Office of Clinical Pharmacology and Biopharmaceutics Review

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

1. Executive Summary

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

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

The pharmacokinetics (PK) of leflunomide was investigated in two clinical efficacy and safety studies (Study 1037 and 3503). The pooled data was then evaluated using the population (POPPK) approach. The objectives of the POPPK analysis were to characterize the steady state

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

1.1 Recommendation:

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

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

Based on the PK data the applicant did include a refined leflunomide treatment regimen to increase the dose of leflunomide to about 100 and 50 % higher than that studied for children with bodyweights < 20 kg and between 20-40 kg. However, they have not requested for this proposed regimen to be included in the label. The clinical division has decided that due to the inadequacy of the efficacy and safety information provided by the applicant, this indication is not recommended in the pediatric population, therefore no dosing recommendations are proposed at this time.

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

1.2 Phase IV Commitments: None were identified.

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3. Summary of CPB Findings

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

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

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

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

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

Pharmacokinetics of M1 in JRA patients

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

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

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

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

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

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

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

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

Dosing Recommendation

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

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

Body Weight (kg)	**Daily Dose** (mg)
10.0 – 19.9	10
20.0 – 40.0	15[a]
> 40.0	20

[a]To be administered as doses of 20 mg and 10 mg on alternating days

The table above shows that the proposed dose is ~ 100 % and 50 % higher than the studied doses for the patients with body weights < 20 kg and between 20-40 kg, respectively. Although the exposure data supports the increased dose, the limited safety data (confirmed with the medical reviewer, Dr. C. Yancey) in the pediatric population do not support the inclusion of these increased doses in the label.

4. QBR

4.1 General Attributes

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

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

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

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

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

Body Weight (kg)	**Daily Dose** (mg)
10.0 – 19.9	10
20.0 – 40.0	15[a]
> 40.0	20

[a]To be administered as doses of 20 mg and 10 mg on alternating days

4.2 General Clinical Pharmacology

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

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

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

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

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

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

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

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

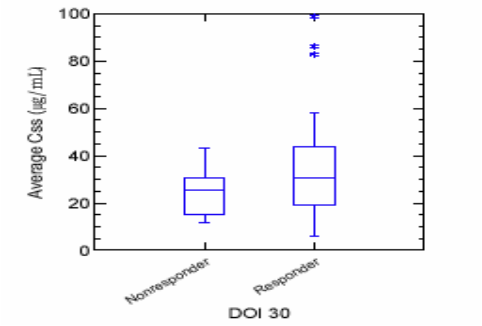
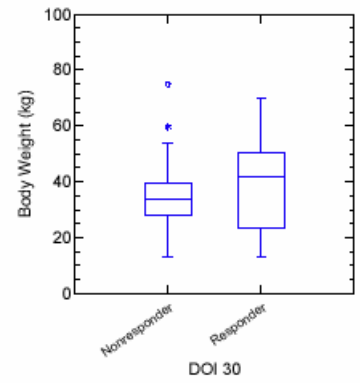


Table: Descriptive Statistics for Css and WT by DOI ≥ 30 % Response

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

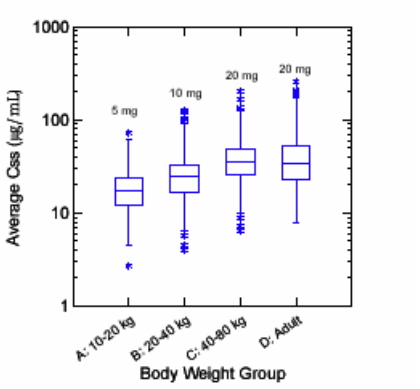
The table above shows that the mean average steady state concentration is 35.0 and 24.2 mcg/mL, for responder (n=32) and non-responder (n=15), respectively. This suggests that a certain exposure may be required to obtain a response to treatment. The graph below shows there was also a trend for the non-responders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



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

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

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



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

Table Descriptive Statistics of the Css Achieved in Study 3503

	Weight (kg) Group		
	<20	**20-40**	**>40**
		Css (μg/mL)	
N	8	19	20
Minimum	6.1	12.0	8.9
Maximum	30.6	98.9	86.4
Median	12.6	26.2	36.7
Mean	**14.5**	**30.0**	**38.9**
SD	7.2	19.3	20.4
C.V.	0.50	0.64	0.52

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

4.3 Intrinsic Factors

Age

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

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

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

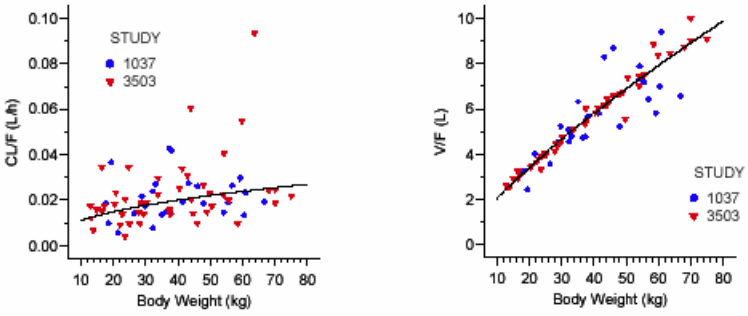
However, results of a CL/F by weight evaluation of the POPPK data demonstrated that pediatric subjects with polyarticular course JRA with body weights < 40 kg have a reduced clearance of M1 relative to adult RA patients as shown in the table below (see Pharmacometrics Review in Appendix by Dr. J. Zheng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

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

Weight

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

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



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

The leflunomide regimens investigated in study 3503 showed a difference in exposure to M1 across the three weight groups. Only the 20 mg daily maintenance dose administered to pediatric subjects weighing > 40 kg achieved systemic exposures comparable to those observed in adults.

To optimally target the desired median steady-state M1 concentration considering the wide inter-subject variability and the formulation strengths available, a refined leflunomide treatment regimen was proposed by the applicant for the pediatric population as follows:

Body Weight (kg)	**Daily Dose** (mg)
10.0 – 19.9	10
20.0 – 40.0	15[a]
> 40.0	20

[a]To be administered as doses of 20 mg and 10 mg on alternating days

The proposed dose is about 100 % and 50 % higher than the studied doses for the subjects with body weights < 20 kg and between 20-40 kg, respectively. Although the increased doses may be supported by the PK analysis, there is no safety data in the pediatric population to support this increased dose (confirmed with the medical reviewer Dr. C. Yancey).

4.4 Extrinsic Factors:

None that were pertinent to the pediatric population were identified.

4.5 Biopharmaceutics:

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

4.6 Analytical Methods:

Were the analytical methods used to determine M1 in biological fluids adequately validated?

Yes, insert details of assay method.

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

Assay Method	HPLC using UV detection @ 292 nm
Analytical Site	Aventis Pharma Deutschland GmBH, DI&A, Germany
Compound	M1 (A771726) the main metabolite of leflunomide
Internal Standard	A782068
Matrix	Plasma
Accuracy *Between-day*	94.8 % - 109.5 %
Imprecision (CV%) *Between-day*	1.7%-6.5%
Standard curve range	0.1-100 mcg/mL
Sensitivity (LOQ)	0.1 mcg/mL (CV% = 4.4 % and Accuracy = 102.3%)
Selectivity	No interfering peaks were observed at the retention time for M1 and its IS.
Stability	Stable in human plasma for at least 53 weeks at –10°C to –30 °C

5. Detailed labeling recommendations:

Applicant's Proposed Recommended Label:

Special Populations

Age and Gender. Neither age nor gender has been shown to cause a consistent change in the *in vivo* pharmacokinetics of M1.

Pediatrics

The pharmacokinetics of M1 following oral administration of leflunomide have been investigated in two separate clinical studies comprising a total of 73 pediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) who ranged in age from 3 to 17 years. The average clearance was estimated to be 21.8 ± 13.5 mL/hr and was weakly correlated to body weight. The average elimination half-life of M1 was 9.1 ± 4.9 days. As in adults, a similarly wide inter-individual variability in pharmacokinetics was observed.

Reviewer's Labeling Recommendations:

Strikethrough indicates deletion and bolded Italics text indicates addition

Special Populations

~~**Age and Gender.** Neither age nor gender has been shown to cause a consistent change in the *in vivo* pharmacokinetics of M1.~~

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

Pediatrics

The pharmacokinetics of M1 following oral administration of leflunomide have been investigated ***in 73 pediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) ranging in age from 3 to 17 years.*** ~~two separate clinical studies comprising a total of 73 pediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) who ranged in age from 3 to 17 years.~~ ***The estimate for M1 clearance demonstrated that children with body weights < 40 kg have a reduced clearance of M1 relative to children with body weights > 40 kg (see table below) and adult rheumatoid arthritis patients.*** ~~The average clearance was estimated to be 21.8 ± 13.5 mL/hr and was weakly correlated to body weight. The average elimination half-life of M1 was 9.1 ± 4.9 days. As in adults, a similarly wide inter-individual variability in pharmacokinetics was observed.~~

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

CLINICAL STUDIES: Clinical Studies in Pediatrics:
The text in bold Italics is our recommended addition to this recommendation by the clinical division

...The response rate to ARAVA in children less than 40 kg was less robust than in children greater than 40 kg suggesting suboptimal dosing in smaller children ***resulting in less than efficacious plasma concentrations***, in spite of reduced clearance of MI (see PK).

6 Appendices
6.1 PM review
See Next Page

PHARMACOMETRIC REVIEW

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

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

The findings of PPK analysis are as the follows:

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

Body Weight (kg)	**Daily Dose** (mg)
10.0 – 19.9	10
20.0 – 40.0	15[a]
> 40.0	20

a: to be administered as doses of 20 mg and 10 mg on alternating days

COMMENTS:

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

2. The proposed dose is about 100% and 50% higher than the studied doses for the subjects with body weight below 20 kg and between 20 to 40 kg, respectively. Even though the increased doses were supported by the pharmacokinetic analysis, no safety data exists at the increased dose in the

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

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

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

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

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

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

Objectives:

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

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

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

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

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

Actual Body Weight (kg)	Loading Dose	Maintenance Dose
<20	100 mg QD x 1	10 mg QOD
20 – 40	100 mg QD x 2	10mg QD
>40	100 mg QD x 3	20 mg QD

Pharmacokinetic Data:

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

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

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

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

Data analysis:

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

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

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

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

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

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

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

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

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

Final Model:

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

Results:

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

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

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

Table 1. The Final PPK Model and Its Parameter Estimates

Parameter	Regression Model and Parameter Estimates (SE)[a]	Inter-Subject Variability (SE)[a], %[b]
CL/F (L/h)	CL/F = θ1*(WT/40)^θ_4	50.4 (22.0)
	θ1 = 0.02 (0.00127)	
	θ4 = 0.43 (0.192)	
V/F (L)	V/F = θ2*(WT/40)^θ_5	18.6 (10.0)
	θ2 = 5.8 (0.23)	
	θ5 = 0.769 (0.0989)	
ka (h^{-1})	θ3= 1.13 (0.455)	171.5 (101.5)
Residual Variability (SE)[c], %	18.2 (6.3)	

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

a SE = Standard error of the estimate

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

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

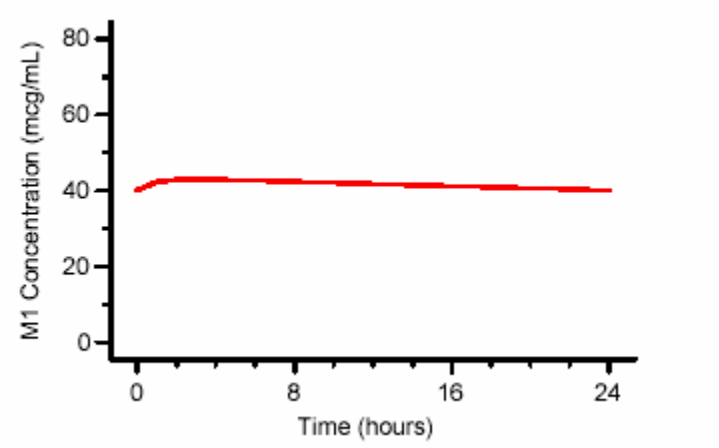
Table 2. Descriptive Summary of the Individual Bayesian POSTHOC PK Parameter Estimates and Demographic Variables Based on the Final PPK Model

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

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

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

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



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

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

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

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

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

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

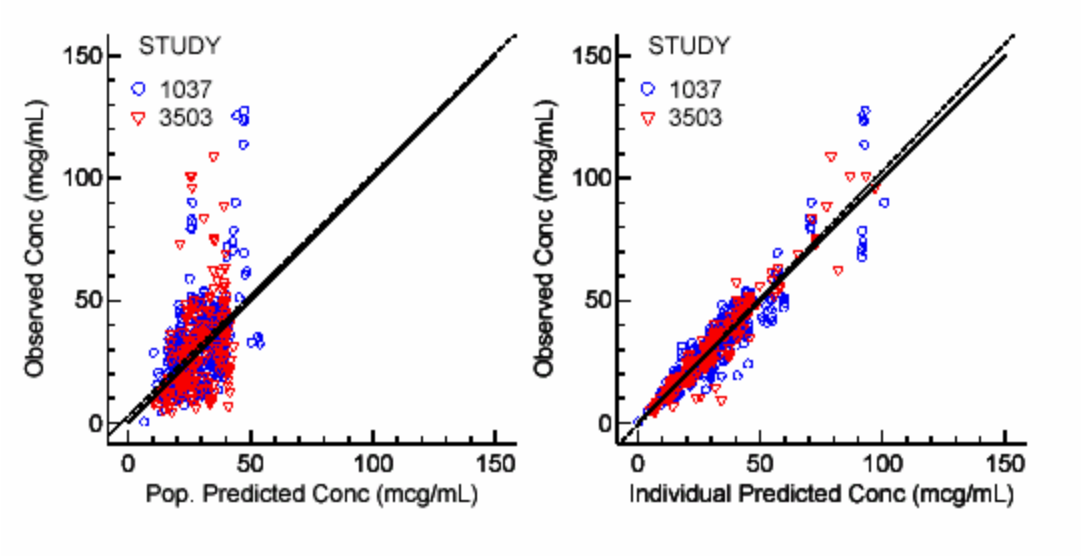
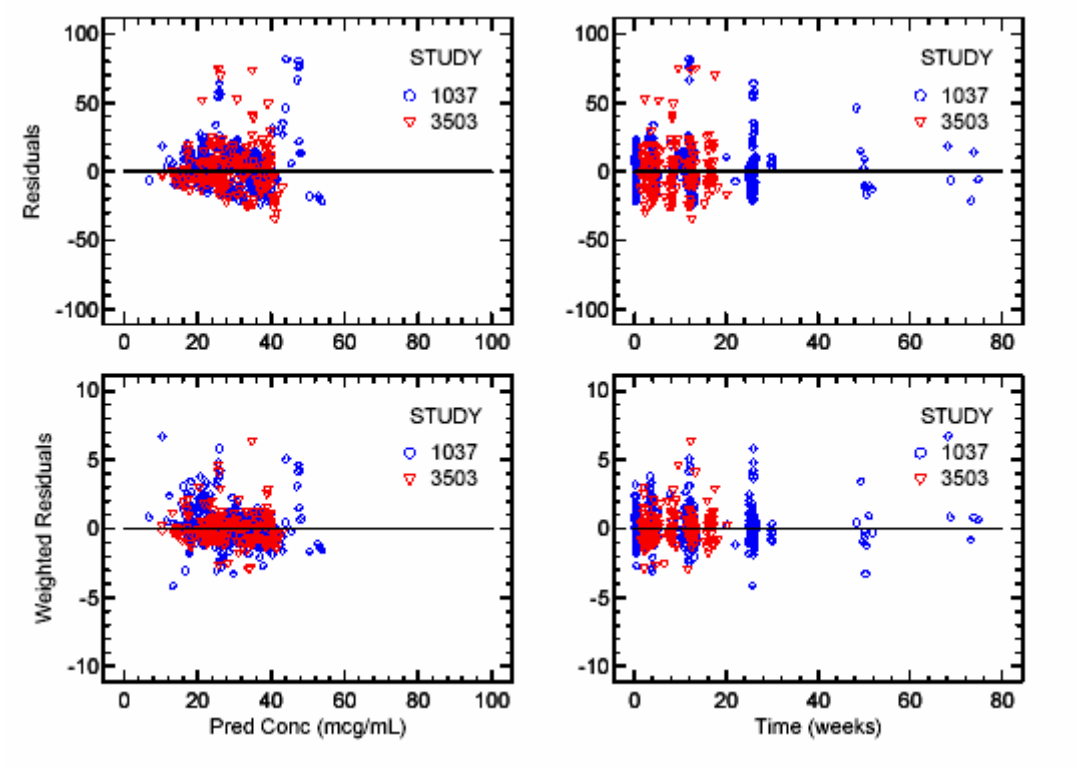


Figure 3. Residuals or Weighted Residuals Versus the Population (Fixed-Effects) Predicted Concentrations (Left) or Time (Right)



Model Validation:

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

- Cross-Study Evaluation:

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

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

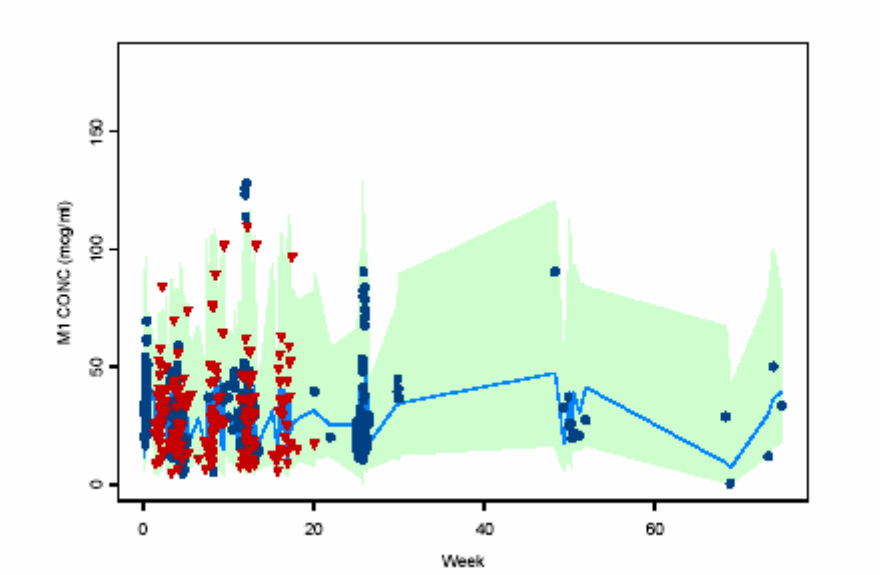
Study	CL/F	V/F	Ka	Exponent[b] For V/F	Exponent[b] for CL/F	ηCL	ηV	ηka	ε
	(L/h)	(L)	(h-1)			(%)	(%)	(%)	(%)
1037	0.0191	5.67	1.07	0.811	0.377	46.7	18.4	170.7	17.7
3503	0.0206	6.37	1a	0.719	0.452	52.7	19.3	0a	19.5
1037+3503	0.020	5.80	1.13	0.769	0.43	50.4	18.6	171.5	18.2

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

- Predictive Check:

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

Figure 4. Predictive Check Using Final PPK Model



- Sensitivity test:

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

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

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

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

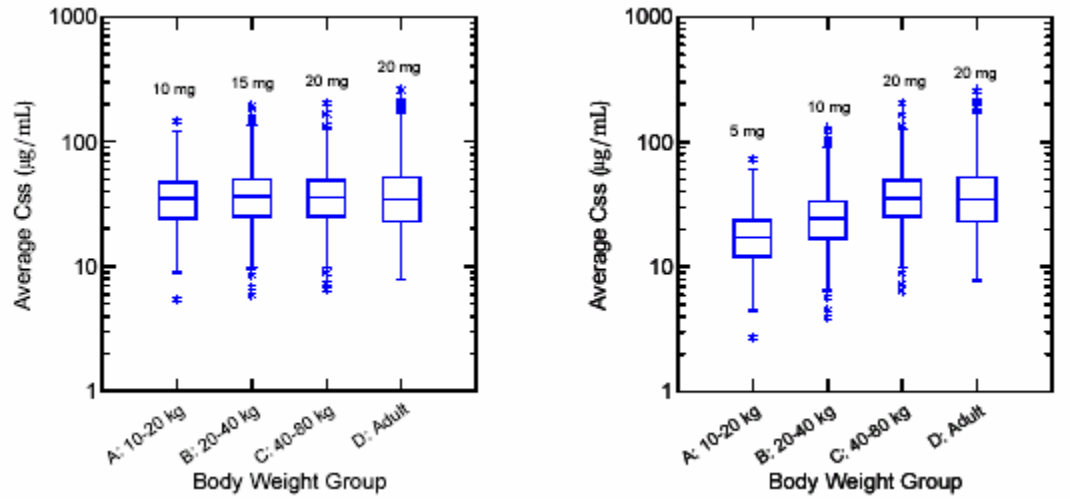
These tests indicated that the PPK analyses were insensitive to the dosing times. This is likely due to the long half-life of M1 (9.14 days, on average) relative to the dosing interval. With such a long half-life and daily dose administration, the fluctuation in M1 plasma concentration at steady-state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

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

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

Dose recommendation for pediatric subjects:
The sponsor conducted simulations in 2000 pediatric subjects according to results of PPK analysis and the recommended doses. The simulated Css at recommended doses and studied doses in Study 3503 for each group including subjects with body weight below 20 kg, body weight between 20-40 kg, body weight above 40 kg, and adults are shown in Figure 5 as a box plot.

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



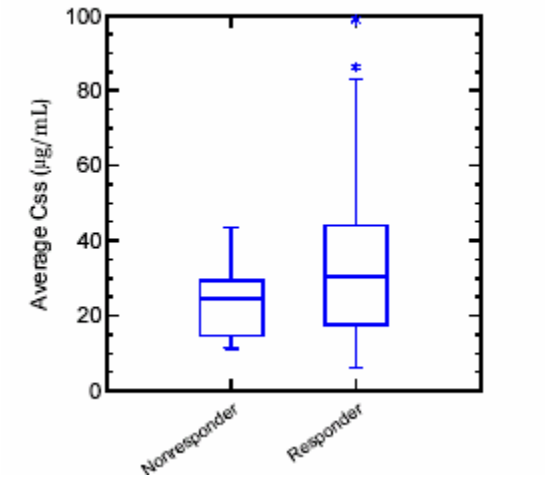
The simulations showed that the recommended doses are more likely to provide comparable exposures across population. However, the studied doses in Study 3503 are likely to provide lower exposure in the subjects with bodyweight below 40 kg than the exposure received in subject with body weight above 40 kg, which could be evidenced by the pharmacokinetic data observed in Study 3503. As shown in Table 5, the mean Css in subjects with body below 20 kg are about 63% lower as compared with mean Css in subjects with body weight above 40 kg.

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

	Body weight		
	<20 kg	**20-40 kg**	**>40 kg**
N	8	19	20
Min	6.1	12.0	8.9
Max	30.6	98.9	86.4
Median	12.6	26.2	36.7
Mean	14.5	30.0	38.9
SD	7.2	19.3	20.4
C.V.	0.50	0.64	0.52

Comparison of PK between responders and non-responders:
Among the 47 subjects treated with leflunomide in study 3503, 32 were categorized as responders and 15 were categorized as non-responders when assessed following 16 weeks of treatment. The model estimated Css for the responders and non-responders are shown in Figure 5.

Figure 5. Estimated Css between responder and non-responder in Study 3503



A clear trend for lower exposures in the group of subjects who failed to respond to leflunomide was observed. The majority of subjects (80%) in the non-responder group had exposures to M1 that were less than the median exposure in the responder group.

Conclusion:

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

Body Weight (kg)	**Daily Dose** (mg)
10.0 – 19.9	10
20.0 – 40.0	15[a]
> 40.0	20

Comments:

1. The studied doses in Study 3503, the mean steady state concentration (Css) at the studied doses, and the proposed doses for approval are shown in the following table. The Css in Study 3503 are 14.5, 30.0, and 38.9 µg/mL in subjects with body weight below 20 kg, 20 to 40 and >40 kg, respectively. The results suggested that the Css at studied doses is lower in subjects with body weight <20 kg than Css in the subjects with bodyweight above 20 kg. Therefore, increased doses from 5 mg daily to 10 mg daily were proposed in subjects with body weight below 20 kg and from 10 mg daily to 15 mg daily for the subjects with body weight between 20 to 40 kg. However, be noted that even at the increased doses, the mean Css in subjects with body weight below 20 kg are expected to be still 26% lower than Css in subjects with body weight above 40 kg.

Body Weight (kg)	**Studies Daily Dose (mg) in Study 3503**	**Css in Study 3503 Mean ± sd (n)**	**Proposed Daily Dose** (mg)
10.0 – 19.9	5	14.5 ± 7.2 (n=8)	10
20.0 – 40.0	10	30.0 ± 19.3 (n=19)	15[a]
> 40.0	20	38.9 ± 20.4 (n=20)	20

Css (μg/mL)=Dose (mg)/CL/F (L/h)/24 (h)
sd= standard deviation
n: the number of subjects

2. The impact of lower exposure in the subjects with body weight below 20 kg on efficacy of the drug may not be able to be evaluated due to the limited sample size (n=8) in the population.
3. The proposed dose is about 100% and 50% higher than the studied doses for the subjects with body weight below 20 kg and between 20 to 40 kg, respectively. Even though the increased doses were supported by the pharmacokinetic analysis, no safety data exists at the increased dose in the pediatric subjects. The increased doses would be acceptable if safety profile is expected to be similar when the exposures are similar between adults and pediatric subjects.
4. Even though the doses used in study 3503 was based on the pharmacokinetic data obtained from study 1037, it appears that the subjects with body weight below 20 kg maybe under dosed because the Css in the subjects with body weight below 20 kg was about 63% lower than Css in the subjects with body weight above 40 kg.
5. The mean average steady state concentration in this study is 35.0 and 24.2 μg/mL, for responder (n=32) and non-responder (n=15), respectively, which may suggest that a certain exposure may be required to respond to the treatment.

Study #: 1037
Title: Phase IB Trial of Leflunomide in Pediatric Subjects with Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Objectives:

- To determine whether therapy with leflunomide warrants further study in patients with polyarticular course juvenile rheumatoid arthritis by obtaining PK and safety data from a small group of patients.
- To collect data regarding preliminary efficacy and improvement (or no deterioration) in physical function and to determine whether therapy with leflunomide warranted further study in subjects with polyarticular course JRA.

Design: It is an open label, multi-center, Phase IB study, 6-months treatment with voluntarily continued study drug administration for up to an additional 24 months provided therapy was well tolerated. Subjects with polyarticular course JRA by American College of Rheumatology (ACR) criteria, regardless of onset type, aged 3 to 17 years, with active disease who were refractory to or intolerant of methotrexate.

Dose: Leflunomide was administered daily according to the following algorithm: a loading dose for 3 days according to body surface area (BSA) measured in square meters (M_2) based on the labeled adult loading dose of 100 mg/day for 3 days and an average adult BSA of 1.73 M^2; maintenance doses were calculated based on a low adult dose of 10 mg/day and an average adult BSA of 1.73 M^2. In subjects without clinical response on or after 8 weeks (based on *Definition of Improvement* [DOI] responder analysis for JRA subjects published by Giannini et al) escalation to the equivalent of leflunomide 20 mg/day per 1.73 M^2 BSA was allowed, at the discretion of the investigator. The final dose algorism is the followings:

BSA m^2	Loading dose for 3 days mg/day	Maintenance dose mg/day	Max maintenance dose mg/day
0.45-0.50	30	5	5
0.51-0.60			10
0.61-0.75	40		
0.76-0.90	50		
0.91-1.00	60		
1.01-1.05		10	15
1.06-1.20	70		
1.21-1.35	80		
1.36-1.50	90		20
1.51-1.73 & up	100		

Data collection: Whole blood samples were collected from each subject at baseline (prior to beginning study treatment), Day 3 (last day of the loading dose), Weeks 4, 12, and 26 during the initial 6-month treatment phase. On Day 3, Weeks 4, 12, and 26, serial samples (prior to dosing, 2, 4, 8 and 24 hours following administration) were collected at each visit. In addition, single samples were to be collected on the following occasions:

- 16 weeks following completion of the initial 6-month treatment phase for subjects not entering the extension
- At Weeks 50 and 74 for subjects continuing treatment in the extension portion of the study
- 16 weeks following treatment discontinuation for any subject withdrawn from the study prior to Week 74

Data analysis: Plasma M1 concentration-time data were pooled with the adult data from Phases I, II, and III and analyzed using a population approach implemented in NONMEM. A one compartment model with first order input previously established in adults was used to describe the pharmacokinetic behavior of M1 with a proportional correction factor for the influence of BSA on clearance and volume in the pediatric population.

Results:

The final number of concentration observations included in the analysis was 494 with an average of 18 (range 5 to 23) plasma M1 concentrations per subject.

The final population pharmacokinetic model was an adaptation of previously developed one compartment model with first order input for M1 using a proportional correction factor for the influence of BSA on CL and V in the pediatric population. BSA was calculated by Du Bois equation as: $BSA = WT^{0.425} HT^{0.725} 0.007184$. Population pharmacokinetic analysis was conducted on the pooled data from Study 1037 and other phase 1/2/3 studies in adults. The relationship between clearance and body surface area, sex, and study population is described as

$$CL = \theta_{Cl} (\frac{BSA}{1.73})^{\theta_{bsa,cl}} (1 + f_{sex,cl})(1 + f_{ph,cl}) \bullet \exp(\eta_{cl})$$

with $f_{sex,cl}$=0 for male and $f_{sex,cl}$= θ_{sex} for female
and $f_{ph,cl}$=0 for phase 3 study, $f_{ph,cl}$= $\theta_{ph1,cl}$ for phase 1 study, $f_{ph,cl}$= $\theta_{ph2,cl}$ for phase 2 study, $f_{ph,cl}$= $\theta_{ph3,cl}$ for study 1037.

The relationship between volume and body surface area, sex, and study population is described as

$$V = \theta_{v} (\frac{BSA}{1.73})^{\theta_{bsa,v}} (1 + f_{sex,v})(1 + f_{ph,v}) \bullet \exp(\eta_{v})$$

with $f_{sex,v}$=0 for male and $f_{sex,v}$= θ_{sex} for female
and $f_{ph,v}$=0 for phase 3 study, $f_{ph,v}$= $\theta_{ph1,v}$ for phase 1 study, $f_{ph,v}$= $\theta_{ph2,v}$ for phase 2 study, $f_{ph,v}$= $\theta_{ph3,v}$ for study 1037.

The final model showed that the clearance (CL) of drug is linearly related with body surface area, indicating that dose might be needed to be adjusted according to the body surface area. However, it is more practical to adjust the dose by body weight, another measure of body size. Therefore, the sponsor used the relationship of BSA=(body weight/70)^0.7 to calculate the body weight at which the dose should be adjusted to ½ and ¼. The corresponding body weight was 26 kg and 10 kg. The midpoint of 1-1/2 and ½-1/4 are ¾ and 3/8 which corresponds to the body weight of 46 kg and 17 kg. A simplified dose recommendation based on the body weight was made and presented in the following table:

Body Weight (kg)	Loading Dose (mg)	Maintenance Dose (mg)
< 20	100 QD x 1	10 QOD
20 – 40	100 QD x 2	10 QD
> 40	100 QD x 3	20 QD

The population pharmacokinetic parameters estimated from the final model are presented in the table below:

	Median	sem	CV%	$sd_{\omega,\sigma}$	95%	
					lower	upper
Structural model						
$\theta_{CL}, (L/h)$	0.025	0.00114	4.56		0.0228	0.0272
$\theta_{V}, (L)$	12.1	0.222	1.83		11.7	12.5
Inter-individual Var.						
ω^2_{CL}	0.375	0.016	4.27	61.2	58.6	63.7
ω^2_{V}	0.0642	0.00619	9.64	25.3	22.8	27.6
Fixed effects						
$\theta_{bsa,Cl}$	1					
$\theta_{bsa,V}$	1					
$\theta_{female,Cl}$	−0.154	0.0392	25.5		−0.231	−0.0772
$\theta_{female,V}$	−0.148	0.0221	14.9		−0.191	−0.105
$\theta_{ph-I,Cl}$	0.383	0.122	31.9		0.144	0.622
$\theta_{ph-I,V}$	0					
$\theta_{ph-II,Cl}$	−0.258	0.0349	13.5		−0.326	−0.19
$\theta_{ph-II,V}$	0.27	0.0352	13		0.201	0.339
$\theta_{1037,Cl}$	0					
$\theta_{1037,V}$	−0.222	0.0503	22.7		−0.321	−0.123
Residual error						
θ_{ph-I}	0.296	0.0634	21.4		0.172	0.42
θ_{ph-II}	0					
θ_{ph-III}	13.2	2.68	20.3		7.95	18.5
θ_{1037}	10.8	12.7	118		−14.1	35.7
σ^2_{ph-I}	0.011	0.00135	12.3	10.5	9.14	11.7
σ^2_{ph-II}	0.039	0.00315	8.08	19.7	18.1	21.3
σ^2_{ph-III}	0.0201	0.00176	8.76	14.2	12.9	15.3
σ^2_{1037}	0.0281	0.0122	43.4	16.8	6.47	22.8

Table 3: NONMEM result of the final model. The data from study HWA486/1037 were fitted together with the data from phase-I, -II, and -III.

Conclusion:

- The final population pharmacokinetic model obtained indicated that BSA-normalized CL in the pediatric subjects with JRA was not different from adults with RA, which supported adjustment of the maintenance dose based on BSA.
- For practical reason, dose adjustment was proposed by body weight instead of BSA. The relationship between BSA and body weight, BSA=(body weight/70)^0.7, was used.
- The proposed doses were shown in the following table:

Body Weight (kg)	Loading Dose (mg)	Maintenance Dose (mg)
< 20	100 QD x 1	10 QOD
20 – 40	100 QD x 2	10 QD
> 40	100 QD x 3	20 QD

Comment: The source of the relationship between BSA and body weight used for proposed dose adjustment was not provided.

6.2 Proposed labeling:

Not included because only change to current label proposed by applicant was under PK and Precautions (pediatric use).

6.3 Individual Study reviews

Please note that the PM review above included a lot of information on the design, objective and analysis of the studies, so they will not be repeated here. Only those areas that were not covered will be inserted here.

Study No. HWA 486/1037

Title: Phase IB Trial of Leflunomide in Pediatric Subjects with Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Population: Twenty-seven subjects (4 M, 23F) were enrolled ranging in age from 6 to 17 years. Weights ranged from 17.8 –66.7 kg. All had failed methotrexate therapy: 15 due to lack of efficacy and 12 as a result of intolerance.

Analytical methods

Plasma was separated from the whole blood samples and analyzed to determine the concentration of the active metabolite of leflunomide (M1). All plasma samples were analyzed for M1 concentration using a validated HPLC method with UV detection. The limit of quantification was 0.1 mcg/mL.

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

Assay Method	HPLC using UV detection @ 292 nm
Analytical Site	Aventis Pharma Deutschland GmBH, DI&A, Germany
Compound	M1 (A771726) the main metabolite of leflunomide
Internal Standard	A782068
Matrix	Plasma
Accuracy *Between-day*	94.8 % - 109.5 %
Imprecision (CV%) *Between-day*	1.7%-6.5%
Standard curve range	0.1-100 mcg/mL
Sensitivity (LOQ)	0.1 mcg/mL (CV% = 4.4 % and Accuracy = 102.3%)
Selectivity	No interfering peaks were observed at the retention time for M1 and its IS.
Stability	Stable in human plasma for at least 53 weeks at –10°C to –30 °C

Data Analysis and Statistical Procedures:

A population PK model was developed using adult and pediatric data (see PM review for details).

Results-Pharmacokinetics

Final POPPK Model: The population pharmacokinetic parameters estimated from the final model are presented in the table below:

Table 11. Estimates of Typical Values at BSA=1.73 M^2 and Inter-Individual Variability for CL and V

Parameter	Population Typical Value	CV%
CL (mL/h)	25.0	61.2
V (L)	12.1	25.3

Individual POSTHOC estimates:

Bayesian estimates for pharmacokinetic parameters were calculated for each subject using the POSTHOC option in NONMEM®. The mean estimates of CL, V, and a calculated elimination half-life ($t_{1/2}$) are presented in the table below (N = 27):

Subject	**WT** (kg)	**Age (years)**	**CL (mL/hr)**	**CL/BSA (mL/hr per M^2)**	**V (L)**	**V/BSA (L per M^2)**	**$T_{1/2}$ (days)**
Mean	40.46	12.3	20.31	16.86	5.79	4.62	9.98
SD	14.29	3.34	9.02	8.54	1.79	0.91	5.72
CV%	35.3	27.2	44.4	50.7	30.9	19.8	57.4
Median	37.4	13	18.78	14.53	5.64	4.46	9.21
Minimum	17.8	6	5.03	6	2.5	3.17	2.37
Maximum	66.7	17	42.63	38.67	9.7	6.64	28.17

Conclusions

Final population PK model obtained indicated that BSA-normalized CL in pediatric subjects (aged 6-17 years old) with polyarticular course JRA was similar to that obtained in adult RA patients. Therefore adjusting the pediatric

maintenance dose to achieve systemic exposure measures comparable to adults using body surface area was supported by this data. An adjusted dosing scheme based on this data was then used for the pivotal efficacy study 3503 in pediatric JRA patients. The dosing recommendation was based on weight for practical reasons no references were provided on how the equation between dose and body weight used for the proposed dose adjustment was derived.

HWA 486/3503

Title: Efficacy and Safety of Leflunomide versus methotrexate in the treatment of Pediatric Patients with Juvenile Rheumatoid Arthritis

Objectives:

Primary objective:

To assess efficacy and safety of leflunomide versus methotrexate in treatment of JRA as assessed by the Percent Improvement Index and JRA DOI 30% Responder Rate at the endpoint or week 16 visit. For subjects terminating early, the endpoint will be the last evaluation prior to week 16 (LOCF). Safety was assessed by adverse events, laboratory tests, vital signs, physical examination.

Secondary objective:

To assess population pharmacokinetics of leflunomide based on plasma levels of the active metabolite

Study design

The study was a multinational, multicenter, double-blind, double-dummy, randomized, parallel, and active controlled study.

Population

Demographic or disease characteristic		Treatment group		
		Leflunomide N=47	**Methotrexate N=47**	**p**
Age (years)	mean (SD)	10.1 (4.0)	10.2 (3.8)	0.9310
< 12 years	n (%)	27 (57.4)	27 (57.4)	0.9495
≥ 12 years	n (%)	20 (42.6)	20 (42.6)	
Sex				
Male	n (%)	12 (25.5)	13 (27.7)	0.6930
Female	n (%)	35 (74.5)	34 (72.3)	
JRA duration (years)	mean (SD)	1.69 (3.2)	1.37 (1.97)	0.6923

Analytical Methods:

Analytical Method Validation for Study No. HWA 486/3503 (Covance Study No. 6339-162)

Assay Method	HPLC using UV detection @ 292 nm
Analytical Site	Covance Laboratories Inc. Madison, Wisconsin
Compound	M1 (A771726) the main metabolite of leflunomide
Internal Standard	A782068
Matrix	Plasma
Accuracy *Between-day*	101 % - 104.5 %
Imprecision (CV%) *Between-day*	1.6%-12.1%
Standard curve range	0.1-100 mcg/mL
Sensitivity (LOQ)	0.1 mcg/mL (CV% = 2 % and Accuracy = 101. %)
Selectivity	No interfering peaks were observed at the retention time for M1 and its IS.
Stability	Stable in human plasma for at least 53 weeks at –10°C to –30 °C

Covance Study No. 6339-164

Assay Method	GC/MS
Analytical Site	Covance Laboratories Inc. Madison, Wisconsin
Compound	TFMA [(trifluoromethyl)-aniline]
Internal Standard	3-TFMA
Matrix	Plasma
Accuracy *Between-day*	98 % - 101.7 %

Imprecision (CV%) *Between-day*	4.0 %-8.6 %
Standard curve range	0.5-50 ng/mL
Sensitivity (LOQ)	0.5 ng/mL (CV% = 3.7 % and Accuracy = 100%)
Selectivity	No interfering peaks were observed at the retention time TFMA
Stability	Stable in human plasma for at least 55 weeks at –10°C to –30 °C

Covance Study No. 6339-165

Assay Method	GC with Nitrogen Selective Detection
Analytical Site	Covance Laboratories Inc. Madison, Wisconsin
Compound	Leflunomide
Internal Standard	H734169
Matrix	Plasma
Accuracy *Between-day*	107.5 % - 111.3 %
Imprecision (CV%) *Between-day*	5.0 %-5.8%
Standard curve range	5-1000 ng/mL
Sensitivity (LOQ)	5 ng/mL (CV % = 2.2 % and Accuracy = 99 %)
Selectivity	No interfering peaks were observed at the retention time for Leflunomide
Stability	Stable in human plasma for at least 61 weeks at –10°C to –30 °C

Statistical procedures

The focus of the pharmacokinetic analysis was the plasma M1 concentrations. Plasma M1 concentration-time data were pooled with the M1 concentration-time data from study HWA486/1037 and analyzed using a population approach implemented in NONMEM ® (see PM review for details)

Results – Pharmacokinetics

Bayesian estimates of the pharmacokinetic parameters were calculated for each subject using the POSTHOC option in NONMEM. The individual estimates of CL/F, V, and a calculated elimination half-life (t½) for the 46 subjects who received leflunomide and had at least 1 measurable M1 level are descriptively summarized in the table below:

Table - Statistical summary of the individual PK parameter estimates using POSTHOC Bayesian estimation in Study 3503

Parameter	**CL/F**	**V/F**	$T_{½}$
	L/h	**L**	**days**
N	46	46	46
Min	0.0042	2.57	2.6
Max	0.0936	9.98	26.5
Median	0.0186	5.39	7.6
Mean	0.0225	5.51	8.9
SD	0.0155	2.04	5.0
%CV	68.7	36.9	55.8

- Although mean CL is similar to adult RA patients, POPPK analysis of the pooled data from both studies indicated pediatric subjects weighing < 20 kg had a reduced clearance compared to the adult RA patients.

Table Descriptive Statistics of the Css Achieved in Study 3503

	Weight (kg) Group		
	<20	**20-40**	**>40**
		Css (□g/mL)	
N	8	19	20
Minimum	6.1	12.0	8.9
Maximum	30.6	98.9	86.4
Median	12.6	26.2	36.7
Mean	14.5	30.0	38.9
SD	7.2	19.3	20.4
C.V.	0.50	0.64	0.52

As shown in the table above, the mean Css in patients with body weights below 20 kg was about 52 % and 63 % lower than that obtained in patients with body weights ranging from 20-40 kg and > 40 kg respectively. There is an imbalance in the sample size of the different weight groups which limits the data interpretation. The actual impact of lower exposure in the subjects with body weights < 20kg on the efficacy of the drug may be difficult to evaluate due to the small sample size of these patients (n=8). With the dosage regimens studied, the systemic exposures to M1 in JRA subjects weighing > 40 kg was comparable to that in adult RA subjects (~34 mcg/mL). However, the M1 exposure was lower in the subjects in the 2 lower weight categories (< 20 kg, 20 – 40 kg). Based on an anlysis between responder and non-responder the mean Css was 35 and 34.2 mcg/mL, for responder (n=32) and non-responder (n=15) respectively. This suggests that a certain exposure may be required for response to treatment.

Any potential effect of crushing the leflunomide tablet and mixing it in applesauce or jam on exposure to M1 could not be determined for study 3503. Only 7 subjects had crushed and mixed some of their doses of leflunomide during the study. Because those subjects who did crush and mix some of their doses tended to be the younger subjects, a meaningful comparison of the M1 concentrations observed for those subjects who crushed some of their doses and those who reported swallowing every dose whole could not be performed.

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/s/

Abi Adebowale
3/4/04 03:44:48 PM
BIOPHARMACEUTICS

Dennis Bashaw
3/5/04 10:05:16 AM
BIOPHARMACEUTICS

Since this review was finalized, additional labeling discussions were held with the sponsor on 3/4/04. The labeling as of this date, while not identical to that in this review is consistent with the reveiw and is acceptable.