)



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.

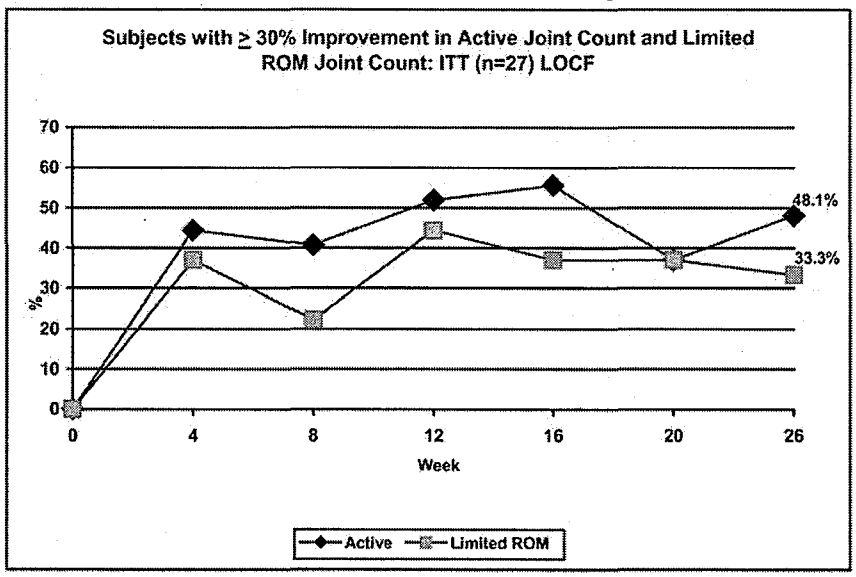
In the responder group (N=27), the mean changes from baseline in both active joints with limited ROM were evident after 4 Weeks of therapy and continued throughout 26 weeks. See **figure 5**, Study HWA486/1037.

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.**

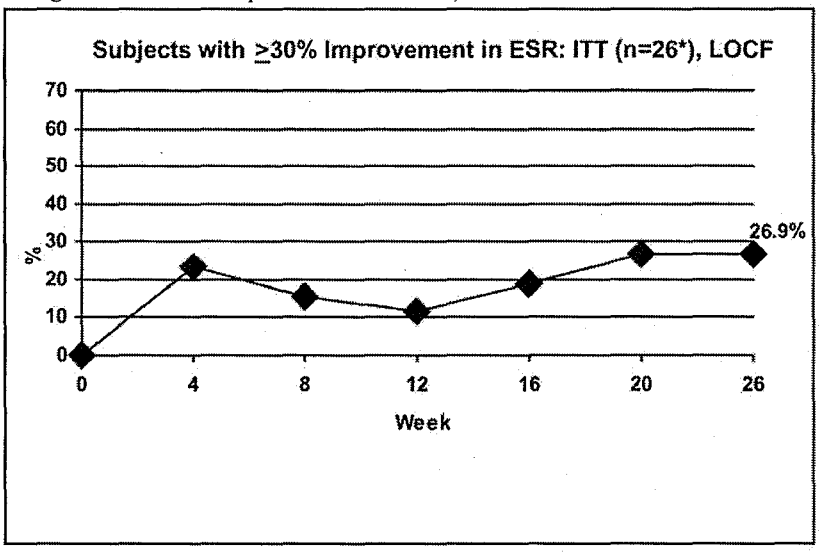
Figure 6. Study HWA 486/1037, ≥ 30 % Improvement in Active Joint Count and Limited ROM: ITT, LOCF. (The following figure is from the sponsor's submission)



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)

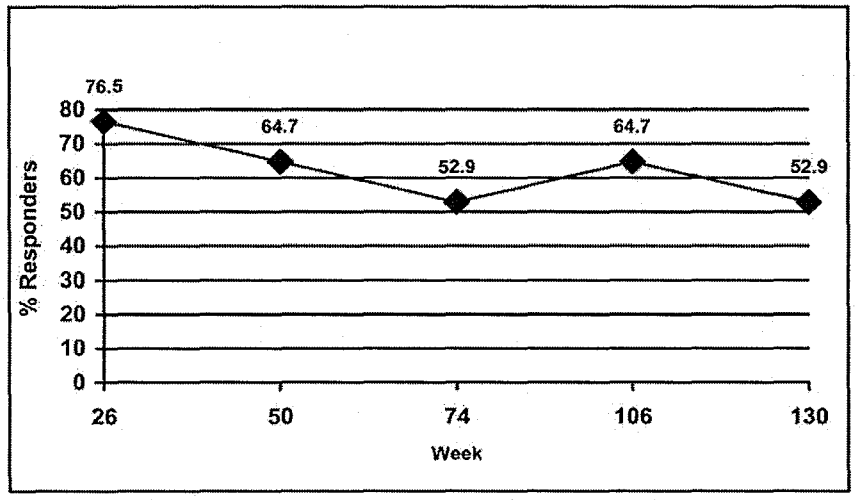
Characteristic	N	%
Time Since JRA Diagnosis		
Mean years	7.39	NA
1 – 2 years	2	11.8
> 2 – 10 years	10	58.8
> 10 years	5	29.4
Type of JRA at Diagnosis		
Polyarticular	12	70.6
Pauciarticular	5	29.4
Mean Duration of Previous Methotrexate Treatment (mos)	32.3	NA
Reason for Methotrexate Discontinuation		
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.

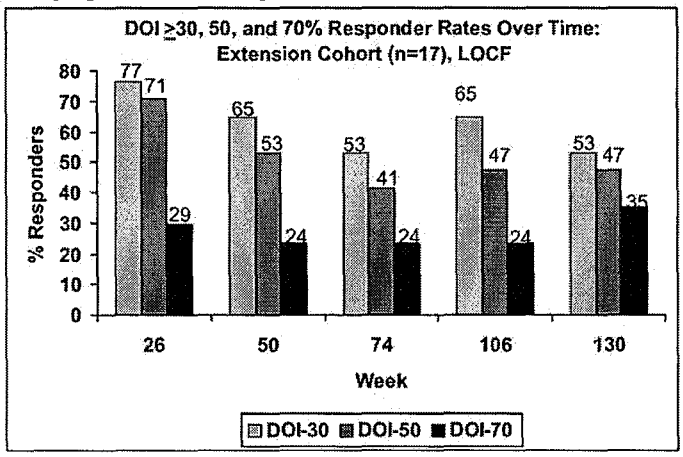
Figure 8. Study HWA 486/1037 JRA DOI ≥ 30 % Over Time: Extension Cohort (n=17), LOCF (The following figure is from the sponsor's submission)



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

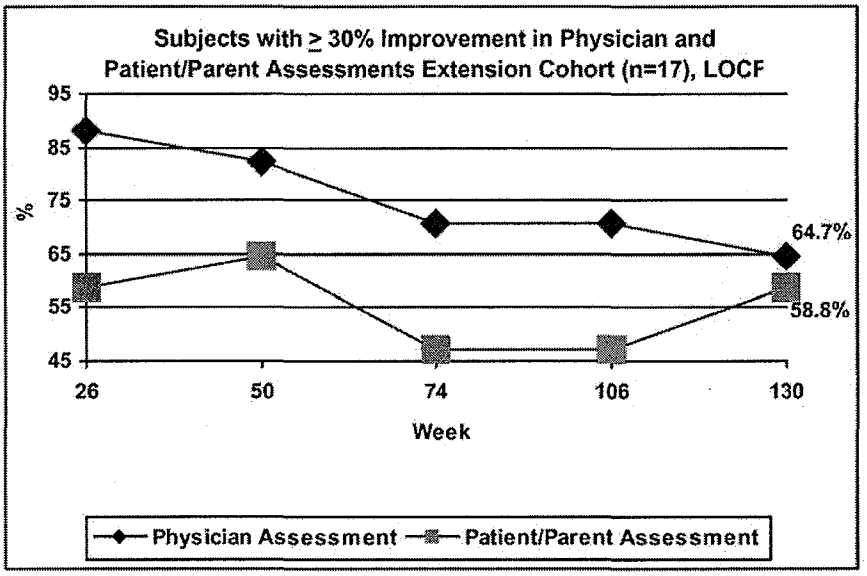
By week 130, only 9 patients (52.9%) in the Extension Study HWA 486/1037, extension cohort were JRA DOI ≥ 30 % responders and 8 (47.1 %) were non-responders. See **figure 9.**

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



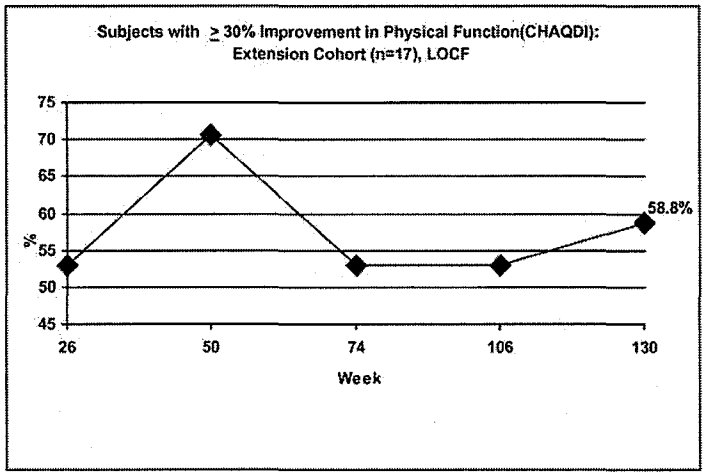
Study HWA 486/1037 patients demonstrated ≥ 30 % improvement in **physician** assessment (64.7%) and **patient/parent assessments** (58.8 %) extension cohort (n=17), LOCF. See **figure 10** for these results.

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**.

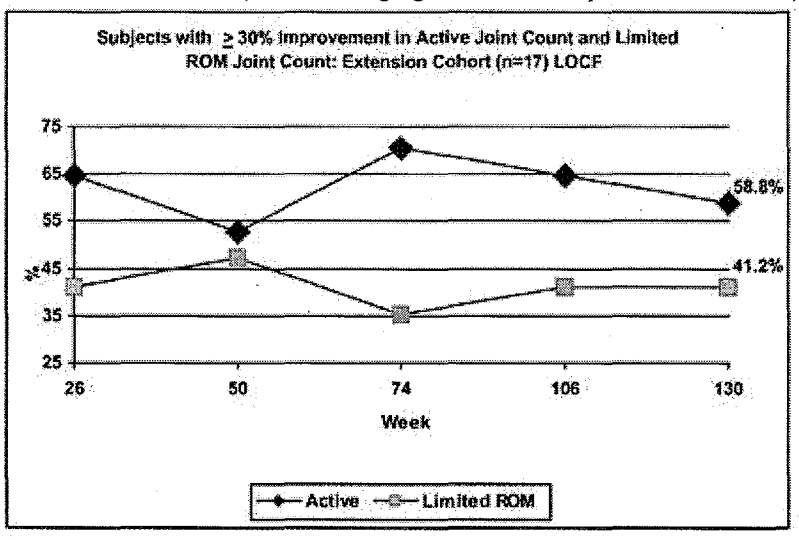
Figure 11. Study HWA 486/1037, ≥ 30 % Improvement in Physical Function
(The following table is from the sponsor's submission)



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.**

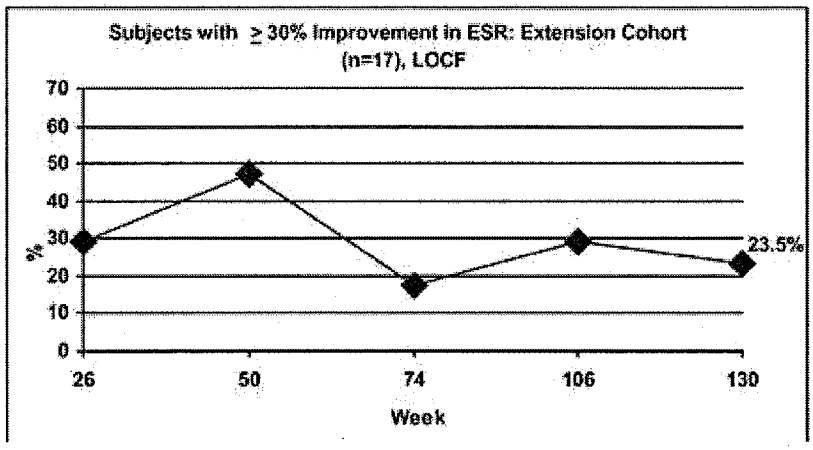
Ten patients (58.8 %) had ≥ 30 % improvement in active joint count at Week 130 which was similar to 11 patients (64.7 %) at Week 26. Seven patients (41.2 %) had ≥ 30 % improvement in limited ROM joint count at Week 130 which was the same percentage (41.1 %) at Week 26. Similarly, 6 to 8 patients (35.3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

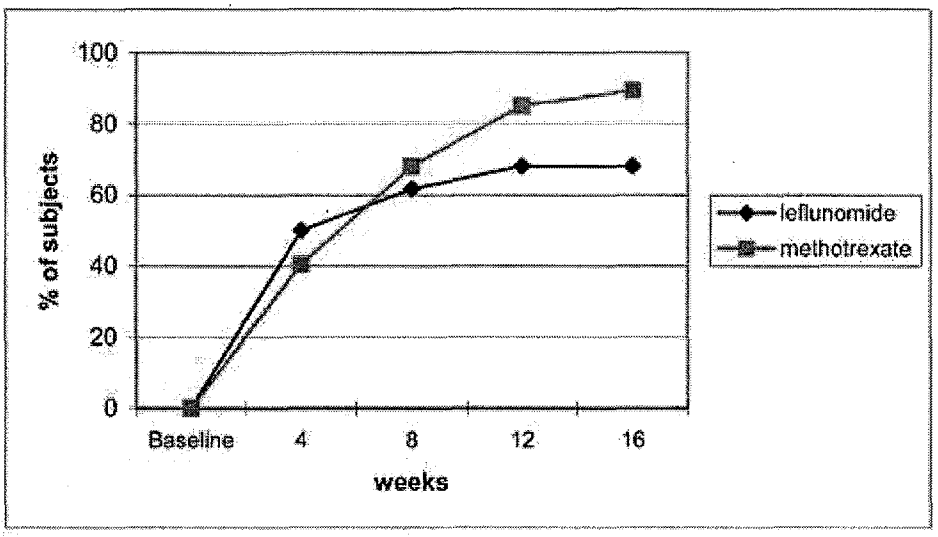
Additional analysis, as noted in **Table 15**, using the JRA DOI ≥ 30 % logistic regression results by subgroup (ITT population), demonstrates that patients weighing ≤ 40 kg and treated with leflunomide (16/27) had 59.3 % response rate versus patients weighing ≤ 40 kg and treated with methotrexate (19/21) 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)

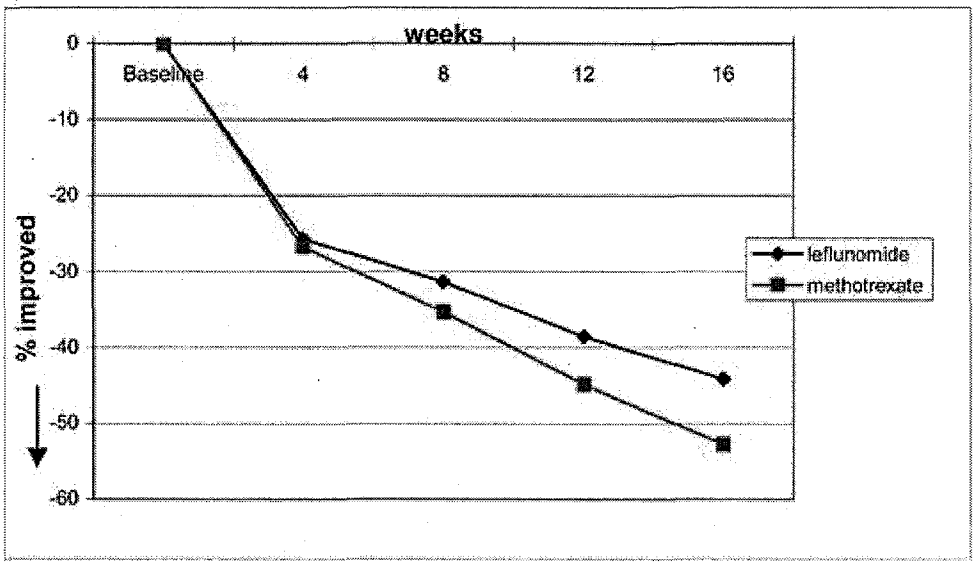


Table 16. Percent Improvement Index for Study HWA486/3503 ITT population. (The following table is from the sponsor's submission)

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.

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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[g]/ 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, 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, or 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 34.2 200;10 18.5	Worsening of JRA	78	No/mod/ hosp/no change/yes	The subject had worsening of arthritis on Day 78 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 or gnosed 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 o nd 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 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 She was hospitalized that day for intensified physiotherapy and i.a. corticosteroid injection. The subject recovered and was discharged 10 days later on d e 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 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 e 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 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 MTX: 12.5 QW not app	Gastrointestinal disturbance (codes to Gastrointestinal disorder NOS)	112	Yes/severe/ hosp/ disc/yes	On Day , e 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 ermatologist'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 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 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 She was hospitalized and arthrocentesis with IA injection (triamcinolone) was performed with recove 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[i]	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.

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/s/

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3/5/04 04:47:07 PM
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Congrats on first NDA-concur