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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	20-938/21-530
Drug Name:	Meloxicam Oral Suspension (Mobic®)
Indication(s):	Juvenile rheumatoid arthritis
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877
Date (s):	Submitted: February 18, 2005
Review Priority:	Accelerated
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D. (HFD-725)
Concurring Reviewer:	Thomas J. Permutt, Ph.D. (HFD-715)
Medical Division:	Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)
Clinical Team:	Tatiana Oussova, M.D. (HFD-170)
Project Manager:	Constantine Markos (HFD170)
Keywords:	NDA review, Clinical studies, Non-Inferiority, Cochran-Armitage test

Table of Contents

(b) (4)

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this NDA submission the sponsor included reports of two double-blind Phase 3 studies (Study #107.235 and Study #107.208) and one open-label Phase 2 study (Study #107.162) to support their claim that the efficacy of daily dose of 0.125 (b) (4) mg/kg of meloxicam oral suspension is non-inferior to those of daily dose of 10 mg/kg of naproxen in terms of the percentage of responders for the treatment of juvenile rheumatoid arthritis for 12 weeks. This reviewer's conclusion was mainly based on results from the two Phase 3 studies. However, results from the Phase 2 study were also considered.

Originally the non-inferiority margin was set to 20% for the first study and 25% for the second study. Non-inferiority was declared if the lower 95% confidence limit on the difference of the percentage of responders between the combined meloxicam arms and the naproxen was greater than the selected margin. In a discussion with this reviewer the medical officer mentioned that comparisons of individual meloxicam dose groups with naproxen group are clinically more meaningful than comparison of the combined meloxicam treatment groups with the naproxen. Due to the medical officer's advice this reviewer compared each individual doses of meloxicam with naproxen. Since there were two doses of meloxicam, this reviewer constructed 97.5% confidence intervals instead of 95% to account for the multiple testing. Also, for appropriate interpretation of integrated results, in this reviewer's analysis both of the studies were analyzed using the same non-inferiority margin of 20%.

Results from the first Phase 3 study showed that at Week 12 the 97.5% lower confidence limits on the difference of the percentage of responders between meloxicam and the naproxen arms were greater than 20% for (b) (4) 0.125 (b) (4), while results from the second Phase 3 study showed that at Week 12 similar 97.5% lower confidence limit was greater than 20% for 0.125 mg/kg arm (b) (4). However for the second study, the 97.5% lower confidence limit between the combined meloxicam arms and the naproxen was greater than 20%. The open label study had only one arm of 0.25 mg/kg of meloxicam. (b) (4)

From results of the submitted studies this reviewer concludes (b) (4) meloxicam (b) (4) established non-inferiority in efficacy to naproxen by Week 12. (b) (4) also maintained the non-inferiority for up to one year. However, this reviewer has the concern that the width of the selected non-inferiority margin may be too wide. Considering about 60% responder of naproxen, a 20% margin may lead to a worst case of 40% responder of meloxicam and yet maintain the non-inferiority status. Also due to ethical reasons none of these studies had placebo control group. A finding of efficacy of meloxicam from a non-inferiority study depends on the efficacy of naproxen. There is historical evidence of efficacy of naproxen at similar doses in apparently similar populations, but without internal validation the question of assay sensitivity cannot be completely dismissed. In a communication to this reviewer, the medical officer mentioned that 10 mg naproxen is the approved dose for JRA in many European countries and the effect size is around 60% and is similar to what we see in adult studies of RA, and the placebo effect size is usually much smaller, between 20-30% as measured by ACR20 completers/responders. Based on this comment of the medical officer, it may be concluded that in this study naproxen has demonstrated considerable effect.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

There were two Phase 3 studies namely, Study #107.235 and Study #107.208, and one Phase 2 study namely, Study #107.162 included in this submission. Study #107.235 was a 12 week double-blind study with a 12 week open-label extension, Study #107.208 was a one year double-blind study, while Study #107.162 was a one year open-label study. Study #107.162 was performed in two phases: a pharmacokinetic phase of 72 hours and a pharmacodynamic phase of 12 weeks. The PD phase was followed by an additional open-label phase of 40 weeks.

The primary objectives of these studies were to compare the efficacy and safety of meloxicam oral suspension with those of naproxen oral suspension (active control) in children with juvenile rheumatoid arthritis.

Results of Study #107.208 were presented in two parts. The first part contains 12 weeks data and the second part contains one year data. Results of Study #107.162 were also presented in two parts. The first part contains 12 weeks data and the second part contains one year data.

1.3 STATISTICAL ISSUES AND FINDINGS

Due to ethical reasons none of these studies had placebo control group. There is historical evidence of efficacy of naproxen at similar doses in apparently similar populations, but without internal validation the question of assay sensitivity cannot be completely dismissed. A discussion on it is included in this reviewer's conclusion.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA submission the sponsor included reports of two double-blind Phase 3 studies namely, Study #107.235 and Study #107.208, and one open-label Phase 2 study namely, Study #107.162 to support their claim that the efficacy of daily dose of 0.125 (b) (4) mg/kg of meloxicam oral suspension is non-inferior to those of daily dose of 10 mg/kg of naproxen for the treatment of juvenile rheumatoid arthritis.

Study #107.235 was a 12 week double-blind randomized parallel group Phase 3 study with a 12 week open-label extension. The dosing groups were as follows:

Group I: Meloxicam 0.125 mg/kg once daily and 0.25 mg/kg once daily after 4 weeks (Mel L)
Group II: Meloxicam 0.25 mg/kg once daily and 0.375 mg/kg once daily after 4 weeks (Mel H)
Group III: Naproxen 5 mg/kg twice daily and 7.5 mg/kg twice daily after 4 weeks (Nap)

The primary object of this study was to compare the efficacy and safety of meloxicam oral suspension with those of naproxen oral suspension (active control) in children with juvenile rheumatoid arthritis.

Study #107.208 was a one year randomized, double-blind, double-dummy, active comparator, parallel group, multicenter, and multinational Phase 3 study in children with established diagnosis of juvenile rheumatoid arthritis. The dosing groups were as follows:

Group I: Meloxicam 0.25 mg/kg daily dose (Mel H)
Group II: Meloxicam 0.125 mg/kg daily dose (Mel L)
Group III: Naproxen 10 mg/kg daily dose (Nap)

The primary object of this study was to establish whether the efficacy and safety of meloxicam oral suspension are comparable to those of naproxen for the treatment of patients with juvenile rheumatoid arthritis.

Study #107.162 was a one year open-label, multicenter, multinational Phase 2 study. The study was performed in two phases: a pharmacokinetic phase of 72 hours and a pharmacodynamic phase of 12 weeks investigating efficacy and safety. The PD phase was followed by an additional open-label phase of 40 weeks, which was aimed at investigating long term safety and efficacy.

The primary aim of this study was to characterize the pharmacokinetics of meloxicam suspension on children with juvenile rheumatoid arthritis. Furthermore, efficacy and safety of a once daily dose of 0.25 mg/kg meloxicam suspension were assessed over a treatment period of up to 52 weeks.

Results of Study #107.208 were presented in two parts. The first part contains 12 weeks data and the second part contains one year data. Results of Study #107.162 were also presented in two parts. The first part contains 12 weeks data and the second part contains one year data.

2.2 DATA SOURCES

The submission was in hard copy. Submitted data was stored in folder http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N20938\S_013\2005-02-18&DOCUMENT_ID=2672485&APPL_NO=020938&APPL_TYPE=N in FDA's Electronic Document Room (EDR).

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 **STUDY # 107.235**

Title: "A 12 week double-blind randomized trial, with a 12 week open-label extension, to investigate the efficacy and safety of meloxicam oral suspension administered once daily and naproxen oral suspension administered twice daily in children with juvenile rheumatoid arthritis".

3.1.1.1 Design and Objectives

This was initially a 12-week double-blind, randomized, active comparator double-dummy, parallel group study in children with established diagnosis of Juvenile Rheumatoid Arthritis (JRA). This was followed by a 12-week open-label extension. The conduct of the trial was divided into three parts namely, screening, treatment, and if required a follow up period. The study population was randomized into three treatment groups in a 1:1:1 ratio. The dosing groups were as follows:

Group I: Meloxicam 0.125 mg/kg once daily and 0.25 mg/kg once daily after 4 weeks (Mel L)
Group II: Meloxicam 0.25 mg/kg once daily and 0.375 mg/kg once daily after 4 weeks (Mel H)

Group III: Naproxen 5 mg/kg twice daily and 7.5 mg/kg twice daily after 4 weeks (Nap)
All patients from meloxicam and naproxen groups were administered the same dose of 0.375 mg/kg of meloxicam suspension daily during the open-label phase.

The primary object of this study was to compare the efficacy and safety of meloxicam oral suspension with those of naproxen oral suspension (active control) in children with JRA.

3.1.1.2 Primary Efficacy Endpoint

The primary efficacy variable was response rate (ACR Pediatric 30) determined at the end of the double-blind phase (12 weeks). Patients with a positive response in the ACR Pediatric 30 are defined as those who have improved from the baseline by at least 30% in three or more of the six core variables with no more than one of the remaining variables worsening by more than 30%.

The JRA core set includes the following six variables:

- Investigator global assessment of overall disease activity (100 mm VAS)
- Parent global assessment of overall well-being (100 mm VAS)
- Number of joints with active arthritis (Out of 75 assessed joints)
- Number of joints with limited range of motion (Out of 75 assessed joints)
- Assessment of functional disability index by Childhood Health Assessment Questionnaire CHAQ (Facial Affective Scale FAS)
- Erythrocyte Sedimentation Rate ESR after one hour (Westergren method).

3.1.1.3 Secondary Efficacy endpoint

Secondary efficacy variables included:

- Investigator global assessment of overall disease activity
- Parent global assessment of overall well-being
- Childhood Health Assessment Questionnaire CHAQ:
    - Functional disability
    - Discomfort
    - Parent global assessment of arthritis
- Number of joints with active arthritis
- Number of joints with limited range of motion
- Erythrocyte Sedimentation Rate ESR
- Final global assessment of efficacy by parent
- Final global assessment of efficacy by investigator
- Withdrawal due to inadequate efficacy
- Acetaminophen consumption.

3.1.1.4 Patients Analyzed

Intent-to-Treat Population: All enrolled patients who were randomized, received study medication and had at least one post-dose efficacy evaluation and those who discontinued the study due to AE or lack of efficacy after taking the first dose and did not provide any post-dose efficacy evaluation.

Reviewer's comment: A more conservative definition of ITT population is all enrolled patients who receive treatment. A total of 209 patients were enrolled in this study. All of these enrolled patients had at least one post-implant examination. Therefore, in this study the protocol defined ITT population is the same as from the more conservative definition stated above.

Evaluable Population: No evaluable population was defined or analyzed.

Safety Population: All patients who received study medication comprised the safety population.

3.1.1.5 Disposition of Patients, Demography, and Baseline characteristics

Summaries of disposition, demography, and baseline characteristics are given in Tables 1, 2, and 3, respectively in the appendix. Two hundred twenty-five patients were enrolled in this study, and 209 were randomized and received treatment. Eighteen of this randomized patients prematurely discontinued during the blinded phase of the trial and 191 completed this phase. These 191 patients continued into the open-label of the trial, where 12 patients prematurely discontinued.

The majority of the patients were female in each treatment group, ranging from 68% to 79 % of the total. Most of the patients were Caucasian (85% to 87%). The age range of patients in the trial was 1 year to 17 years with mean age in treatment groups ranged from 9.3 years to 9.9 years. No statistically significant difference was found in any of the demographic characteristics.

The percentage of patients reporting a history of uveitis at the screening visit was 4.8% for the Mel L group, 5.6% for the Mel H group, and 2.7% for the Nap group. The percentages of patients having four or less joints with active arthritis at baseline were 54.8%, 54.2%, and 65.3% for the Mel L, Mel H, and Nap treatment groups, respectively. The average durations of arthritis disease were 34.0, 31.7, and 37.9 months for the Mel L, Mel H, and Nap treatment groups, respectively. The average numbers of joints with active arthritis at baseline were 8.0, 6.9, and 6.1 for the Mel L, Mel H, and Nap treatment groups, respectively. The average numbers of joints with limited range of motion at baseline were 7.2, 6.1, and 6.6 for the Mel L, Mel H, and Nap treatment groups, respectively. . The overall disease sub-type at onset (present during the first 6 months of the disease) was 47.8% pauci-articular arthritis, 43.5% poly-articular arthritis, and 8.6% systemic arthritis.

3.1.1.6 Sample size determination and Efficacy Analysis

3.1.1.6.1 Determination of sample size

The sample was calculated assuming a 50% response rate for the combined meloxicam treatment groups. A sample size of 60 patients (120 total) was found to ensure a one-sided alpha 0.05 non-inferiority for a difference of 0.2 in proportion responding with an 80% power.

Reviewer's Comments:

1) *This reviewer verified the sponsor's sample size calculations assuming 50% response rate, 20% margin, and 80% power with 2:1 ratio (combined meloxicam vs. naproxen). This reviewer's calculated sample size showed 120 for combined meloxicam and 60 patients for naproxen.*
2) *The non-inferiority margin of 20% looks too wide for the desired non-inferiority of meloxicam to naproxen. A clinical judgment regarding this is needed.*

3.1.1.6.2 Primary Efficacy Analysis

The primary efficacy was performed at Week 12 based on intent-to-treat patients. The primary comparison was between the two meloxicam groups combined and the naproxen group. Differences, expressed in terms of the point estimate and corresponding confidence intervals were the basis for conclusions about the difference in efficacy between meloxicam and naproxen. The interpretation of the study results was dependent on the validity of the sponsor's assumption that the difference between the two meloxicam regimens is relatively small. Before their analysis the sponsor compared the two meloxicam regimens to test the validity of their assumption, also each meloxicam regimen was compared to naproxen to further aid in interpretation of the primary analysis.

The proportion of responders in JRA Pediatric 30 and its 95% confidence interval was calculated for each treatment group. For comparisons between the combined meloxicam groups and naproxen, as well as for each of the two meloxicam groups versus naproxen, the difference in the proportions and its 95% confidence interval were calculated. The calculations were based on Cochran's test for binomial response adjusting for JRA Subtype (poly-articular or pauci-articular).

3.1.1.6.3 Handling of dropouts or missing data

If a patient discontinued the study after taking the first dose of medication due to AE or lack of efficacy and did not provide any post-dose efficacy evaluation, the patient was considered a treatment failure and was included in the intent-to-treat analysis. These dropouts were considered as non-responders for determining the JRA ACR Pediatric 30. For the other efficacy assessment at Weeks 4, 8, 12, 18, and 24 missing values were replaced by the last observation carried forward (LOCF).

3.1.1.6.4 Secondary Efficacy analysis

As a secondary analysis, logistic regression was applied to the primary efficacy variable with factors treatment, center, JRA subtype, and other prognostic variables. Change from baseline for the secondary efficacy variables were performed using the analysis of variance (ANOVA) models with treatment, center and JRA subtype as factors. Treatment means, differences and their 95% confidence intervals were estimated using the Least-Square means (LSMEANS). In calculating the LSMEANs, each center and JRA subtype was weighted according to the observed number of patients (using the observed margin OM option). ANOVA models with interaction terms were used to explore the possibility of heterogeneity in treatment effect and to aid in interpretation of main results.

The proportional odds model with treatment, center and JRA subtype as factors were applied to estimate the treatment difference. Also, the proportion favorable responses (good or satisfactory) for each treatment and the difference in proportions were estimated along with 95% confidence intervals.

Safety analyses were based on patients taking at least one dose of medication and providing safety information. The AEs were summarized separately as overall, by body system, by preferred term, and by time to onset. The SAEs and the patient discontinuation reasons, in particular those due to AEs were summarized separately.

3.1.1.7 Sponsor's Results and Conclusions

3.1.1.7.1 Primary efficacy outcome

Following table shows the results of ACR Pediatric 30 responder analysis.

Summary of JRA Core Set Outcome Responders (ACR Pediatric 30)
ITT Population
Study #107.235

			Responders			Comparison vs. Naproxen*		
Week	Treatment@	Total	N	Rate	(95% CI)	Diff (SE)	(95% CI)	p-value
Week 4	Meloxicam L	62	26	41.9	(29.7, 54.2)	-6.3(12.9)	(-31.6, 18.9)	0.6225
	(b) (4)							
	Naproxen	75	36	48.0	(36.7, 59.3)			
Week 8	Meloxicam L	62	35	56.5	(44.1, 68.8)	-10.6(10.7)	(-31.6, 10.4)	0.3226
	(b) (4)							
	Naproxen	75	50	66.7	(56.0, 77.3)			
Week 12	Meloxicam L	62	43	69.4	(57.9, 80.8)	1.7(9.7)	(-17.2, 20.6)	0.8607
	(b) (4)							
	Naproxen	75	51	68.0	(57.4, 78.6)			

@: Meloxicam L = meloxicam low dosage, (b) (4) (b) (4)

*: Cochran's test for binomial response stratified by pauci or polyarticular JRA
Source Data: Section 15, Table 15.2.1: 1

Source: Table 11.4.1.1:1 of sponsor's analysis

The percentages of patients demonstrating response at Week 12 were 69%, (b) (4) and 68% for Mel L, (b) (4) and Nap treatment groups, respectively. For the 147 patients that had a response in the ACR Pediatric 30 endpoint: 40 (27%) patients had a 30% increase in three components; 42 (29%) patients had a 30% increase four components; 48 (33%) patients had a 30% increase five components; and 17 (12%) patients had a 30% increase in all six components.

This table also shows the differences in proportions of ACR Pediatric 30 responders between the meloxicam treatments versus naproxen and the 95% confidence intervals. These results are also demonstrated in Figure 1. The results show that the (b) (4) Mel L treatment group, (b) (4) had higher proportion of responders than the naproxen treatment group. (b) (4)

Reviewer's Comment: Since there was no placebo control group in this study, the true efficacy of the naproxen or meloxicam could not be evaluated, which may relate to the validity of the study.

3.1.1.7.2 Secondary Efficacy outcome

Outcomes of the secondary efficacy endpoints are given in the following table. No statistically significant difference between the meloxicam and naproxen treatment groups was found in any of the secondary efficacy endpoint.

Outcomes of the secondary efficacy endpoints
Study #107.235

		Treatment Group		
Endpoint	**Variable**	**Mel L**	(b) (4)	**Nap**
Investigator global assessment of overall disease activity	mean reduction	17.5		17.8
Parent global assessment of well-being	Mean improvement	16.0		16.9
Number of joints with active arthritis	Mean reduction	4.4		4.2
Number of joints with limited range	Mean reduction	1.8		2.2
Functional disability as measured by CHAQ	Mean reduction	0.36		0.34
Erythrocyte sedimentation rate	Percent change from baseline	≤5%		≤5%
Discomfort (or pain) as measured by CHAQ	Mean reduction	0.16		0.19
Parent global assessment of arthritis as measured by CHAQ	Mean improvement	17.6		14.7
Parent and investigator final global assessments of efficacy	"satisfactory" or "good"	>80%		>80%

Source: This reviewer created this table from the sponsor's report texts.

Acetaminophen consumption

Acetaminophen usage as a rescue medication was not significantly different between meloxicam versus naproxen treatments. The treatment means ranged from a low of 8.3 mg/day for Mel L at Week 8 to a high of 40.6 mg/day for naproxen as Week 2.

ACR Pediatric 30 response during the 12 weeks of open-label treatment

Following table shows the results or ACR responders from the 12 weeks open-label extension period.

ACR Pediatric 30 Responders by Visit for ITT Patients
Study #107.235

		Responder					
		No		Yes		Total	
Treatment	Visit No.	N	%	N	%	N	%
Mel L	2.00	62	100.00	0	0.00	62	100.00
	3.00	39	62.90	23	37.10	62	100.00
	4.00	36	58.06	26	41.94	62	100.00
	5.00	27	43.55	35	56.45	62	100.00
	6.00	19	30.65	43	69.35	62	100.00
	7.00	16	25.81	46	74.19	62	100.00
	8.00	14	22.58	48	77.42	62	100.00
[redacted] (b) (4)							
Nap	2.00	75	100.00	0	0.00	75	100.00
	3.00	39	52.00	36	48.00	75	100.00
	4.00	39	52.00	36	48.00	75	100.00
	5.00	25	33.33	50	66.67	75	100.00
	6.00	24	32.00	51	68.00	75	100.00
	7.00	26	34.67	49	65.33	75	100.00
	8.00	17	22.67	58	77.33	75	100.00

Source: Table 6.1.1 of sponsor's analysis

Note: Visit #6 = End of Week 12 of the double-blind phase, Visit #7 = End of Week 6 of the open-label phase, Visit #8 = End of Week 12 of the open-label phase

During the 12-week open-label treatment all patients receive meloxicam at a dose of 0.375 mg/kg/day. The percentage of ACR Pediatric 30 responders in Mel L group was 69.4% at the end of double-blind treatment (Week 12), 74.2% after 6 weeks of open-label treatment, and 77.4 after 12 weeks of open-label treatment. [redacted] (b) (4) The percentage of ACR Pediatric 30 responders in naproxen group was 68.0% at the end of double-blind treatment (Week 12), 65.3% after 6 weeks of open-label treatment, and 77.3 after 12 weeks of open-label treatment.

At Week 12 the percentages of patients having at least 30% improvement in the "number of joints with active arthritis" were 75.8%, [redacted] (b) (4) and 78.7% in the Mel L, [redacted] (b) (4) and Nap treatment groups, respectively; the percentages of patients having at least 30% improvement in the "investigator global assessment of overall disease activity" were 72.6%, [redacted] (b) (4) and 77.3% in the Mel L, [redacted] (b) (4) and Nap treatment groups, respectively; the percentages of patients having at least 30% improvement in the "parent global assessment of overall well-being" were 56.5%, [redacted] (b) (4) and 57.3% in the Mel L, [redacted] (b) (4) and Nap treatment groups, respectively; the percentages of patients having at least 30% improvement in the "parent number of joints with limited range of motion" were 61.3, [redacted] (b) (4) and 48.0% in the Mel L, [redacted] (b) (4) and Nap treatment groups, respectively; and the percentages of patients having at least 30% improvement in the "functional disability index in CHAQ" were 64.5%, [redacted] (b) (4) and 56.0% in the Mel L, [redacted] (b) (4) and Nap treatment groups, respectively.

3.1.1.8 Reviewer's Findings and Conclusions

The sponsor considered the comparison of the combined meloxicam treatment groups with the naproxen as the primary analysis. In a discussion with this reviewer, the medical officer mentioned that comparisons of individual meloxicam dose groups with naproxen group are clinically more meaningful than comparison of the combined meloxicam treatment groups with the naproxen. The sponsor performed such comparisons of the individual meloxicam treatment groups with naproxen as additional analysis without mentioning of any adjustment for multiple testing.

Due to the medical officer's advice and also to verify the sponsor's analysis, this reviewer reanalyzed the primary efficacy variable ACR Pediatric 30 using the Cochran-Armitage method. Since there were two meloxicam doses, this reviewer constructed 97.5% confidence intervals instead of 95% confidence intervals to account for the multiple testing. Following table shows this reviewer's results.

ACR Pediatric 30 Responders by Visit for ITT Patients
Study #107.235
Reviewer's Table

Visit	Treatment Group	No. of Patients Treated	No. of Responders	Percentage of Responders	Difference Mel - Nap	97.5% CI Mel vs. Nap
Week 4 D-B	Meloxicam L	62	26	41.94	-6.06	(-25.33, 13.30)
	(b) (4)					
	Naproxen	75	36	48.00		
Week 12 D-B	Meloxicam L	62	43	69.35	1.35	(-16.78, 19.26)
	(b) (4)					
	Naproxen	75	51	68.00		
Week 6 O-L	Meloxicam L	62	46	74.19	8.86	(-9..22, 26.36)
	(b) (4)					
	Naproxen	75	49	65.33		
Week 12 O-L	Meloxicam L	62	48	77.42	0.09	(-16.73 ,16.40)
	(b) (4)					
	Naproxen	75	58	77.33		

Note: D-B = Double-Blind, and O-L = Open-Label. In this Table the D-B percentages were calculated from the submitted data. Since the data of open label part were not submitted, the O-L percentages were copied from sponsor's Table #6.1.1.

(b) (4) . The lower dose (b) (4) maintained this non-inferiority up to the end (Week 12) of the open-label extension of the study. (b) (4) (b) (4) From these results this reviewer concludes (b) (4) meloxicam showed non-inferior efficacy to naproxen and retained for reasonably long time.

3.1.2 **STUDY # 107.208 (12 WEEKS DATA)**

Title: "A one year double-blind trial to investigate the efficacy and safety of meloxicam oral suspension 0.25 mg/kg and 0.125 mg/kg administered once daily in comparison to naproxen oral suspension 5 mg/kg administered twice daily in children with Juvenile Rheumatoid Arthritis".

3.1.2.1 Design and Objectives

This was a randomized, double-blind, double-dummy, active comparator, parallel group, multicenter, and multinational trial in children with established diagnosis of Juvenile Rheumatoid Arthritis (JRA). The conduct of the trial was divided in three parts namely, screening, treatment, and if required a follow-up period. The study population was randomized into three treatment groups in a 1:1:1 pattern as follows:

Group I: Meloxicam 0.25 mg/kg daily dose (Mel H)
Group II: Meloxicam 0.125 mg/kg daily dose (Mel L)
Group III: Naproxen 10 mg/kg daily dose (Nap)

The treatment period was of one year duration. However, after 12 weeks the primary analysis was performed in a way to keep the trial team blind and the trial was ongoing. After one year the final analysis was performed with a focus on safety data.

The primary object of this study was to establish whether the efficacy and safety of meloxicam oral suspension are comparable to those of naproxen for the treatment of patients with JRA.

3.1.2.2 Efficacy Endpoints

The primary and the secondary efficacy variable were the same as in Study #107.235.

3.1.2.3 Patients Analyzed

Intent-to-Treat Population: ITT population included all treated patients.

Evaluable Population: No evaluable population was defined or analyzed.

Safety Population: All patients who received study medication comprised the safety population.

3.1.2.4 Disposition of Patients, Demography, and Baseline characteristics

The summaries of disposition, demography, and baseline characteristics are given in Table 4 and Table 5, respectively in the appendix. Two hundred twenty-five patients were randomized and received treatment. Fifteen of this randomized patients prematurely discontinued during the first 12 weeks of the trial. Among the discontinued patients, 5 were due to adverse events (AE), 3 were due to lack of efficacy, and 7 were due to administrative reasons.

Majority of the patients were female in each treatment group, ranging from 66% to 77 % of the total. The age range of patients in the trial was 1 year to 16 years with mean age in treatment groups ranged from 7.5 years to 9.0 years. No statistically significant difference was found in any of the demographic characteristics.

Base line disease characteristics for all patients are presented in, and Table 6 and Table 7 in the appendix. The percentage of patients reporting a history of uveitis at the screening visit was 12.3% for the Mel L group, 9.5% for the Mel H group, and 7.7% for the Nap group. The disease sub-type at onset in combined treatment groups was 77.8% pauci-articular arthritis, 20.4% poly-articular arthritis, and 1.2% systemic arthritis. The average durations of arthritis disease were 41.6, 30.0, and 27.7 months for the Mel L, Mel H, and Nap treatment groups, respectively. The average numbers of joints with active arthritis at baseline were 6.2, 7.3, and 6.7 for the Mel L, Mel H, and Nap treatment groups, respectively. The average numbers of joints with limited range of motion at baseline were 6.1, 6.6, and 6.5 for the Mel L, Mel H, and Nap treatment groups, respectively.

3.1.2.5 Sample size determination and Efficacy Analysis

3.1.2.5.1 Determination of sample size

The original objective of this study was to test equivalency of meloxicam and naproxen. However, the sample size calculations by the sponsor for a formal equivalence analysis lead to an unfeasibly high patient number. Therefore, alternatively the sponsor decided to calculate the sample size for a superiority test with $\alpha=\beta=0.05$. In contradiction to the usual approach, the aim of this analysis is that the null hypothesis on interest in not rejected (quasi-equivalence).

A 6-month trial (R97-2518) by the sponsor showed that the incidence for the efficacy parameter "response" was 63.3% with methotrexate (MTX). This effect was about 23% over placebo. The sponsor assumed that an active NSAID, after a treatment period of 3 months, would show a responder rate of about 50% based on the half of the difference between the MTX and the placebo effect. Consequently, the sponsor assumed a 50% responder rate for naproxen in this prospective trial.

To detect with a power of 95% a difference (delta) of $\pm 25\%$ between the treatment groups, a sample size of about 103 patients per treatment would be needed for Fisher's exact test (two-sided, $\alpha=0.05$). Assuming a drop-out rate of 15% a sample size of 118 patients per treatment group or a total of about 360 patients was regarded sufficient.

Originally it was planned to recruit all 360 patients in the present trial. However, later on it was decided to split the trial into two trials. One to be performed in Europe with the aim to recruit 180 patients (Study #107.208) and the remaining 180 patients to be recruited in Study #107.235 running with a similar design in the USA. The results from the 3 month double-blind phase from both trials should have been evaluated together in the final 3 month report of the present trial #107.208. However, trial #107.235 could not recruit a sufficient number of patients within the planned recruitment period. Therefore, in consultation with the French regulatory agency, the design of this study was changed. The study was decided to be a "stand alone" trial and instead of quasi-equivalence the agency advised for a superiority analysis based on the assumption that the selected naproxen dose was a placebo like treatment.

A new sample size calculation was performed to meet this new design. In the new calculation the sponsor assumed a difference in responder rate of 23% between meloxicam and placebo. Given that the efficacy of naproxen is slightly better than placebo the sponsor considered a difference (delta) of 20% between the naproxen group and the pooled meloxicam groups. For a test with 90% power a sample 219 patients (73 in naproxen and 146 in the combined meloxicam group) was calculated. This target was met in this study (Study #107.208). In practice a total of 226 were randomized and 225

patients were treated (73 in naproxen and 152 in the combined meloxicam group) in this study. No reason was mentioned in the final report why one patient did not receive medication.

Reviewer's Comments:

1) *This reviewer verified the sponsor's sample size calculations assuming 60% response rate, 20% margin, and 90% power with 2:1 ratio (meloxicam vs. naproxen). This reviewer's calculated sample size showed 155 for meloxicam and 78 patients for naproxen.*
2) *As this reviewer comment in the previous study, the non-inferiority margin of 20% looks too wide for the desired non-inferiority of meloxicam to naproxen. A clinical judgment regarding this is needed.*

3.1.2.5.2 Primary Efficacy Analysis

The primary efficacy was performed at Week 12 based on intent-to-treat patients. The Chi-Square test was used as the overall test. Unadjusted Fisher's exact test was used for the paired comparisons. Logistic regression was used, if necessary, to analyze potential confounder variables.

3.1.2.5.3 Handling of dropouts or missing data

The LOCF/WCF was used where appropriate.

3.1.2.5.4 Secondary Efficacy analysis

All secondary efficacy parameters were evaluated by means of descriptive statistics in an exploratory manner.

Safety analyses were based on patients taking at least one dose of medication and providing safety information. The AEs were summarized separately as overall, by body system, by preferred term, and by time to onset. The SAEs and the patient discontinuation reasons, in particular those due to AEs were summarized separately.

3.1.2.6 Sponsor's Results and Conclusions

3.1.2.6.1 Primary efficacy outcome

Following table shows the results of ACR Pediatric 30 responder analysis.

Summary of JRA Core Set Outcome Responders ACR Pediatric 30
ITT Population (Twelve Weeks Data)
Study 107.208

		Responder (LOCF)				Total	
		No		Yes			
		N	%	N	%	N	%
Treatment	Visit Number						
Melox Low	Week 4	38	52.05	35	47.95	73	100.00
	Week 12 (EOT)	27	36.99	46	63.01	73	100.00
(b) (4)							
Naproxen	Week 4	41	52.56	37	47.44	78	100.00
	Week 12 (EOT)	28	35.90	50	64.10	78	100.00
(b) (4)							

Source: Table 6.1.1 of sponsor's analysis

The percentages of patients demonstrating response were 63%, (b) (4) and 64% for Mel L, (b) (4) and Nap treatment groups, respectively. The pooled meloxicam groups had an ACR Pediatric 30 response rate of 61%. The pooled meloxicam groups were not superior to the naproxen group. The Chi-Squire p-value for this test was p=0.6012.

Following the original analysis plan, the sponsor also performed the equivalency test of meloxicam and naproxen. According to the original analysis the null hypotheses could not be rejected with Type I error of 5% and Type II error of 5%. Figure 2 in the appendix shows the estimated difference of the treatment groups with the 95% confidence intervals for both meloxicam treatments versus naproxen, and the pre-define difference (delta) of ±25%. (b) (4) .

Reviewer's Comments:

1) *The naproxen dose of 10 mg / kg daily in this study was the same as naproxen doses in Study #107.235, where the effect of naproxen was not considered as placebo like. Both in Studies #107.235 and #107.208 the naproxen had response rate of more than 60%. Therefore the assumption of placebo like response rate for naproxen may not be a reasonable one. In Studies #107.235 a formal non-inferiority test was performed with non-inferiority margin of 20%. A similar analysis of data from this study is more meaningful and helpful to unify the results.*
2) *Since there was no placebo control group in this study the true efficacy of the naproxen or meloxicam could not be made, which may relate to the validity of the study.*

3.1.2.6.2 Secondary Efficacy outcome

Outcomes of the secondary efficacy endpoints are given in the following table. No statistically significant difference between the meloxicam and naproxen treatment groups was found in any of the secondary efficacy endpoint.

Outcomes of the Secondary Efficacy Endpoints (Twelve Weeks Data)
Study #107.208

		Treatment Group		
Endpoint	**Variable**	**Mel L**	**Mel H**	**Nap**
Investigator global assessment of overall disease activity	mean reduction	17.5	(b) (4)	16.4
Parent global assessment of well-being	Mean improvement	15.8		15.5
Number of joints with active arthritis	Mean reduction	3.3		2.8
Number of joints with limited range	Mean reduction	2.7		2.44
Functional disability as measured by CHAQ	Mean reduction	.27		0.30
Erythrocyte sedimentation rate	Percent change from baseline	2.1		5.6
Child assessment of discomfort (or pain) as measured by CHAQ	Mean reduction	0.13		0.17
Parent global assessment of arthritis	Mean improvement	19.1		20.0
Parent global assessment of pain	Mean improvement	17.4		17.3
Parent and investigator final global assessments of efficacy	"satisfactory" or "good"	>80%		>80%

Source: This reviewer created this table from sponsor's report texts.

Steinbrocker functional classification

At the beginning of the trial, the percentage of Stage I classification (the patient is not impaired in her/his daily activities judged by the investigator) was 19 for Mel L, (b) (4) and 17 for Nap treatment groups. After 12 weeks of treatment the percentages of Stage I classification was 47 for Mel L, (b) (4) and 35 for Nap treatment groups.

3.1.2.7 Reviewer's Findings and Conclusions

To uniformly analyze the data of this study and data form Study #107.235 and also to verify the sponsor's analysis this reviewer reanalyzed the primary efficacy variable ACR Pediatric 30 using the Cochran-Armitage method. Since there were two meloxicam doses, this reviewer constructed 97.5% confidence intervals instead of 95% confidence intervals to account for the multiple testing.

Following shows this reviewer's analysis results.

ACR Pediatric 30 Responders by Visit for ITT Patients
Study #107.208
Reviewer's Table

Visit	Treatment Group	No. of Patients Treated	No. of Responders	Percentage of Responders	Difference Mel - Nap	97.5% CI Mel vs. Nap
Week 4	Meloxicam L	73	35	47.95	0.51	(-17.82, 18.74)
	(b) (4)					
	Naproxen	78	37	47.44		
Week 12	Meloxicam L	73	46	63.01	-1.09	(-18.76, 16.67)
	(b) (4)					
	Naproxen	78	50	64.10		
Month 6	Meloxicam L	73	49	67.12	1.74	(-15.70, 19.08)
	(b) (4)					)
	Naproxen	78	51	65.38		
Month 9	Meloxicam L	73	52	71.23	2.00	(-14.93, 18.75)
	(b) (4)					
	Naproxen	78	54	69.23		
Month 12	Meloxicam L	73	56	76.71	2.35	(-13.77, 18.35)
	(b) (4)					
	Naproxen	78	58	74.36		

Note: In this Table the Week 4 and Week 12 percentages were calculated from the submitted data. Since the data of visit after Week 12 were not submitted, the percentages of responders after Week 12 were copied from sponsor's Table #6.1.1.

Using the proposed non-inferiority margin of 25%, results of reviewer's analysis showed that (b) (4) meloxicam established non-inferiority to Naproxen at Week 12 of the double blind phase. It should be noted that at week 12 the meloxicam low dose group (b) (4) non-inferiority using a margin of 20% as was used in Study #107.23. (b) (4) . From these results this reviewer concludes (b) (4) meloxicam showed non-inferior efficacy to naproxen and retained for reasonably long time.

3.1.3 STUDY # 107.208 (ONE YEAR DATA)

In this section I will review the one-year follow-up data from Study #107.208. The primary objects of this part of the study was to establish whether efficacy and safety of once daily doses of 0.125 mg/kg meloxicam oral suspension are different from 5 mg/kg naproxen oral suspension given bid over a period of one year in the treatment on patients with JRA. The main criterion to evaluate efficacy was the analysis of the responders ACR Pediatric 30 at 3, 6, 9, and 12 months on intent-to-treat population.

3.1.3.1 Disposition of Patients

The summary of disposition is given in Table 8 in the appendix. Two hundred twenty-five patients were randomized and received treatment. Fifteen of this randomized patients prematurely discontinued during the first 12 weeks of the trial. Another 28 patients discontinued during the extension period. Therefore, a total of 43 patients discontinued from the entire study. In the extension period of the study 5 patients (6.8%) discontinued the trial from the Mel H treatment

group, 12 patients (16.4%) discontinued the trial from the Mel L treatment group, and 11 patients (14.1%) discontinued the trial from the Nap treatment group. In entire study 11 patients (14.9%) discontinued the trial from the Mel H treatment group, 15 patients (20.5%) discontinued the trial from the Mel L treatment group, and 17 patients (21.8%) discontinued the trial from the Nap treatment group. The difference of percentage of discontinued patients due to adverse event or lack of efficacy in the extension period between Mel H (5.4%) and Nap (16.7%) was statistically significant (p=0.0382). Also the difference of percentage of discontinued patients due to adverse event or lack of efficacy in the entire study between Mel H (8.1%) and Nap (23.1%) was statistically significant (p=0.0141).

3.1.3.1.1 Primary Efficacy Analysis

The Chi-Square test was used for the overall test. Unadjusted Fisher's exact test was used for the paired comparisons response rates. For other efficacy parameters summary statistics were calculated. Exploratory analyses were also performed using standard statistical methods. A non-confirmatory treatment comparison at Month 12 was performed using the analysis of covariance with treatment and baseline value as main effects in the model.

3.1.3.1.2 Handling of dropouts or missing data

For primary efficacy analysis the last observation carried forward (LOCF) was used for imputation of missing values. Also for sensitivity analysis the primary efficacy data were reanalyzed by assuming all dropouts as non-responders. This method was referred to as the worst case analysis (WCA).

3.1.3.1.3 Safety data analysis

Safety analyses were based on patients taking at least one dose of medication and providing safety information. The AEs were summarized separately as overall, by body system, by preferred term, and by time to onset. The SAEs and the patient discontinuation reasons, in particular those due to AEs were summarized separately.

3.1.3.2 Sponsor's Results and Conclusions

3.1.3.2.1 Primary efficacy outcome

Following table shows the ACR Pediatric 30 responder analysis results at month 3, 6, 9, and 12.

Responder Rate Over Visits ACR Pediatric 30
LOCF for Missing Values
Study #107.208 (One year)

		Responder (LOCF)				Total	
		No		Yes			
		N	%	N	%	N	%
Treatment	Visit Number						
(b) (4)							
Melox Low	Week 12	27	36.99	46	63.01	73	100.00
	Month 6	24	32.88	49	67.12	73	100.00
	Month 9	21	28.77	52	71.23	73	100.00
	Month 12 (EOT)	17	23.29	56	76.71	73	100.00
Naproxen	Week 12	28	35.90	50	64.10	78	100.00
	Month 6	27	34.62	51	65.38	78	100.00
	Month 9	24	30.77	54	69.23	78	100.00
	Month 12 (EOT)	20	25.64	58	74.36	78	100.00
(b) (4)							

Source: Table 6.1.1 of sponsor's analysis

The responder rates in different treatment groups at Month 12 were about 75% and were quite comparable. However, the Nap showed slightly lower responder rates at Months 3, 6, and 9. Mel L group had the highest responder rates at Month 12 (b) (4)

With this worst case approach, both meloxicam doses continued to perform better than naproxen at month 6, 9, and 12. However, the observed differences were not statistically significant. Table 9 in the appendix shows the results.

3.1.3.2.2 Secondary Efficacy outcome

Following table shows the results of secondary efficacy analyses expressed as the mean differences from baseline and the percent-decrease of the observed mean values compared to the observed baseline mean values from Week 12 to Month 12.

Secondary Efficacy Endpoints as Absolute Change and Mean % Decrease from Baseline by Treatment Groups Over Time
Study #107.208

Parameter	Time point	Mel L			(b) (4)	Nap		
		Mean	SD	% ch.		Mean	SD	% ch.
Global assessment of disease activity by investigator	week12	-17.7	17.8	47.7		-16.4	18.4	43.7
	month 6	-18.5	18.2	49.9		-18.6	20.9	49.5
	month 9	-18.7	18.0	50.5		-21.1	19.9	56.0
	month 12*	-21.7	19.6	58.5		-23.1	20.5	61.5
Parent global assessment of overall well-being	week12	-15.8	20.4	42.8		-15.5	23.6	40.8
	month 6	-14.5	23.2	39.5		-19.1	22.8	50.4
	month 9	-16.8	24.5	45.6		-19.5	23.7	51.3
	month 12*	-18.7	23.8	50.8		-21.1	24.9	55.6
Number of joints with active arthritis	week12	-3.3	6.8	52.4		-2.8	5.5	42.4
	month 6	-3.6	6.9	57.5		-3.2	6.5	47.6
	month 9	-3.6	6.9	58.4		-3.8	7.2	57.0
	month 12*	-3.7	7.0	59.3		-3.8	6.9	57.2
Number of joints with limited range of motion	week12	-2.7	5.0	44.9		-2.4	5.0	37.5
	month 6	-2.9	5.2	47.2		-2.9	6.2	44.4
	month 9	-3.0	5.2	49.2		-2.9	6.5	45.0
	month 12*	-3.3	5.0	53.9		-3.2	6.5	49.1
ESR	week12	0.5	8.5	-2.1		-0.9	11.4	5.5
	month 6	-1.3	9.4	8.8		-2.1	12.9	11.2
	month 9	-1.0	10.2	6.7		-2.8	13.3	13.7
	month 12*	-2.1	8.7	13.4		-3.9	14.4	18.5
Childhood Health Assessment Questionnaire	week12	-0.3	0.4	42.7		-0.3	0.4	36.9
	month 6	-0.3	0.4	43.5		-0.4	0.5	47.7
	month 9	-0.3	0.4	54.6		-0.4	0.5	54.3
	month 12*	-0.4	0.5	58.9		-0.5	0.5	59.7
Childrens assessment of discomfort	week12	-0.1	0.3	28.4		-0.2	0.3	38.6
	month 6	-0.2	0.3	34.8		-0.2	0.3	41.2
	month 9	-0.2	0.3	36.0		-0.2	0.3	38.0
	month 12*	-0.2	0.3	41.4		-0.2	0.3	47.5

Source: Table 14.22 of sponsor's analysis

Secondary Efficacy Endpoints as Absolute Change and Mean % Decrease from Baseline by Treatment Groups Over Time Study #107.208 (Continued)

Parameter	Time point	Mel L			(b) (4)	Nap		
Parents global assessment of arthritis	week12	-19.1	21.9	46.8		-20.0	22.9	45.4
	month 6	-19.6	24.5	48.1		-23.3	23.0	52.9
	month 9	-22.5	23.4	55.1		-25.2	23.9	57.2
	month 12*	-23.9	23.6	58.6		-26.0	26.5	59.2
Parents global assessment of pain	week12	-17.4	22.7	49.6		-17.3	26.3	45.4
	month 6	-17.8	26.6	50.8		-21.1	25.0	55.4
	month 9	-19.9	23.7	56.9		-20.5	27.7	54.0
	month 12*	-21.6	22.3	61.7		-22.2	27.1	58.3

Source: Appendix 16.1.9.2: TABLES 6.3.2, 6.4.2, 6.5.2, 6.6.2, 6.7.2, 6.8.2, 6.9.2, 6.10.2, 6.11.2

Source: Table 14.2:2 of sponsor's analysis

Results did not show any remarkable differences. All treatments treatment induced mean improvements to baseline on an order of magnitude mostly between 50% and 60% at Month 12. Only the improvement in ESR remained below 20% (b) (4) . The only significant difference observed on secondary endpoint s was in favor of Mel L (b) (4) for the reduction of number of joints with limitation in movement at Month 12.

3.1.3.3 Reviewer's Findings and Conclusions

This reviewer's analyses results of 12 months data are included along with reviewer's analysis of 12 weeks data.

3.1.4 STUDY # 107.162 (12 WEEKS DATA)

Title: "An open trial to investigate pharmacokinetics as well as efficacy and safety of 0.25 mg/kg meloxicam suspension administered once daily in children with Juvenile Rheumatoid Arthritis over a treatment period of up to 52 weeks"

This submitted report contains only 12 week data of 12 month trial. The 12 month data was discussed separately.

Under an amendment (Amendment #2) due to a SAS format issue the joints cervical spine and DIP of toes out of 75 examined joints were not counted in the respective results. The following efficacy endpoints were affected from this SAS format issue: responder analysis, number of joints with limited range of motion, number of joints with active arthritis.

Under a separate amendment (Amendment #1) the following change was done:

At the screening visit the rheumatoid factor was determined. In the statistical analysis each value >0 U/ml for the rheumatoid factor was interpreted as positive. Further investigation revealed that values for the rheumatoid factor less than 30 U/ml resp. 20 U/ml had to be considered as negative according to normal ranges provided by the laboratories. Therefore, the SA and SDL were corrected accordingly.

3.1.4.1 Design and Objectives

This was an open, multicenter, multinational trial. The trial had to be performed in two phases: a pharmacokinetic (PK) phase of 72 hours duration and a pharmacodynamic (PD) phase investigating efficacy and safety of 12 weeks duration. The PD phase was followed by an additional open treatment phase of 40 weeks duration which was aimed at investigating long term safety and efficacy (SE). A total of 40 male and female children suffering from JRA between age 2 and 16 years were planned to be included. Of these at least eight patients had to be between 2 and 6 years and at least eight patients had to be between 7 and 16 years. The dose level of all patients was 0.25 mg/kg.

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

3.2.1.1 Study # 107.235

The population evaluated for safety included 209 patients: 62 in the Mel L group, 72 in the Mel H group, and 75 in the Nap group. During the double blind phase, 146 of 209 (69.9%) patients experienced one or more AEs. The frequency of patients experiencing an AE was slightly higher in Mel H group (75%) and Nap (72%0 compared to Mel L group (61%). During the open-label phase 96 of 191 (50.3) patients experienced an AE. Less than 4.1% AEs were severe in intensity. The number of patients with AEs that resulted in an intervention (discontinuation or reduction of study drug) was relatively small, ranging from 0% to 4.1%. Five patients experienced SAEs in the trial. One patient was receiving naproxen 15mg/kg/day during the double-blind phase and the remaining 4 patients experienced SAEs during the open label phase of the trial while receiving meloxicam 0.375 mg/kg/day. No death occurred during the trial.

Table 13 in the appendix summaries AEs experienced by more than or equal to 2% of the patients.

3.2.1.2 Study # 107.208

One hundred and fifty six of 225 patients experienced one or more AE during screening and treated period. Out of which 33 patients had one or more AE during the screening period and 149 patients had one or more AE during the 12 weeks treatment period: 44 in the Mel L group, 51 in the Mel H group, and 54 in the Nap group. The observed AEs mainly consisted of infections and infestations, gastrointestinal, respiratory, musculoskeletal, and general disorders. No death occurred.

Tables 14 and 15 in the appendix summaries frequently affected AEs by organs and AE type, respectively. The overall frequency of musculoskeletal AEs was highest in the Mel H group 24 events), and the number of patients with infections and infestations was highest in the Nap group (28 events). The most frequently observed AEs were mild infections. The three patients with severe AEs had an aggravated arthritis (Mel H), and a uveitis and a joint swelling with limited range of movement, respectively. Most of the AEs (50/53) were judged by the investigator as treatment unrelated.

3.2.1.3 Study # 107.162

The summary of the AEs experienced by the patients is given in Table 16 in the appendix. Twenty four of 36 patients (66.7%) reported an AE during the study. Three patients (8.1%) reported AEs during screening. Most observed AEs were gastro-intestinal disorders (11 patients, 30.6%), respiratory system disorders (1 patients, 33.3%), and disorders of the body as a whole (8 patients, 22.2%). No death occurred during the study.

3.2.2 REVIEWER'S ANALYSIS OF SAFETY DATA

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

4 FINDINGS IN SPACIAL/SUBGROUP POPULATIONS

4.1 SPONSOR'S SUB-GROUP ANALYSIS

4.1.1 STUDY #107.235

4.1.1.1 Sub-group analysis by Age

The sponsor analyzed the ACR Pediatric 30 responses stratifying by age (≤ 6, and 7-17 years). Table 17 in the appendix shows the results. No apparent difference in treatment effect was found between age groups.

4.1.1.2 Sub-group analysis by Gender

The sponsor analyzed the ACR Pediatric 30 responses stratifying by gender. Table 17 in the appendix shows the results. No apparent difference in treatment effect was found between gender groups.

4.1.1.3 Sub-group analysis by Race

The sponsor did not analyze the data stratifying by race.

4.1.1.4 Analysis by Other Special/Subgroup populations

The sponsor analyzed the data sub-grouping by disease type (Pauci-articular or Poly-articular), number of active joints at baseline (≤4 joints or ≥5 joints), country of origin (Brazil, Mexico, Argentina, Ukraine, or USA), and Methotrexate (No or Yes). Table 17 in the appendix shows the results. No apparent difference in treatment effect was found in the strata of these subgroups.

4.1.2 STUDY #107.208

4.1.2.1 Sub-group analysis by Age

The sponsor analyzed the ACR Pediatric 30 responses stratifying by age (≤ 6, and 7-16 years). Table 18 in the appendix shows the results. The response in 7-16 year group is slightly higher but no apparent significant difference in treatment effect was found between age groups.

4.1.2.2 Sub-group analysis by Gender

The sponsor analyzed the ACR Pediatric 30 responses stratifying by gender. Table 19 in the appendix shows the results. No apparent difference in treatment effect was found between genders groups.

4.1.2.3 Sub-group analysis by Race

The sponsor did not analyze the data stratifying by race.

4.1.2.4 Analysis by Other Special/Subgroup populations

The sponsor analyzed the data sub-grouping by disease type (Pauci-articular or Poly-articular), number of active joints at baseline (≤4 joints or ≥5 joints), and Methotrexate (No or Yes).

Responder's rate classified by number of active joints at baseline

Table 20 in the appendix shows the responder rates by number of active joints at baseline. All treatment appeared to be more effective in the patients with more than four joints affected at baseline compared to the class with two or less joints.

Responder's rate classified by use of methotrexate as concomitant medication MXT

The percentage of responders for patients with MXT as concomitant medication was 60.0 for Mel L, (b) (4) and 56.5 for Nap treatment groups, while the percentage of responders for patients without MXT as concomitant medication was 63.8 for Mel L, (b) (4) and 67.3 for Nap treatment groups. No statistically significant difference between treatment groups was found.

Treatment Results classified by poly and pauci-articular assessment

The percentage of responders in pauci-articular sub-group was 60.0 for Mel L, (b) (4) and 60.8 for Nap treatment groups, while the percentage of responders in poly-articular sub-group was 67.9 for Mel L, (b) (4) and 70.4 for Nap treatment groups. Table 21 in the appendix shows the results of secondary efficacy endpoints classified by poly and pauci-articular assessment at baseline. Groups separated approximately by one third of the patients with poly- and two thirds with pauci-articular disease. The results show that (b) (4) the poly-articular sub-group got better benefit compared to the pauci-articular group. In general the (b) (4) compared to both Mel L and Nap groups in all parameters except ESR.

4.1.3 STUDY #107.162 (12 WEEKS DATA)

The sponsor did not perform any subgroup analysis.

4.2 REVIEWER'S SUB-GROUP ANALYSIS

This reviewer performed subgroup analysis by age, gender, race, baseline RA type, number of active joints, and use of methotrexate following similar analysis method as was used in the primary efficacy analysis. Tables 22 and 23 show this reviewer's results for Studies #107.235 and #107.208, respectively. Result show that for most of the sub-groups the lower 97.5% confidence intervals were below 20% (not establishing non-inferiority). The result could be attributed to the small sample size in each sub-group. To verify the small sample effect this reviewer analyzed the pooled data of Studies #107.235 and #107.208. Table 24 in the appendix shows the results. Results show that as the sample increased in most sub-groups meloxicam showed non-inferior efficacy compared to naproxen. However, besides this increased sample size, neither of the meloxicam L (b) (4) showed non-inferior efficacy in subgroup with methotrexate non-user using non-inferiority margin of 20%.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this NDA submission the sponsor included reports of two double-blind Phase 3 studies (Study #107.235 and Study #107.208) and one open-label Phase 2 study (Study #107.162) to support their claim that the efficacy of daily dose of 0.125 (b) (4) mg/kg of meloxicam oral suspension is non-inferior to those of daily dose of 10 mg/kg of naproxen in terms of the percentage of responders for the treatment of juvenile rheumatoid arthritis for 12 weeks. This reviewer's conclusion was mainly based on results from the two Phase 3 studies. However, results from the Phase 2 study were also considered.

Originally the non-inferiority margin was set to 20% for the first study and 25% for the second study. Non-inferiority was declared if the lower 95% confidence limit on the difference of the percentage of responders between the combined meloxicam arms and the naproxen was greater than the selected margin. In a discussion with this reviewer the medical officer mentioned that comparisons of individual meloxicam dose groups with naproxen group are clinically more meaningful than comparison of the combined meloxicam treatment groups with the naproxen. Due to the medical officer's advice this reviewer compared each individual doses of meloxicam with naproxen. Since there were two doses of meloxicam, this reviewer constructed 97.5% confidence intervals instead of 95% to account for the multiple testing. Also, for appropriate interpretation of integrated results, in this reviewer's analysis both of the studies were analyzed using the same non-inferiority margin of 20%.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Results from the first Phase 3 study showed that at Week 12 the 97.5% lower confidence limits on the difference of the percentage of responders between meloxicam and the naproxen arms were greater than 20% for (b) (4) 0.125 (b) (4) mg/kg (b) (4), while results from the second Phase 3 study showed that at Week 12 similar 97.5% lower confidence limit was greater than 20% for 0.125 mg/kg arm (b) (4). However for the second study, the 97.5% lower confidence limit between the combined meloxicam arms and the naproxen was greater than 20%. The open label study had only one arm of 0.25 mg/kg of meloxicam. (b) (4)

From results of the submitted studies this reviewer concludes (b) (4) meloxicam (b) (4) established non-inferiority in efficacy to naproxen by Week 12. (b) (4) also maintained the non-inferiority for up to one year. However, this reviewer has the concern that the width of the selected non-inferiority margin may be too wide. Considering about 60% responder of naproxen, a 20% margin may lead to a worst case of 40% responder of meloxicam and yet maintain the non-inferiority status. Also due to ethical reasons none of these studies had placebo control group. A finding of efficacy of meloxicam from a non-inferiority study depends on the efficacy of naproxen. There is historical evidence of efficacy of naproxen at similar doses in apparently similar populations, but without internal validation the question of assay sensitivity cannot be completely dismissed. In a communication to this reviewer, the medical officer mentioned that 10 mg naproxen is the approved dose for JRA in many European countries and the effect size is around 60% and is similar to what

we see in adult studies of RA, and the placebo effect size is usually much smaller, between 20-30% as measured by ACR20 completers/responders. Based on this comment of the medical officer, it may be concluded that in this study naproxen has demonstrated considerable effect.

M. Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Thomas Permutt, Ph.D.
Team Leader

cc:
Archival NDA 20-938
HFD-170/Division File
HFD-170/Dr. Rappaport
HFD-550/Dr. Hertz
HFD-550/Dr. Oussova
HFD-550/ Mr. Constantine
HFD-715/ Chron
HFD-715/ Dr. Nevius
HFD-715/ Dr. Wilson
HFD-715/ Dr. Permutt
HFD-725/Dr. Rahman.
HFD-700/Dr. Anello

6 APPENDIX

Table 1: Disposition of Patients
Study #107.235

	Mel L N (%)	Mel H N (%)	Nap N (%)	Mel T N (%)	Total N (%)
Enrolled					225
Randomized and treated in double-blind	62	72	75	134	209
Prematurely discontinued	4 (6.5)	9 (12.5)	5 (6.7)	13 (9.7)	18 (8.6)
Adverse event	0 (0.0)	2 (2.8)	1 (1.3)	2 (1.5)	3 (1.4)
Lack of efficacy	1 (1.6)	5 (6.9)	2 (2.7)	6 (4.5)	8 (3.8)
Non compliant with protocol	1 (1.6)	1 (1.4)	0 (0.0)	2(1.5)	2 (1.0)
Lost to follow up	0 (0.0)	1 (1.4)	1 (1.3)	1 (0.7)	2 (1.0)
Consent withdrawn	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)
Others	1 (1.6)	0 (0.0)	1 (1.3)	1 (0.7)	2 (1.0)
Treated in open-label	58 (93.5)	63 (87.5)	70 (93.3)	121 (90.3)	191 (91.4)
Prematurely discontinued	6 (9.7)	2 (2.8)	4 (5.3)	8 (6.0)	12 (5.7)
Adverse event	4 (6.5)	1 (1.4)	3 (4.0)	5 (3.7)	8 (3.8)
Lack of efficacy	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.7)	1 (0.5)
Non compliant with protocol	1 (1.6)	0 (0.0)	0 (0.0)	1(0.7)	1 (0.5)
Lost to follow up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	1 (1.6)	0 (0.0)	1 (1.3)	1 (0.7)	2 (1.0)
Others	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 10.1:1 of sponsor's analysis

Table 2: Demographic Characteristics
Study #107.235

	Mel L	Mel H	Nap	Mel T	Total
Total Treated	62(100.0)	72(100.0)	75(100.0)	134(100.0)	209(100.0)
Sex					
Male	13(21.0)	23(31.9)	20(26.7)	36(26.9)	56(26.8)
Female	49(79.0)	49(68.1)	55(73.3)	98(73.1)	153(73.2)
Race					
White	54(87.1)	63(87.5)	64(85.3)	117(87.3)	181(86.6)
Black	5(8.1)	5(6.9)	6(8.0)	10(7.5)	16(7.7)
Asian	3(4.8)	4(5.6)	5(6.7)	7(5.2)	12(5.7)
Hispanic					
Yes	18(29.0)	19(26.4)	25(33.3)	37(27.6)	62(29.7)
No	44(71.0)	53(73.6)	50(66.7)	97(72.4)	147(70.3)
Age Group					
<=6 Years	19(30.6)	19(26.4)	22(29.3)	38(28.4)	60(28.7)
7-17 Years	43(69.4)	53(73.6)	53(70.7)	96(71.6)	149(71.3)
Calc. Age					
N	62	72	75	134	209
Mean	9.3	9.4	9.9	9.4	9.5
SD	4.5	4.4	4.7	4.4	4.5
Min	1.0	1.0	1.0	1.0	1.0
Max	16.0	17.0	17.0	17.0	17.0
Height(cm)					
N	62	72	74	134	208
Mean	130.0	135.3	135.8	132.9	133.9
SD	27.6	25.1	24.9	26.3	25.8
Min	29.0	83.0	84.0	29.0	29.0
Max	170.0	183.0	177.0	183.0	183.0
Weight(kg)					
N	62	72	75	134	209
Mean	34.1	37.0	37.5	35.6	36.3
SD	16.8	21.6	19.1	19.5	19.3
Min	10.0	11.0	11.2	10.0	10.0
Max	74.0	139.1	87.0	139.1	139.1

Source Data: Section 15, Table 15. 1.4: 1

Source: Table 11.2:1 of sponsor's analysis

Table 3: Baseline Characteristics
Study #107.235

	Mel L N (%)	Mel H N (%)	Nap N (%)	Mel T N (%)	All N (%)
Total Treated	62(100.0)	72(100.0)	75(100.0)	134(100.0)	209(100.0)
Age Group					
<=6 Years	19(30.6)	19(26.4)	22(29.3)	38(28.4)	60(28.7)
7-17 Years	43(69.4)	53(73.6)	53(70.7)	96(71.6)	149(71.3)
History of Uveitis					
No	53(85.5)	61(84.7)	69(92.0)	114(85.1)	183(87.6)
Yes	3(4.8)	4(5.6)	2(2.7)	7(5.2)	9(4.3)
Unknown	6(9.7)	7(9.7)	4(5.3)	13(9.7)	17(8.1)
Presence of Uveitis at Baseline by Slit					
No	57(91.9)	67(93.1)	72(96.0)	124(92.5)	196(93.8)
Yes	5(8.1)	4(5.6)	2(2.7)	9(6.7)	11(5.3)
Unknown	0(0.0)	1(1.4)	1(1.3)	1(0.7)	2(1.0)
Onset Type of Disease					
Pauci-articular	28(45.2)	35(48.6)	37(49.3)	63(47.0)	100(47.8)
Poly-articular	28(45.2)	34(47.2)	29(38.7)	62(46.3)	91(43.5)
Systemic	6(9.7)	3(4.2)	9(12.0)	9(6.7)	18(8.6)
Current Type of Disease by Investigator					
Pauci-articular	22(35.5)	31(43.1)	33(44.0)	53(39.6)	86(41.1)
Poly-articular	40(64.5)	41(56.9)	42(56.0)	81(60.4)	123(58.9)
Systemic	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Joints with Active Arthritis at Baseline					
<=4 Joints	34(54.8)	39(54.2)	49(65.3)	73(54.5)	122(58.4)
>=5 Joints	28(45.2)	33(45.8)	26(34.7)	61(45.5)	87(41.6)
JRA Duration (Months)					
N	62	72	75	134	209
Mean	34.0	31.7	37.9	32.8	34.6
SD	33.6	41.8	44.8	38.1	40.6
Min	0.0	0.0	0.0	0.0	0.0
Max	125.9	186.8	184.2	186.8	186.8

Source Data: Section 15, Tables 15. 1.4: 1, 15. 1.4: 3 and 15.1.4: 9

Source: Table 11.2:2 of sponsor's analysis

Table 4: Disposition of Patients
Study #107.208 (Twelve Weeks Data)

	Mel L	Mel H	Nap	Total
Treated	73	74	78	225
Continued	70	68	72	210
Discontinued due to Adverse Event (AE)	1	1	3	5
Discontinued due to lack of efficacy	0	1	2	3
Discontinued due to administrative reasons	2	4	1	7
Discontinued due to other reasons	0	0	0	0

Source: Table 10.1:1 of sponsor's analysis

Table 5: Demographic Characteristics
Study #107.208

	Mel L (N=73)	Mel H (N=74)	Nap (N=78)	Total (N=225)
Age (years)	8.9 ± 3.8	9.0 ± 3.9	7.5 ± 3.7	8.5 ± 3.9
Age 0 – 6 years (n)	23 (31.5%)	20 (27.0%)	37 (47.4%)	80 (35.6%)
Age 7 – 16 years (n)	50 (68.5%)	54 (73.0%)	41 (52.6%)	145 (64.4%)
Weight (kg)	33.8 ± 14.9	32.9 ± 14.9	28.8 ± 15.4*	31.8 ± 15.2*
Height (cm)	136.5 ± 22.5**	133.7 ± 23.1**	126.7 ± 21.8**	132.2 ± 22.7**
Sex male	24 (32.9%)	25 (33.8%)	18 (23.1%)	67 (29.8%)
Sex female	49 (67.1%)	49 (66.2%)	60 (76.9%)	158 (70.2%)

* N=76, N=223, respectively
** N=71,N=73,N=76, N=220, respectively

Source: Table 11.2:1 of sponsor's analysis

Table 6: History of Diagnosis Under Study
Study #107.208

		Mel L (N=73)	Mel H (N=74)	Nap (N=78)	Total (N=225)
Duration of disease [months]		41.6 ± 40.6	30.0 ± 33.4	27.7 ± 24.9	33.0 ± 33.8
Presence of uveitis		9 (12.3%)	7 (9.5%)	6 (7.7%)	22 (9.8%)
Trial diagnosis onset type	Pauciarticular	60 (82.2%)	59 (79.7%)	56 (71.8%)	175 (77.8%)
	Polyarticular	13 (17.8%)	12 (16.2%)	21 (26.9%)	46 (20.4%)
	Systemic	0	3 (4.1%)	1 (1.3%)	4 (1.8%)
Trial diagnosis recent type	Pauciarticular	49 (67.1%)	42 (56.8%)	46 (59.0%)	137 (60.9%)
	Polyarticular	24 (32.9%)	32 (43.2%)	32 (41.0%)	88 (39.1%)
	Systemic	0	0	0	0

Source: Table 11.2:2 of sponsor's analysis

Table 7: Disease Activity at Baseline
Study #107.208

Mean ± SD	Mel L (N=73)	Mel H (N=74)	Nap (N=78)	Mel T* (N=147)	p-value
Global assessment disease activity investigator (mm)	37.1 ± 19.6	38.5 ± 21.6	37.6 ± 17.9	37.8 ± 20.6	0.9032
Parent global assessment of overall well-being (mm)	36.9 ± 20.1	38.7 ± 23.3	38.0 ± 19.5	37.8 ± 21.7	0.8624
Childhood Health Assessment Questionnaire (unit)	0.64 ± 0.59	0.76 ± 0.64	0.80 ± .061	0.70 ± 0.62	0.2318
Number of active joints at baseline (N)	6.22 ± 8.37	7.28 ± 8.28	6.68 ± 7.86	6.76 ± 8.31	0.7305
Number of joints with LOM (N)	6.10 ± 8.50	6.65 ± 7.86	6.50 ± 7.98	6.37 ± 8.16	0.9128
ESR (mm/h Westergren)	16.2 ± 14.7	21.4 ± 22.8	20.5 ± 18.6	18.8 ± 19.3	0.2089
Parents global assessment of arthritis (mm)	40.8 ± 21.9	42.7 ± 22.8	44.0 ± 22.0	41.7 ± 22.3	0.6761
Parents global assessment of pain (mm)	35.0 ± 22.4	39.0 ± 24.6	38.1 ± 23.4	37.1 ± 23.6	0.5592
Childrens assessment of discomfort (FAS)	0.46 ± 0.25	0.45 ± 0.25	0.45 ± 0.24	0.45 ± 0.25	0.9758

* Mel T = pooled meloxicam groups

Source: Table 11.2:3 of sponsor's analysis

Table 8: Patient Disposition
Study #107.208 (One year data)

	Mel L	Mel H	Nap	Total
Treated	73 (100%)	74 (100%)	78 (100%)	225 (100%)
Planned Treatment Duration Completed*	58 (79.5%) 70 (95.9%)	63 (85.1%) 68 (91.9%)	61 (78.2%) 72 (92.3%)	182 (80.9%) 210 (93.3%)
Discontinued due to Adverse Event (AE)*	7 (9.6%) 1 (1.4%)	3 (4.1%) 1 (1.4%)	10 (12.8%) 3 (3.8%)	20 (8.9%) 5 (2.2%)
Discontinued due to lack of efficacy*	2 (2.7%) 0	1 (1.4%) 1 (1.4%)	3 (3.8%) 2 (2.6%)	6 (2.7%) 3 (1.3%)
Discontinued due to administrative reasons*	4 (5.5%) 2 (2.7%)	5 (6.8%) 4 (5.4%)	4 (5.1%) 1 (1.3%)	13 (5.8%) 7 (3.1%)
Discontinued due to other reasons*	2 (2.7%) 0	2 (2.7%) 0	0 0	4 (1.8%) 0

Source: Appendix 16.1.9.2, Table 1.1 and U03-1429, section 10, Table 10.1: 1
*The first row is related to the whole trial, the second row to the first 12 weeks

Source: Table 10.1:1

Table 9: Responder Rate Over Visits – ACR WCA
Assuming All Dropouts as Non-Responders
Study #107.208 (One year)

		Responder WCA				Total	
		No		Yes			
		N	%	N	%	N	%
Treatment	Visit Number						
(b) (4)							
Melox Low	Week 12	28	38.36	45	61.64	73	100.00
	Month 6	26	35.62	47	64.38	73	100.00
	Month 9	26	35.62	47	64.38	73	100.00
	Month 12 (EOT)	23	31.51	50	68.49	73	100.00
Naproxen	Week 12	28	35.90	50	64.10	78	100.00
	Month 6	31	39.74	47	60.26	78	100.00
	Month 9	32	41.03	46	58.97	78	100.00
	Month 12 (EOT)	29	37.18	49	62.82	78	100.00
(b) (4)							

Source: Table 6.1.25 of sponsor's analysis

Table 10: Disposition of Patients
Study #107.162

Enrolled	37
Randomized	36
PK+PD	18
PD	18
Prematurely discontinued during PD Phase	2
Completed 12 weeks	34
Prematurely discontinued during PD Phase	3
Completed 52 weeks	31

Source: Figure 10.1:1 of sponsor's analysis

Table 11: Demographic Data for All Patients
Study #107.162

		Total N = 36	Germany N = 13	Mexico N = 23
Age (years)		8.4 ± 3.7	6.1 ± 2.7	9.8 ± 3.5
Age group	**2-6 years**	9 (25.0 %)	6 (46.2 %)	3 (13.0 %)
	7-16 years	27 (75.0 %)	7 (53.8 %)	20 (87 %)
Height (cm)		126.7 ± 19.6	119.8 ± 16.8	130.7 ± 20.4
Sex	**male**	14 (38.9 %)	7 (53.8 %)	7 (30.4 %)
	female	22 (61.1 %)	6 (46.2 %)	16 (69.6 %)
Weight (kg)		27.19 ± 11.8	24.32 ± 10.1	28.81 ± 12.58

Source: Table 11.2:1 of sponsor's analysis

Table 12: History of Trial Indication JRA for All Patients
Study 107.162

	Total N = 36	Germany N = 13	Mexico N = 23
Duration of disease (years)	2.5 ± 2.4	2.1 ± 2.8	2.7 ± 2.1
Duration of disease (months)	29.7 ± 28.3	25.5 ± 33.7	32.2 ± 25.2
Number of affected joints	4.9 ± 5.4	1.8 ± 1.0	6.7 ± 6.0
Trial diagnoses onset type			
pauciarticular	24 (66.7 %)	12 (92.3 %)	12 (52.2 %)
polyarticular	12 (33.3 %)	1 (7.7 %)	11 (47.8 %)
systemic	0	0	0
Trial diagnoses current type			
pauciarticular	14 (38.9 %)	10 (76.9 %)	4 (17.4 %)
polyarticular	22 (61.1 %)	3 (23.1 %)	19 (82.6 %)
systemic	0	0	0

Source: Table 11.2:2 of sponsor's analysis

Table 13: Summary of Adverse Events Experienced by More Than or Equal to 2% of the Patients Safety Population Study #107.235

MedDRA System Organ Class / MeDRA Preferred Term	Meloxicam Low				Meloxicam High				Naproxen				Open Label	
	.125 mg		.25 mg		.25 mg		.375 mg		10 mg		15 mg		.375 mg	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Treated	62	100.0	61	100.0	72	100.0	67	100.0	75	100.0	74	100.0	191	100.0
Total with any Adverse Event	30	48.4	28	45.9	45	62.5	33	49.3	36	48.0	42	56.8	96	50.3
Blood and lymphatic system disorders	0	0.0	0	0.0	3	4.2	0	0.0	0	0.0	0	0.0	1	0.5
Lymphadenopathy	0	0.0	0	0.0	3	4.2	0	0.0	0	0.0	0	0.0	0	0.0
Ear and labyrinth disorders	1	1.6	1	1.6	0	0.0	2	3.0	0	0.0	0	0.0	1	0.5
Ear pain	1	1.6	1	1.6	0	0.0	2	3.0	0	0.0	0	0.0	0	0.0
Eye disorders	1	1.6	0	0.0	1	1.4	1	1.5	2	2.7	4	5.4	3	1.6
Uveitis NOS	1	1.6	0	0.0	1	1.4	0	0.0	0	0.0	2	2.7	1	0.5
Gastrointestinal disorders	12	19.4	4	6.6	16	22.2	8	11.9	16	21.3	15	20.3	19	9.9
Abdominal pain NOS	0	0.0	0	0.0	2	2.8	0	0.0	1	1.3	5	6.8	1	0.5
Abdominal pain upper	3	4.8	2	3.3	5	6.9	1	1.5	5	6.7	3	4.1	3	1.6
Constipation	0	0.0	0	0.0	0	0.0	2	3.0	2	2.7	2	2.7	1	0.5
Diarrhoea NOS	3	4.8	1	1.6	4	5.6	0	0.0	2	2.7	2	2.7	3	1.6
Dyspepsia	1	1.6	0	0.0	1	1.4	2	3.0	1	1.3	1	1.4	1	0.5
Mouth ulceration	0	0.0	0	0.0	0	0.0	0	0.0	2	2.7	1	1.4	0	0.0
Nausea	2	3.2	0	0.0	3	4.2	1	1.5	2	2.7	1	1.4	0	0.0
Pharyngolaryngeal pain	2	3.2	1	1.6	1	1.4	2	3.0	0	0.0	2	2.7	4	2.1
Toothache	0	0.0	0	0.0	2	2.8	1	1.5	0	0.0	1	1.4	1	0.5
Vomiting NOS	5	8.1	3	4.9	5	6.9	0	0.0	4	5.3	1	1.4	5	2.6
General disorders and administration site conditions	5	8.1	1	1.6	0	0.0	4	6.0	4	5.3	9	12.2	14	7.3
Pyrexia	3	4.8	1	1.6	0	0.0	4	6.0	3	4.0	5	6.8	9	4.7
Immune system disorders	0	0.0	2	3.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Seasonal allergy	0	0.0	2	3.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Source: Table 12.2.2:2 of sponsor's analysis

Table 13 (Continued): Summary of Adverse Events Experienced by More Than or Equal to 2% of the Patients
Safety Population
Study #107.235

MedDRA System Organ Class / MedDRA Preferred Term	Meloxicam Low				Meloxicam High				Naproxen				Open Label	
	.125 mg		.25 mg		.25 mg		.375 mg		10 mg		15 mg		.375 mg	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Infections and infestations	6	9.7	15	24.6	16	22.2	18	26.9	13	17.3	26	35.1	59	30.9
Fungal infection NOS	0	0.0	0	0.0	2	2.8	3	4.5	0	0.0	0	0.0	0	0.0
Influenza	0	0.0	1	1.6	3	4.2	0	0.0	2	2.7	4	5.4	8	4.2
Localised infection	0	0.0	0	0.0	1	1.4	0	0.0	3	4.0	0	0.0	2	1.0
Nasopharyngitis	1	1.6	2	3.3	1	1.4	1	1.5	2	2.7	4	5.4	7	3.7
Otitis media NOS	0	0.0	1	1.6	0	0.0	1	1.5	1	1.3	1	1.4	4	2.1
Pharyngitis NOS	0	0.0	0	0.0	0	0.0	6	9.0	1	1.3	2	2.7	6	3.1
Pharyngitis streptococcal	0	0.0	1	1.6	0	0.0	0	0.0	1	1.3	2	2.7	4	2.1
Respiratory tract infection NOS	1	1.6	1	1.6	1	1.4	1	1.5	1	1.3	1	1.4	6	3.1
Respiratory tract infection viral NOS	0	0.0	2	3.3	0	0.0	2	3.0	0	0.0	1	1.4	5	2.6
Upper respiratory tract infection NOS	1	1.6	2	3.3	4	5.6	2	3.0	1	1.3	3	4.1	11	5.8
Urinary tract infection NOS	1	1.6	0	0.0	0	0.0	0	0.0	0	0.0	3	4.1	2	1.0
Injury, poisoning and procedural complications	2	3.2	3	4.9	4	5.6	2	3.0	2	2.7	3	4.1	11	5.8
Abrasion NOS	0	0.0	1	1.6	1	1.4	1	1.5	0	0.0	0	0.0	5	2.6
Musculoskeletal and connective tissue disorders	5	8.1	3	4.9	2	2.8	5	7.5	3	4.0	4	5.4	13	6.8
Arthralgia	4	6.5	2	3.3	2	2.8	2	3.0	2	2.7	1	1.4	4	2.1
Juvenile rheumatoid arthritis	0	0.0	0	0.0	0	0.0	2	3.0	0	0.0	0	0.0	3	1.6
Neck pain	0	0.0	2	3.3	0	0.0	0	0.0	0	0.0	1	1.4	0	0.0
Pain in limb	1	1.6	2	3.3	0	0.0	0	0.0	0	0.0	2	2.7	1	0.5
Nervous system disorders	8	12.9	7	11.5	8	11.1	3	4.5	6	8.0	5	6.8	15	7.9
Headache NOS	8	12.9	7	11.5	6	8.3	1	1.5	4	5.3	4	5.4	11	5.8

Source: Table 12.2.2:2 of sponsor's analysis

Table 13 (Continued): Summary of Adverse Events Experienced by More Than or Equal to 2% of the Patients Safety Population Study #107.235

MedDRA System Organ Class / MeDRA Preferred Term	Meloxicam Low				Meloxicam High				Naproxen				Open Label	
	.125 mg		.25 mg		.25 mg		.375 mg		10 mg		15 mg		.375 mg	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Psychiatric disorders	0	0.0	1	1.6	3	4.2	0	0.0	0	0.0	1	1.4	2	1.0
Insomnia	0	0.0	0	0.0	3	4.2	0	0.0	0	0.0	1	1.4	1	0.5
Respiratory, thoracic and mediastinal disorders	3	4.8	3	4.9	4	5.6	4	6.0	5	6.7	5	6.8	14	7.3
Cough	2	3.2	2	3.3	1	1.4	1	1.5	0	0.0	2	2.7	4	2.1
Dyspnoea NOS	0	0.0	1	1.6	0	0.0	0	0.0	2	2.7	0	0.0	1	0.5
Rhinitis NOS	1	1.6	0	0.0	1	1.4	1	1.5	0	0.0	2	2.7	3	1.6
Rhinorrhoea	0	0.0	0	0.0	1	1.4	2	3.0	0	0.0	0	0.0	2	1.0
Skin and subcutaneous tissue disorders	4	6.5	4	6.6	6	8.3	6	9.0	4	5.3	3	4.1	9	4.7
Rash NOS	0	0.0	0	0.0	3	4.2	2	3.0	1	1.3	1	1.4	2	1.0

Source Data: Section 15, Table 15.3.2: 1

Source: Table 12.2.2:2 of sponsor's analysis

Table 14: Summary of frequently Occurred AEs by Organs Study #107.208

MedDRA System Organ Class	Mel L	Mel H	Nap
Gastrointestinal	17 (23.3%)	**20 (27.0%)**	16 (20.5%)
Respiratory	12 (16.4%)	13 (17.6%)	**18 (23.1%)**
General	9 (12.3%)	8 (10.8%)	**12 (15.4%)**
Infections and Infestations	19 (26.0%)	19 (25.7%)	**28 (35.9%)**
Skin	1 (1.4%)	3 (4.1%)	**6 (7.7%)**
Musculo-skeletal	4 (5.5%)	**14 (18.9%)**	5 (6.4%)
Nervous system	**8 (11.0%)**	4 (5.4%)	2 (2.6%)

Source: Table 12.2.2.2:1 of sponsor's analysis

Table 15: Summary of Frequently Occurred AEs by Decreasing Frequency
Safety Population
Study # 107.208

MedDRA Preferred Term	Mel L	Mel H	Nap
Rhinitis NOS	7 (9.6%)	7 (9.5%)	**11 (14.1%)**
Pyrexia	8 (11.0%)	8 (10.8%)	**9 (11.5%)**
Cough	5 (6.8%)	6 (8.1%)	**9 (11.5%)**
Headache NOS	**8 (11.0%)**	4 (5.4%)	2 (2.6%)
Pharyngitis	4 (5.5%)	3 (4.1%)	**7 (9.0%)**
Diarrhea NOS	**6 (8.2%)**	5 (6.8%)	4 (5.1%)
Bronchitis NOS	2 (2.7%)	1 (1.4%)	**6 (7.7%)**
Pharyngolaryngeal pain	**5 (6.8%)**	4 (5.4%)	2 (2.6%)
Nasopharyngitis	2 (2.7%)	**4 (5.4%)**	3 (3.8%)
Joint swelling	1 (1.4%)	**4 (5.4%)**	1 (1.3%)

Source: Table 12.2.3:1 of sponsor's analysis

Table 16: Summary of Adverse Events
Study #107.162 (12 Weeks data)

WHO System Organ Class WHO Preferred Term	Treatment at Onset					
	Screening		Meloxicam Susp.		Total	
	N	%	N	%	N	%
Summary data						
Total treated	37	100.0	36	100.0	37	100.0
Total with any adverse event	3	8.1	24	66.7	24	64.9
Body as a whole - general disorders	**0**	**0.0**	**8**	**22.2**	**8**	**21.6**
Accident household	0	0.0	1	2.8	1	2.7
Fever	0	0.0	3	8.3	3	8.1
Influenza-like symptoms	0	0.0	4	11.1	4	10.8
Oedema mouth	0	0.0	1	2.8	1	2.7
Central & peripheral nervous system disorders	**0**	**0.0**	**1**	**2.8**	**1**	**2.7**
Headache	0	0.0	1	2.8	1	2.7
Collagen disorders	**0**	**0.0**	**1**	**2.8**	**1**	**2.7**
Arthritis rheumatoid Aggravated	0	0.0	1	2.8	1	2.7
Gastro-intestinal system disorders	**2**	**5.4**	**11**	**30.6**	**12**	**32.4**
Abdominal pain	2	5.4	3	8.3	4	10.8
Constipation	1	2.7	0	0.0	1	2.7
Diarrhoea	0	0.0	7	19.4	7	18.9
Food poisoning	0	0.0	3	8.3	3	8.1
Gastroenteritis	0	0.0	2	5.6	2	5.4
Nausea	0	0.0	2	5.6	2	5.4
Vomiting	1	2.7	1	2.8	1	2.7
Musculo-skeletal system disorders	**0**	**0.0**	**1**	**2.8**	**1**	**2.7**
Arthritis aggravated	0	0.0	1	2.8	1	2.7
Reproductive disorders, female	**0**	**0.0**	**1**	**2.8**	**1**	**2.7**
Vulva disorder	0	0.0	1	2.8	1	2.7
Resistance mechanism disorders	**0**	**0.0**	**4**	**11.1**	**4**	**10.8**
Abscess	0	0.0	1	2.8	1	2.7
Infection	0	0.0	1	2.8	1	2.7
Infection parasitic	0	0.0	1	2.8	1	2.7
Varicella	0	0.0	1	2.8	1	2.7

Source: Table 12.2.2:1 of sponsor's analysis

Table 16 (Continued): Summary of Adverse Events
Study # 107.162

WHO System Organ Class WHO Preferred Term	Treatment at Onset					
	Screening		Meloxicam Susp.		Total	
	N	%	N	%	N	%
Respiratory system disorders	**1**	**2.7**	**12**	**33.3**	**13**	**35.1**
Bronchitis	0	0.0	3	8.3	3	8.1
Coughing	0	0.0	1	2.8	1	2.7
Pharyngitis	0	0.0	10	27.8	10	27.0
Rhinitis	0	0.0	1	2.8	1	2.7
Upper resp. tract infection	1	2.7	0	0.0	1	2.7
skin and appendages disorders	**0**	**0.0**	**2**	**5.6**	**2**	**5.4**
Nail disorder	0	0.0	2	5.6	2	5.4
Urinary system disorders	**0**	**0.0**	**1**	**2.8**	**1**	**2.7**
Dysuria	0	0.0	1	2.8	1	2.7

Source: Table 12.2.2:1 of sponsor's analysis

Table 17: Subgroup Analysis of ACR Pediatric 30 Responses at Week 12
ITT Patients
Study #107.235

		Meloxicam L*		(b) (4)	Naproxen		(b) (4)
Subgroup		N	Responder		N	Responder	
Current Type Inv.	Pauciarticular	22	15 (68.2)		33	23 (69.7)	
	Polyarticular	40	28 (70.0)		42	28 (66.7)	
Active Joints at	<= 4 Joints	34	24 (70.6)		49	34 (69.4)	
Baseline	>= 5 Joints	28	19 (67.9)		26	17 (65.4)	
Country	Brazil	4	3 (75.0)		5	3 (60.0)	
	Mexico	3	1 (33.3)		5	4 (80.0)	
	Argentina	6	4 (66.7)		6	5 (83.3)	
	Ukraine	14	11 (78.6)		13	12 (92.3)	
	USA	35	24 (68.6)		46	27 (58.7)	
Age	<=6	19	15 (78.9)		22	15 (68.2)	
	7-17	43	28 (65.1)		53	36 (67.9)	
Gender	Male	13	8 (61.5)		20	13 (65.0)	
	Female	49	35 (71.4)		55	38 (69.1)	
Methotrexate use	No	39	26 (66.7)		51	38 (74.5)	
	Yes	23	17 (73.9)		24	13 (54.2)	

Source: Table 11.4.1.1:2 of sponsor's analysis

Table 18: Responder Rate by Age Group (Week 12)
Study #107.208

		Responder (LOCF)					
		No		Yes		Total	
		N	%	N	%	N	%
Treatment	Age Group						
Melox Low	0 - 6 Years	9	39.13	14	60.87	23	100.00
	7 - 16 Years	18	36.00	32	64.00	50	100.00
							(b) (4)
Naproxen	0 - 6 Years	15	40.54	22	59.46	37	100.00
	7 - 16 Years	13	31.71	28	68.29	41	100.00
							(b) (4)

Source: Table 6.1.3 of sponsor's analysis

Table 19: Responder Rate by Gender (Week 12)
Study #107.208

		Responder (LOCF)					
		No		Yes		Total	
		N	%	N	%	N	%
Treatment	Sex						
Melox Low	Male	7	29.17	17	70.83	24	100.00
	Female	20	40.82	29	59.18	49	100.00
							(b) (4)
Naproxen	Male	6	33.33	12	66.67	18	100.00
	Female	22	36.67	38	63.33	60	100.00
							(b) (4)

Source: Table 6.1.2 of sponsor's analysis

Table 20: Responder Rates for Treatment Groups Classified According to Their Number of Active Joints at Baseline
Study #107.208

Treatment	Number of joints with active arthritis	Total N (=100%)	Responder (%)
Mel L (N=73)	0 - 2 Joints	21	10 (47.6%)
	3 - 4 Joints	24	17 (70.8%)
	> 4 Joints (Poly)	28	19 (67.9%)
	Pauci	45	27 (60.0%)
			(b) (4)
Nap (N=78)	0 - 2 Joints	23	15 (65.2%)
	3 - 4 Joints	28	16 (57.1%)
	> 4 Joints (Poly)	27	19 (70.4%)
	Pauci	51	31 (60.8%)
			(b) (4)

Source: Table 14.2:1 of sponsor's analysis

Table 21: Treatment Results in Secondary Efficacy Endpoints Classified by Poly-articular and Pauci-articular Assessment
Study #107.208

Parameter	Mel L (N=73)		(b) (4)	Nap (N=78)	
	Pauci (N=49)	Poly (N=24)		Pauci (N=46)	Poly (N=32)
Global assessment of disease activity by investigator	-15.61	-21.96		-11.35	-23.75
Parent global assessment of overall well-being	-12.18	-23.13		-13.04	-19.00
Childhood Health Assessment Questionnaire	-0.27	-0.28		-0.24	-0.39
Number of joints with active arthritis	-1.80	-6.25		-1.41	-4.88
Number of joints with limited range of motion	-1.53	-5.21		-1.17	-4.25
ESR	0.92	-0.30		0.27	-2.77
Parents global assessment of arthritis	-16.90	-23.50		-19.15	-21.13
Parents global assessment of pain	-14.73	-22.79		-18.87	-14.97

Source: Table 14.2:4 of sponsor's analysis

Table 22: Number of Responders per Treatment Group at Week 12 by Sub-Group
Study #107.235
Reviewer's Table

subgroup	dose	a1	n1	a2	n2	L975%	U975%
Female							(b) (4)
Male							
Female	Mel_L Vs. Nap	35	49	38	55	-18.20	22.57
Male	Mel_L Vs. Nap	8	13	13	20	-42.69	34.30
0 - 6 Years							(b) (4)
7 - 11 Years							
12 - 17 Years							
0 - 6 Years	Mel_L Vs. Nap	15	19	15	22	-21.98	41.34
7 - 11 Years	Mel_L Vs. Nap	15	20	16	24	-23.98	38.89
12 - 17 Years	Mel_L Vs. Nap	13	23	20	29	-42.05	18.41
Asian							(b) (4)
Black							
White							
Asian	Mel_L Vs. Nap	1	3	4	5	-94.62	38.87
Black	Mel_L Vs. Nap	5	5	3	6	-17.48	90.95
White	Mel_L Vs. Nap	37	54	44	64	-19.84	19.35
Pauci-articular							(b) (4)
Poly-articular							
Pauci-articular	Mel_L Vs. Nap	15	22	23	33	-31.73	26.58
Poly-articular	Mel_L Vs. Nap	28	40	28	42	-20.91	26.36
<=4 Joints							(b) (4)
>=5 Joints							
<=4 Joints	Mel_L Vs. Nap	24	34	34	49	-22.88	23.69
>=5 Joints	Mel_L Vs. Nap	19	28	17	26	-26.59	31.61
Methotrexate No							(b) (4)
Methotrexate Yes							
Methotrexate No	Mel_L Vs. Nap	26	39	38	51	-27.40	11.37
Methotrexate Yes	Mel_L Vs. Nap	17	23	13	24	-8.70	46.02

Table 23: Number of Responders per Treatment Group at Week 12 by Sub-Group
Study #107.208
Reviewer's Table

subgroup	dose	a1	n1	a2	n2	L975c	U975c
Female							(b) (4)
Male							
Female	Mel_L Vs. Nap	29	49	38	60	-22.82	14.29
Male	Mel_L Vs. Nap	17	24	12	18	-24.76	34.61

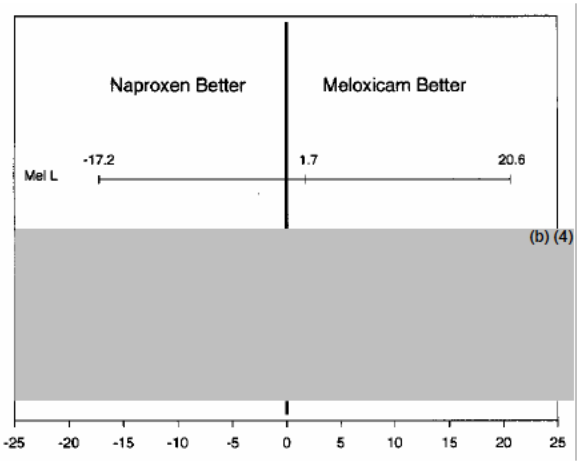
0 - 6 Years	[redacted]						
7 - 11 Years							
12 - 17 Years							
0 - 6 Years	Mel_L Vs. Nap	14	23	22	37	-24.72	26.52
7 - 11 Years	Mel_L Vs. Nap	18	28	17	26	-26.95	24.71
12 - 17 Years	Mel_L Vs. Nap	14	22	11	15	-39.04	22.48
Not-Specified	[redacted]						
White							
Asian	Mel_L Vs. Nap	0	1	0	0	.	.
Not-Specified	Mel_L Vs. Nap	5	7	7	8	-60.20	29.52
White	Mel_L Vs. Nap	41	65	43	70	-14.95	18.40
Pauci-articular	[redacted]						
Poly-articular							
Pauci-articular	Mel_L Vs. Nap	30	49	27	46	-17.76	22.26
Poly-articular	Mel_L Vs. Nap	16	24	23	32	-30.80	19.57
<=4 Joints	[redacted]						
>=5 Joints							
<=4 Joints	Mel_L Vs. Nap	27	45	31	51	-20.58	19.09
>=5 Joints	Mel_L Vs. Nap	19	28	19	27	-27.18	22.46
Methotrexate No	[redacted]						
Methotrexate Yes							
Methotrexate No	Mel_L Vs. Nap	37	58	37	55	-21.14	14.52
Methotrexate Yes	Mel_L Vs. Nap	9	15	13	23	-29.53	34.66

Table 24: Number of Responders per Treatment Group at Week 12 by Sub-Group
Studies #107.235 and #107.208 Integrated
Reviewer's Table

subgroup	dose	a1	n1	a2	n2	L975c	U975c
Female	Mel_L Vs. Nap	64	98	76	115	-15.38	13.87
Male	Mel_L Vs. Nap	25	37	25	38	-22.88	26.24
Female	[redacted]						
Male							
0 - 6 Years	Mel_L Vs. Nap	29	42	37	59	-15.74	27.43
7 - 11 Years	Mel_L Vs. Nap	33	48	33	50	-19.43	24.01
12 - 17 Years	Mel_L Vs. Nap	27	45	31	44	-29.39	16.76
0 - 6 Years	[redacted]						
7 - 11 Years							
12 - 17 Years							
Asian	Mel_L Vs. Nap	1	4	4	5	-95.64	29.43
Black	Mel_L Vs. Nap	5	5	3	6	-9.02	88.30
Not-S	Mel_L Vs. Nap	5	7	7	8	-65.22	35.60
White	Mel_L Vs. Nap	78	119	87	134	-12.89	14.14

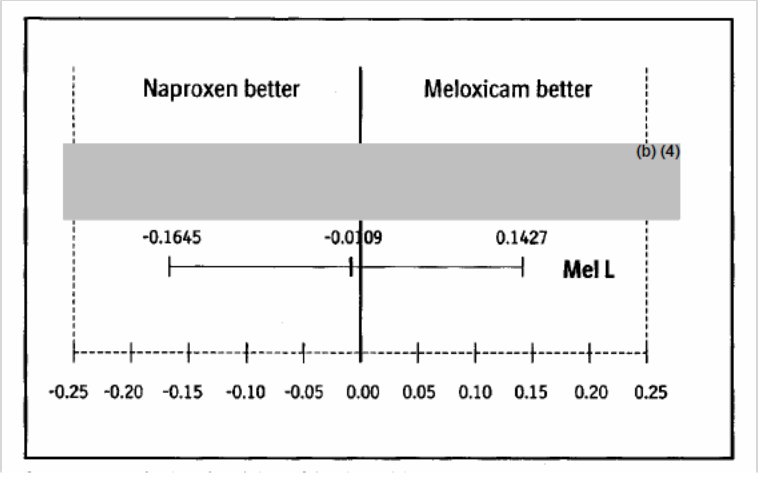
Asian							(b) (4)
Black							
Not-S							(b) (4)
White							
Pauci-articular	Mel_L Vs. Nap	45	71	50	79	-18.06	18.08
Poly-articular	Mel_L Vs. Nap	44	64	51	74	-18.19	18.04
Pauci-articular							(b) (4)
Poly-articular							
<=4 Joints	Mel_L Vs. Nap	51	79	65	100	-16.80	15.88
>=5 Joints	Mel_L Vs. Nap	38	56	36	53	-20.22	20.20
<=4 Joints							(b) (4)
>=5 Joints							
Methotrexate No	Mel_L Vs. Nap	63	97	75	106	-20.67	9.11
Methotrexate Yes	Mel_L Vs. Nap	26	38	26	47	-11.24	35.95
Methotrexate No							(b) (4)
Methotrexate Yes							

Figure 1
Point Estimates of Treatment Differences and 95% Confidence Intervals for Week 12 ACR
ACR Pediatric 30 Response
ITT Patients
Study #107.235 (U04-3227-01)



Source: Figure 11.4.1.1:2 of sponsor's analysis

Figure 2
Point Estimates of Treatment Differences and 95% Confidence Intervals for Week 12 ACR Pediatric 30 Response
ITT Patients
Study 107.208



Source: Figure 11.4.1.1:2 of sponsor's analysis

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

/s/

Atiar Rahman
7/14/05 12:36:56 PM
BIOMETRICS

Thomas Permutt
7/14/05 05:17:23 PM
BIOMETRICS
concur