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Arava-000235-Article 45-II-28
EPAR Assessment Report

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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SCIENTIFIC DISCUSSION

Introduction

This submission concerns a type II variation to Arava in response to the EMEA letter dated 25 March 2005 on the submission of data concerning the use of medicinal products in children.
Of the many subtypes of juvenile rheumatoid arthritis (JRA), active polyarticular course JRA (APC-JRA) is widely regarded as the paediatric equivalent to adult RA. Both conditions share many clinical and pathophysiological features. APC-JRA is the second most frequent type of paediatric RA, affecting approximately 20 to 40% of all children with JRA. The European League of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) both recognise this subtype of paediatric arthritis and have established the key diagnostic criteria and pattern of joint involvement which characterise each of the major variants of JRA, including APC-JRA.
Currently the repertoire of medicinal products approved for the treatment of JRA in Europe is limited. Only two compounds are available in Europe, methotrexate (MTX), a Disease-Modifying Anti-Rheumatic Drug (DMARD) and etanercept, a biological. The efficacy of MTX in JRA has been demonstrated since 1992. Compared to placebo, MTX was shown to have improved efficacy with an acceptable safety profile in children with APC-JRA. However, the frequency and severity of side effects increase with higher doses, and drug resistance to MTX may develop when used over the long term.
Etanercept is a genetically engineered fusion protein that binds the pro-inflammatory cytokine tumor necrosis factor (TNF) and lymphotoxin-α, inhibiting their activity. It has been established that TNF-α inhibition by etanercept is effective at controlling APC-JRA with acceptable tolerability. Etanercept is approved in Europe for second-line therapy of JRA.

Leflunomide is a DMARD approved for the treatment of adult RA. Leflunomide is an isoxazole immunomodulatory agent with a unique mechanism of action. It inhibits *de novo* pyrimidine synthesis by reversibly blocking the enzyme dihydroorotate dehydrogenase, resulting in antiproliferative effects on activated lymphocytes important in the pathogenesis of rheumatic diseases like RA.
Due to the similarities between APC-JRA and adult RA, it was anticipated that patients with APC-JRA might also benefit from treatment with leflunomide. The Marketing Authorisation Holder (MAH) has therefore completed clinical trials to evaluate the pharmacokinetics (PK), safety and efficacy profile of leflunomide in the treatment of APC-JRA in paediatric population between the ages of 3 and 17 years.

Please note that according to the concept paper from the CHMP on points to consider on clinical investigation of medicinal products for the treatment of JIA, issued on 26 February 2004 (CPMP/EWP/422/04), the terms juvenile chronic arthritis and JRA have been replaced by JIA. However, as the clinical program with leflunomide in children with JRA was initiated prior to this paper, all of the documentation of this dossier refers to JRA instead of JIA.

For this application the following (concept) guidelines are applicable: concept paper from the CHMP on points to consider on clinical investigation of medicinal products for the treatment of JIA, issued on 4-7-2005 (CPMP/EWP/422/04), and ICH Topic E11 Clinical investigations of medicinal products in the paediatric population (CHMP/ICH/2711/99).

Clinical aspects

A clinical program to evaluate the efficacy and safety of leflunomide in paediatric patients with APC-JRA was implemented. Two studies (**HWA486/1037** and **HWA486/3503**) were conducted in children with JRA. Both studies were followed by an extension study to gather further data on the durability of efficacy over the long term. In addition, to assess efficacy and safety of leflunomide in this population, the pharmacokinetic of leflunomide and its active metabolite were assessed based on data collected from blood samples taken in both studies, and analysed collectively after completion of both studies. One of the objectives of the PPK (population pharmacokinetics) analysis was to determine appropriate *dose recommendations* for leflunomide use in the JRA population.

Clinical efficacy

Study design

Study HWA486/1037, performed in children (6 to 17 years), was a Phase Ib, open label study in subjects with APC-JRA who had previously failed to respond to, or were intolerant of, MTX therapy. This pilot study collected preliminary data on efficacy and improvement (or no deterioration) in physical function as a secondary objective in order to determine whether therapy with leflunomide warranted further study in subjects with APC-JRA. The primary objective was to obtain PK and safety data on leflunomide. Study 1037 was 6 months in duration and was followed by an extension of 24 months (Study 1037x).

Study HWA486/3503 was a Phase III, randomised, double-dummy, double-blind study in children (3 to 17 years) performed in 32 study centres in the US, Canada, New Zealand, Australia, and Europe comparing leflunomide to MTX with folic acid supplementation in subjects naïve to both MTX and leflunomide. The design was used as the current US FDA regulations and ethical considerations do not permit placebo-controlled trials in children if there is a valid approved comparator (MTX, sulfasalazine and etanercept are all approved for the treatment of JRA in the US). Study 3503 was 4 months in duration and was followed by an extension of 8 months (Study 3504). The double-blind of study 3503 was maintained during the extension phase of Study 3504 (see table below).

Table 1 - Key features of clinical trials of leflunomide in JRA

	Study 1037	**Study 1037 Extension**	**Study 3503**	***Study 3504*** **(Extension to Study 3503)**
Design	Open label, multicenter		Randomized, double-dummy, double-blind, parallel group, multicenter	
Comparator	None		Methotrexate	
Duration	6 months	24 months	4 months	8 months
Number of patients	27	17	94 (47 Lef and 47 Mtx)	70 (33 Lef and 37 Mtx)
Principal inclusion criteria	Age 6 - 17 years Diagnosis of APC-JRA (defined as a minimum of 5 active joints with at least 5 swollen joints and at least 3 joints with limited motion plus pain and/or tenderness) *Previous failure with or intolerance to methotrexate*		Age 3 - 17 years Diagnosis of APC-JRA (defined as a minimum of 5 active joints with at least 5 swollen joints and at least 3 joints with limited motion plus pain and/or tenderness) Methotrexate and leflunomide naive	
Treatment	Loading dose of leflunomide according to body surface area (BSA)1 for 3 days Maintenance dose of leflunomide according to BSA2		<u>Leflunomide + methotrexate placebo.</u> Leflunomide dose according to body weight: <20 kg: 100 mg loading dose for 1 day followed by 10 mg qd maintenance dose every other day 20–40 kg: 100 mg loading dose for 2 days followed by 10 mg qd maintenance dose >40 kg: 100 mg loading dose for 3 days followed by 20mg qd maintenance dose <u>Methotrexate + leflunomide placebo</u> Methotrexate dose 0.5 mg/kg/wk (~15 mg/m2/wk) po to a maximum of 25 mg/wk.	
Principal efficacy criteria	JRA Definition of Improvement (DOI) ≥30% responder status		JRA DOI ≥30% responder status Percent Improvement Index (PII)	

Lef = leflunomide, Mtx = methotrexate, qd = every day, po = orally
1Proportional to a 100 mg/day dose for an adult with a body surface area (BSA) of 1.73 m². 2Proportional to a 10 mg/day dose for an adult with a BSA of 1.73 m²; from 8 weeks of therapy, the dose of leflunomide could be increased at the discretion of the investigator to the equivalent of 20 mg/day in a 1.73 m² adult.

All studies were conducted in accordance with good clinical practice (GCP), as required by the ICH E6 Guideline for GCP, 1 May, 1996, in agreement with the Declaration of Helsinki and standard operating procedures for clinical investigation and documentation in force at Aventis worldwide.

<u>Efficacy variables</u>
The <u>primary efficacy variable</u> in both studies was the Definition of Improvement (DOI), a responder analysis in JRA published by Giannini et al. (1997). A subject was considered a responder if >30% improvement (from baseline) occurred in >3 of 6 variables, with no more than 30% worsening (from baseline) in any one variable. The 6 outcome measures used to calculate the DOI are as follows:

1. Physician's global assessment of disease severity.
2. Subject or parent global assessment of overall well-being.
3. Physical function, using the Child Health Assessment Questionnaire Disability Index (CHAQDI).
4. Number of joints with active arthritis, as defined by ACR criteria.
5. Number of joints with limited range of motion (ROM) excluding sternoclavicular and sacroiliac joints.
6. Erythrocyte Sedimentation Rate (ESR).

A second primary efficacy variable was used in Study 3503/3504, the Percent Improvement Index (PII). The PII was defined as the average percentage change from baseline over the six outcome measures assessed. In the event that the mean percent change was positive (=worsening) the % improvement was set to zero.[1]

Secondary efficacy variables included mean changes in the 6 individual components of the DOI (and PII in 3503/3504) as well as:

Table 2 – Study specific secondary efficacy variables

Study 1037/1037x	***Study 3503/3504***
• Swollen joint count defined as inflamed joints with synovial thickness and/or effusions, without ankylosis1. • Joint severity score, as the sum of: – all joints with swelling (62 joints assessed), – pain on motion (71 joints assessed), – tenderness (71 joints assessed), – limitation of motion (67 joints assessed).	• C-reactive protein (CRP) • Subject/parent assessment of pain on a visual analog scale (VAS).

1 62 joints were assessed for swelling excluding the hip, subtalar, sacroiliac, lumbar spine, thoracic spine, and cervical spine.

Statistics

Efficacy was assessed in both studies in the intent-to-treat (ITT) population defined as all subjects enrolled who received at least one dose of study drug with one post baseline assessment. Where there were missing data the Last Observation Carried Forward (LOCF) procedure was applied. Supportive efficacy was assessed in the extension cohort of Study 1037x for the extension phase months 6 to 30. Due to the small sample size and open label treatment in Study 1037, it was prospectively defined that formal statistical testing of the safety and efficacy data would not be performed. The primary endpoint for this study was at the end of the 6-month treatment period (26 weeks). The efficacy data from the extension phase are presented and summarised as supporting efficacy information.

The primary efficacy analysis in Study 3503 evaluated PII and DOI ≥ 30% at Week 16 and evaluated the durability of efficacy in the extension subjects from Week 16 to Week 48 of treatment (Week 0 to Week 32 of the extension) in its extension study 3504.

Initially the study was designed as an equivalence study with one primary endpoint the PII. There where two major amendments from a methodological perspective. Following discussion with the FDA, the JRA DOI 30% responder rate became a co-primary endpoint (amendment 4, 30-05-2002) and the study was converted from an equivalence study to a superiority study (amendment 6 initiated 09-04-2003) after which the last patients entered the study at 28-05-2003).

[1] As part of a sensitivity analysis additional definitions of % Improvement were explored incorporating patients with < 30% worsening , with <100% worsening and any change. Results were robust (data not shown).

The primary hypothesis was that there where treatment difference between leflunomide and MTX in the primary endpoints. In the event that superiority was not achieved with respect to the PII non-inferiority was opted for with a non-inferiority margin of 12.5%.

A sample size of 37 subjects per group was calculated as necessary to observe a difference in the mean PII of 15% or greater, with a standard deviation of 23% (power 0.80). 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 % Improvement Index is greater than or equal to –12.5%.

The between-group comparisons conducted at Week 16 as well as at Week 48 of treatment (extension Week 32), and for each visit since the start of study treatment in Study 3503, used an analysis of variance (ANOVA) with treatment and site (pooled) as fixed effects for the PII, and the Cochran Mantel-Haenszel procedure controlling for site (pooled) for the JRA DOI ≥ 30%, responder rates.

To assess durability of efficacy, a within-group comparison of mean values at Week 16 versus Week 48 (study end-point) of treatment and other time-points (secondary efficacy analysis) was conducted using ANOVA, with visit and subject as fixed effects, for the PII, and a McNemar test for the responder rates.

Subgroup analyses were predefined in Study 3503 to investigate the consistency of effect across various subgroups. Subgroups concerned age, sex, race, duration of JRA, baseline swollen joint count and endpoint dose. For the PII, ANOVA was used with treatment, centre, background variable and treatment by background variable interaction as fixed effects. For the JAR DOI responders a logistic regression was used for the same covariates.

Results

Dose response studies

Results of the population pharmacokinetics (PPK) analysis were used to determine appropriate dose recommendations for leflunomide use in the JRA population (see section 2.3 "Pharmacokinetics"). The optimal daily dose of leflunomide based on body weight is shown in table 3:

Table 3 - **Optimal daily doses of leflunomide as suggested by PK modeling**

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

Nevertheless, only 5 and 10 mg regimens have been clinically tested (10 mg every other day for children under 20 kg and 10 mg per day for children between 20 and 40 kg).

Study populations

Table 4 · **Disposition of subjects in all studies**

Population	Number (%) of subjects					
	Study 1037	Extension 1037	Study 3503		Extension 3504	
	Lef	Lef	Lef	Mtx	Lef	Mtx
ITT/Safety population	27 (100.0)	17 (100.0)	47 (100.0)	47 (100.0)	33 (100.0)	37[a] (100.0)
Discontinued	10 (37.0)	8 (47.1)	5 (10.6)	3 (6.3)	9 (27.3)	6 (16.2)
Completed study therapy	17 (63.0)	9 (52.9)	42 (89.4)	44 (93.6)	24 (72.7)	31 (83.8)

Lef = leflunomide, Mtx = methotrexate

[a] 2 subjects in the methotrexate group that entered the 3504 extension study and took 3504 study medication, did not have any efficacy assessments and were excluded from the efficacy evaluable population.

Source data: *Module 5.3, CSR 1037, Table 1*; *Module 5.3, CSR 3503, Table T2* and *Module 5.3, CSR 3504, Table T2.*

Due to the small number of subjects remaining in the 1037 extension study by the time any subjects had completed 130 weeks of treatment, the study was ended before all remaining subjects had the opportunity to complete 130 weeks of treatment. At that time, 3 (17.7%) subjects had completed 130 weeks and the 6 (35.3%) others still remaining had not. During the extension phase, 8 (47.1%) subjects withdrew (5 lack of efficacy, 1 adverse event and 2 for other reasons).
Sixteen subjects who completed Study 3503 did not enrol in extension Study 3504 (9 leflunomide and 7 MTX subjects). During the extension phase, 15 of the 70 subjects withdrew, the reasons for which were lack of efficacy (5 leflunomide, 0 MTX), an adverse event (1 leflunomide, 5 MTX), withdrew consent (1 leflunomide, 1 MTX), progression of disease (1 leflunomide, 0 MTX) and other reasons (1 leflunomide, 0 MTX).

Baseline characteristics
All 27 subjects in Study 1037 had APC-JRA and had failed MTX therapy (15 due to lack of efficacy and 12 as a result of intolerance) and all 94 subjects in Study 3503 were MTX naïve at the start of the study (see further, table). Mean age in study 1037 was 12.3 yrs in the Leflunomide group (85% female) and 13.3 yrs in the MTX group (83% female) and in study 3503 10.1 yrs in the Leflunomide group (75% female) and 10.2 yrs in the MTX group (72% female).
In Study 1037, the pattern of disease at onset of JRA in the ITT subjects was polyarticular in 19, pauciarticular in 6, and systemic in 2 subjects. Eight subjects were RF+. Mean disease duration was 7.0 years. Concomitant medications included non-steroidal anti-inflammatory drugs (NSAIDs) in 22 (81.5%), corticosteroids in 18 (66.7%) and both in 16 (59.3%) subjects.
Subjects in Study 3503 were required to have polyarticular course JRA at baseline. The majority of subjects in both treatment groups had polyarticular JRA at onset of disease. Ten subjects were RF+. The mean disease duration was approximately 1.5 years with a median duration of 0.33 years, and all but 6 subjects were DMARD-naïve.

Mean baseline levels for physician's global assessment of disease severity, subject or parent global assessment of overall well-being, CHAQDI, number of joints with active arthritis, number of joints with limited ROM and Erythrocyte Sedimentation Rate (ESR) were in **study 1037** 5.58, 4.37, 1.33, 14.85, 20.59, 43.54, respectively. The baseline levels of these measures in study 3503 were summarized in table 5:

Table 5 . JRA history and status (ITT subjects)

Characteristic	Treatment group		Probability
	Leflunomide N=47	Methotrexate N=47	
JRA type at onset n (%)			
Pauciarticular	10(21.3)	8 (17.0)	0.6358
Polyarticular	36 (76.6)	39 (83.0)	
Systemic	1 (2.1)	0 (0.0)	
JRA duration (years)			
Mean (SD)	1.69 (3.210)	1.37 (1.970)	
Median	0.33	0.33	0.6923
Range	0.0 – 15.33	0.0 – 9.00	
Number	47	47	
Active joint count			
Mean (SD)	14.4 (7.91)	14.0 (9.93)	
Median	13	11	0.9995
Range	0 – 32	2 – 47	
Number	47	47	

Table 5 (cont.) JRA history and status (ITT subjects)

Characteristic	Treatment group		Probability
Limited ROM[a] joint count			
Mean (SD)	7.7 (6.44)	8.0 (6.64)	
Median	7	7	0.3774
Range	0 – 32	0 – 31	
Number	47	47	
MD global assessment score			
Mean (SD)	55.1 (18.33)	47.3 (19.27)	0.1792
Median	55	42	
Range	14 – 95	20 – 92	
Number	47	47	
Patient global assessment			
Mean (SD)	39.6 (28.13)	36.5 (23.79)	0.9533
Median	34	34	
Range	2 – 96	2 – 100	
Number	47	47	
Disability index (CHAQ DI)			
Mean (SD)	1.03 (0.707)	1.11 (0.737)	0.4687
Median	0.9	1.0	
Range	0.0 – 3.0	0.0 – 2.8	
Number	47	47	
ESR (mm/hr)			
Mean (SD)	30.8 (18.16)	34.5 (21.74)	0.2342
Median	20	22	
Range	20 – 114	20 – 104	
Number	43	45	
≤ 20 mm/hr N (%)	23 (53.5)	22 (48.9)	0.8673
≥ 20 mm/hr N (%)	20 (46.5)	23 (51.5)	
CRP (mg/L)			
Mean (SD)	19.57 (22.82)	13.80(25.63)	0.3152
Median	10.40	3.70	
Range	0.0 – 94.5	0.0– 124.0	
Number	47	46	

Treatment duration and exposure

In study 1037, mean duration of leflunomide therapy was 22 weeks (1 to 30 weeks). Mean loading dose was 79.63 mg and mean maintenance dose 12.22 mg. The dose of study drug was increased in 20 subjects (74.1%). In 2 subjects subsequent dose reductions were required due to adverse events. Over the 130 weeks of treatment in the extension Study 1037x, the extension cohort was exposed to leflunomide for a mean duration of 95.9 weeks. The treatment exposure to leflunomide in the extension cohort over the entire 30 month study period was 31.2 patient years.

In study 3503, there were no significant differences between the groups in mean study duration or drug exposure. Leflunomide dose was reduced in 1 subject (adverse event) and MTX dose was reduced

in 2 subjects (1 due to adverse event) while the MTX dose was increased in 1 subject and leflunomide placebo dose increased in 1 subject.
Over the 48 weeks of treatment in the extension Study 3504, the duration of exposure to study medication in the extension population was comparable between the treatment groups. The largest proportion of extension subjects received study medication for 337 to 364 days in both treatment groups.

Primary efficacy
In study 1037, one-third of subjects in the ITT efficacy analysis were responders at week 4 (9/27) and week 8 (10/27). These results increased to 14/27 or 51.9% at Week 12, the maximum response rate, which was sustained through Week 26 (see figure below).

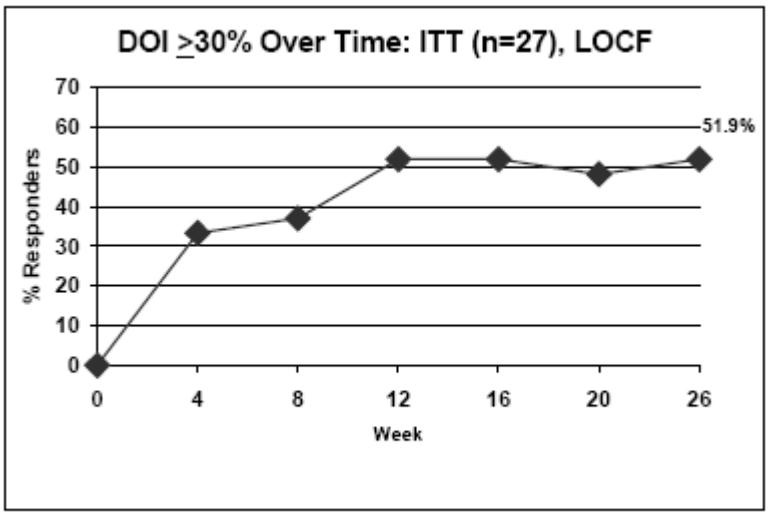


Figure 1. DOI ≥30% Over Time: ITT (n=27), LOCF

Although 14 subjects were DOI >30% responders after 26 weeks of therapy using LOCF, 17 subjects entered the extension phase. Thirteen of the 17 subjects who entered the extension phase were responders at Week 26. During the long-term extension of Study 1037, DOI response rates were maintained in the 17 subjects who entered this phase of the study. After 30 months of treatment, 52.9% of subjects reached the target of a DOI response of 30%. No additional subjects withdrew for lack of efficacy during the extension.

In study 3505, two primary efficacy outcome variables were assessed, DOI response rates at 30% and PII. Improvement occurred with subjects achieving a DOI of 30% response after approximately 2 months and remaining responders thereafter. At endpoint, after 16 weeks of treatment, a DOI response of 30% had been achieved in 89.4% of MTX subjects and 68.1% of leflunomide subjects and the adjusted mean improvement in the PII was –44.4% in the leflunomide group and –52.9% in the MTX group (see table below). The difference in response rates was statistically significant in favour of MTX for the DOI ≥ 30% (p=0.02), but not for the PII (p=0.18). One patient in each treatment arm discontinued the study for lack of efficacy. The DOI ≥ 30% responder rate and the PII achieved at Week 16 were maintained in both treatment groups throughout the extension Study 3504 but the difference between treatment groups for DOI ≥ 30% was no longer statistically significant in the Study 3504 efficacy evaluable population at endpoint (Week 48) of the extension (p=0.15).

Table. 6

A Patients disposition

	Lef	**MTX**	**Difference[B], CI $_{95\%}$, p-value**
Study 3503			
$n_{randomised\ in\ study\ 3503}$	47	47	
$n_{completed\ study\ 3503}$	42	44	
$n_{entering\ extension\ study\ 3504}$	33	35+2[A]	
$n_{entering\ completing\ study\ 3504}$	24	31	

[A] Two subjects entering provided no data

B Results DOI >= 30% responder rate

	Lef	MTX	Difference[B], CI 95% , p-value
Study 3503			
n_{itt}	47	47	
Responders			
- At week 8	61.7	68.1	- 6.4 -25.7 ; 12.9 p=0.46
- At week 12	68.1	85.1	-17.0 -33.8 ; - 0.2 p=0.09
- At week 16[C]	**68.1**	**89.4**	**-21.3 -37.3 ; -5.3 p=0.02**
Study 3504[#]			
$n_{continuing}$ [&]	33	35	
Responders			
- At week 16	78.8	91.4	12.6 Not presented
- At week 32	81.8	94.3	12.5 Not presented
- At week 40	81.8	91.3	9.5 Not presented
- At week 48	78.8	91.3	12.5 Not presented p=0.15

[A] Responder defined as a subject with an at least 30% improvement from baseline in 3 out of the 6 variables (i.e Global assessment by physician (VAS), by patient/parent (VAS), number of active joints, number of joints with limited range of motion plus pain and/or tenderness, functional assessment based on CHAQ Disability Index and ESR) and no more than 30% worsening in any other item.
[B] Cochran-Mantel-Haenzsel procedure controlling for site.
[C] Primary endpoint

Double blind extension of study 3503,
& Based on for which data were available, n not necessarily the same group of subjects

C Results improvement index

	Lef	MTX	Difference[B], CI 95% , p-value
Study 3503			
n_{itt}	47	47	
% Improvement index[A]			
At week 4	-25.56	-26.62	1.06 -9.27 ; 11.39 p = 0.84
At week 8	-31.26	-35.51	4.25 -6.51 ; 15.01 p = 0.43
At week 12	-38.63	-44.85	6.22 -5.55 ; 17.98 p = 0.30
At week 16[C]	**-44.41**	**-52.87**	**8.46 -3.86 ; 20.77 p = 0.18**
Study 3504[#]			
$n_{continuing}$ [&]	33	35	
% Improvement index[&]			
At week 16	-54.66	-57.96	3.30 Not presented
At week 32	-56.19	-61.35	5.16 Not presented
At week 40	-54.87	-61.57	6.70 Not presented
At week 48	-55.36	-65.51	10.15 Not presented p=0.21

[A] The % Improvement Index was the mean percent changes from baseline for the following items Global assessment by physician (VAS), by patient/parent (VAS), number of active joints, number of joints with limited range of motion plus pain and/or tenderness, functional assessment based on CHAQ Disability Index and ESR. In the event that the mean percent change was positive (=worsening) the % improvement was set to zero.[2]
[B] Analysis of variance with treatment and site effects
[C] Primary endpoint
double blind extension of study 3503,
& based on for which data were available.

[2] As part of a sensitivity analysis additional definitions of % Improvement were explored incorporating patients with < 30% worsening , with <100% worsening and any change. Results were robust (data not shown).

Primary efficacy subgroups

Table 7 – Primary efficacy results at endpoint in all studies (ITT populations and extension cohorts)

Variable	Study 1037	Study 1037x	Study 3503			Study 3504		
	Lef	Lef	Lef	Mtx	p-value	Lef	Mtx	p-value
Number of subjects	27	17	47	47		33[a]	35[a]	
PII	NA	NA	-44.4%	-52.9%	0.1758	-53.5%	-63.0%	0.2060
DOI ≥30% responder rate	51.9%	52.9%	68.1%	89.4%	0.0156	78.8%	91.4%	0.1533

Lef = leflunomide, Mtx = methotrexate

[a] Number of subjects for whom there was at least one on-treatment set of the 6 core variables after the completion visit of Study 3503.

Source data: *Module 5.3, CSR 1037, Table 19; Module 5.3, CSR 3503, Table 31* and *Table 35; Module 5.3, CSR 3504, Table 46* and *Table 50*

Data assessed as a function of age and weight for both efficacy outcome measures in Study 3503 demonstrated no statistically significant difference in effect size between the two treatment arms for any of the subgroups. The data indicate that age and body weight had an effect on the response. Younger (<12 years), lighter (<20 kg) subjects showed a better response in the MTX group compared to the leflunomide group than older, heavier subjects, indicating that younger, lighter children were not responding as well to the leflunomide treatment as their older, heavier counterparts. This is consistent with the results of the PPK analysis, which demonstrated that the mean exposure to M1 (the primary metabolite) obtained in responders was about 59% greater than what was achieved in those children <20 kg, suggesting that the doses administered to subjects who weighed <20 kg may have resulted in less efficacious plasma concentrations (see table 8 below).

Table 8 – Subgroup analysis of primary efficacy variables in Study 3503 at week 16

Subgroup	N		PII			DOI ≥30%		
	Lef	Mtx	Lef	Mtx	p-value[a]	Lef	Mtx	p-value[a]
Age								
<12 years	27	27	-44.8%	-57.5%	0.4224	66.7%	92.6%	0.3989
≥12 years	20	20	-43.0%	-45.8%		70.0%	85.0%	
Weight								
<20 kg	8	8	-46.3%	-66.9%	0.6623	59.3%	90.5%	0.2387
20-40 kg	19	13	-41.8%	-49.5%				
≥40 kg	20	26	-46.3%	-50.9%		80.0%	88.5%	

Lef = leflunomide, Mtx = methotrexate

[a] A logistic regression analysis was comparing subgroups, where the p-value is based on logistic regression fitting treatment, subgroup, continent and subgroup by treatment interaction into the model.

Source data: *Module 5.3, CSR 3503, Table T63* and *Table T66*

The results of the within-group comparison of the PII at Week 16 compared to Week 48 to evaluate durability of efficacy, showed that the improvement seen in each treatment group at Week 16 was maintained at Week 48 (see table 9).

Table 9 – PII: within-group comparison of Weeks 16 and 48 (Extension cohort)

Timepoint	Week 16			Week 48			Difference: Week 16 – Week 48		p-value[a]
	N	Adj mean	SE	N	Adj mean	SE	Adj mean	95% CI	
Leflunomide	33	-54.66	3.169	33	-55.36	3.169	0.70	-8.43; 9.83	0.8774
Methotrexate	35	-57.96	2.723	35	-65.51	2.723	7.55	-0.27; 15.38	0.0580

N=number of subjects for whom data were available; adj mean=adjusted mean; CI=confidence interval for differences of adjusted means
[a] ANOVA with treatment and pooled site as effects.
Source data: *Module 5.3, CSR 3504, Table T22*

This is also supported by DOI ≥30% responder rates: in the Leflunomide group, the DOI ≥30% responder rate was 78.8 and 78.8% at week 16 and 48 respectively, in the MTX group 91.4 and 91.4%, respectively.

Secondary efficacy

In Study 1037, improvements were observed in all secondary outcome variables with the exception of the number of joints with reduced mobility (see table below). Improvements were observed from Week 4 and sustained throughout the 26-week treatment period. During the 30-month extension, most of these parameters continued to improve, and a reduction in the number of joints with limited mobility was seen after a total of thirty months' treatment.

In Study 3503, improvements were observed in all the secondary outcome variables in both the leflunomide and MTX groups (see table below). The time to achieve a response during Study 3503 was similar in the 2 treatment groups, with a median time to reach a DOI ≥ 30% response of 52 days in the leflunomide groups and 56 days in the MTX group. The improvements achieved after 4 months of treatment in Study 3503 were sustained over the course of the long-term extension Study 3504, and subjects continued to improve over the following 8 months of treatment: by Week 48 of treatment an additional 1 leflunomide subject had achieved a DOI response of 50% and an additional 6 leflunomide subjects and 4 MTX subjects achieved a response rate of 70%. No statistically significant differences were observed between the 2 treatment groups at any of the time points for any secondary variable during the extension Study 3054.

Table 10 – **Secondary efficacy results in all studies: adjusted mean change from baseline at endpoint (ITT populations and extension cohorts)**

Variable	Study 1037	Extension 1037	Study 3503		Extension 3504	
	Lef	Lef	Lef	Mtx	Lef	Mtx
Number of subjects	27	17	47	47	33	35
DOI ≥50% at study end	44.4%	47.1%	59.6%	76.6%	75.8%	85.7%
DOI ≥70% at study end	18.5%	35.3%	42.6%	59.6%	72.7%	77.1%
Physician's global assessment (mm)	-21.4	-20.5	-31.5	-32.1	-38.0	-35.8
Subject/parent global assessment (mm)	-9.9	-12.8	-15.9	-22.0	-23.3	-23.7
CHAQDI	-0.26	-0.36	-0.44	-0.39	-0.51	-0.55
Active joint count	-4.63	-6.94	-8.1	-8.9	-9.3	-10.5
Swollen joint count	-7.48	-10.12	NA		NA	
Joints with limited range of motion	0.63	-2.41	-5.2	-5.3	-6.8	-6.5
Erythrocyte sedimentation rate (mm/hour)	-5.31	-5.18	-6.5	-7.2	-4.4	-8.6
Severity score	-12.96	-23.76	NA		NA	
VAS Pain score (mm)	NA	NA	-15.9	-23.0	-19.3	-26.9
C-reactive protein (mg/L)	NA	NA	-3.86	-11.4	-7.9	1.2

Lef = leflunomide, Mtx = methotrexate, NA: not assessed.

Subgroup analysis

Regarding the following issues, the MAH did additional subgroup analysis to investigate:

- The influence of corticosteroids on efficacy results for the percent improvement index (PII) and the Definition of Improvement 30% (JRA DOI 30%) variables,
- The influence of Rheumatoid Factor (RF) positivity/negativity on efficacy results for the PII and the JRA DOI 30% parameters,
- The response rate of JRA patients treated with placebo in different placebo-controlled studies.

Concerning studies HWA486/3503 (4-month study) and HWA486/3504 (8-month study), on basis of these subgroups it was concluded that differences in mean PII parameter and JRA DOI 30% between leflunomide and MTX are consistent across levels of each subgroup. There was no evidence that the durability of response was different by level of each subgroup variable.

A summarise of the placebo effect observed in different placebo-controlled clinical studies conducted in JRA population to test MTX, sulfasalazine or etanercept was presented. The magnitude of the placebo effect in the different studies ranged from 16 to 36% and magnitude of effect of active controls was for etanercept[1] 80 %, MTX[2] 48% and sulphasalazine[3] 44%.

1. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
2. Woo P, Southwood TR, Prieur AM, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849-57.
3. van Rossum MA, Fiselier TJ, Franssen MJ, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum 1998;41:808-16.

2.1 Clinical safety

This overview discusses all adverse events that were treatment-emergent (TEAEs), i.e. were not present at baseline and occurred on treatment or during the post-treatment follow-up period; or, if present at baseline, worsened during treatment or the follow-up period. The safety data from study 1037 and its long-term extension (a total of 30 months of treatment) were combined for a single analysis, whereas separate analyses were performed for the data from study 3503 (4 months of treatment) and its extension (study 3504, 8 months of treatment).
The safety population in study 1037 comprised all 27 subjects who received at least one dose of study drug. During the 6-month treatment period, this safety population was exposed to study drug for a mean duration of 22 weeks or 154.3 days and 88.8% of subjects received study drug >85 days. Seventeen subjects participated in the extension phase (extension cohort) and received at least one dose of study drug. During the entire 30-month study, the extension cohort was exposed to study drug for a mean duration of 95.9 weeks or 671.12 days and 82.4% received study drug >518 days.
In study 3503, there were 94 subjects in the safety population, 47 subjects in each treatment group. During the 4-month treatment period, mean exposure was 115 days in the leflunomide group and 116 days in the MTX group. There were 70 subjects in the safety population of the extension Study 3504, 33 leflunomide subjects and 37 MTX subjects. During the entire 12 months of treatment, the mean duration of exposure to study drug was 338 days in the leflunomide group and 349 days in the MTX group.

The majority of subjects (>80%) reported at least 1 TEAE in each of the studies, regardless of the treatment assignment (see table 11).

Table 11 – **Incidence of adverse events in all studies (Safety populations)**

Type of adverse event	Number (%) of subjects				
	Study 1037/1037x (N = 27)	Study 3503 (N = 47)		Study 3504 (N = 33)	
	Lef	Lef	Mtx	Lef	Mtx
Treatment duration	30 months	4 months		8 months	
Any adverse event	26 (96.3)	43 (91.5)	38 (80.9)	29 (87.9)	31 (83.8)
Serious adverse events	7 (26.0)	10 (21.3)	0 (0.0)	4 (12.1)	9 (24.3)
Possibly-related TEAEs	26 (96.3)	30 (63.8)	21 (44.7)	12 (36.4)	15 (40.5)
Possibly-related serious TEAEs	3 (11.1)	3 (6.4)	0 (0.0)	1 (3.0)	4 (10.8)
TEAEs leading to treatment discontinuation	2 (7.4)	3 (6.4)	1 (2.1)	1 (3.0)	5 (13.5)
TEAEs leading to treatment interruption	11 (40.7)	5 (10.6)	2 (4.3)	2 (6.1)	4 (10.8)
TEAEs leading to dose reduction	3 (11.1)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)
ALT or AST >1.2 x ULN	6 (22.2)	7 (14.9)	15 (31.9)	5 (15.2)	11 (29.7)

Lef = leflunomide, Mtx = methotrexate, ALT: alanine transaminase; AST: aspartate transaminase; ULN=upper limit of normal range

A similar pattern was observed in leflunomide subjects in study 3503. However, the frequency of individual adverse events was systematically lower than in the previous study, which is to be expected due to the longer duration of study 1037. The nature and frequency of adverse events reported in subjects receiving MTX was very similar, although the incidence of headache and alopecia was somewhat lower. Possibly-related TEAEs were reported in 69.8% (30/43) of leflunomide subjects and 55.3% (21/38) of MTX subjects. During the long-term extension (study 3504), the pattern and frequency of adverse events were essentially comparable to those seen in study 3503 (see table 12).

Table 12 - Incidence of TEAEs in ≥7 subjects in any study

Preferred term	Number (%) of subjects				
	Study 1037	Study 3503		Study 3504	
		Leflunomide	Methotrexate	Leflunomide	Methotrexate
Total population	27 (100.0)	47 (100.0)	47 (100.0)	33 (100.0)	37 (100.0)
Any adverse event	26 (96.3)	43 (91.5)	38 (80.9)	29 (87.9)	31 (83.8)
Headache	17 (63.0)	18 (38.3)	11 (23.3)	7 (21.2)	5 (13.5)
Respiratory infections[1]	17 (63.0)	--[1]	--[1]	--[1]	--[1]
Abdominal pain	11 (40.7)	12 (25.5)	5 (10.6)	5 (15.2)	2 (5.4)
Rheumatoid arthritis[2]	10 (37.0)	0 (0.0)	0 (0.0)	2 (6.1)	1 (2.7)
Diarrhoea	10 (37.0)	7 (14.9)	8 (17.0)	4 (12.1)	1 (2.7)
Nausea	10 (37.0)	10 (21.3)	12 (25.5)	2 (6.1)	2 (5.4)
Rash	9 (33.3)	3 (6.4)	3 (6.4)	0 (0.0)	2 (5.4)
Alopecia	8 (29.6)	7 (14.9)	3 (6.4)	3 (9.1)	0 (0.0)
Dizziness	7 (25.9)	3 (6.4)	2 (4.3)	0 (0.0)	0 (0.0)
Nasopharyngitis[1]	--[1]	12 (5.3)	3 (6.4)	3 (9.1)	1 (2.7)
Pharyngitis	7 (25.9)	0 (0.0)	4 (8.5)	0 (0.0)	2 (5.4)
Increased cough	7 (25.9)	5 (10.6)	0 (0.0)	1 (3.0)	5 (13.5)
Rhinitis	7 (25.9)	3 (6.4)	1 (2.1)	3 (9.1)	2 (5.4)
ALT or AST > 1.2 x ULN	6 (22.2)	7 (14.9)	15 (31.9)	5 (15.2)	11 (29.7)

ALT: alanine transaminase; AST: aspartate transaminase; ULN=upper limit of normal range
[1] In study 1037, respiratory infections were grouped together, whereas in Studies 3503 and 3504 these are subdivided. Nasopharyngitis (the most common) is listed here for these studies.
[2] Juvenile arthritis in Study 3504.

Serious AEs
Thirteen serious AEs were reported in 7 (26.0%) subjects in study 1037 and its extension, one of which (JRA flare) occurred prior to receiving leflunomide. Two of the serious TEAEs (possible gastritis and anemia) occurred in 2 subjects during the first 26 weeks of therapy and the remaining 10 serious TEAEs in 5 subjects during the extension phase. The events were classified as serious because they were considered medically important and/or they required hospitalization. Five of the events were considered possibly related to study drug, and all 13 events resolved.
In study 3503, 11 serious TEAEs were reported in 10 leflunomide subjects and no MTX subjects reported a serious TEAE. The majority of the serious TEAEs were not considered possibly related to treatment and of mild or moderate intensity. Three subjects discontinued treatment as a result of the serious adverse event. All serious TEAEs apart from the cases of Crohn's disease and pytiriasis resolved during the study period. During the extension Study 3504, 5 serious TEAEs were reported in 4 leflunomide subjects. One of these (colitis) was considered possibly treatment-related and led to treatment discontinuation. In addition, 16 serious TEAEs were reported in 9 MTX subjects. In 4 of these subjects, including 3 cases of transaminase elevations, the events were considered to be treatment-related.

No deaths, malignancies, or pregnancies were reported in any of the studies. In Study 3503, overdoses were reported in 1 leflunomide subject (use of a 20 mg maintenance dose rather than 10 mg), and 1 methotrexate subject (unplanned ingestion of 22.5 mg). None of these overdoses were associated with the occurrence of adverse events.

Transaminase elevations and liver function
In study 1037, 6 (22.2%) subjects presented clinically significant elevations (>1.2 x ULN) in alanine transaminase (ALT), aspartate transaminase (AST) or both, 4 of which were reported as adverse events and 1 of which was serious.
In study 3503, elevated transaminases were reported in 7 (14.9%) leflunomide subjects compared to 15 (31.9%) MTX subjects. Four cases in each group were reported as AEs. Transaminase levels

normalized by the end of the study in 4 leflunomide subjects and in 11 MTX subjects, and remained above 2 x ULN in only 1 subject in each treatment group.
In the extension study 3504, the incidence of elevated transaminases was lower in the leflunomide treatment group (5 subjects, 15.2%) compared to the MTX group (11 subjects, 29.7%). Moreover, transaminase levels in all the leflunomide subjects remained below 2 x ULN, whereas 5 MTX subjects reported ALT levels above this limit, including 1 subject with an elevation >8 x ULN. For 3 of the methotrexate subjects, transaminase elevations were considered serious adverse events and treatment was discontinued. In all of the leflunomide patients (5/5) and 9 of the 11 methotrexate subjects, transaminase levels subsequently normalized.

Pharmacokinetics

Two studies (**HWA486/1037** and **HWA486/3503**) were conducted in children with JRA. Both studies were followed by an extension study to gather further data on the durability of efficacy over the long term. In addition, to assess efficacy and safety of leflunomide in this population, the pharmacokinetic (PK) of leflunomide and its active metabolite were assessed based on data collected from blood samples taken in both studies, and analyzed collectively after completion of both studies. One of the objectives of the population pharmacokinetics (PPK) analysis was to determine appropriate *dose recommendations* for leflunomide use in the JRA population.

The objectives of study 1037 were to determine whether therapy with leflunomide warranted further study in subjects with polyarticular course JRA by primarily obtaining pharmacokinetic and safety data and secondarily obtaining preliminary efficacy and functional data in a small group of subjects. As a pilot study the dose selection in study 1037 was based on the target M1 concentration range from adult experience and pharmacokinetic parameters scaled by body surface area. A population PK model was developed to describe the data and the relationship between the estimated pharmacokinetic parameters and demographic data in the JRA patient population. A simplified leflunomide dose regimen according to specific body weight categories was derived for study 3503.

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 randomised, 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 1037 was conducted in pediatric subjects (aged 3-17 year) with active, polyarticular course juvenile rheumatoid arthritis who had previously failed or were intolerant of methotrexate therapy. Eligible subjects for study 3503 were pediatric patients 3 to 17 years of age with active, polyarticular course JRA, irrespective of onset type, who were naïve to treatment with either leflunomide or methotrexate.
In study 1037, 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 (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 [1997]) escalation to the equivalent of leflunomide 20 mg/day per 1.73 m^2 BSA was allowed, at the discretion of the investigator. 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 in table PK 1.

Table PK 1.

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

In 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. In study 3503, two blood samples were obtained for determination of leflunomide, M1 (the primary metabolite),

and TFMA (4-trifluoromethylaniline, a minor metabolite) 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.

Nonlinear mixed effect modeling (NONMEM) methods were applied to analyse the pooled data of the two studies. Only the M1 levels were used in the PPK modeling and the population mean and the variances of the pharmacokinetic parameters of M1 were obtained. The covariates including body surface area (BSA), body weight (WT), AGE, and SEX were tested to determine their influence on the PK of M1. Apparent oral total clearance (CL/F), apparent volume of distribution (V/F) and input rate constant (ka) were estimated for each individual subject by using the POSTHOC Bayesian approach based on the final optimal population model and individual specific PK information. The half-life of the apparent terminal disposition phase (t1/2) was to be calculated from the CL and V.
The pharmacostatistical models were fitted to the data by the first order conditional estimation method (FOCE) with interaction. The NONMEM stepwise regressions were applied to determine the impact of the covariates including BSA, WT, AGE and SEX on the pharmacokinetics of M1. The final optimal model selected was evaluated by goodness-of-fit plots, cross-study comparisons, and a predictive check.

The PK evaluable population consisted of 73 subjects (27 subjects in study 1037 and 46 subjects in study 3503). Of these, 57 subjects were female and 16 were male, with ages ranging from 3 to 17 years. The weight ranged from 13 to 75 kg and the body surface area (BSA) from 0.56 to 1.83 m^2. A total of 674 observations were included in the PPK database. Of these, 493 observations were collected from study 1037 and 181 from study 3503. The number of observations per subject ranged from 1 to 23, with an average of 9.2 observations per subject. By comparison, more sparse PK samples were collected in study 3503 (mean: 3.9 observations per subject) than those in study 1037 (mean: 18.3 observations per subject). In study 1037 only M1 plasma levels were determined, while in study 3503, plasma levels of parent could not be detected in any subject and only low TFMA levels could be detected in some subjects.

M1 disposition was well described by a one-compartment model with first order input. Inter-subject variability was described by an exponential error model on the structural PK parameters, while the residual variability was described by a proportional error model.

The population PK parameters estimates of the final 'optimal' model are summarised in table PK 2, and the descriptive individual Bayesian Posthoc pharmacokinetic parameter estimated of the final model in table PK 3.

Table PK 2. The final "optimal" PPK Model and its parameter estimates

parameter	Regression Model and Parameter Estimates (SE)[a]	Inter-Subject Variability (SE)[a], %[b]
CL/F (l/h)	$CL/F = \theta_1*(WT/40)^{\theta 4}$ $\theta_1 = 0.02$ (0.00127) $\theta_4 = 0.43$ (0.192)	50.4 (22.0)
V/F (l)	$V/F = \theta_2*(WT/40)^{\theta 5}$ $\theta_2 = 5.8$ (0.23) $\theta_5 = 0.769$ (0.0989)	18.6 (10.0)
k^a (h^{-1})	$\theta_3 = 1.13$ (0.455)	1721.5 (101.5)
Residual variability (SE)[c], %	18.2 (6.3)	

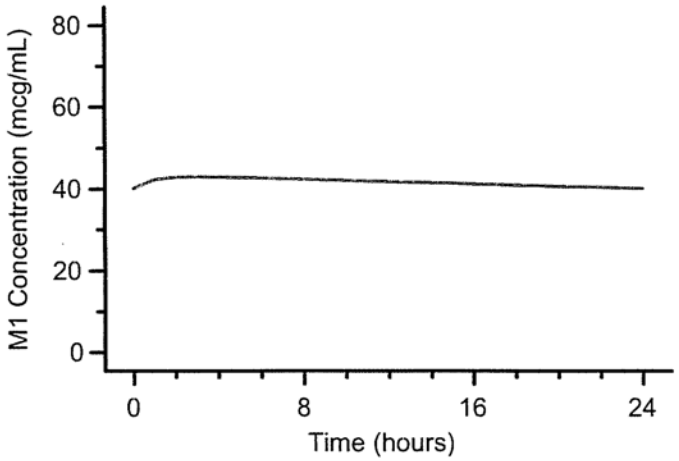
WT is the actual body weight in kg. θs are the regression parameters estimated by NONMEM
a SE = Standard error of the estimate
b Estimate expressed as percent coefficient of variation (%CV)
c Residual variation in the M1 plasma concentration, C (µg/ml), expressed as percent coefficient of variation (%CV)

Table PK 3. 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)	T½ (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	26.5	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

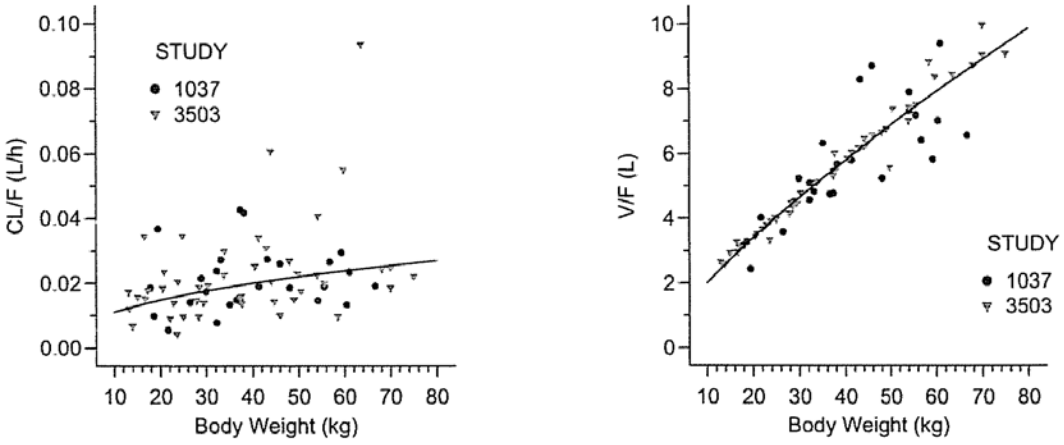
According to the final "optimal" model with WT as the sole covariate, the CL/F and V/F were estimated to be 0.020 l/h and 5.8 l, respectively, in a typical pediatric patient with a body weight of 40 kg. Administration of 20 mg leflunomide daily to the typical 40 kg pediatric patient would produce the following steady-state M1 concentration-time profile:

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



The NONMEM stepwise regression revealed that CL/F was weakly correlated with body size (WT or BSA), and V/F was strongly correlated with body size (see figures below). Sex or age was not a significant covariate once body size was taken into consideration. A rather weak correlation between the $t_{1/2}$ of M1 and WT is demonstrated, indicating that the dosing interval of leflunomide should remain 24 hours for the pediatric population.

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



The difference in CL/F between the two extremes of body weight (70 and 14 kg, respectively) is approximately 50%, indicating that reduction of the maintenance dose by one half is only needed for pediatric patients weighing approximately 14 kg or less.
Results of a CL/F by weight evaluation of the PPK data demonstrated that pediatric APC-JRA patients with body weights <40 kg have a reduced clearance (CL) of M1 compared to those >40 kg (see table PK 3).

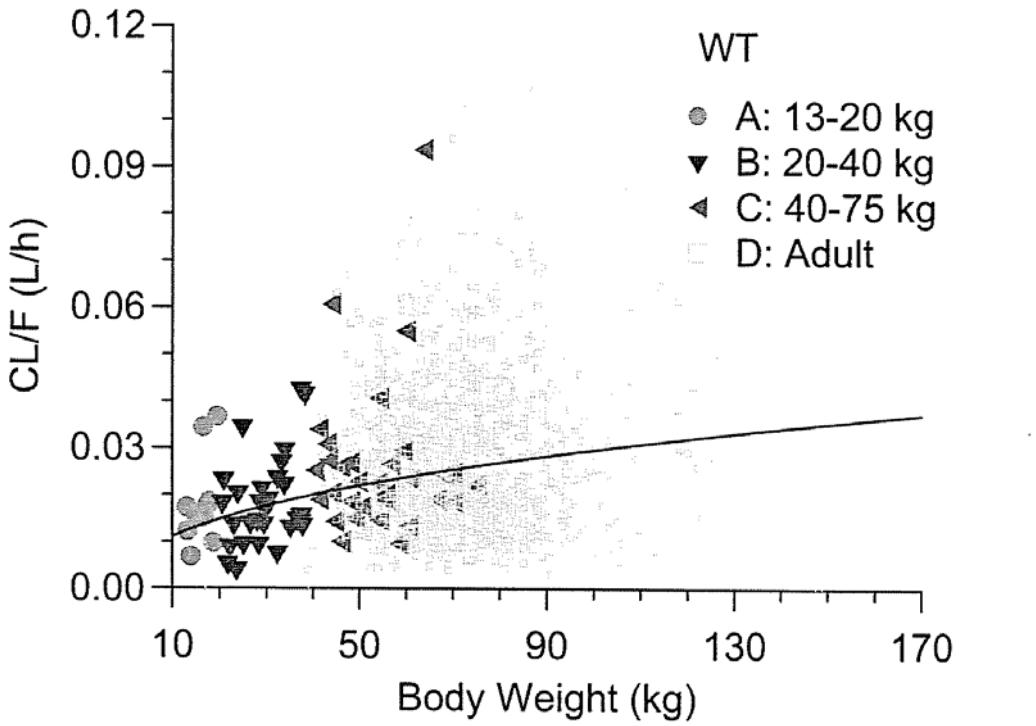
Table PK 3. PK results from study 1037 and 3503

Body weight (kg)	Cl (ml/h)		Css (µg/ml)[a]	
	n	mean ± sd	n	mean ± sd
< 20	10	18 ± 9.8	8	14.5 ± 7.2
20 – 40	30	18 ± 9.5	19	30.0 ± 19.3
> 40	33	26 ± 16.0	20	38.9 ± 20.4

a: data from study 3503 only.
Cl=clearance; Css = concentration at steady state

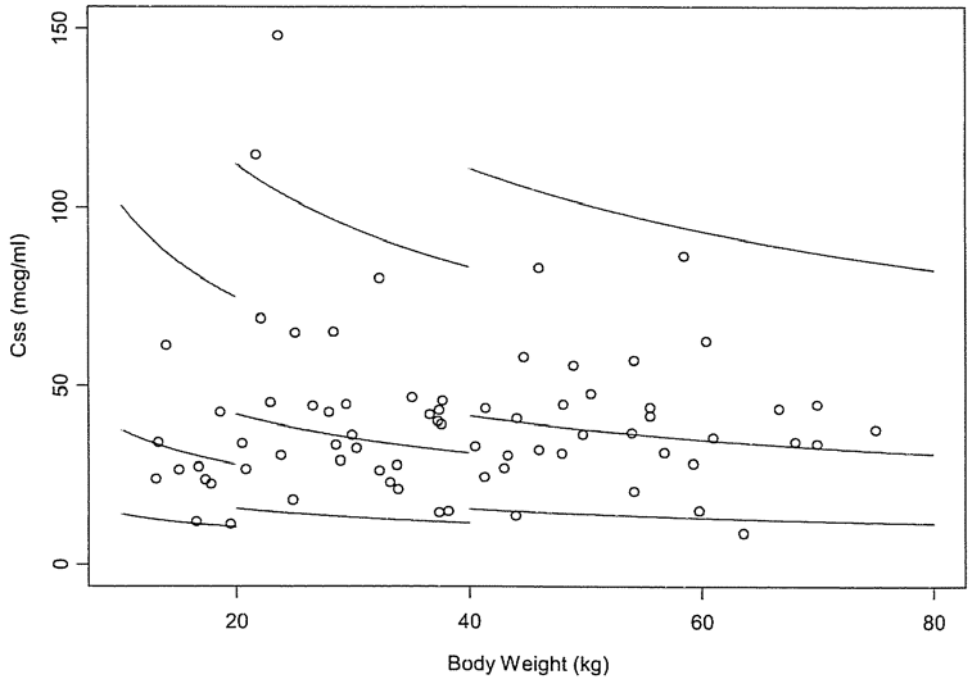
Previous obtained data in adults indicated that median values for Cl/F, Css and body weight in a total of 1171 adult patients with RA (Phase II and III combined data) were 0.024 l/h, 34 µg/ml and 70 kg, respectively. Based upon the final model obtained in this PPK analysis a Cl/F of 0.0254 l/h was predicted for a person weighing 70 kg. The relationship between Cl/F and WT in the JRA population (n=73) and adult RA patients (n=1171) is depicted in the figure below.

Individual Bayesian POSTHOC Estimates of CL/F Versus Body Weight



As body size and V/F is strongly correlated, in case a loading dose is administered, this should be adjusted for pediatric patients. However as a loading dose has been associated with acute tolerability problems, a loading dose is not recommended in pediatrics.
The figure below shows the typical Css (middle line) and the 95% prediction interval (outer lines) plotted against body weight (WT) after doses of 10, 15 and 20 mg, respectively, from left to right. Targeting a median Css of 34 µg/ml for all pediatric patients on average, a dose of 10 mg daily should be recommended for pediatric patients weighing 10 to 20 kg, 15 mg daily for pediatric patients weighing 20 to 40 kg, and 20 mg daily for those weighing >40 to 80 kg. If the above refined leflunomide dose recommendations for pediatrics were applied, the Css, as indicated by open circles in the figure, in the vast majority of the 73 JRA patients would have fallen within the 95% prediction interval with a median of approximately 34 µ/ml.

Predicted C_{ss} for Refined Leflunomide Dose Recommendations Using the Inter-Subject Variability Estimate for Clearance



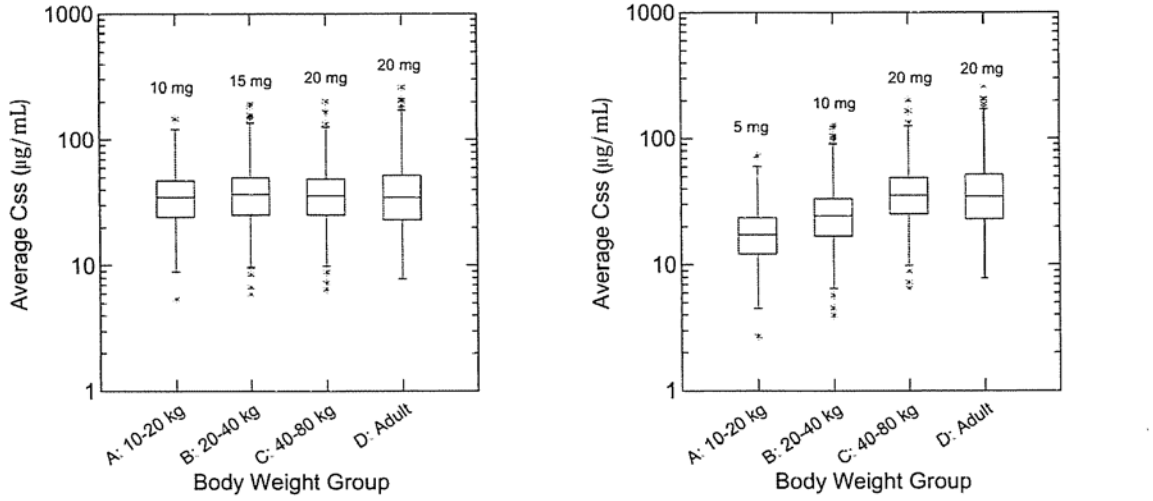
To test the validity of recommending these doses, a simulation of 2000 replicate "patients" was made by
adding a random term (exp(ήi)) to the relationship for Cl and weight:

$$Cli = 0.020 \times (WT/40)^{0.43} \times (\exp(ήi))$$

where WT had a uniform distribution from 10 to 80 kg, and ήi had a normal distribution with a mean of zero and an SD of 0.5. The Css was calculated by assigning a dose of 10 mg for subjects weighing 10 to
20 kg, 15 mg for subjects weighing 20 to 40 kg, and 20 mg daily for subjects weighing >40 to 80 kg. The dosing interval in all weight groups was specified to be 24 hours.

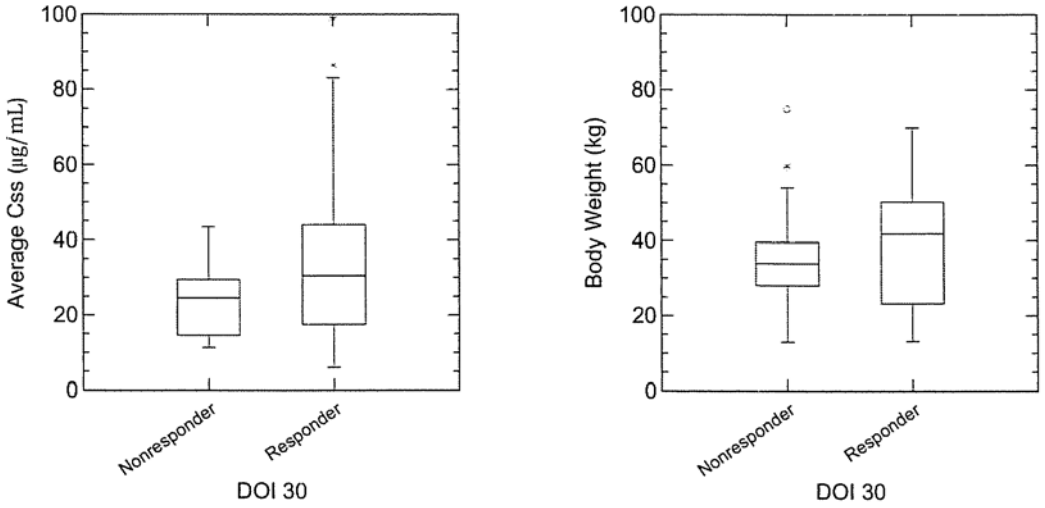
The left box-whisker plots below show that the Css for M1 in the JRA population using the refined regimens are successful in achieving similar M1 exposures as they lie within the range of M1 exposures observed in adult RA patients. However in the right panel, the leflunomide regimens investigated in study 3503 clearly were not equivalent for 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. Consequently, the leflunomide doses prescribed for subjects < 20 kg and between 20 and 40 kg were possibly too low in study 3503.

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 C_{ss}



Among the 47 subjects treated with leflunomide in study 3503, 32 were categorised as responders, as measured by DOI>30%, and 15 were categorized as non-responders when assessed following 16 weeks of treatment. To examine whether the non-responders had lower exposures to M1 and were possibly also in the lower weight groups (therefore under-dosed), the model-predicted Css based on the regimens of study 3503 and individual body weights were separately plotted against response status (i.e., responder or non-responder), one of the co-primary efficacy endpoints in study 3503.

Study 3503: Model-Predicted C_{ss} and Body Weight Versus DOI>30% Response



Total number of subjects is 47. The CL/F value for Subject 1103001 who provided no M1 concentration data was calculated based on her body weight.

The left panel reveals a clear trend for lower exposures in the group of subjects who failed to respond to leflunomide. 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. The right panel revealed a similar but less pronounced trend for the non-responders to be those subjects in the lower weight groups. The observation that the leflunomide doses studied in the subjects who weighed less than 40 kg were sub-optimal appears to be supported both on PK and efficacy grounds.

In conclusion, based upon the results of the population pharmacokinetics, a leflunomide target Css of 34 µg/ml was obtained in pediatrics by a dose of 10 mg for subjects weighing 10 to 20 kg, 15 mg for subjects weighing 20 to 40 kg, and 20 mg daily for subjects weighing >40 to 80 kg.

Overall discussion and benefit/risk assessment

The MAH has submitted data from two studies conducted in children with JRA. Study HWA486/1037 was a Phase Ib, open label study in subjects who had previously failed to respond to, or were intolerant of, MTX therapy. Study HWA486/3503 was a Phase III, randomised, double-dummy, double-blind study comparing leflunomide to MTX in subjects naïve to both MTX and leflunomide. Both studies were followed by an extension study to gather further data on the durability of efficacy over the long term.

Taking into account previous studies conducted in children, and the concept paper from the CHMP on points to consider on clinical investigation of medicinal products for the treatment of JIA (CPMP/EWP/422/04) studies HWA486/1037 and HWA486/3503 were well designed and adequate outcome measures were used.

The consequence of the changing from equivalence study to a superiority study was that the sample size was re-adjusted from 240 subjects to 90 subjects. A justification of this amendment was not given but it appears there was a wish to stop the trial (over March 2002- May 2003, 94 subjects were recruited whereas another 1-2 year would be needed to recruit up to 240 subjects in case non-inferiority was opted for). However, there was no mentioning in the amendment that in the event superiority was not observed, non-inferiority was opted for only in the study report. Further the extrapolation of the 12.5% non-inferiority margin of percentage change is questionable and at least would have needed a justification.
However these major methodological flaws are overruled by the results. MTX seems to be superior to lelflunomide after 16 weeks treatment and non-inferiority for leflunomide has not been demonstrated. The CHMP did not raise an objection in this respect. The methods of analyses are agreed by CHMP.

A well established and extensive population pharmacokinetic analysis was carried out. The results indicate that leflunomide Cl/F by weight evaluation that pediatric APC-JRA patients with body weights < 40 kg have a reduced clearance (CL) of M1 compared to those >40 kg. A dose reduction in these subjects seems necessary to obtain a similar exposure/steady state concentration. The population pharmacokinetics analysis indicate that a leflunomide target Css of 34 µg/ml (similar to the Css observed in the adult population) will be obtained in pediatrics by a dose of 10 mg for subjects weighing 10 to 20 kg, 15 mg for subjects weighing 20 to 40 kg, and 20 mg daily for subjects weighing > 40 to 80 kg.

Following the concept paper from the CHMP on points to consider on clinical investigation of medicinal products for the treatment of JIA (CPMP/EWP/422/04), dose section should be based on recommended dose in adults of an appropriate pharmacokinetic parameter, most commonly AUC for chronic dosing. Subsequently, well planned dose ranging studies should be carried out before the confirmatory clinical trials are undertaken. However, the guideline ICH Topic E11 Clinical investigations of medicinal products in the paediatric population (CHMP/ICH/2711/99) indicates that when the medicinal product is to be used in the paediatric population for the same indication as those studied and approved in adults, the disease process is similar in adults and paediatric patients, in such cases pharmacokinetic studies in paediatric patients together with safety studies may provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults. In the case of leflunomide in children with JCA, no formal dose finding studies were conducted but on basis of PK analysis 5 and 10 mg regimens have been clinically tested. This approach is considered to be sufficient because active polyarticular course JRA is widely regarded as the paediatric equivalent to adult RA. But on basis of the results of the population PK analysis the chosen doses appeared to be too low to achieve similar Css as observed in adults.

Disease characteristics at baseline were similar between the groups and the included patients describe a moderate to severe disease activity.

The subjects continuing in study 3504 from subjects completing study 3503, 20% did not entered study 3504. No conclusion with respect to equal efficacy can be drawn.

The two studies suggest some effect of leflunomide in the treatment of JRA in children who have intolerance for MTX or who are MTX naïve, however, placebo controlled studies are lacking and the efficacy of lelfunomide was lower than that for MTX. After 16 weeks treatment, the difference in response rates was statistically significant in favour of MTX for the DOI ≥ 30% (p=0.02), but not for the PII (p=0.18). The DOI ≥ 30% responder rate and the PII achieved at Week 16 were maintained in both treatment groups throughout the extension study 3504 but the difference between treatment groups for DOI ≥ 30% was no longer statistically significant in study 3504 efficacy evaluable population at endpoint (Week 48) of the extension (p=0.15). The difference in efficacy favouring MTX was particularly noticeable in lighter (≤ 40 kg) and younger (<12 years) subjects. Based on the fact that the M1 concentration was lower in subjects ≤ 40 kg, it seems that the lighter subjects were under-dosed compared to subjects > 40 kg.
Taking into account that the numbers of patients that used oral corticosteroids treatments or that had a positive rheumatoid factor in each study were small, based on subgroup analyses it seems that neither the corticosteroid co-medications nor the presence of RF influenced the efficacy outcomes in study 3503 and its extension study 3504.

Although it seems that response rates observed in leflunomide treated patients are higher in comparison to the response rate values observed in placebo-treated patients, values of placebo effects obtained from previously conducted clinical studies cannot replace a head to head comparison in a clinical trial designed to compare leflunomide vs. placebo.

The pattern of adverse events of leflunomide and MTX seems to be similar. However, it is seems that lighter subjects (the proportion of leflunomide subjects weighing <40 kg was 15% larger than those weighing >40 kg) were under-dosed (compared to subjects >40kg) due to the fact that the M1 concentration was lower in subjects ≤ 40 kg, and, therefore, this may also have influenced the safety data.

Based on the review of the data on safety and efficacy for Arava conducted in patients with Juvenile Rheumatoid Arthritis and comparing the safety and efficacy of leflunomide with that of MTX, the CHMP concluded that the efficacy and safety of Arava in patients under 18 years age group was not established.