CLINICAL REVIEW

Application Type	20-938/S-013 21-530/S-001
Submission Number	013
Submission Code	SE1
Letter Date	February 18, 2005
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Reviewer Name	Tatiana Oussova
Review Completion Date	July 15, 2005
Established Name	Meloxicam
(Proposed) Trade Name	Mobic
Therapeutic Class	NSAID/COX-2
Applicant	Boehringer Ingelheim
Priority Designation	P
Formulation	Tablets 7.5 mg and 15 mg, Oral Suspension 7.5 mg/5 mL
Indication	Juvenile Rheumatoid Arthritis (JRA)
Intended Population	Pediatric Population 2-17 yrs.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

With this submission, Boehringer Ingelheim is seeking approval for Mobic (meloxicam) Tablets 7.5 mg and 15 mg and Oral Suspension 7.5 mg/5 mL administered once daily for the treatment of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in pediatric population aged 2 through 17 years (b) (4) Mobic is approved in the U.S. for the relief of the signs and symptoms of osteoarthritis (OA) and the adult rheumatoid arthritis (RA). Establishing efficacy in JRA for meloxicam is based on having demonstrated efficacy in adult RA. The Sponsor has submitted this supplemental NDA in response to a Pediatric Written Request (WPR) dated Nov 22, 2004. The studies in the pediatric program were performed in response to and in accordance with the WR.

In this submission, the Sponsor provided an adequate evidence of the efficacy of meloxicam 0.125 mg/kg/day (b) (4) for the treatment of the signs and symptoms of JRA. Three doses of meloxicam were studied (0.125 mg/kg/day, 0.250 mg/kg/day and 0.375 mg/kg/day) and compared against active control naproxen in doses 10 and 15 mg/kg/day. (b) (4)

(b) (4)

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This reviewer concludes that there is an adequate evidence of the efficacy and acceptable safety of meloxicam 0.125 mg/kg/day (b) (4) for the treatment of the signs and symptoms of juvenile rheumatoid arthritis and recommends an approval for (b) (4) 0.125 mg/kg/day (b) (4) using tablets or oral suspension formulation.

1.2 Recommendation on Postmarketing Actions

The Sponsor needs to continue to monitor safety data of the product including use in the pediatric population.

1.3.1 Brief Overview of Clinical Program

According to the WPR, one pivotal study **107.235** and one supportive study **107.208** were submitted in support of the JRA indication. Both studies were double blind, three-arm active controlled (two dosages of meloxicam and one dosage of naproxen) of three or more months duration evaluating the efficacy, safety and dose response of meloxicam oral suspension in pauci- and polyarticular JRA patients. In addition, PK study 107.168 was also included with this submission to provide additional data on safety.

Both efficacy studies utilized FDA recommended endpoints, had sufficient sample size and were of sufficient duration (12 weeks). In both of these studies, the JRA patients were balanced fairly equally between pauci- and polyarticular arthritis, and were evenly distributed between the ages of 2 and <17 years, with approximately one third of the patients being less than 6 years of age as requested in WPR.

1.3.2 Efficacy

In pivotal trial 107.235, meloxicam at doses of 0.125 (b) (4) mg/kg/d (meloxicam L) (b) (4) is comparable to treatment with the active comparator naproxen, administered 5 mg/kg twice daily and increased to 7.5 mg/kg twice daily throughout the 12 weeks of treatment for the primary efficacy endpoint of the ACR Pediatric 30 responder rate. The responders' rate for the primary endpoint ACR Pediatric 30 responders at Week 12 (%, 90% confidence interval) was (b) (4) 69.4% (57.9, 80.8) and naproxen treatment 68.0% (57.4, 78.6). (b) (4)

Subgroup analysis for effect of arthritis type course, age, gender, and MTX usage on the response to the treatment did not show any significant interaction.

Assessment of the individual components of the ACR core set parameters revealed that the number of joints with active arthritis and investigator's global assessment of overall disease activity had the highest proportion of responders (b) (4). The only core set parameter that did not change substantially over the 12-week course of treatment (b) (4) was the ESR. All other individual core set parameters demonstrated improvement over the 12 weeks of therapy (b) (4).

Additional secondary endpoints assessed showed improvement (b) (4) without significant difference between meloxicam (b) (4) and naproxen group.

In supportive trial 107.208, meloxicam at doses of 0.125 (b) (4) was comparable to treatment with naproxen at a dose of 10 mg/kg/d at 12 weeks of treatment for the primary efficacy endpoint of the ACR Pediatric 30 responder rate. The Pediatric ACR responder rate (%, 90% confidence interval) for (b) (4) meloxicam (b) (4) was 63.0% (51.9, 74.1) (b) (4) compared to 64.1% (53.5, 74.8) for the naproxen dose group. The efficacy response demonstrated during the first 12 weeks was sustained during the 40 week double-blind extension (b) (4).

(b) (4)
(b) (4)

1.3.3 Safety

The meloxicam JRA development program included an overall total of 470 patients with pauci- and polyarticular course JRA studied in 3 Trials: 107.235, 107.208 and 107.162.

Within these 3 trials there were a total of 387 patients with JRA who received meloxicam and a total of 153 patients who received naproxen. Among these patients there were 70 patients who received both naproxen and meloxicam because of the open-label extension design of Trial 107.235 where all patients were administered the highest dose of meloxicam.

There were several analyses performed on data available. The dataset was examined by treatment received (meloxicam vs. naproxen) regardless of dose, duration, or trial design (double-blind or open-label). In addition, integrated data from the 2 controlled trials (107.235 and 107.208) was analyzed by dose and after 4 and 12 weeks of data (short term data). Separate analysis of the data was performed from the 12 week open-label extension (meloxicam 0.375 mg/kg/day) from Trial 107.235 and the up to 1 year data from Trial 107.208 (double-blind) and Trial 107.162 (open-label; meloxicam 0.250 mg/kg/day).

This reviewer concludes that the safety profile of meloxicam is comparable to that of naproxen over the course of these trials. Adverse events were representative of those expected in a pediatric population in general, or as part of the natural history of JRA, or with treatment with nonsteroidal anti-inflammatory agents. Analysis of AEs by subgroup including age, gender, concomitant use of methotrexate, race and disease course (pauci- and polyarticular), did not reveal any readily discernible differences between the meloxicam- and naproxen-treated groups.

Analysis of the safety profile for those patients treated in the trials (either double-blinded or open-labelled) for the long term (up to 1 year) did not suggest any duration of treatment – associated qualitative differences in the AE profile (compared to the short term data).

Assessment for possible growth and development-related adverse events or weight change over time for up to 1 year of treatment does not suggest that meloxicam or naproxen has any significant negative effect on growth and development.

Based on this reviewer's assessment of the data presented with this application, the tolerability and safety profile of meloxicam at doses over the range of 0.125 mg/kg to 0.375 mg/kg once per day is **comparable** to that of naproxen over the range of 10 mg/kg to 15 mg/kg in 2 equally divided doses per day for the treatment of the signs and symptoms of pauci- and polyarticular JRA for up to 1 year as studied in clinical trials with the exception of 0.375 mg/kg/ dose indication that it might increase systolic blood pressure in children.

However, because of the safety concerns raised in reviews of adult RA and OA trials with 22.5 mg meloxicam dose which is equal to 0.375 mg/kg/d pediatric dose and the lack of additional appreciable efficacy with this dose, 0.375 mg/kg/d dose cannot be recommended for an approval for the indication of JRA.

1.3.4 Dosing Regimen and Administration

The meloxicam doses selected for study in the JRA clinical program were derived from the experience with adult doses (7.5 mg, 15 mg and 22.5 mg per day) which had been shown to be effective in rheumatoid arthritis in two 12 week placebo controlled trials (107.258 and 107.183). Based on a 60 kilogram adult, the adult doses discussed above translate on a mg/kg basis to the following pediatric doses: 0.125 mg/kg/d (7.5 mg/d), 0.25 mg/kg/d (15 mg/d), and 0.375 mg/kg/d (22.5 mg/d)

Based on the JRA population PK data, meloxicam oral suspension exposures at 0.125 mg/kg/d, 0.25 mg/kg/d, and 0.375 mg/kg/d in children are comparable to the exposures seen in adults dosed once a day with 7.5 mg, 15 mg and 22.5 mg meloxicam.

Bioequvalency of oral suspension to tablets was established earlier in adult development program therefore both tablets and oral suspension would be approved for use under this application.

This reviewer recommends a (b) (4) dose of 0.125 mg/kg/d. (b) (4) .

1.3.5 Drug-Drug Interactions

No new data was submitted with this supplemental application

1.3.6 Special Populations

Pediatric population was studies under this development program

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Juvenile rheumatoid arthritis (JRA) is a term used in the United States for a heterogeneous group of chronic inflammatory arthritides that occur in childhood.

Juvenile rheumatoid arthritis is defined as the onset before age 16 of persistent synovitis in one or more joints for at least 6 weeks (3 months is preferable), with all other causes being excluded. The prevalence is 1 in 1000 and the incidence is 1.4 in 10,000 in the United States. Although onset before 6 months of age is unusual, the highest frequency occurs between 1 and 3 years of age, especially of the pauciarticular form in girls.

JRA is subdivided into pauciarticular (four or fewer joints), polyarticular (more than four joints), and systemic (accompanied by spiking fevers) onset types, depending upon the presentation in the first 6 months of disease.

Pauciarticular (oligoarticular) JRA, defined as synovitis in four or fewer joints over the first 6 months of symptoms, occurs in 40 to 60 % of children with JRA. The ratio of males to females is 1:6.5; the usual age of onset is 1 to 3 years. Typically, the child has few symptoms and an insidious onset. A quarter of these children will report no pain and come to medical attention after joint swelling is incidentally found. The knee is most frequently involved, followed by the ankle, and then the small joints of the hand, but almost any joint can be affected. Isolated hip or neck arthritis occurs rarely, although it may also portend evolution into ankylosing spondylitis or psoriatic arthritis. Asymptomatic uveitis (inflammation of the uveal tract—iris, ciliary body, and choroid) develops in approximately 20% of children with pauciarticular JRA, and more frequently in patients with a positive antinuclear antibody (ANA) test.

Polyarticular JRA, defined as involvement of at least five joints during the first 6 months, is found in 30 to 40% of children with JRA. Females predominate with two peak ages of onset: 1 to 3 years of age and early adolescence. Both large and small joints can be affected; presentations vary from scattered joint involvement to symmetric synovitis of nearly all joints in the body. Involvement of the cervical spine, hips, shoulders, and temporomandibular joints (TMJ) is common. In most patients, the onset is insidious and accompanied by fatigue. Some patients have low-grade fever, weight loss, and rheumatoid nodules.

Systemic-onset disease, defined as the occurrence of fever and other systemic findings that often precede the onset of joint disease, affects about 10 to 20% of children with JRA.
Males and females are affected equally. The age of onset peaks at 5 to 10 years but spans infancy through adulthood. The key finding is daily fever, which, although erratic, usually spikes once or twice a day, rising above 39.3°C (103°F) and falling to normal. The peak of the fever curve is often in the evening and may be accompanied by intense arthralgia and myalgia. When the

temperature is normal, the child may feel quite well only to appear ill again when the fever spikes. Frequently, the fever precedes arthritis by weeks or months. Because JRA is a diagnosis of exclusion, patients with systemic-onset disease usually have an appropriately extensive evaluation to rule out infection and malignancy.

Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3 carboxamide-1,1-dioxide) is an NSAID of the enolic acid class. The anti-inflammatory activity of meloxicam is produced by inhibition of the enzyme cyclo-oxygenase (COX) resulting in inhibition of prostaglandin biosynthesis. Two isoforms of cyclooxygenase have been detected. The constitutive form (COX-1) is responsible for the cytoprotective and thrombotic actions of prostaglandins whereas COX-2 is induced in fibroblasts, macrophages, synoviocytes, chondrocytes, and some other cells by pro-inflammatory stimuli and cytokines. Meloxicam inhibits the cyclo-oxygenases with IC50 values (concentrations that inhibit an effect by 50%) of 1.9 nanomolar (nM) and 5.77 nM for COX-2 and COX-1, respectively. Thus, meloxicam shows selectivity with regard to COX-2 inhibition with an IC50 ratio of 0.33 (COX-2 vs. COX-1) compared with a ratio of 33 and 31 for piroxicam and indomethacin, respectively. In addition to COX inhibition, meloxicam inhibits leukocyte migration and influences leukocyte function.

Meloxicam is approved for the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. The recommended once-a- day doses are 7.5 to 15 mg in OA and 15 mg in RA. Meloxicam is currently available in the US market in the form of tablets and an oral suspension (7.5 mg/5 mL).

2.2 Currently Available Treatment for Indications

The pharmacologic agents used to treat JRA typically are grouped into five categories:

- nonsteroidal anti-inflammatory drugs (NSAIDs)
- slow-acting antirheumatic drugs (SAARDs) or disease-modifying antirheumatic drugs (DMARDs)
- glucocorticoids
- cytotoxic or immunosuppressive agents
- biologic response modifiers

NSAIDs play an important role in the treatment of Juvenile rheumatoid Arthritis (JRA), especially during its initial stages. In approximately one third of patients, the disease is controlled satisfactory with NSAIDs alone. In the majority of patients, NSAIDs are used in conjunction with disease-modifying anti-rheumatic agents (DMARDs) as adjunctive therapy. In practice, it is generally observed that patient responses to NSAIDs are variable and unpredictable. A child may fail to respond to one drug and yet respond to another. Apart from aspirin, only **a few NSAIDs have been approved for use in children (e.g., naproxen, tolmetin, ibuprofen and Vioxx that have been withdrawn from the market) in the USA**.

2.3 Availability of Proposed Active Ingredient in the United States

Meloxicam is currently available in the US market in the form of tablets and an oral suspension (7.5 mg/5 mL).

2.4 Important Issues With Pharmacologically Related Products

Please, see NDA 20-938 and 21-530 reviews.

2.5 Presubmission Regulatory Activity

Please, see NDA 20-938 and 21-530 clinical reviews.

Meloxicam was approved in the United States on April 13, 2000 for the relief of signs and symptoms of osteoarthritis in adults, at doses of 7.5 and 15 mg daily. On July 16, 2004 the 7.5 mg and 15 mg daily doses were also approved for the treatment of signs and symptoms of adult rheumatoid arthritis (RA).

An oral suspension formulation of meloxicam was developed to allow easy, once-daily administration on a weight-adjusted basis for use in children (as well as the elderly and other individuals who have difficulty swallowing capsules or tablets). The oral suspension formulation has been shown to be bioequivalent to meloxicam capsules in healthy adults

(NDA 21-530; approved 1 June 2004). The oral suspension was also shown to be dose-proportional over the dose range equivalent of 7.5 mg, 15 mg, up to 22.5 mg.

As with other NSAIDs, establishing efficacy in JRA for meloxicam is based on having demonstrated efficacy in adult RA. The formulation used in clinical trials supporting the JRA indication has been approved (NDA 21-530) for use in adults.

In August 2004, the sponsor submitted a Proposed Pediatric Study Request containing studies that have been conducted with the purpose of bridging safety and efficacy data from the studies in RA and JRA and that resulted in the FDA issuing a Written Pediatric Request.

In response to a Written Request dated November 22, 2004, the Sponsor submitted a supplement to NDA 20-938/NDA 21-530 for determination of Pediatric Exclusivity and supporting the use of meloxicam tablets and oral suspension in treating the signs and symptoms of JRA. Pediatric Exclusivity was granted on April 13, 2005.

2.6 Other Relevant Background Information

Meloxicam has been given an orphan drug designation (Designation Request # 02-1606; November 22, 2002).

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

There is no additional toxicology, CMC or pharmacology information about meloxicam submitted in this supplement.

Please, see NDA 21-530 and NDA 20-938 reviews.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The JRA development program consisted of 3 clinical trials involving 470 JRA patients conducted using the meloxicam oral suspension formulation (7.5 mg/5 mL).

Study 107.235 (Pivotal Study, conducted in the US and 4 other countries)

The study is a 12 -week randomized double-blind, active-controlled comparison of the safety and efficacy of meloxicam oral suspension compared to naproxen oral suspension in treating the signs and symptoms of JRA with a 12 week open-label extension.

Two doses of meloxicam oral suspension are compared to the labeled dose of naproxen oral suspension. Per FDA request, the study incorporates a forced up-titration of all dose-groups at 4-weeks. All patients in study 107.235 (including those who were randomized to naproxen oral suspension) receive 0.375 mg/kg day meloxicam oral suspension for the duration of the open-label extension. Naproxen **15 mg/kg/day** is a dose closer to that prescribed by most rheumatologists in the US however it exceeds the registered dose of 10 mg/kg/day in some of the European countries.

Study 107.208 (conducted in Europe)

A one year double-blind randomized trial to investigate the efficacy and safety of meloxicam oral suspension 0.25mg/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.

Study 107.162 (Phase 2 Exploratory Study)

An open trial to investigate pharmacokinetics as well as efficacy and safety of 0.25 mg/kg meloxicam syrup administered once daily (not to exceed a daily dose of 15 mg) in children with Juvenile Rheumatoid Arthritis over a treatment period of up to 52 weeks. The trial was designed as an open label trial with three phases: pharmacokinetics (single dose), efficacy (at 12 weeks) and a safety extension (40 weeks duration).

Table 1. Description of clinical JRA efficacy and safety studies

Study ID	107.235			107.208			107.162
Number of Study Centers	37			34			3
Locations	United States, Mexico, Argentina, Brazil, Ukraine			Austria, Belgium, France, Germany, Italy, Russia, UK			Germany, Mexico
Study start	December 2000			September 2000			January 1998
Enrollment status, date	completed, June 2003			completed, January 2003			completed, May 2000
Total entered/ enrolment goal	209/180			226 (225 treated)/180			36/36
Design	Randomized, double-blind, double-dummy, parallel group, open label extension			Randomized, double-blind double-dummy parallel group			open label one treatment group
Control type	active comparator			active comparator			uncontrolled
Study & Control Drugs, dose, route & regimen	Meloxicam L: 0.125 mg/kg (4 weeks), then 0.25 mg/kg/day Meloxicam H: 0.25 mg/kg/day (4 weeks), then 0.375 mg/kg/day Naproxen: 10 mg/kg (4 weeks), then 15 mg/kg divided in 2 daily doses open label: Meloxicam 0.375 mg/kg/day			Meloxicam L: 0.125 mg/kg/day Meloxicam H: 0.25 mg/kg/day Naproxen: 10 mg/kg divided in 2 daily doses			Meloxicam 0.25 mg/kg/day - one treatment group only
Study Objective	Efficacy, Safety and Pharmacokinetics			Efficacy and Safety			Pharmacokinetics , Efficacy, Safety
# subjects by arm	Mel L	Mel H	Nap	Mel L	Mel H	Nap	
entered	62	72	75	73	74	78	36
completed (week 12)	58	63	70	70	68	72	34
completed (trial)	52	61	66	58	63	61	31
Duration	12 weeks, plus 12 weeks open label			1 year			1 year
Gender M/F	56/153			67/158			14/22
Median Age (range)	10 (1-17)			8 (1-16)			8 (2-15)
Primary endpoints	ACR Pediatric 30 responders at 12 weeks			ACR Pediatric 30 responders at 12 weeks			Pharmacokinetic assessment

4.2 Review Strategy

Studies 107.235 and 107.208 were reviewed individually for efficacy assessment. All three studies were reviewed for safety assessment, individually and as ISS. Adult safety assessment from previous submissions was consulted in this review.

4.3 Data Quality and Integrity

The studies 107.208, 107.235, and 107.116 were conducted and reported according to the principles of Good Clinical Practices (GCP), FDA regulations and the BI standard operating procedures reflecting those guidelines/regulations.

The following steps were taken by the sponsor, the CROs and at the study sites to ensure accurate, consistent, and complete data collection:

- Prior to study initiation, field monitors (CRAs) visited each center to assure that the Investigator and his or her staff was qualified to conduct the trial and that the facilities and equipment were adequate for study conduct.

- Training meetings were held for all participating Operating Units (OPUs) prior to study initiation. At the meetings, the protocol, CRFs, drug supplies, and laboratory procedures were reviewed in detail.

- Initiation visits were conducted by the CRAs to ensure that study materials were received by and properly stored at the study sites. This visit also served as an avenue to discuss any questions the study staff may have had. Sites were not allowed to begin enrolling patients until an initiation visit was conducted.

An Investigator Site File containing all pertinent information required to implement and conduct the trial was prepared for each Investigator. Case Report Forms (CRFs) designed to collect all safety and efficacy data as specified by the protocol, were supplied for each patient. The field monitors reviewed all patient charts, case report forms, and written informed consents. The accuracy of the data was verified by reviewing the above referenced documents. A monitoring manual was prepared by the clinical team and served as an informative guideline regarding study procedures for the CRAs.

Following site initiations, the field monitoring staff visited each study site approximately every 4-6 weeks. The purpose of the visits was to ensure that the CRFs were maintained and current and that the trial was being conducted in compliance with the protocol. Any change in staff at a study site was noted. Completed CRFs were retrieved and sent to the Boeheringer Ingelheim International Sites for data entry and review. Following each site visit, a Trip Report was generated by the CRA, reviewed by the clinical team, and filed in the Clinical Trial Master File (CTMF).

A protocol-specific Trial Data Management and Analysis Plan (TDMAP) was prepared by the Trial Data Manager, Trial Statistician and the Trial Clinical Monitor. The document contained guidelines for the identification and resolution of problems relating to data quality and safety issues, including protocol violations which affected efficacy and safety measures. The TDMAP also contained a description of data flow, data handling, rules, analysis data set specifications, and the requirements for reporting data. All data contained in the CRFs was entered into the database using double data entry and verified to assure accuracy. The TDMAP was updated throughout the trial as the need arose.

The Data Management Unit Specialist and the Clinical Team addressed data queries. Any discrepancies, which could not be handled internally, were sent via Data Clarification Form (DCF) to the Investigator for resolution. The Investigator returned the original DCF with the resolution and maintained a copy of the DCF with the resolution and Investigator signature within the patients' clinical data binder. In-house changes made to the database were acceptable if the missing or appropriate information appeared elsewhere in the CRFs. These changes were documented on a Document of Change (DOC) form, which was forwarded to the Investigator on an ongoing basis, to be maintained with the patient's clinical trial binder.

Reviewer's comments:

- *For an additional information, please, see DSI site inspection report (it is not in DFS at the time of this review)*

4.4 Compliance with Good Clinical Practices

The studies were conducted in accordance with the provisions of the Declaration of Helsinki (originally adopted in Helsinki in 1964) and its amendments (Hong Kong, 1989; Republic of South Africa, 1996), in accordance with Good Clinical Practice (GCP), the International Conference on Harmonization Guidelines (ICH) for GCP (ICH E6), US requirements on experimentation on human subjects, (Title 21 CFR, Parts 50, 54, 56, 312) and with other relevant local guidelines.

Good Clinical Practice audits were performed by Boehringer Ingelheim in accordance with ICH Harmonised Tripartite Guideline for GCP.

4.5 Financial Disclosures

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is a subsidiary of Boehringer Ingelheim GmbH, a privately-held company. It is not publicly traded, has no equity available to investigators and does not provide compensation to investigators based on the outcome of studies conducted on its behalf. No investigators can have or own a proprietary interest in a product owned by the company.

The Sponsor provided an FDA form 3454 certifying that there were no disclosable financial arrangements with the investigators or sub-investigators listed for either study. No listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

Please, see review by Dr. Chandra Chaurasia
There is no additional toxicology, CMC or pharmacology information about meloxicam submitted in this supplement

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental application proposes to add the indication for the **treatment of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)** in pediatric patients from (b) (4) through 17 years old.

6.1.1 Methods

The pivotal study 107.235 and supportive study 107.208 were used in the efficacy portion of this review to examine the efficacy of meloxicam oral suspension to support the proposed indication. See Section 6.1.3 for complete description of studies.

6.1.2 General Discussion of Endpoints

The primary efficacy variable used in these studies was the rate of responders according to the JRA core set outcome criteria definition of improvement (also known as ACR Pediatric 30) measured at the end of Week 12. Responders were defined as those who improved at 12 weeks of treatment by at least 30% in three or more of the six variables with no more than one of the remaining variables worsened by more than 30%. The six variables were: (1) investigator global assessment of overall disease activity, (2) parent global assessment of overall well-being, (3) number of joints with active arthritis, (4) number of joints with limited range of motion, (5) functional disability index in CHAQ (Childhood Health Assessment Questionnaire), and (6) erythrocyte sedimentation rate (ESR).

This definition of improvement is accepted by American College of Rheumaotlogy (ACR) as a uniform definition that helps standardize the conduct and reporting of clinical trials and combines aspects of the articular examination with true outcome (functional ability and parent/patient assessment of overall well-being).

It is considered to be robust enough to cover all types of JRA, focusing on central features of arthritis, function, and overall well-being. The definition of improvement shows high sensitivity and specificity, and low false- positive and false-negative rates.

One of the main issues with this endpoint is that there is no firm conclusion about the discriminant ability of the definition under placebo-controlled trial because of the lack of adequate data sets.

6.1.3 Study Design

Study 107.235 (Pivotal Study)
This was a 12-week, randomized, double-blind, active-control, forced-titration study in 180 patients with a 12- week open-label extension. It was conducted in multiple international sites. It compared the safety and efficacy of meloxicam oral suspension to naproxen oral suspension in treating the signs and symptoms of JRA.
Upon entry into the trial, patients were randomized to one of three dose groups: 0.125mg/kg/day meloxicam oral suspension, 0.25 mg/kg/day meloxicam oral suspension or 5 mg/kg BID naproxen oral suspension.
At 4-weeks, all patients were up-titrated to the next dose level, e.g., 0.125 mg/kg/day meloxicam oral suspension patients started taking 0.25 mg/kg/day, 0.25 mg/kg/day meloxicam oral suspension patients started taking 0.375 mg/kg/day and 5 mg/kg BID naproxen oral suspension patients started taking 7.5 mg/kg BID.
A 12-week open-label extension followed the 12-week double-blind phase of the study. All patients in study 107.235 (including those who were randomized to naproxen oral suspension) received 0.375 mg/kg day meloxicam oral suspension for the duration of the open-label extension. PK information was derived at steady state from a subset of 20 patients at the end of the open-label extension period.
Patients who were taking NSAIDs at the screening visit (Visit 1) were required to observe a washout period and thus to be without NSAID therapy immediately prior to randomization.

Inclusion criteria

1. Male or female outpatients aged 2 to 16 years (Per Amendment 2: aged 2-17 years)
2. Diagnosis of idiopathic arthritis of childhood by ILAR criteria:
    - Age of onset less than 16 years
    - Arthritis in one or more joints defined as swelling, or-if no swelling present, limitation in range of joint movement with joint pain or tenderness, which is not due to primary mechanical disorders
    - Duration of the disease equal or greater than 6 weeks
    - Type of disease during the first 6 months classified as polyarthritis (5 joints or more; rheumatoid factor positive or negative), pauciarthritis (4 joints or fewer) or systemic arthritis
3. Pauciarticular, extended pauciarticular or polyarticular current course of disease
4. Active arthritis as defined above of at least 2 joints

5. At least 2 other abnormal variables of any of the 5 remaining core set parameters. An "abnormal" physician or parent rating is defined as at least 10 mm on a 100 mm Visual Analog Scale (VAS). An abnormal CHAQ score is greater than 0. (Per Amendment 2: clarification of wording: Per physician and parent rating must be at least 10 mm on a 100 mm VAS scale and the CHAQ score more than 0)
6. Patients requiring therapy with NSAID , i.e. the patient fits into one of the following categories:
   - New onset patient
   - Patient in remission, but experiencing a flare and now requiring an NSAID
   - Patient with insufficient therapeutic effect (ITE) or intolerability to another NSAID (other than naproxen) and now must be changed
   - Patient treated with NSAID, without ITE or intolerability, but decides to enroll
7. Written informed consent given by parent (s) or the subject's legally authorized representative in accordance with local legislation and the International Counsel on Harmonization Good Clinical Practices (ICH GCP) Guidelines
8. Active assent given by the patient if the child is capable of understanding the given information (applies to children who have reached an intellectual age of 7 years or greater) as required by the IRB

Exclusion criteria

1. Patients with systemic course of JRA (intermittent fever with or without rash or other organ involvement) or with active systemic involvement
2. All rheumatic conditions not covered by the inclusion criteria
3. Any finding indicating that the patient has a clinically significant disease other than JRA that could interfere with the evaluation of the safety and efficacy of the trial medication
4. Patients weighing 9 kg or less
5. Patients with abnormal, clinically relevant laboratory values not related to their JRA
6. Pregnancy or breast-feeding
7. Females of child-bearing potential who are sexually active and not using adequate contraception (e.g., intrauterine device, contraceptive pills, Depo-Provera, implant or double-barrier device) for at least 3 months prior to, and for the duration of trial participation. It should be noted that NSAID might interfere with the effectiveness of intrauterine devices
8. History of bleeding disorders, gastrointestinal bleeding or cerebrovascular bleeding
9. Active peptic ulcer within the last 6 months
10. Treatment with more than one SAARD/DMARD (slow-acting antirheumatic drug/disease-modifying antirheumatic drug) during the 3 months prior to study entry (Per Amendment 2: treatment with more than two SAARD/DMARD (slow-acting antirheumatic drug/disease-modifying antirheumatic drug) during the 3 months prior to study entry)
11. Change in treatment with SAARD/DMARDs during the 3 months prior to study entry or intended change during trial duration

12. Change in treatment with corticosteroids during the 3 months prior to study entry or intended change during trial duration
13. One of the following therapies during the 3 months prior to study entry or intended use during trial treatment period (Per Amendment 2: Any of the following therapies when exceeding the specified dose during the 3 months prior to study entry or intended use during trial treatment period):
    - Systemic treatment (except for intra-articular injections) with corticosteroids at a dose higher than 10 mg/day or 0.2 mg/kg/day (prednisone equivalent), respectively (whichever is lower)
    - Treatment with hydroxychloroquine at a dose higher than 10 mg/kg/day
    - Treatment with cyclosporine at a dose higher than 5 mg/kg/day
    - Treatment with methotrexate at a dose higher than 15 mg/m²/week (Per Amendment 2: treatment with methotrexate at a dose higher than 1 mg/kg/week (30 mg/m²/week)
    - Treatment with cytotoxic agents other than methotrexate, gold compounds, D-penicillamine, sulfasalazine, glucosamine and investigational products (Per Amendment 2: Sulfasalazine was allowed as a concomitant drug during the trial; wording clarified by deleting methotrexate)
14. Treatment with Enbrel during the month prior to study entry or intended use during trial (Per Amendment 2: Treatment with Enbrel at a stable dose for at least three months prior to study entry was allowed in the trial)
15. Treatment with Remicade during the 2 months prior to study entry or intended use during trial
16. Intra-articular injections of corticosteroids the month prior to study entry and intended injections during the first 4 weeks of the trial treatment period
17. Patients requiring concomitant administration of other NSAIDs (including topical forms but excluding ophthalmic forms) as routine treatment or analgesics agents except acetaminophen (not to exceed the maximum recommended dose fro the age group, i.e., 2-5 years of age=1200 mg/day and >=6 years=75 mg/kg/day or maximum of 4 gm/day) as rescue medication. There is a washout period of:
    - 1 day for acetylsalicylic acid, ibuprofen, nimesulide and tolmetin
    - 3 days for short acting NSAIDs such as naproxen and celecoxib
    - 7 days for long acting NSAIDs such as piroxicam, rofecoxib and meloxicam
18. Patients requiring treatment with anticoagulants, phenothiazines, lithium or ACTH
19. Patients with insufficient therapeutic effect or intolerability to naproxen or meloxicam
20. Known or suspected hypersensitivity to any of the trial medications or their excipients
21. Patients requiring chronic H2 antagonist therapy

22. History of asthma, nasal polyps, angioneurotic edema or urticaria following the administration of aspirin or NSAIDs
23. Surgical procedure planned to be performed during the course of the trial
24. Participation in a clinical trial of an investigational drug during this trial or within 30 days or six half lives (whichever is greater) prior to entering the trial
25. Previous participation in this trial
26. Patients with known drug or alcohol abuse
27. Patients, parent(s) or legal authorized representative unable to understand and to comply with the terms of the protocol
28.

Criteria for Efficacy:

Primary: Rate of responders in the JRA core set outcome criteria. Responders were defined as those who improved at 12 weeks of treatment by at least 30% in three or more of the six variables with no more than one of the remaining variables worsened by more than 30%. The six variables were: (1) investigator global assessment of overall disease activity, (2) parent global assessment of onerall well-being, (3) number of joints with active arthritis, (4) number of joints with limited range of motion, (5) functional disability index in CHAQ (Childhood Health Assessment Questionnaire), and (6) erythrocyte sedimentation rate (ESR).

Secondary: Disease activity by investigator; number of joints with active arthritis, number of joints with limited range of motion, parent global assessment of overall well-being assessment of functional disability by means of CHAQ, ESR, final global assessment of efficacy by parent, final global assessment of efficacy by investigator, withdrawals due to inadequate efficacy, acetaminophen consumption.

Criteria for Safety: Incidence and intensity of adverse events, withdrawal due to adverse events, laboratory parameters, slit lamp eye exam, final global assessment of tolerability by parent and investigator, physical exam, additional physician visits due to gastrointestinal adverse event (GI-AE), hospital stay due to gastrointestinal serious adverse event (GI-SAE), hospital stay due to adverse events related to study drug administration, vital signs.

Reviewer's comments:

- *The study design, duration, entry criteria appear appropriate for the indication thought and was discussed at length with the Division during development stage*
- *The calculation of the appropriate pediatric doses were derived from the doses studied for treatment of rheumatoid arthritis in adults and standardized by weight. Daily doses of 0.125, 0.25 and 0.375 mg/kg/ body weight of meloxicam were calculated based on a mean ratio of 1:60 of the adult doses.* (b) (4)

- *Endpoints chosen are commonly accepted for this indication and population as discussed in 6.1.2.*
- *This study is not using a placebo arm due to ethical concerns, however a standard background therapy is allowed. The choice of an active comparator (naproxen) appears appropriate and is commonly used in similar studies since there are very few NSAIDs approved for pediatric use, and naproxen is one of them.*

Study 107.208

Title: A one year double-blind trial to investigate the efficacy and safety of meloxicam oral suspension 0.25mg/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.
Objective: Assess the efficacy and safety of meloxicam oral suspension in children with JRA.
Population: N= 219 patients (73 per treatment group), 2 to 16 years of age with pauciarticular and polyarticular forms of JRA.
Study Design: This was a one year randomized, double-blind, parallel, active-control, fixed dose comparison of meloxicam oral suspension and naproxen oral suspension in treating the signs and symptoms of JRA. This study was conducted outside the United States. Two doses of meloxicam oral suspension (0.125 mg/kg/day and 0.25 mg/kg/day) were compared to naproxen oral suspension (5 mg/kg BID). Patients were randomized to receive one of the treatments mentioned for one year.
Pre-specified interim analysis at 12 weeks was performed.

Criteria for Efficacy:

Primary: Same as for trial 107.235.

Secondary: Disease activity by investigator; number of joints with active arthritis, number of joints with limited range of motion, parent global assessment of overall well-being assessment of functional disability by means of CHAQ, ESR, final global assessment of efficacy by parent, final global assessment of efficacy by investigator, withdrawals due to inadequate efficacy, acetaminophen consumption and the change in functional classification (Steinbrocker classification).

Criteria for Safety:

Same as for trial 107.235.

Efficacy Findings

Since there is only one pivotal study 107.235 with one supportive study 107.208 provided with this application in support of JRA indication, this section of the review presents individual study results.

Study 107.235

The sample size for the pivotal Trial 107.235 was selected to obtain adequate information on meloxicam dosing and safety in the JRA population. With a planned sample size of 60 patients in each treatment group, a total of 120 patients would be exposed to meloxicam oral suspension providing dosing information during the double-blind period. As illustrated in Table 2 below, calculated sample size is presumably sufficient to insure a **one-sided alpha 0.05 non-inferiority for a difference of 0.2 in proportion responding with a power of 80%.**

Table 2.

Sample sizes for Trial 107.235 comparing meloxicam (both doses combined) with naproxen, assuming a response rate of 0.50

α (one-sided)	0.05	0.05	0.05	**0.05**	0.025	0.025	0.025
Δ	0.1	0.15	0.2	(b) (4)	0.1	0.15	0.2
Power (%)	80	80	80	**80**	80	80	80
N per group	232	104	58	**60**	295	131	74
Total N	696	312	174	**180**	885	393	222

Source: U04-3227, Appendix16.1.1.1

The 107.235 trial was sized on the basis of assumptions that meloxicam would be effective over the range of doses that were used and would be therapeutically equivalent to naproxen. Thus, **the primary comparison between meloxicam and naproxen was specified as both doses combined versus naproxen.** The assumption of efficacy across the range of doses was based on experience with doses from 7.5 mg to 22.5 mg in adult RA. The efficacy results obtained in the open label Trial 107.162 provided a basis for the assumption of equivalence to naproxen based on historical data. **The pre-defined delta of (b) (4)% could not be supported by results of placebo controlled trials because no placebo controlled NSAID trials in JRA with the JRA DOI 30 endpoint have been conducted**.

Multiplicity was addressed by reducing the primary objective for efficacy to a single comparison between treatment groups. While the trial included three treatment groups, there was only one primary prospectively specified comparison. **With the objective of showing that a dosing range for meloxicam was not inferior to naproxen, all meloxicam patients combining the two doses were compared to naproxen patients with respect to ACR Pediatric 30. The two meloxicam regimens were compared to test the validity of this assumption, and each meloxicam regimen was compared to naproxen to further aid in interpretation of the primary analysis.**

	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

The actual sample size for the trial was 209 patients (62, 72, and 75 patients per treatment group). No patients with mono-articular JRA participated in the pivotal Trial 107.235.

At FDA request, the study utilized a forced escalation design at week 4 to permit assessment of the full range of doses of meloxicam by starting at the 2 lowest doses and raising the dose to the highest planned (0.375 mg/kg/day).

Demographics and other

baseline characteristics

Table 3.

Demographic characteristics for ITT population

Reviewer's comments:

- *The majority of patients were females, ranging from 68% to 79% of the total in each of the treatment groups. Most patients were Caucasians (85% to 87%).*
- *Approximately 30% of patients in each group were under the age of 6 years as required in WPR.*
- *No significant demographic differences between treatment groups were observed that could impact on the interpretation of the study results.*

Table 4.

Baseline disease characteristics for ITT population

	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

Reviewer's comments:

- *There were more patients with a history of uveitis in each of meloxicam groups (4.8% and 5.6%) compared to naproxen group (2.7%). The same applies to the presence of uveitis at baseline by ophthalmologic exam (8.1%, 5.6% and 2.7%, respectively). It is unknown whether or not those imbalances could have an effect on the study outcome.*

- *There were more patients with systemic onset type of disease in naproxen group (12%) compared to each of meloxicam group (9.7% and 4.2%) but less patients with polyarticular onset type of disease (38.7% vs. 45.2% and 47.2%).*

- *There were fewer patients with current pauciarticular type of disease in mel L group (35.5%) compared to mel H and naproxen groups (43.1% and 44.0%, respectively). There were fewer patients with more than 4 joints with active arthritis at baseline in naproxen group (34.7%) compared to meloxicam groups (45.2% and 45.8%). The impact those differences might have had on the outcome is impossible to assess.*

Table 5.

Summary of baseline JRA core set efficacy endpoints for ITT population

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Endpoint	Treatment@	N	Mean	S.D.	Min	25th	Med	75th	Max
Inv. Disease Act.	Mel L	62	39.42	16.05	12	28.00	36.00	49.00	78.00
									(b) (4)
	Nap	75	35.73	15.73	5	24.00	34.00	44.00	75.00
Parent well-being	Mel L	62	41.10	20.75	2	27.00	41.00	54.00	91.00
									(b) (4)
	Nap	75	42.73	21.36	2	30.00	39.00	60.00	85.00
Active Arthritis	Mel L	62	8.00	8.54	2	3.00	4.00	10.00	44.00
									(b) (4)
	Nap	75	6.11	5.73	2	3.00	4.00	7.00	32.00
Limited Motion	Mel L	62	7.19	10.31	0	2.00	4.00	8.00	68.00
									(b) (4)
	Nap	75	6.59	9.59	0	2.00	3.00	5.00	42.00
Func. Dis. (CHAQ)	Mel L	62	0.95	0.68	0	0.38	0.75	1.50	2.50
									(b) (4)
	Nap	75	0.91	0.59	0	0.38	0.88	1.38	2.50
ESR	Mel L	59	20.35	18.72	1	7.00	15.00	27.00	80.00
									(b) (4)
	Nap	74	18.28	15.82	0	6.63	14.00	23.00	82.00

@: Mel L = meloxicam low dosage, (b) (4) Nap = naproxen
ESR measured at Visit 1, all others measured at Visit 2.
Source data: Appendix 16.1.9.2 Table 6.3.1, 6.4.1, 6.5.1, 6.6.1, 6.7.1, 6.8.1

Reviewer's comments:

- *Individual efficacy measurements that comprise the JRA core set of outcome criteria appear balanced across the three treatment groups*

- *They suggest most patients experienced JRA symptoms in the range of mild-to moderate severity*

- *The baseline assessment of functional status utilizing the Child Health Assessment Questionnaire (CHAQ) indicated that patients had some difficulty in their daily activities with mean scores* (b) (4) *0.91 for naproxen and 0.95 for meloxicam L. The functional disability was assessed on a scale from 0 to 3 (0= no difficulty, 1= some difficulty, 2=much difficulty, 3=unable to do).*

Prior NSAID use was common in all patient groups. The most commonly used NSAID was naproxen (n=120/209, 58.4%), followed by ibuprofen (n=101, 48.3%) and diclofenac (n=52, 24.9%). At Visit 1, instructions were given for proper washout of any NSAIDs that patient was taking at the time.

Table 6.

History (up to 5 years prior to study start) of NSAID use in Trial 107.235

	Meloxicam 0.125 mg/kg*	**Meloxicam 0.25 mg/kg***	**Naproxen 10mg/kg***	**Total**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Total number of patients	**62 (100)**	**72 (100)**	**75 (100)**	**209 (100)**
Acetylsalicylic acid	6 (9.7)	9 (12.5)	5 (6.7)	20 (9.6)
Celecoxib	2 (3.2)	1 (1.4)	4 (5.3)	7 (3.3)
Diclofenac	22 (35.5)	23 (31.9)	17 (22.7)	62 (30.1)
Etodolac	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
Ibuprofen	30 (48.4)	39 (54.2)	32 (42.7)	101 (48.3)
Indomethacin	9 (14.5)	8 (11.1)	13 (17.3)	30 (14.4)
Ketoprofen	0 (0.0)	1 (1.4)	2 (2.7)	3 (1.4)
Meloxicam	2 (3.2)	1 (1.4)	3 (4.0)	6 (2.9)
Mefenemic acid	0 (0.0)	3 (4.26)	0 (0.0)	4 (1.9)
Nabumetone	0 (0.0)	4 (5.6)	1 (1.3)	5 (2.4)
Naproxen	**35 (56.5)**	**45 (62.5)**	**42 (56.0)**	**120 (58.4)**
Nimesulide	8 (12.9)	5 (6.9)	5 (6.7)	18 (8.6)
Phenylbutazone	0 (0.0)	3 (4.2)	0 (0.0)	3 (1.43)
Piroxicam	1 (1.6)	2 (2.8)	2 (2.7)	5 (2.4)
Rofecoxib	5 (8.1)	7 (9.7)	10 (13.3)	22 (10.5)
Sulindac	3 (4.8)	2 (2.8)	4 (5.3)	9 (4.3)
Tolmentin	0 (0.0)	1 (1.4)	1 (1.3)	2 (1.0)
Trilisate	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)

* Dose at randomization
Source: U04-3227 Appendix 16.2, Lisiting 4.6

Concomitant medications

Sulfasalazine and etanercept were allowed as concomitant drugs during the trial. The maximum allowed dose of metotrexate (MTX) was increased to 1 mg/kg/wk.

Table 7. Washout of NSAIDs prior to randomization in Trial 107.235

	Meloxicam 0.125 mg/kg*	Meloxciam 0.25 mg/kg*	Naproxen 10 mg/kg*	Total
	N (%)	N (%)	N (%)	N (%)
Total number of patients	62 (100)	72 (100)	75 (100)	209 (100)
Acetylsalicylic acid	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)
Celecoxib	2 (3.2)	0 (0.0)	2 (2.7)	4 (1.9)
Diclofenac	6 (9.7)	7 (9.7)	2 (2.7)	15 (7.2)
Etodolac	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
Ibuprofen	8 (12.9)	10 (13.8)	8 (10.8)	26 (12.4)
Indomethacin	1 (1.6)	1 (1.4)	1 (1.4)	3 (1.4)
Ketoprofen	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
Meloxicam	2 (3.2)	0 (0.0)	2 (2.7)	4 (1.9)
Nabumetone	0 (0.0)	3 (4.2)	0 (0.0)	3 (1.4)
Naproxen	18 (29.0)	22 (30.6)	23 (31.1)	63 (30.1)
Nimesulide	3 (4.8)	3 (4.2)	3 (4.1)	9 (4.3)
Rofecoxib	3 (4.8)	6 (8.4)	6 (8.1)	15 (7.2)
Sulindac	2 (3.2)	2 (2.8)	2 (2.7)	6 (2.9)
Tolmentin	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
Total number of patients with NSAID washout	45 (72.6)	57 (79.2)	51 (68.0)	153 (73.2)
No washout necessary	16 (25.8)	12 (16.7)	20 (27.0)	48 (23.0)
No washout observed	1 (1.6)	3 (4.2)	4 (5.4)	8 (3.8)

Source: U04-3227 Appendix 16.2, Lisiting 4.6

Table 8

Patient disposition in the JRA study population (up to Week 12), trial 107.235

	Mel L N (%)	Mel H N (%)	Nap N (%)	Trial 107.235 N (%)
Number of patients treated	62	72	75	209 (100)
Patient Disposition				
Planned Treatment Duration Completed	58 (93.5)	63 (88.9)	70 (94.7)	191 (91.4)
Total Number of Discontinuations	4 (6.5)	9 (12.5)	5 (6.7)	18 (8.6)
Disc. due to Adverse Event	0 (0.0)	2 (2.8)	1 (1.3)	3 (1.4)
Disc. due to Lack of Efficacy	1 (1.6)	5 (6.9)	2 (2.7)	8 (3.8)
Disc. due Non-Compliance with Protocol	1 (1.6)	1 (1.4)	0 (0.0)	2 (1.0)
Disc. - Lost to Follow-up	0 (0.0)	1 (1.4)	1 (1.3)	2 (1.0)
Disc - Consent Withdrawn	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Disc. Other	1 (1.6)	0 (0.0)	1 (1.3)	2 (1.0)

Source: End of Text Tables 2.7.4.7.3.2, 2.7.4.7.3.3, Appendix 16.1.9.2, Table 1.1 and Appendix 16.2, Listing 1.1

Reviewer's comments:

- *Most patients stayed in trial 107.235, however, the discontinuation rate due to all causes was twice as high in Meloxicam high dose group that in other two groups.*
- *Discontinuation due to adverse events was **twice as high in Meloxicam high dose** group compared to Naproxen group though the numbers are very small to make a definite conclusion. There were no discontinuations due to adverse events in Meloxicam low dose group.*
- *Unexpectedly, discontinuations due to lack of efficacy were highest in Meloxicam high dose group, followed by Naproxen group and then Mel low dose group.*
- *Numbers of patients lost to follow-up and withdrawn consent are very low and is not a concern with this trial.*

The primary endpoint, ACR Pediatric 30 responders, is defined as those patients who have improved from baseline by at least 30% in three or more of the six variables, measured at the end of week 12, with no more than one of the remaining variables worsened by more than 30%.

Table 9
Summary of JRA core set outcome responders (ACR30) for ITT population (LOCF)

	Responders					Comparison vs.Naproxen		
Week	Treatment	Total	N	Rate	(95% CI)	Diff (SE)	(95% CI)	p-value
Week 4	Mel. 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	Mel. 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	Mel. 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)
Source Data: Section 15, Table 15.2.1:1

Reviewer's comments:

- (b) (4)

The percentage of ACR30 responders (b) (4) increased from Week 4 to Week 8 and from Week 8 to Week 12. The ACR30 response at Week 4 reflected the efficacy response after four weeks of treatment with the initial titration dosage: 0.125 mg/kg for Mel L group (b) (4) and 10 mg/kg for the Nap group. (b) (4)

Each of the 95% confidence intervals for the treatment differences of meloxicam versus naproxen had the lower bound of the confidence interval greater than pre-defined difference of -20%.

The change from baseline in each of the six components of the ACR pediatric 30 endpoint is presented under secondary endpoints section. The components for the number of joints

with active arthritis and investigator global assessment of overall disease activity had the highest proportions of responders for each of the three treatment groups. At week 12, the percentage of patients having at least 30% improvement in the "number of joints with active arthritis" was 75.8%, (b) (4) and 78.7% in the Mel L (b) (4) and Nap treatments, respectively; in the " investigator global assessment of overall disease activity"-72.6%, (b) (4) and 77.3% Mel L, (b) (4) and Nap treatments, respectively.

At week 12, the percentage of patients having at least 30% improvement

- in the "**parent global assessment of overall well-being**" was 56.6%, (b) (4) and 57.3% in the Mel L (b) (4) and Nap treatments, respectively;
- in the "**number of joints with limited range of motion**" was 61.3%, (b) (4) and 48% in the Mel L, (b) (4) and Nap treatments, respectively;
- in the "**functional disability index in CHAQ**" was 64.5%, (b) (4)% and 56.0% in the Mel L, (b) (4) and Nap treatments, respectively.

The component of the ACR Pediatric 30 endpoint that had the lowest proportion of responders was the ESR variable, with 23.7%, (b) (4) and 25.7% responders in the Mel L, (b) (4) and Nap treatments, respectively.

Additional analyses evaluated the effect of arthritis type (current course) country, age, gender, and methotrexate usage on the response to treatment. No significant treatment –by-factor interaction was found for each of the factors examined, i.e., arthritis type, country, age, gender, and methotrexate usage.

Table 9. Subgroup analysis of ACR pediatric 03 Response at Week 12 for ITT population (LOCF)

		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 baseline	<=4 joints	34	24 (70.6)	49	34 (69.4)
	>=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)
MTX use	No	39	26 (66.7)	51	38 (74.5)
	Yes	23	17 (73.9)	24	13 (54.2)

Meloxicam L=meloxicam low dosage, (b) (4)
Source Data: Section 15, Table 15.2.1:3

Reviewer's comments:

- [redacted]
- *Interestingly, patients on background MTX therapy had substantially lower responders rate in Naproxen group (54.2%) compared to* [redacted] *meloxicam* [redacted] *73.9% for Mel L).*

Secondary endpoints

ACR Pediatric 50

At week 12, the percentage of patients demonstrating a response for the ACR Pediatric 50 endpoint was 56.5% for Meloxicam L, [redacted] and 52% for Naproxen. No significant differences between naproxen and meloxicam treatments for the ACR Pediatric 50 were observed.

Similar to responses seen for ACR30 endpoint with meloxicam, the percentage of ACR50 responders within each treatment group increased from Week 4 to Week 8 and from Week 8 to Week 12.

ACR Pediatric 70

At week 12, the percentage of patients demonstrating a response for the ACR Pediatric 70 endpoint was 30.6% for Meloxicam L, [redacted] and 26.7% for Naproxen. No significant differences between naproxen and meloxicam treatments for the ACR Pediatric 70 were observed.

Investigator Global Assessment of Disease Activity

The mean investigator global assessment of disease activity at baseline was 39.4 for meloxicam L, [redacted] and 35.7 for naproxen. The mean reduction in disease activity was 17.5 (44.4%) for meloxicam L, 22.1 [redacted] and 17.8 (49.7%) for naproxen [redacted]

Parent Global Assessment of Well-being

The mean global assessment of overall well-being at baseline was 41.1 for meloxicam L, [redacted] and 42.7 for naproxen. The mean improvement in overall well-being at Week 12 was 16.0 (39.0%) for meloxicam L, [redacted] and

16.9 (39.6%) for naproxen [redacted]

Number of Joints with Active Arthritis

The number of joints with active arthritis at baseline was 8.0 for meloxicam L, [redacted] and 6.1 for naproxen. The mean reduction in the number of joints with active arthritis achieved by Week 12 was 4.4 (55.5%) for meloxicam L, [redacted] and 4.2 (69.4%) for naproxen and [redacted]

Number of Joints with Limited Range of Motions

The average number of joints with limited range of motions at baseline was 7.2 for meloxicam L, [redacted] and 6.6 for naproxen. The mean reduction in the number of joints with limited range of motions achieved by Week 12 was 1.8 (25.6%) for meloxicam L, 2.3 (37.3%) [redacted] and 2.2 (33.7%) for naproxen [redacted]

Functional Disability as measured by CHAQ

The functional disability of patients improved for all treatment groups. The mean reduction in the disability index was 0.36 for meloxicam L, [redacted] and 0.34 for naproxen which corresponds to percent reductions of 38%, [redacted] and 37%, respectively. No significant treatment differences were observed for functional disability.

Erythrocyte Sedimentation Rate (ESR)

The mean ESR **did not change substantially** over the 12 weeks of treatment, the percentage of change from baseline for ESR was 5% or less for all treatment groups (+0.1% for meloxicam L, [redacted] and +2.3% for naproxen).

Reviewer's comments:

- *As pointed out by the ACR, "The lack of valid, widely available laboratory markers of inflammation in children with JRA leaves the core set with only the ESR as a biochemical marker of response. Some children enrolled in trials of second-line agents have a normal ESR throughout the baseline values thus compromising the utility of the definition of improvement" that is why perhaps there were no substantial changes with this variable*

- *The results seen in this trial (no significant changes in ESR observed) are similar to results seen in adult RA trials*

Discomfort (or pain) as measured by CHAQ

The discomfort, i.e., presence and severity of pain, improved in each treatment group over the 12 weeks of study. The mean reduction in discomfort was 0.16 for meloxicam L, (b) (4) and 0.19 for naproxen. No significant treatment differences were observed.

Parent's global assessment of arthritis as measured by CHAQ

The parent's global assessment of arthritis improved in each treatment group over the 12 weeks of study. This endpoint assesses how well the child was doing on a scale from zero (doing very well) to 100 (doing very poorly). The mean improvement in arthritis was 17.6 for meloxicam L, (b) (4) and 14.7 for naproxen. No significant treatment differences were observed.

Acetaminophen consumption

As seen in **Table 10**, acetaminophen consumption as a rescue medication was not significantly different between meloxicam versus naproxen treatment however numerically naproxen group consumed more acetaminophen (mg/day) as any other treatment groups.

Table 10.
Analysis of acetaminophen consumption (mg/day) for ITT patients at week 12

Treatment	N	Mean	(SE)	LSMean	(SE)	95% CI	P-value
Mel L	59	14.44	(7.06)	-7.69	(9.52)	(-26.5,11.08)	0.4201
(b) (4)							
Naproxen	73	22.13	(6.36)				

Source: End of Text Table 2 7 3 6 2 10 1 1

Reviewer's comments:

- (b) (4)

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

During the 12-week open-label treatment phase all patients received meloxicam at a dose of **0.375 mg/kg/day**. (b) (4)

The percentage of ACR30 responders in the meloxicam 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. (b) (4)

(b) (4)

The percentage of ACR30 responders in the 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.

Reviewer's comments:

- (b) (4)
- *Switching from naproxen to meloxicam resulted in initial decrease rate of responders with subsequent increase in responder's rate above the rate observed at the end of naproxen treatment*

Study 107.208

232 patients were enrolled into study 107.208, 226 patients were randomized and 225 patients were treated. 210 patients completed the study.

Patients were randomized to meloxicam 0.125 mg/kg once a day, meloxicam 0.25 mg/kg once a day, or naproxen 5 mg/kg administered twice daily (1:1:1 randomization) and treated for one year. The meloxicam doses chosen involved the dose (0.25 mg/kg/day) used (b) (4) in the 107.162 trial, and a dose (0.125 mg/kg/day) below that. The naproxen dose (10 mg/kg/day) selected was the registered dose available for use in clinical trials in the European countries that participated. The primary endpoint was the rate of responders by ACR Pediatric 30 (JRA Definition of Improvement (DOI) 30) criteria after 12 weeks of treatment.

While the trial included three treatment groups, there was only one primary prospectively specified comparison. With the objective of showing that a dosing range for meloxicam was not inferior to naproxen, all meloxicam patients combining the two doses were compared to naproxen patients with respect to ACR Pediatric 30.

In Trial 107.208 less than 4% of patients had fewer than 2 joints with active arthritis (2 patients had 0 and 7 had one joint with active arthritis out of the 226 randomized patients).

Table 11. Patient disposition in the JRA study population for study 107.208 (up to Week 12)

	Meloxicam Low (L)	Meloxicam High (H)	Naproxen	Total
Number of patients treated	73	74	78	225
Patient Disposition				
Planned Treatment Duration Completed	70	68	72	210
Disc. due to Adverse Event (AE)	1	1	3	5
Disc. due to Lack of Efficacy	0	1	2	3
Disc. due to administrative reasons	2	4	1	7

Source: End of Text Tables 2.7.4.7.3.2, 2.7.4.7.3.3 and U00-1833, Appendix 16.1.9.2, Table 1.1 and Appendix 16.2, Listing 1.1

The reasons for discontinuations due to AEs were vomiting (Mel L), worsening of disease under study (Mel H), and hematoma, worsening of disease under study (uveitis) and a combination of facial swelling, hyperemia and tongue swelling in the 3 naproxen patients.

Table 12. Demographic data for all patients in study 107.208

	Mel L (N=73)	Mel H (N=74)	Naproxen (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%)	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
Male	24 (32.9%)	25 (33.8%)	18 (23.1%)	67 (29.8%)
Female	49 (67.1%)	49 (66.2%)	60 (76.9%)	158 (70.2%)

Source: Appendix 16.1.9.2, Table 4.1.1

Reviewer's comments:

- *Patients in Naproxen group appear to be slightly younger, and proportion of patients under 6 years of age is substantially larger in Naproxen group.*
- *Patients in Naproxen group had a lower height and lower weight, perhaps due to a higher proportion of younger patients*
- *The proportion of females in Naproxen group was lower compared to Meloxicam groups.*
- *Due to these observed imbalances between the treatment groups, the pre-specified prognostic factors (age and sex) were investigated by the Sponsor in a confounder analysis (see Statistical Review).*

Table 13. History of diagnosis under study

		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: Appendix 16.1.9.2, Table 4.2, 4.3

Reviewer's comments:

- *The mean duration of disease before randomization was shortest for the naproxen group and the longest for meloxicam L group. This could be due to a larger proportion of younger population in naproxen group. Uveitis at baseline was slightly more common in both meloxicam groups compared to naproxen group.*
- *Unlike Trial 107.235, Mel L group had a highest proportion of patients with current pauciarticular type of disease (67.1%) compared to Mel H (56.8%) and Naproxen (59.0%) groups. The implication of above-mentioned imbalances on the study results is unknown.*

Table 14. Disease activity at baseline

Mean±SD	Mel L (N=73)	Mel H (N=74)	Nap (N=78)	p-value
Global assessment of disease activity investigator (mm)	37.1±19.6	38.5±21.6	37.6±17.9	0.9032
Parent global assessment of overall well-being (mm)	36.9±20.1	38.7±23.3	38.0±19.5	0.8624
Childhood Health Assessment Questionnaire (unit)	0.64±0.59	0.76±0.64	0.80±0.61	0.2318

Number of active joints at baseline (N)	6.22±8.37	7.28±8.28	6.68±7.86	0.7305
Number of joints with LOM (N)	6.10±8.50	6.65±7.86	6.50±7.98	0.9128
ESR (mm/h)	16.2±14.7	21.4±22.8	20.5±18.6	0.2089
Parent global assessment of arthritis (mm)	40.8±21.9	42.7±22.8	44.0±22.0	0.6761
Parent global assessment of pain (mm)	35.0±22.4	39.0±24.6	38.1±23.4	0.5592
Children's assessment of discomfort (FAS)	0.46±0.25	0.45±0.25	0.45±0.24	0.9758

Source: Appendix 16.1.9.2

Reviewer's comments:

- *Disease activity parameters did not differ significantly between the groups.*
- *Parent global assessment of pain (mm) and Children's assessment of discomfort (FAS) were added to the list of measurements however were not included into the composite ACR Pediatric 30 endpoint .*

Table 15. Medication history

		Mel L (N=73)	Mel H (N=74)	Nap (N=78)	Total (N=225)
Number of patients on MTX	In history	21 (28.8%)	22 (29.7%)	30 (38.5%)	73 (32.4%)
	At baseline	15 (20.5%)	19 (25.7%)	23 (29.5%)	57 (25.3%)
Number of patients on any DMARD at baseline		18 (24.7%)	21 (28.4%)	29 (37.2%)	68 (30.2%)

Reviewer's comments:

- *MTX was the most common background DMARD both in history and during the trial, and more common in naproxen group compared to meloxicam groups*

Table 16. Responder rate over visits

		Responder (LOCF)			
		No		Yes	
		N	%	N	%
Treatment	Visit Number				
Meloxicam L (N=73)	Week 4	38	52.05	35	47.95
	Week 12	27	36.99	**46**	**63.01**
					(b) (4)
Naproxen	Week 4	41	52.56	37	47.44

(N=78)	**Week 12**	28	35.90	**50**	**64.10**

Reviewer's comments:

- *Naproxen had the highest proportion of responders (64.1%)*
- *Meloxicam 0.125 mg/kg/d group showed a higher response rate compared to meloxicam 0.25 mg/kg/d group (63.1% and* (b) (4) *respectively)*
- (b) (4)

Table 17. Responder rate by age group (Week 12)

		Responder (LOCF)			
		No		Yes	
		N	%	N	%
Treatment	Age Group				
Meloxicam L (N=73)	0-6 years (N=23)	9	39.13	14	**60.87**
	7-16 years (N=50)	18	36.00	32	**64.00**
(b) (4)					
Naproxen (N=78)	0-6 years (N=37)	15	40.54	22	**59.46**
	7-16 years (N=41)	13	31.71	28	**68.29**

Reviewer's comments:

- *Overall, older groups seem to have a slightly higher proportion of responders compared to younger groups* (b) (4).

Table 18. Responder rate by treatment with MTX taken during trial (Week 12)

		Responder (LOCF)			
		No		Yes	
		N	%	N	%
Treatment	Methotrexate				
Meloxicam L (N=73)	No (N=58)	21	36.21	37	63.79
	Yes (N=15)	**6**	**40.00**	**9**	**60.00**
(b) (4)					
Naproxen (N=78)	No (N=55)	18	32.73	37	67.27
	Yes (N=23)	**10**	**43.48**	**13**	**56.52**

Reviewer's comments:

- *This is an interesting observation. It appears that patients on methotrexate as a background therapy have slightly lower responders' rate than patients without MTX. One plausible explanation for this could be that patients being put on methotrexate are likely to have a higher baseline disease activity and those usually tend to have a poorer response. It seems unlikely that a combination of a DMARD +NSAID would produce a lower response than NSAID alone.*

Secondary efficacy variables

Table 19.
Secondary efficacy endpoints (LOCF) as absolute change and mean % decrease from baseline for treatment groups at week 12

Parameter	Mel L			Mel H			Nap		
	Mean	SD	% ch.	Mean	SD	% ch.	Mean	SD	% ch.
Global assessment of disease activity by investigator	- 17.7	17.8	47.7	(b) (4)			-16.4	18.4	43.7
Parent global assessment of overall well-being	- 15.8	20.4	42.8				- 15.5	23.6	40.8
Childhood Health Assessment Questionnaire	- 0.27	0.4	43.8				- 0.30	0.44	37.5
Number of joints with active arthritis	- 3.26	6.83	52.4				- 2.83	5.49	42.4
Number of joints with limited range of motion	-2.74	5.05	44.9				- 2.44	4.98	37.5
ESR	0.51	8.49	- 2.1				- 0.93	11.4	5.6
Parents global assessment of arthritis	- 19.1	21.9	46.8				-20.0	22.9	45.4
Parents global assessment of pain	- 17.4	22.7	49.6				- 17.3	26.3	45.4
Childrens assessment of discomfort	- 0.13	0.28	28.3				- 0.17	0.28	37.8

Source: Appendix 16.1.9.2: TABLES 6.3.4, 6.4.4, 6.5.4, 6.6.4, 6.7.4, 6.8.4, 6.9.4, 6.10.4, 6.11.4, Appendix 16.1.9.1.3: TABLE 1

Reviewer's comments:

- (b) (4)
- (b) (4)

Table 20.
Treatment Results in Secondary Efficacy Endpoints Classified by Polyarticular and Pauciarticular Assessment (Study 107.208)

Parameter	Mel L (N=73)		Mel H (N=74)	Nap (N=78)	
	Pauci (N=49)	Poly (N=24)	(b) (4)	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

Reviewer's comments:

- *Overall, the improvement (compared to baseline) is better in polyarticular course of disease subgroups* (b) (4) *compared to pauciarticular. This could indicate that either pauciarticular course of disease is less responsive to treatment with NSAIDs or there is less "room" for improvement with pauciarticular course since there are less joints involved in this type of disease.*

Table 21.
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%)
Mel H (N=74)	(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%)
Mel T (N=147)	(b) (4)		

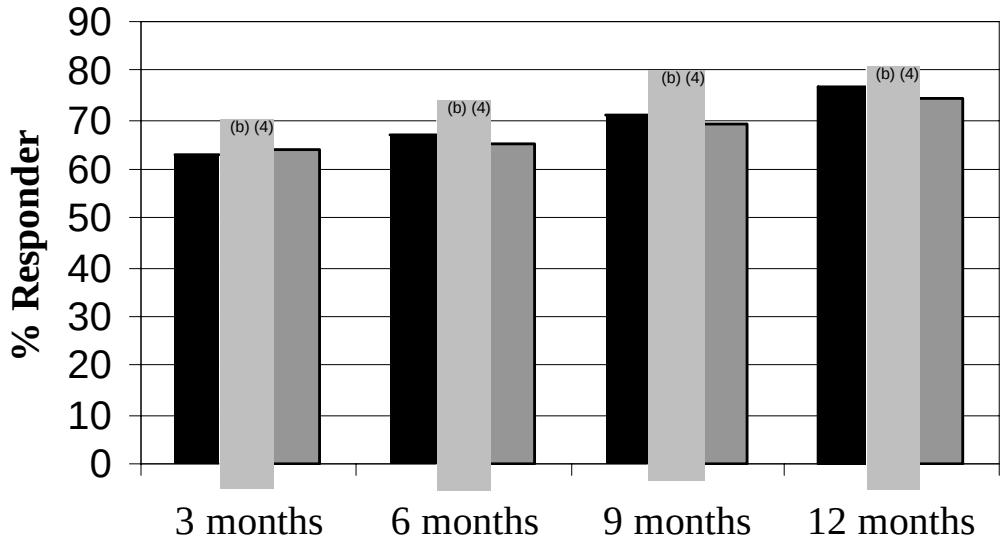
Source: Table 14.2:1 of sponsor's analysis

Reviewer's comments:

- *The response rate is higher in polyarticular type of disease groups* (b) (4)
- (b) (4)

Persistence of Efficacy and/or Tolerance Effects

The primary endpoint of the trial was the ACR Pediatric 30 responder rate after treatment of 12 weeks. Beyond 12 weeks treatment up to one year, the responder rates continued to increase in all treatment groups. There was no statistically significant difference between treatment groups at each timepoint and within each treatment group over time. **Figure 22** shows the ACR Pediatric 30 response rates at months 3, 6, 9, and 12 (LOCF). The values for the ACR Pediatric 30 responders over time, together with the 95% confidence intervals are presented in **Table 23.**



Source: U03-1727, Appendix 16.1.9.2, Table 6.1.1

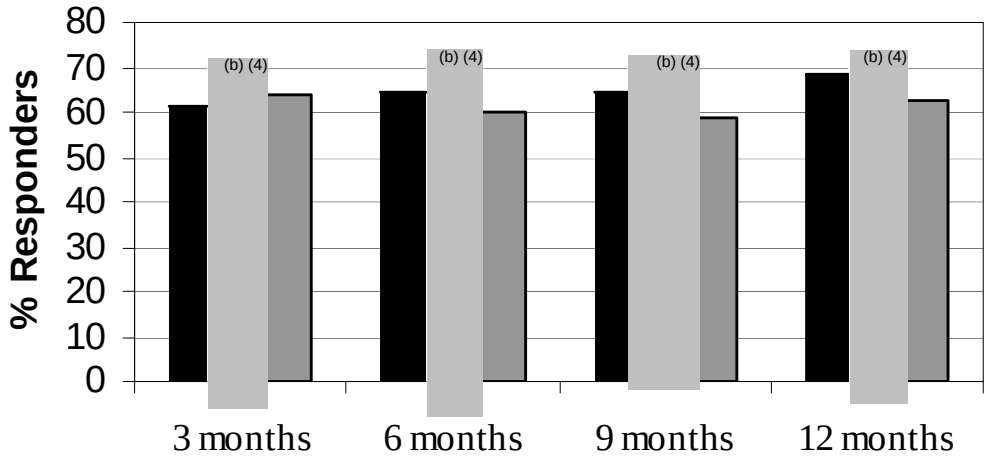
Figure 22 **ACR Pediatric 30 responder rates for meloxicam 0.125 mg/kg (black), meloxicam 0.25 mg/kg (white) and naproxen 10 mg/kg (grey) over time (LOCF) in Trial 107.208**

Table 23. ACR Pediatric 30 Responder rates) [95% Confidence Intervals] by treatment group over time (LOCF) in Trial 107.208

Time	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg	Naproxen 10mg/kg
3 months	63.0% [51.9%,74.1%]	(b) (4)	64.1% [53.5%,74.8%]
6 months	67.1% [56.4%,77.9%]		65.4% [54.8%,75.9%]
9 months	71.2% [60.9%,81.6%]		69.2% [59.0%,79.5%]
12 months	76.7% [67.0%,86.4%]		74.4% [64.7%,84.1%]

Source: U03-1727, Appendix 16.1.9.2, STATDOC 6.1.12, 6.1.13 (for month 6-12) and U03-1429, chapter 11.4.1.1 (for month 3)

Due to the fact that treatment in Trial 107.208 continued for up to 1 year and there were an appreciable number (43/225, 19.1%) of patients who discontinued treatment over time, **all dropouts were counted as non-responders, irrespective of their actual responder status. With this worst case approach, the ACR Pediatric 30 response rates for both meloxicam dose groups were numerically better than those for the naproxen dose group at months 6, 9, and 12. The observed differences are not statistically significant.** The result of the worst case approach is shown in **Figure 24**.



Source: U03-1727, Appendix 16.1.9.2, Table 6.1.25

Figure 24 ACR Pediatric 30 responder rates for meloxicam 0.125 mg/kg (black), meloxicam 0.25 mg/kg (white) and naproxen 10 mg/kg (grey) over time (worst case approach) in Trial 107.208

Overall, these data indicate that there is no loss of the therapeutic effect of meloxicam or naproxen over a treatment period of 1 year.

Reviewer's comments:

- (b) (4)

Table 25. **Individual core set parameters for the ACR Pediatric 30 (LOCF) as mean absolute change and mean % change from baseline by treatment groups at 3 and 12 months in Trial 107.208**

Endpoint	Time point	Meloxicam 0.125 mg/kg			Meloxicam 0.25mg/kg			Naproxen 10mg/kg		
		Mean	SD	% ch	Mean	SD	% ch	Mean	SD	% ch
Global assessment of disease activity by investigator	3 months	-17.7	17.8	47.7	(b) (4)			-16.4	18.4	43.7
	12 months	-21.7	19.6	58.5				-23.1	20.5	61.5
Parent global assessment of overall wellbeing	3 months	-15.8	20.4	42.8				-15.5	23.6	40.8
	12 months	-18.7	23.8	50.8				-21.1	24.9	55.6
Number of joints with active arthritis	3 months	-3.3	6.8	52.4				-2.8	5.5	42.4
	12 months	-3.7	7.0	59.3				-3.8	6.9	57.2
Number of joints with limited range of motion	3 months	-2.7	5.0	44.9				-2.4	5.0	37.5
	12 months	-3.3	5.0	53.9				-3.2	6.5	49.1
ESR	3 months	0.5	8.5	-2.1				-0.9	11.4	5.5
	12 months	-2.1	8.7	13.4				-3.9	14.4	18.5
Childhood Health Assessment Question-naire	3 months	-0.3	0.4	42.7				-0.3	0.4	36.9
	12 months	-0.4	0.5	58.9				-0.5	0.5	59.7

Source: U03-1727, Section 14, Table 14.2: 2

Reviewer's comments:

- *Sustainability of the effect over 12-months period is seen in each of the six components of the ACR pediatric 30 endpoint* (b) (4)
- *There is no significant difference between treatment groups*

6.1.5 Clinical Microbiology
Not applicable

6.1.6 Efficacy Conclusions

Two double blind, three-arm active controlled (two dosages of meloxicam and one dosage of naproxen) studies of three or more months duration evaluating the efficacy, safety and dose response of meloxicam oral suspension in pauci- and polyarticular JRA patients were submitted with this application in support of the indication for JRA.

Both efficacy studies utilized FDA recommended endpoints, had sufficient sample size and were of sufficient duration (12 weeks). In both of these studies, the JRA patients were balanced fairly equally between pauci- and polyarticular arthritis, and were evenly distributed between the ages of 2 and <17 years, with approximately one third of the patients being less than 6 years of age as requested in WPR.

In pivotal trial 107.235, meloxicam (b) (4) 0.125 (b) (4) was comparable to treatment with the active comparator naproxen, administered 5 mg/kg twice daily and increased to 7.5 mg/kg twice daily at week 4 and continued throughout the additional 8 weeks of treatment for the primary efficacy endpoint of the ACR Pediatric 30 responder rate. The responders' rate for the primary endpoint ACR Pediatric 30 responders at Week 12 (%, 90% confidence interval) was (b) (4)
meloxicam L 69.4% (57.9, 80.8) and **naproxen** treatment **68.0%** (57.4, 78.6). (b) (4)

(b) (4)
.

Subgroup analysis for effect of arthritis type course, age, gender, and MTX usage on the response to the treatment did not show any significant interaction.

Assessment of the individual components of the ACR core set parameters revealed that the number of joints with active arthritis and investigator's global assessment of overall disease activity had the highest proportion of responders (b) (4)
The only core set parameter that did not change substantially over the 12-week course of treatment (b) (4) was the ESR. All other individual core set parameters demonstrated improvement over the 12 weeks of therapy (b) (4).

(b) (4)

In supportive trial 107.208, meloxicam (b) (4) 0.125 (b) (4) mg/kg/d was comparable to treatment with naproxen at a dose of 10 mg/kg/d at 12 weeks of treatment

for the primary efficacy endpoint of the ACR Pediatric 30 responder rate. The Pediatric ACR responder rate (%, 90% confidence interval) for (b) (4) **meloxicam** (b) (4) **63.0%** (51.9, 74.1) (b) (4) compared to **64.1%** (53.5, 74.8) for the **naproxen** dose group. (b) (4)

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The efficacy response demonstrated during the first 12 weeks was sustained during the 40 week double-blind extension (b) (4).

There are two concerns with the trials design and analysis: one is the lack of placebo arm against which the effect of an active comparator naproxen could be compared, and the second one is the width of the selected non-inferiority margin of 20%.

Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in the armamentarium used to treat JRA, especially during its initial stages. In approximately one third of patients, the disease is controlled satisfactory with NSAIDs alone. In the majority of patients NSAIDs are used in conjunction with disease modifying anti-rheumatic agents (DMARDs) as adjunctive therapy. In practice, it is generally observed that patient's responses to NSAIDs are variable and unpredictable; a child may fail to respond to one drug and yet respond to another.

Only a few NSAIDs have been tested for safety and efficacy or have been approved for use in children with JRA. This relative lack of therapeutic alternatives presents a significant concern since most NSAIDs are being used off-label in children with JRA. Although a placebo-controlled trial design has significant scientific merit, utilizing a placebo in children with JRA is considered unethical. Because of these concerns, there have not been any placebo-controlled NSAID studies in JRA since 1983.
RA Guidance for Industry (February, 1999) recognizes this problem and accepts active-controlled studies as adequate.

Naproxen was chosen as an active comparator because it is one of the few NSAIDs approved for treatment of JRA, has a well-documented safety and efficacy profile based on previous clinical trials data, is frequently used for the treatment of JRA, and is available in liquid suspension to match meloxicam oral suspension. Of note, naproxen has been approved for JRA indication using a study design that utilized aspirin as an active comparator. Both studies in this application consistently showed the effect size of naproxen around 60% as measured by ACR Pediatric30 responders' rate that is similar to that of naproxen in VIOXX JRA studies and to the effect size of naproxen in adult RA studies utilizing ACR20 responder criteria, and the placebo effect size is usually much smaller, between 20-30% as measured by ACR20 responders.

In addition, there were two double-blind placebo controlled adult RA trials (107.258 and 107.183) submitted previously in support of adult RA indication where meloxicam showed sufficient evidence of efficacy. Of note, the effect size of meloxicam observed in those trials is comparable to that observed in current JRA trials, and the primary end-point used in adult RA trials (ACR20) is similar to the primary end-point used in JRA trials (ACR pediatric 30). The meloxicam doses selected for study in the JRA clinical program were derived from the experience with adult doses (7.5 mg, 15 mg and 22.5 mg per day) which had been shown to be effective in adult RA trials 107.258 and 107.183. Based on a 60 kilogram adult, the adult doses discussed above translate on a mg/kg basis to the following pediatric doses: 0.125 mg/kg/d (7.5 mg/d), 0.25 mg/kg/d (15 mg/d), and 0.375 mg/kg/d (22.5 mg/d).

Based on the JRA population PK data, meloxicam oral suspension exposures at 0.125 mg/kg, 0.25 mg/kg/d, and 0.375 mg/kg in children are comparable to the exposures seen in adults dosed once a day with 7.5 mg, 15 mg and 22.5 mg meloxicam.

Non-inferiority design used in both JRA studies is viewed by this reviewer as an acceptable approach. It would be nice to see another drug to be superior to naproxen in this type of trials, but that is not what we see in reality. What's important is to have another NSAID available with an efficacy comparable to naproxen and an acceptable safety profile that will provide a treating physician with an additional choice. There is no common agreement on what would constitute an acceptable non-inferiority margin, and the Sponsor was not given clear instructions on what would be considered an acceptable margin during study design discussions, nor was it spelled out in WPR. In this reviewer's opinion 20% non-inferiority margin is expectable. In addition, statistical reviewer concluded that "From results of the submitted studies this reviewer concludes that both of the meloxicam doses established non-inferiority in efficacy to naproxen by Week 12. Both of these doses also maintained the non-inferiority for up to one year."

In summary, the trials conducted by the Sponsor are the largest ones that have been conducted using NSAIDs in this indication. Based on results of the trials in the JRA program (107.235, 107.208), this reviewer concludes that there is a sufficient evidence of efficacy for the 0.125 (b) (4).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety evaluation was performed by reviewing ISS and safety data from individual trials.

The analysis performed in ISS combined all doses of meloxicam in one group and compared it with naproxen. Therefore, the individual data from trial 107.235 that utilized the highest dose of meloxicam (0.375 mg/kg/day) was reviewed separately where

appropriate to evaluate whether or not there is a higher incidence of AEs associated with a higher dose.

The program of meloxicam in JRA included 3 trials: 107.162, 107.208 and 107.235. Trial 107.162 was a one year, open-label study of meloxicam 0.250 mg/kg/day. Trial 107.208 was a one year, double-blind study of 3 treatment arms: meloxicam 0.125 mg/kg/day, meloxicam 0.250 mg/kg/day and naproxen 10 mg/kg/day. Trial 107.235 had 2 phases: a 12 week, double-blind study of 3 treatment arms with a forced escalation of dose within each arm after 4 weeks (i.e., meloxicam 0.125 mg/kg/day increased to 0.250 mg/kg/day after 4 weeks, meloxicam 0.250 mg/kg/day increased to 0.375 mg/kg/day after 4 weeks and naproxen 10 mg/kg/day increased to 15 mg/kg/day after 4 weeks) followed by a 12 week, open-label extension with all patients treated with meloxicam 0.375 mg/kg/day.

There were a total of 387 patients with JRA who received meloxicam and a total of 153 patients who received naproxen in the 3 JRA clinical trials (107.162, 107.208 and 107.235). These numbers of patients include **daily** administered doses of meloxicam from 0.125 mg/kg (up to 7.5 mg) to 0.375 mg/kg (up to 22.5 mg) and of naproxen from 10 mg/kg (up to 500 mg) to 15 mg/kg (up to 750 mg).

Table 26. Enumeration of subjects with meloxicam and comparator in JRA clinical trials

	Meloxicam			Naproxen	
	0.125 mg/kg	0.25 mg/kg	0.375 mg/kg	10 mg/kg	15 mg/kg
Active controlled trials (integrated at 4 and 12 weeks)[1]					
Up to 4 weeks	135	146		153	
Up to 12 weeks	73	136	72	78	75
Up to 1 year	73	74		78	
Open label trial/phase[2]					
Up to 12 weeks			191		
Up to 1 year		36			

1 Clinical Trials 107.235 and 107.208. In clinical Trial 107.235 patients were treated in double-blind phase (active controlled) for 12 weeks and then treated for an additional 12 weeks in an open label extension. The same patient may be counted in more than one row (duration of treatment).

2 Clinical Trial 107.162 and open label phase of 107.235. The patients treated in the open label extension phase of 107.235 are the same patients treated during the double-blind phase.

Source: Table 2.7.4.7.1.2-6

Table 27 below summarizes the number of patients exposed and the duration of exposure to meloxicam and naproxen. In this table the total number of patients exposed to meloxicam is given as 385 versus the total exposed of 387 because 2 patients (pt. no. 7549 and 8045 in Trial 107.162) were lost to follow-up and a precise duration of meloxicam treatment could not be provided. Note that the median duration of therapy with meloxicam was approximately twice that with naproxen reflecting the 1 year of treatment in the open-label Trial (107.162) with only meloxicam and the open-label extension with only meloxicam for all patients in Trial 107.235.

Table 27. Duration of therapy: Integrated Trials 107.162, 107.208 and 107.235

	Meloxicam Total N=385	Naproxen Total N=153
Duration (days)		
Mean	223.7	202.1
SD	122.7	136.4
Minimum	1.0	4.0
Maximum	424.0	385.0
Median	170.0	94.0

Table 28 presents the disposition of patients in the combined studies.

Table 28. Subject disposition: Integrated Trials 107.162, 107.208 and 107.235

	Treatment Groups			
	Meloxicam		Naproxen	
Number of Patients Treated	N =387	%	N = 153	%
Completed Planned treatment Duration	331	85.5	131	85.6
Discontinued due to AE Study Disease Worsening	7	1.8	3	2.0
Discontinued due to Other AE Disease Worsening	1	0.3	0	0
Discontinued due to Other AE	12	3.1	8	5.2
Discontinued due to Lack of Efficacy	11	2.8	5	3.3
Discontinued due to Administrative Reason[1]	20	5.2	5	3.3
Other	5	1.3	1	0.7

1 Administrative reasons include non compliance with protocol, lost to follow-up and withdrawal of consent
Source: Table 2.7.4.8.3.1

Reviewers' comments:

- *Majority of patients completed the studies.*
- *Subjects' disposition appears balanced across combined meloxicam groups and naproxen except for discontinuation due to administrative reason which is higher in meloxicam groups.*

Table 29. Demographic Profile of Patients: Integrated Trials 107.162, 107.208, 107.235

	Treatment Groups			
	Meloxicam		Naproxen	
	N =387	%	N = 153	%
Age (years)				
Mean ± SD	9.2 ± 4.2		8.6 ± 4.4	
Range	1 - 17		1 - 17	
Groups				
0 - 6	111	28.7	59	38.6
7 - 11	146	37.7	50	32.7
12 - 17	130	33.6	44	28.8
Gender				
Female	270	69.8	115	75.2
Male	117	30.2	38	24.8
Race				
Asian	13	3.4	5	3.3
Black	15	3.9	6	3.9
Caucasian	320	82.7	134	87.6
Missing	16	4.1	8	5.2
Weight (kg)				
Mean ± SD	34.21 ± 17.23		33.12 ± 17.81	
Range	10 – 139.1		11.2 - 87.0	

Source: Table 2.7.4.8.4.1

There are no substantive differences or imbalances observed between the 2 treatment groups with respect to these demographic characteristics. The patients in both treatment groups are fairly evenly distributed across the three age groups with the naproxen treatment group having the most patients in the 0-6 years of age group (39%), and the meloxicam treatment group having the most in the 7-11 years of age group (38%). Although these trials studied pediatric age groups, as expected with patients with JRA there was a high frequency of concomitant medication use. The majority of concomitant medication use involved commonly used pediatric medications such as antibiotics. Two important concomitant medication classes used by patients with JRA are systemic corticosteroids and disease modifying anti-rheumatic drugs (DMARDs). Concomitant

DMARD and systemic steroid were used by both treatment groups. There was a slightly lower use of DMARDs in the naproxen treatment group (28%) compared to the meloxicam treatment group (34%). Use of concomitant systemic steroid also was slightly lower in the naproxen treatment group (8%) compared to the meloxicam treatment group (14%).

Table 30. Concomitant medications for all patients: Integrated Trials 107.162, 107.208, 107.235

	Meloxicam	Naproxen
Total patients treated	387	153
No. (%) of patients with any concomitant therapy	320 (82.7)	106 (69.3)
No. (%) of patients with any concomitant systemic steroid therapy	55 (14.2)	12 (7.8)
No. (%) of patients with any concomitant injectable steroid therapy	9 (2.3)	3 (2.0)
No. (%) of patients with any concomitant DMARD therapy	131 (33.9)	42 (27.5)

Source: Tables 2.7.4.8.7.1-3

7.1.1 Deaths

There were no deaths in this development program.

7.1.2 Other Serious Adverse Events

Table 31 shows the serious adverse events by treatment observed in the integrated trials 107.162, 107.208 and 107.235. The total number of patients developing any serious adverse event while treated with meloxicam was 19/387 (4.9%), compared to 11/153 (7.2%) of patients treated with naproxen. The types of serious adverse events experienced were diverse with very few occurrences of any one preferred term. Only one term appeared with a frequency of equal to or greater than 1% [Juvenile arthritis in the naproxen-treated group at a frequency of 1.3% (2/153)]. As expected, the most commonly occurring events by system organ class were Infections and infestations [4/387 (1.0%) of patients in the meloxicam-treated group and 5/153 (3.3%) of patients in the naproxen-treated group] and Musculoskeletal and connective tissue disorders [8/387 (2.1%) of the meloxicam-treated group and 3/153 (2.0%) of the naproxen-treated group].

Table 31.

Serious Adverse Events: Integrated Trials 107.162, 107.208 and 107.235 by treatment at onset
MedDRA Syten Organ Class and Preferred Term

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Melox. Total		Naprox. Total	
	N	%	N	%
Summary Data				
Total Treated	387	100.0	153	100.0
Total with any Serious Adverse Event	19	4.9	11	7.2
Congenital, familial and genetic disorders	1	0.3	0	0.0
Congenital foot malformation	1	0.3	0	0.0
Eye disorders	1	0.3	1	0.7
Optic neuritis retrobulbar	1	0.3	0	0.0
Uveitis	0	0.0	1	0.7
Visual acuity reduced	1	0.3	0	0.0
Gastrointestinal disorders	3	0.8	0	0.0
Abdominal pain	3	0.8	0	0.0
General disorders and administration site conditions	2	0.5	0	0.0
Disease progression	2	0.5	0	0.0
Infections and infestations	4	1.0	5	3.3
Acute tonsillitis	1	0.3	0	0.0
Appendicitis	1	0.3	1	0.7
Bronchitis	1	0.3	0	0.0
Gastroenteritis	0	0.0	1	0.7
Infection	1	0.3	0	0.0

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Melox. Total		Naprox. Total	
	N	%	N	%
Infections and infestations				
Pneumonia	1	0.3	0	0.0
Sepsis	0	0.0	1	0.7
Varicella	0	0.0	1	0.7
Viral infection	0	0.0	1	0.7
Injury, poisoning and procedural complications	1	0.3	0	0.0
Accident	1	0.3	0	0.0
Injury	1	0.3	0	0.0
Road traffic accident	1	0.3	0	0.0
Investigations	2	0.5	0	0.0
Alanine aminotransferase increased	1	0.3	0	0.0
Aspartate aminotransferase increased	1	0.3	0	0.0
Body temperature increased	1	0.3	0	0.0
Musculoskeletal and connective tissue disorders	8	2.1	3	2.0
Arthralgia	1	0.3	1	0.7
Arthritis	1	0.3	1	0.7
Arthropathy	2	0.5	0	0.0
Back pain	1	0.3	0	0.0
Epiphysiolysis	0	0.0	1	0.7

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Melox. Total		Naprox. Total	
	N	%	N	%
Musculoskeletal and connective tissue disorders				
Joint swelling	1	0.3	1	0.7
Juvenile arthritis	1	0.3	2	1.3
Rheumatoid arthritis	2	0.5	0	0.0
Systemic lupus erythematosus	1	0.3	0	0.0
Psychiatric disorders	1	0.3	1	0.7
Abnormal behaviour	0	0.0	1	0.7
Affect lability	0	0.0	1	0.7
Depression	1	0.3	0	0.0
Mental disorder	0	0.0	1	0.7
Respiratory, thoracic and mediastinal disorders	1	0.3	1	0.7
Adenoidal hypertrophy	0	0.0	1	0.7
Pneumonitis	1	0.3	0	0.0
Tonsillar hypertrophy	0	0.0	1	0.7
Skin and subcutaneous tissue disorders	0	0.0	1	0.7
Henoch-Schonlein purpura	0	0.0	1	0.7

Reviewer's comments:

- *There were no unexpected events for any of the treatment groups*
- *Since the types of serious adverse events experienced were diverse with very few occurrences of any one preferred term, no definite conclusions can be made. From this reviewer point of view, the overall range of SAEs observed in either group does not present a significant concern.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 32 shows treatment discontinuations due to adverse events by treatment at onset for integrated Trials 107.162, 107.208 and 107.235. The frequency of patients with an adverse event leading to treatment discontinuation was 19/387 (4.9%) for the meloxicam-treated group and 13/153 (8.5%) for the naproxen-treated group. The preferred terms cited as leading to discontinuation were diverse with very few occurrences of any one term. The most frequently occurring preferred terms included Vomiting [4/387 (1.0%) for meloxicam and 0/153 (0.0%) for naproxen], Juvenile arthritis [4/387 (1.0%) for meloxicam and 0/153 (0.0%) for naproxen] and Abdominal pain [2/387 (0.5%) for meloxicam and 1/153 (0.7%) for naproxen]. All of the other terms occurred only one time. Not unexpectedly, the most commonly occurring events by system organ class were Gastrointestinal disorders [6/387 (1.6%) for meloxicam and 2/153 (1.3%) for naproxen] and Musculoskeletal and connective tissue disorders [6/387 (1.6%) for meloxicam and 2/153 (1.3%) for naproxen].

Table 32

Treatment discontinuations due to Adverse Events: Integrated Trials 107.162, 107.208 and 107.235 by treatment at onset
MedDRA Sytem Organ Class and Preferred Term

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Melox. Total		Naprox. Total	
	N	%	N	%
Summary Data				
Total Treated	387	100.0	153	100.0
Total with Adverse Events Leading to Treatment Discontinuation	19	4.9	13	8.5
Congenital, familial and genetic disorders	0	0.0	1	0.7
Pseudoporphyria	0	0.0	1	0.7
Eye disorders	0	0.0	1	0.7
Uveitis	0	0.0	1	0.7
Gastrointestinal disorders	6	1.6	2	1.3
Abdominal pain	2	0.5	1	0.7
Abdominal pain upper	1	0.3	1	0.7
Nausea	0	0.0	1	0.7
Vomiting	4	1.0	0	0.0
General disorders and administration site conditions	1	0.3	1	0.7
Asthenia	0	0.0	1	0.7
Disease progression	1	0.3	0	0.0
Infections and infestations	1	0.3	2	1.3
Acute tonsillitis	0	0.0	1	0.7
Pneumonia	1	0.3	0	0.0
Sepsis	0	0.0	1	0.7

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Melox. Total		Naprox. Total	
	N	%	N	%
Investigations	3	0.8	1	0.7
Alanine aminotransferase increased	1	0.3	0	0.0
Aspartate aminotransferase increased	1	0.3	0	0.0
Blood bilirubin increased	1	0.3	0	0.0
Hepatic enzyme increased	1	0.3	0	0.0
Liver function test abnormal	0	0.0	1	0.7
Musculoskeletal and connective tissue disorders	6	1.6	2	1.3
Arthralgia	1	0.3	0	0.0
Arthritis	1	0.3	0	0.0
Back pain	0	0.0	1	0.7
Joint range of motion decreased	0	0.0	1	0.7
Joint swelling	0	0.0	1	0.7
Juvenile arthritis	4	1.0	0	0.0
Myalgia	0	0.0	1	0.7
Osteochondrosis	0	0.0	1	0.7
Nervous system disorders	1	0.3	1	0.7
Headache	1	0.3	0	0.0
Paraesthesia	0	0.0	1	0.7
Skin and subcutaneous tissue disorders	1	0.3	3	2.0

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Melox. Total		Naprox. Total	
	N	%	N	%
Skin and subcutaneous tissue disorders				
Henoch-Schonlein purpura	0	0.0	1	0.7
Swelling face	0	0.0	1	0.7
Urticaria	1	0.3	1	0.7
Vascular disorders	0	0.0	2	1.3
Haematoma	0	0.0	1	0.7
Hyperaemia	0	0.0	1	0.7

Reviewer's comments:

- *The overall rate of treatment discontinuation due to adverse events was twice as high in naproxen group than in meloxicam all doses combined; however there were no a single adverse event that raised a concern due to high frequency*
- *Cases with increased liver function tests were reviewed further and do not cause additional concern*

7.1.3.2 Adverse events associated with dropouts

There were a total of 11 discontinuations due to AE in Trial 107.235 [1 additional patient, patient no. 12032 discontinued due to withdrawn consent but also developed an AE – Upper abdominal pain, at the time. Three of the discontinuations were SAEs (patient nos. 12172, 12339 and 12366).

There were a total of 20 discontinuations due to AEs in Trial 107.208. Four of these discontinuations (Patient Nos. 3007, 3014, 3231 and 3408) were SAEs.

Also, see section 7.1.3.1

7.1.3.3 Other significant adverse events

None

7.1.4 Other Search Strategies

See 7.1.5.6

7.1.5 Common Adverse Events

The total number (frequency) of patients who experienced any AE during the trials was approximately equally distributed between the meloxicam and naproxen treatment groups (284/387 [73.4%] and 120/153 [78.4%], respectively). **The five most frequently occurring preferred terms (PTs) included pyrexia, headache, rhinitis, abdominal pain and cough**. Generally, the AE profile for meloxicam and naproxen were similar and are representative of those expected in a pediatric population in general, or as part of the natural history of JRA, or with treatment with a nonsteroidal anti-inflammatory agent. See **Table 33** in section 7.1.5.4.

7.1.5.1 Eliciting adverse events data in the development program

The Sponsor collected all adverse events (defined as any untoward medical occurrence regardless of a causal relationship to study treatment) that occurred after informed consent for participation in the trials had been obtained. These were obtained by asking the patient (or their guardian) "How have you felt since your last clinic visit?" and were captured on the CRF by noting "Are there any events/symptoms which occurred since the last visit? - Yes or No". Safety laboratory test results or physical examination findings that led to an action with the study drug or to a therapeutic intervention (e.g., concomitant medication added or changed) and was not associated with an already reported adverse event symptom or diagnosis were also captured as an AE. Worsening of a pre-existing condition was also considered an AE if it met the criteria for a serious AE (see below), action was taken with study drug, treatment was required, or the investigator believed that the patient had shown a clear deterioration from baseline symptoms.

An adverse event was considered a **serious AE** (SAE) when it met any of the following criteria: resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was deemed serious for any other reason, e.g. cancer. A significant adverse event did not fulfil the aforementioned seriousness criteria, but because of its nature was considered medically "significant" in a specific trial(s). For Trials 107.235, 107.208 and 107.162 **significant AEs** were defined as perforation, ulceration, or bleeding (PUB) of the upper gastrointestinal tract (stomach or duodenum) and thrombocytopenia of <50,000 platelets/mm^3. All AEs, serious and non-serious, were fully documented on the appropriate case report form (Adverse Event Report Form). For each AE, the investigator provided the onset, duration, intensity, treatment required, outcome and action taken with the investigational drug. The investigator was requested to provide a determination of the relationship of the investigational drug to all AEs.

All adverse events (AEs) that occurred while on treatment and within 14 days after a patient discontinued treatment were considered treatment- emergent AEs. Pre-existing conditions and AEs that worsened during this period were also considered treatment-emergent.

Reviewer's comments:

- *Methods of eliciting AEs appear adequate to collect information on a broad range of possible AEs*

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Treatment –emergent AEs were coded by MedDRA (version 6.1) System Organ Class (SOC) and Preferred Term (PT).

7.1.5.3 Incidence of common adverse events

See **Table 33** in section 7.1.5.4

7.1.5.4 Common adverse event tables

Table 33. Number (%) of patients with adverse events (MedDRA Preferred Term) equal to or greater than 2% within meloxicam and naproxen treatment groups (5 most commonly occurring shown in bold**) in Integrated Trials 107.162, 107.208 and 107.235. Adverse events are assigned to treatment at onset and are listed by system organ class in alphabetical order.**

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Meloxicam		Naproxen	
	N	%	N	%
Total Treated	387	100.0	153	100.0
Total with any Adverse Event	284	73.4	120	78.4
Blood and lymphatic system disorders				
Lymphadenopathy	3	0.8	3	2.0
Eye disorders				
Conjunctivitis	5	1.3	3	2.0
Uveitis	8	2.1	7	4.6
Gastrointestinal disorders				
Abdominal pain	33	8.5	17	**11.1**
Abdominal pain upper	14	3.6	10	6.5
Constipation	3	0.8	6	3.9
Diarrhea	32	8.3	8	5.2
Nausea	13	3.4	9	5.9
Stomatitis	3	0.8	4	2.6
Vomiting	28	7.2	9	5.9
General disorders and administration site conditions				
Influenza-like illness	11	2.8	0	0.0
Pyrexia	46	11.9	21	**13.7**
Infections and infestations				
Acute tonsillitis	9	2.3	4	2.6
Bronchitis	14	3.6	8	5.2
Bronchitis acute	3	0.8	3	2.0
Ear infection	5	1.3	4	2.6
Gastroenteritis	10	2.6	6	3.9
Influenza	21	5.4	8	5.2
Nasopharyngitis	25	6.5	11	7.2
Otitis media	6	1.6	6	3.9
Pharyngitis	35	9.0	10	6.5
Pharyngitis streptococcal	6	1.6	4	2.6
Respiratory tract infection	11	2.8	2	1.3
Respiratory tract infection viral	10	2.6	1	0.7
Upper respiratory tract infection	23	5.9	8	5.2
Urinary tract infection	6	1.6	3	2.0
Varicella	5	1.3	3	2.0
Investigations				
Body temperature increased	9	2.3	3	2.0

Source: Table 2.7.4.8.6.1.1

(continued) (Page 2 of 2)

MedDRA system organ class MedDRA preferred term	Treatment at Onset			
	Meloxicam		Naproxen	
	N	%	N	%
Musculoskeletal and connective tissue disorders				
Arthralgia	17	4.4	7	4.6

	Treatment at Onset			
	Meloxicam		Naproxen	
Arthritis	9	2.3	3	2.0
Back pain	3	0.8	3	2.0
Joint swelling	13	3.4	2	1.3
Juvenile arthritis	14	3.6	3	2.0
Pain in extremity	4	1.0	3	2.0
Nervous system disorders				
Headache	46	**11.9**	13	8.5
Respiratory, thoracic and mediastinal disorders				
Cough	27	7.0	16	**10.5**
Epistaxis	4	1.0	5	3.3
Pharyngolaryngeal pain	23	5.9	6	3.9
Rhinitis	30	7.8	18	**11.8**
Skin and subcutaneous tissue disorders				
Pruritis	2	0.5	3	2.0
Rash	7	1.8	5	3.3
Vascular disorders				
Haematoma	1	0.3	4	2.6

Source: Table 2.7.4.8.6.1.1

Reviewer's comments:

- *Adverse events seem to be representative of those expected in a pediatric population in general, or as part of the natural history of JRA, or with treatment with nonsteroidal anti-inflammatory agents.*

7.1.5.5 Identifying common and drug-related adverse events

There were 37/387 (9.6%) of patients when treated with meloxicam and 19/153 (12.4%) of patients when treated with naproxen who experienced any AE perceived to be related to the study drug. As expected, the **most commonly occurring study drug-related AEs were within the SOC of Gastrointestinal disorders**. The gastrointestinal AEs included Abdominal pain [11/387 (2.8%) for meloxicam and 4/153 (2.6%) for naproxen], Abdominal pain upper [6/387 (1.6%) for meloxicam and 5/153 (3.3%) for naproxen], Vomiting [8/387 (2.1%) for meloxicam and 1/153 (0.7%) for naproxen] and Nausea [4/387 (1.0%) for meloxicam and 2/153 (1.3%) for naproxen]. **All other AEs affected only 1 to 2 patients (<1.0%).**

7.1.5.6 Additional analyses and explorations

Subgroup analyses of adverse events

Age

Overall, in the 2-6 years of age subgroup, 89/111 (80.2%) of patients when treated with meloxicam and 48/59 (81.4%) of patients when treated with naproxen developed any AE.

In the 7-11 years of age subgroup, 102/146 (69.9%) of patients when treated with meloxicam and 42/50 (84.0%) of patients when treated with naproxen developed any AE. In the 12-17 years of age subgroup, 93/130 (71.5%) of patients when treated with meloxicam and 30/44 (68.2%) of patients when treated with naproxen developed any AE.

In light of the relatively small numbers of patients in each group (after subgrouping according to age and treatment), there were no clinically meaningful discrepancies of AE incidences by SOC and PT among the age groups and between the 2 treatments (meloxicam and naproxen) within an age group. There were, as expected, some trends toward differences of frequencies of particular AEs between age groups consistent with those AEs usually viewed as age-related (e.g., lower incidences of headaches in the 2-6 years of age group relative to that in the 12-17 years of age group, higher incidences of pyrexia in the 2-6 years of age group relative to that in the 12-17 years of age group). Generally, the relative frequencies of SOC and PT AEs for each of the age groups reflected that observed for the entire population of patients. Typical of the spectrum of affected SOC for the entire population of patients, the **most commonly affected SOCs within age-specific groups were Infections and infestations, Gastrointestinal disorders and Respiratory, thoracic and mediastinal disorders.** As previously noted, a frequently affected SOC in the 2-6 years of age group was General disorders and administration site conditions (because of the higher frequency of pyrexia) and in the 12-17 years of age group the SOC Nervous system disorders (because of the higher frequency of headache).

The SAEs did not demonstrate an age-specific subgroup effect. No particular age-specific subgroup was observed to be at increased risk for discontinuing treatment due to an AE.

Gender

Overall, 80/117 (68.4%) males and 204/270 (75.6%) females treated with meloxicam and 28/38 (73.7%) males and 92/115 (80.0%) females treated with naproxen experienced any adverse event during the trials. In light of the relatively small numbers of males compared to females, there were **no appreciable clinically relevant differences in frequency of adverse event preferred terms by gender**.

Concomitant Use of Methotrexate

As methotrexate is the most commonly used DMARD to treat patients with JRA, the Sponsor assessed whether patients with or without concomitant use of methotrexate experienced a difference in incidence of adverse events in the trials. There were a total of 158 patients with concomitant methotrexate and 382 without concomitant methotrexate in the trials. Of the patients taking concomitant methotrexate, 69/111 (62.2%) of patients treated with meloxicam and 29/47 (61.7%) of patients treated with naproxen experienced any adverse event. Of the patients not taking concomitant methotrexate, 189/276 (68.5%) of patients treated with meloxicam and 91/106 (85.8%) of patients treated with naproxen experienced any adverse event. In light of the relatively small and unbalanced numbers of patients in each group, there were **no clinically relevant differences in incidences of adverse event preferred terms.** In particular, there were no noted differences in the

frequency of Blood and lymphatic system disorders, Gastrointestinal disorders, Infections and infestations and Investigations.

Adverse Events of Interest

Historically, use of NSAIDs has been associated with adverse events affecting specific organ systems. In particular, treatment with an NSAID can be associated with gastrointestinal, bleeding and skin-related adverse events. Overall, 118/387 (30.5%) of patients treated with meloxicam and 64/153 (41.8%) of patients treated with naproxen developed any of the AEs of interest. There was only 1 patient identified with pseudoporphyria (patient treated with naproxen). Gastrointestinal disorder AEs affected 96/387 (24.8%) of patients treated with meloxicam and 47/153 (30.7%) of patients treated with naproxen. The **most commonly occurring Gastrointestinal disorder AEs** of interest included **abdominal pain** (meloxicam group 33/387 [8.5%] vs naproxen group 17/153 [11.1%]), **abdominal pain upper** (meloxicam group 14/387 [3.6%] vs naproxen group 10/153 [6.5%]), **diarrhea** (meloxicam group 32/387 [8.3%] vs naproxen group 8/153 [5.2%]), **nausea** (meloxicam group 13/387 [3.4%] vs naproxen group 9/153 [5.91%]), and **vomiting** (meloxicam group 28/387 [7.2%] vs naproxen group 9/153 [5.9%]). Skin and subcutaneous tissue disorder AEs of interest affected 20/387 (5.2%) of patients treated with meloxicam and 13/153 (8.5%) of patients treated with naproxen. The most commonly occurring skin-related AE of interest was Rash (meloxicam group 7/387 [1.8%] vs naproxen group 5/153 [3.3%]). The other skin-related AEs of interest occurred relatively infrequently. The bleeding-related AEs of interest occurred as a group relatively infrequently including a diverse number of specific PTs.

Race

Incidences of AEs were examined by racial subgrouping and treatment (meloxicam and naproxen) at onset in the integrated trials (see Tables 2.7.4.8.6.4.4.1). Racial subgroupings included N.A. (not available; n=24), white (n=454), black (n=21), Asian (n=18) and other (n=23). French regulations prohibited collection of racial information from patients participating in France in Trial 107.208, accounting for the 24 patients listed as N.A.. In Trial 107.162 (open-label of meloxicam 0.250 mg/kg/day) there were 13 patients listed as white (from Germany) and 23 listed as “other” (interpreted at the time as Mexican without further designation of race or ethnicity). Note that the numbers of patients of the other races given here include some individuals counted twice, once for naproxen during the open-label phase of Trial 107.235 and once for meloxicam during the open-label extension of Trial 107.235. **In general, there are too few patients in each of the non-white racial subgroups to be able to detect any clinically meaningful differences.** Incidences observed for the white subgroup reflected the findings observed for the complete integrated subject population.

Given the relatively small numbers of Hispanic patients, there are no clinically meaningful differences observed.

Disease Course (Pauci- and Polyarticular)

The disease course of JRA may affect the incidence of adverse events. As polyarticular course of JRA is typically associated with a higher disease burden and is usually treated more aggressively with disease modifying anti-rheumatic drugs (DMARDs), the spectrum of AEs may differ from that experienced by patients with a pauci-articular course of JRA. Also, polyarticular course of JRA is clinically more analogous to adult onset of RA and therefore with NSAID treatment may display a pattern of AEs comparable to that described in adults. The subtyping of JRA course (pauci- vs. polyarticular) assigned in this analysis reflects the investigators' characterization of the patient's recent or current disease.

Of those patients characterized as having pauciarticular course JRA, 137/188 (72.9%) when treated with meloxicam and 67/79 (84.8%) when treated with naproxen experienced an AE. Of those patients characterized as having polyarticular course JRA, 147/199 (73.9%) when treated with meloxicam and 53/74 (71.6%) when treated with naproxen manifested an AE. Generally, the spectrum of AE PTs were diverse and well balanced between the two disease course types and within a disease course between the 2 treatments (meloxicam and naproxen). **In light of the relatively small numbers in each group there does not appear to be any clinically relevant differences between the AE incidences in each disease course type.**

7.1.6 Less Common Adverse Events

No additional separate data were provided

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Only laboratory parameters that were measured in all 3 integrated trials (107.162, 107.208 and 107.235) are included in this analysis. Laboratory values are presented here as normalized values. In the database the lab results are expressed as original value (value as reported by the lab), converted value (a value that has been converted by linear transformation to the preferred unit of measurement as per <converted value> = a*<original value> + b with a = parameter and b=unit specific conversion factor) and normalized value (a value that has been linear transformed with respect to the standard reference range as per <normalized value> = L + (<converted value> - 1)*(H-L)/(h-l) with H,L=boundaries of standard (new) reference range and h,l=boundaries of original reference range as provided by lab). Given this conversion, a normalized value may be negative while the original value was positive.

Also, in cases of repeated laboratory testing with a defined interval for a visit, the last laboratory value within the interval was used for calculation of the descriptive statistics. For ease of integration and simplicity of display of the integrated laboratory data from the three JRA trials (107.162, 107.208 and 107.235), the tables and listings in this document

will present visit number according to a defined interval (range in days) relative to Day 1 (day of randomization).

Table 34. Definition of visit intervals for integrated Trials 107.162, 107.235 and 107.208

Visit Number	Label	Interval (Days)
1	Baseline	From -99998 to 1
2	Week 12 (<= 105 days)	2 - 105
3	M6 (<= 203 days)	106 - 203
4	M9 (<= 294 days)	204 - 294
5	M12 (<= 379 days)	295 - 379
6	FU	380 - 99999

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Descriptive statistics for the hematology parameters (hematocrit, hemoglobin, red blood cell count, white blood cell count and platelet count) for the integrated trials (107.162, 107.235 and 107.208) were performed. For each of the hematology parameters, baseline values were not essentially different among the meloxicam or naproxen treatment group and mean differences compared to baseline were small and likely not clinically meaningful for each of the two treatment groups. Both treatment groups had a slight decrease in mean platelet counts from baseline over time: meloxicam -13,000 and naproxen -10,000 platelets at M12 which could be consistent with reduced systemic inflammation associated with response to regular treatment with DMARDs, systemic steroids and NSAIDs.

The key findings based on the descriptive statistics of hematocrit values from this population as a whole and the data from individual patients are: 1) of the total of 59 patients with possible clinically significant decrease of hematocrit at “baseline”

(defined as less than or equal to 37 % for males and less than or equal to 32% for females), 46 were male and 13 were female; most of the males had hematocrit values just below the defined cut-off; and 2) these patients did not develop further decreases (and in many instances actually showed increases) in hematocrit during subsequent on-treatment testing.

For the electrolytes (sodium, potassium) there were no appreciable differences in the baseline values for each treatment group and the mean differences between baseline and at end of treatment for all treatment groups were small and likely clinically insignificant.

Mean differences of the values of liver transaminases [aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT)], alkaline phosphatase and total bilirubin at baseline and after treatment for the two treatment groups were relatively small and unlikely to be clinically meaningful. There was a slight tendency for alkaline phosphatase to increase in both treatment groups with a greater increase observed over time on naproxen compared to meloxicam; at M12 mean difference from baseline was 41 U/L and 8 U/L for naproxen and meloxicam respectively. In Trial 107.208 there were 9/221 (4.1%) patients with increased alkaline phosphatase compared to 2/205 (1.0%) from Trial 107.235. This difference in frequency is likely due to the variability usually observed for this parameter in pediatric-aged populations in which rapid growth phases are reflected in markedly increased values of bone-derived alkaline phosphatase.

For the renal function parameter, serum creatinine there were no appreciable mean differences of the results obtained at baseline and after treatment for the two treatment groups.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

To be captured as a possibly clinically significant laboratory abnormality, 2 criteria needed to be met: 1) the abnormal value needed to meet the required level of abnormality (see Table); and 2) the baseline value did not meet the criteria for a possible clinically significant laboratory abnormality. If the baseline value was missing it was considered to be within the normal range.

Table 35. Criteria for clinically significant abnormalities based on normalized lab values for integrated trials 107.208 and 107.235

Functional Group/ Parameter	Direction	Criterion	Standard Unit
HAEMATOLOGY			
Haematocrit	Decrease	MALE LE 37 OR FEMALE LE 32	%
Haemoglobin	Decrease	MALE LE 11.5 OR FEMALE LE 9.5	g/dL
Red blood cell ct.	Decrease	LAB < 3	10^12/L
White blood cell ct.	Decrease	LAB < 3	10^9/L
	Increase	LAB > 20.1	10^9/L
Platelets	Decrease	LAB LE 75	10^9/L
	Increase	LAB GE 700	10^9/L
ELECTROLYTES			
Sodium	Decrease	LAB < 130	mmol/L
	Increase	LAB > 150	mmol/L
Potassium	Decrease	LAB < 3	mmol/L
	Increase	LAB > 5.5	mmol/L
ENZYMES			
AST/GOT, SGOT	Increase	LAB GE 3 x ULN	U/L
ALT/GPT, SGPT	Increase	LAB GE 3 x ULN	U/L
Alkaline phosphatase	Increase	LAB > 400	U/L
SUBSTRATES			
Creatinine	Increase	LAB GE 2	mg/dL
Bilirubin, total	Increase	LAB GE 2	mg/dL
DIFFERENTIAL_ABSOLUTE			
ANC	Decrease	LAB < 1.96	10^9/L
SUBSTRATES			
Blood urea nitrogen	Increase	LAB GE 30	mg/dL

In the integrated trials, the naproxen treatment group had 19/78 (24.4%) of patients with a possible clinically significant decrease in hematocrit and 5/79 (6.3%) of patients with a possible clinically significant decrease in red blood cell count compared to meloxicam (49/373 (13.1%) and 10/374 (1.9%), respectively). For hemoglobin, meloxicam had 5.6% versus naproxen 3.8% of patients with possible clinically significant decrease. This is explained by the number of patients whose hematocrit values just achieved the cut-off for a possibly clinically significant decrease without achieving the defined cut-off for hemoglobin. Decreases in white blood cell count were infrequent in both the meloxicam (1.9%) and naproxen (3.8%) treatment groups. There were no patients who experienced a possible clinically significant change in platelets in either treatment group.

Table 36. Frequency of patients (N%) with possible clinically significant abnormalities for integrated trials 107.208 and 107.235 up to 4 weeks

Hematology

Parameter/ Treatment	N	Decrease	Increase
Haematocrit			
Mel.125mg/kg	112	7 (6.3)	0
Mel.250mg/kg	120	8 (6.7)	0
Nap 10 mg/kg	125	12 (9.6)	0
Haemoglobin			
Mel.125mg/kg	113	2 (1.8)	0
Mel.250mg/kg	122	2 (1.6)	0
Nap 10 mg/kg	127	0	0
Red blood cell ct.			
Mel.125mg/kg	113	2 (1.8)	0
Mel.250mg/kg	121	0	0
Nap 10 mg/kg	127	1 (0.8)	0
White blood cell ct.			
Mel.125mg/kg	113	0	0
Mel.250mg/kg	122	0	0
Nap 10 mg/kg	127	0	0
Platelets			
Mel.125mg/kg	111	0	0
Mel.250mg/kg	119	0	0
Nap 10 mg/kg	126	0	0

up to 12 weeks

Parameter/ Treatment	N	Decrease	Increase
Haematocrit			
Mel.125mg/kg	69	11 (15.9)	0
Mel.250mg/kg	131	15 (11.5)	0
Mel.375mg/kg	69	5 (7.2)	0
Nap 10 mg/kg	74	12 (16.2)	0
Nap 15 mg/kg	75	8 (10.7)	0
Haemoglobin			
Mel.125mg/kg	70	3 (4.3)	0
Mel.250mg/kg	132	3 (2.3)	0
Mel.375mg/kg	69	1 (1.4)	0
Nap 10 mg/kg	75	3 (4.0)	0
Nap 15 mg/kg	75	1 (1.3)	0
Red Blood Cell Ct.			
Mel.125mg/kg	70	4 (5.7)	0
Mel.250mg/kg	132	2 (1.5)	0
Mel.375mg/kg	69	0	0
Nap 10 mg/kg	75	6 (8.0)	0
Nap 15 mg/kg	75	0	0
White Blood Cell Ct.			
Mel.125mg/kg	70	0	0
Mel.250mg/kg	132	2 (1.5)	0
Mel.375mg/kg	69	0	0
Nap 10 mg/kg	75	3 (4.0)	0
Nap 15 mg/kg	75	0	0
Platelets			
Mel.125mg/kg	70	0	0
Mel.250mg/kg	131	0	0
Mel.375mg/kg	69	0	0
Nap 10 mg/kg	75	0	0
Nap 15 mg/kg	75	0	1 (1.3)

up to 1 yr (trial 107.208)

Parameter/ Treatment	N	Decrease	Increase
Haematocrit			
Mel.125mg/kg	70	14 (20.0)	0
Mel.250mg/kg	72	16 (22.2)	0
Nap 10 mg/kg	75	21 (28.0)	0
Haemoglobin			
Mel.125mg/kg	71	8 (11.3)	0
Mel.250mg/kg	72	4 (5.6)	0
Nap 10 mg/kg	76	3 (3.9)	0
Red Blood Cell Ct.			
Mel.125mg/kg	71	6 (8.5)	0
Mel.250mg/kg	72	3 (4.2)	0
Nap 10 mg/kg	76	6 (7.9)	0
White Blood Cell Ct.			
Mel.125mg/kg	71	1 (1.4)	0
Mel.250mg/kg	72	3 (4.2)	0
Nap 10 mg/kg	76	3 (3.9)	0
Platelets			
Mel.125mg/kg	71	0	0
Mel.250mg/kg	72	0	0
Nap 10 mg/kg	76	0	0

For electrolytes, there were a few patients in both the meloxicam (6.1%) and naproxen (5.3%) treatment groups who experienced a clinically significant decrease in sodium. Similar proportions in both treatment groups also had increases suggesting this was test to test variability around the lower and upper limits of the normal range. Increases in creatinine were infrequent (<1%) in both groups.

Table 37. Frequency of patients (N%) with possible clinically significant abnormalities

for integrated trials 107.208 and 107.235

up to 4 weeks

Electrolytes

Parameter/ Treatment	N	Decrease	Increase
Sodium			
Mel.125mg/kg	108	0	1 (0.9)
Mel.250mg/kg	120	3 (2.5)	0
Nap 10 mg/kg	122	3 (2.5)	0
Potassium			
Mel.125mg/kg	107	0	0
Mel.250mg/kg	119	0	1 (0.8)
Nap 10 mg/kg	122	1 (0.8)	4 (3.3)

up to 12 weeks

Parameter/ Treatment	N	Decrease	Increase
Sodium			
Mel.125mg/kg	68	4 (5.9)	1 (1.5)
Mel.250mg/kg	131	5 (3.8)	1 (0.8)
Mel.375mg/kg	70	0	1 (1.4)
Nap 10 mg/kg	74	5 (6.8)	4 (5.4)
Nap 15 mg/kg	75	0	0
Potassium			
Mel.125mg/kg	68	0	2 (2.9)
Mel.250mg/kg	131	0	3 (2.3)
Mel.375mg/kg	70	0	3 (4.3)
Nap 10 mg/kg	73	1 (1.4)	5 (6.8)
Nap 15 mg/kg	75	0	1 (1.3)

up to 1 yr (trial 107.208)

Parameter/ Treatment	N	Decrease	Increase
Sodium			
Mel.125mg/kg	69	14 (20.3)	4 (5.8)
Mel.250mg/kg	72	8 (11.1)	3 (4.2)
Nap 10 mg/kg	76	7 (9.2)	6 (7.9)
Potassium			
Mel.125mg/kg	69	0	4 (5.8)
Mel.250mg/kg	72	1 (1.4)	4 (5.6)
Nap 10 mg/kg	75	1 (1.3)	8 (10.7)

For enzymes (AST, ALT and alkaline phosphatase), more patients had a clinically significant increase in alkaline phosphatase (defined as greater than 400 U/L) in the naproxen (8.7%) compared to the meloxicam (5.3%) treatment group. It is likely that in the age group studied, these elevated values may be related to bony growth and not to liver involvement. Increases in ALT and AST were infrequent (<~ 1%) in both treatment groups. Possible significant increases in total bilirubin were infrequent (1 patient in the meloxicam group and 2 patients in the naproxen group).

Table 38. Frequency of patients (N%) with possible clinically significant abnormalities

for integrated trials 107.208 and 107.235

Enzymes

Up to 4 weeks

Parameter/ Treatment	N	Decrease	Increase
AST/GOT, SGOT			
Mel.125mg/kg	110	0	0
Mel.250mg/kg	120	0	0
Nap 10 mg/kg	124	0	0
ALT/GPT, SGPT			
Mel.125mg/kg	111	0	0
Mel.250mg/kg	122	0	0
Nap 10 mg/kg	125	0	1 (0.8)
Alkaline phosphatase			
Mel.125mg/kg	109	0	2 (1.8)
Mel.250mg/kg	122	0	0
Nap 10 mg/kg	123	0	5 (4.1)

Parameter/ Treatment	N	Decrease	Increase
Creatinine			
Mel.125mg/kg	112	0	0
Mel.250mg/kg	121	0	0
Nap 10 mg/kg	122	0	0
Bilirubin, total			
Mel.125mg/kg	107	0	0
Mel.250mg/kg	117	0	0
Nap 10 mg/kg	121	0	1 (0.8)

up to 12 weeks

Parameter/ Treatment	N	Decrease	Increase
AST/GOT, SGOT			
Mel.125mg/kg	66	0	0
Mel.250mg/kg	131	0	0
Mel.375mg/kg	70	0	0
Nap 10 mg/kg	73	0	0
Nap 15 mg/kg	75	0	0
ALT/GPT, SGPT			
Mel.125mg/kg	69	0	1 (1.4)
Mel.250mg/kg	133	0	0
Mel.375mg/kg	70	0	0
Nap 10 mg/kg	74	0	0
Nap 15 mg/kg	75	0	1 (1.3)
Alkaline Phosphatase			
Mel.125mg/kg	69	0	2 (2.9)
Mel.250mg/kg	132	0	1 (0.8)
Mel.375mg/kg	70	0	0
Nap 10 mg/kg	73	0	5 (6.8)
Nap 15 mg/kg	75	0	2 (2.7)

Parameter/ Treatment	N	Decrease	Increase
Creatinine			
Mel.125mg/kg	70	0	0
Mel.250mg/kg	131	0	0
Mel.375mg/kg	70	0	1 (1.4)
Nap 10 mg/kg	75	0	0
Nap 15 mg/kg	75	0	0
Bilirubin, Total			
Mel.125mg/kg	68	0	0
Mel.250mg/kg	130	0	0
Mel.375mg/kg	70	0	0
Nap 10 mg/kg	71	0	2 (2.8)
Nap 15 mg/kg	75	0	0

up to 1 yr (trial 107.208)

Parameter/ Treatment	N	Decrease	Increase
AST/GOT, SGOT			
Mel.125mg/kg	69	0	0
Mel.250mg/kg	70	0	0
Nap 10 mg/kg	74	0	0
ALT/GPT, SGPT			
Mel.125mg/kg	71	0	1 (1.4)
Mel.250mg/kg	72	0	0
Nap 10 mg/kg	75	0	0
Alkaline Phosphatase			
Mel.125mg/kg	71	0	7 (9.9)
Mel.250mg/kg	72	0	7 (9.7)
Nap 10 mg/kg	75	0	11 (14.7)

Parameter/ Treatment	N	Decrease	Increase
Creatinine			
Mel.125mg/kg	71	0	0
Mel.250mg/kg	72	0	0
Nap 10 mg/kg	76	0	1 (1.3)
Bilirubin, Total			
Mel.125mg/kg	71	0	1 (1.4)
Mel.250mg/kg	72	0	0
Nap 10 mg/kg	73	0	2 (2.7)

Reviewer's comments:

- *Reviewing listing of all possible clinically significant abnormalities revealed three cases of increased bilirubin: one-in patient on meloxicam 0.125 mg (2.7 at month 9 visit) and two on naproxen 10 mg (one-2.8 at week 4 visit, and one-5.9 at week 12 visit)*

- *No other changes in laboratory parameters of appreciable clinical significance were identified*

- *Analysis of the safety profile for the long term (up to 1 year) did not suggest any duration of treatment –associated qualitative differences in the AE profile compared to the short term data.*

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Below are the narratives of patients who discontinued the trials due to laboratory abnormalities.

1. 95 days post first dose of study drug, while receiving meloxicam 0.25mg/kg/day), the patient was found to have elevated liver function tests (AST 88 U/L, reference range 0-53; ALT 112 U/L, reference range 0-56.

2. The patient had elevated liver function at screening and throughout the trial. The investigator indicated that the elevated value at screening was related to therapy with indomethacin and repeat tests prior to starting of naproxen were within normal limits. However AST and ALT were abnormal again at Days 27 and 55 after start of trial drug. 86 days after first dose of study drug and while the patient was taking naproxen

15 mg/kg/day, AST was 6.5 times the upper limit of normal and ALT was 8 times the upper limit of normal.

3. The patient's total bilirubin started to increase around Week 6 of the trial (1.13 mg/dl) while on Meloxicam 0.125 mg/kg/d. At Week 8, the bilirubin level had increased to 2.2mg/dl, and at Week 11, it was 2.34.

Reviewer's comments:

- *Those are known side effects of NSAIDs and the numbers of patients who discontinued the trials due to abnormal lab values do not raise additional concerns.*

7.1.7.4 Additional analyses and explorations

None

7.1.7.5 Special assessments

None

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Table 39 displays the vital sign data over time for the meloxicam and naproxen treatment groups. There was no appreciable change in pulse rate, diastolic or systolic blood pressure with either of the two treatments.

Table 39. Vital Sign Mean and Standard Deviation (SD) over time for Integrated Trials 107.162, 107.208, 107.235

	Meloxicam			Naproxen		
	Baseline	12 Weeks	12 Months	Baseline	12 Weeks	12 Months
Pulse (bpm)	85.6 ± 13.4 (N=379)	85.5 ± 12.7 (N=360)	83.9 ± 11.0 (N=140)	85.8 ± 14.3 (N=150)	86.5 ± 14.2 (N=146)	87.2 ± 13.0 (N=59)
Systolic BP (mmHg)	101.8 ± 11.4 (N=374)	101.2 ± 12.4 (N=359)	102.0 ± 13.0 (N=141)	102.4 ± 13.2 (N=148)	101.3 ± 11.4 (N=143)	102.1 ± 12.7 (N=59)
Diastolic BP (mmHg)	62.6 ± 9.5 (N=374)	62.8 ± 9.4 (N=359)	63.5 ± 10.1 (N=141)	61.7 ± 8.8 (N=148)	61.4 ± 9.1 (N=143)	61.7 ± 9.7 (N=59)

Source: Table 2.7.4.8.10.1.1

In Trial 107.235 physical examination including assessment of vital signs was performed during the screening visit and not on Day 1 just prior to initiation of treatment with study drug. Therefore, for some patients the assessment at the screening visit may have taken place while being treated with a NSAID prior to the washout phase. In Trial 107.208 physical examination including assessment of vital signs was performed on Day 1 just prior to initiation of treatment with study drug and after, if applicable, washout of the previously used NSAID. To assess whether the "baseline" vital sign values from these two trials can be combined, the Sponsor first compared the mean "baseline" values from each individual trial. Descriptive statistics for "baseline" systolic and diastolic blood pressures from Trials 107.208 and 107.235 are shown below in **Table 40**. The vital sign measurements at "baseline" are generally comparable between the trials and among the different treatment groups. In Trial 107.208 the treatment group that received meloxicam 0.250 mg/kg/d had a somewhat higher diastolic blood pressure and in Trial 107.235 the treatment group that received naproxen 15 mg/kg/d had a slightly higher mean systolic blood pressure with a higher upper end of range value. Mean pulse rate was very consistent across the trials and treatment groups.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 40. Descriptive statistics of baseline* blood pressure readings and pulse rate from Trials 107.208 and 107.235

	Systolic BP (mmHg)				Diastolic BP (mm Hg)			Pulse (beats per min.)	
Trial 107.208	N	Mean ± SD	Range	Median	Mean ± SD	Range	Median	N	Mean ±SD
Mel 0.125 mg/kg/d	70	100.7±11.3	70-126	100.0	62.8±8.8	40-80	61.5	70	85.8±13.3
Mel 0.250 mg/kg/d	73	102.7±10.9	80-130	100.0	65.4±10.1	40-95	65.0	72	85.3±11.3
Nap 10 mg/kg/d	77	101.1±10.5	80-130	100.0	61.6±7.9	50-90	60.0	77	86.4±13.3
Trial 107.235									
Mel 0.250 mg/kg/d#	61	102.2±11.6	70-126	100.0	60.3±8.8	40-80	60.0	61	87.3±15.4
Mel 0.375 mg/kg/d#	68	102.9±12.3	78-137	102.0	62.0±9.4	40-84	60.0	71	84.6±13.6
Nap 15 mg/kg/d#	71	103.9±15.5	76-177	100.0	61.8±9.6	40-80	60.0	73	85.1±15.3

*In Trial 107.235 vital sign measurements obtained at screening visit
Final treatment dose during double-blind phase of Trial 107.235
Source: Table 2.7.4.7.11.1.2 (107.208) and Table 2.7.4.7.11.1.3 (107.235)

With comparability of the "baseline" mean values for blood pressure and pulse established, the Sponsor then integrated the data from the two trials for the period of up to Week 12 (visit corresponding to 71 to 105 days after randomization) of treatment and calculated mean difference from baseline for each treatment group. The results are shown below in **Table 41**. For each treatment group the mean difference from baseline was relatively small and not likely to be clinically relevant especially given the relatively small numbers of patients studied and the degree of variability observed.

Table 41. Blood pressure and pulse mean difference to baseline for up to Week 12 by final treatment for integrated Trials 107.235 and 107.208

	Systolic BP (mm Hg)		Diastolic BP (mm Hg)	Pulse (beats per min.)	
Final Treatment	N	Mean ± SD	Mean ± SD	N	Mean ± SD
Mel 0.125 mg/kg	66	1.1 ± 9.0	0.5 ± 9.4	67	- 1.5 ± 12.5
Mel 0.250 mg/kg	120	-1.8 ± 10.4	- 0.3 ± 10.2	117	- 2.2 ± 12.1
Mel 0.375 mg/kg	59	2.5 ± 11.8	0.2 ± 11.2	62	1.8 ± 9.7
Nap 10 mg/kg	69	-0.5 ± 9.0	0.1 ± 7.8	69	1.2 ± 10.7
Nap 15 mg/kg	68	-07 ± 10.2	- 0.5 ± 7.7	70	0.2 ± 9.9

Source: Tables 2.7.4.7.11.1.1

Reviewer's comments:

- *It appears that there is an increase of 2.5mm Hg in mean systolic BP in Meloxicam 0.375 mg group compared to other treatment groups at 12 weeks of treatment however consequences of this increase are unknown*

In Trial 107.208, mean differences from baseline for blood pressure and pulse measurements obtained over a 12 month period were small (both increases and decreases observed) for both meloxicam and naproxen treatments. There were no dose response effects observed for the two doses of meloxicam studied (0.125 mg/kg/day and 0.250 mg/kg/day).

Table 42.

Vital Signs: Descriptive Statistics for Trial 107.208 over time (up to one year) including difference to baseline

			Value at visit						Difference from baseline					
Endpoint	Treatment	Visit	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Systolic BP (mmHg)	Mel.125mg/kg	Baseline	70	100.7	11.3	70	100.0	126						
		W4 <= 42 d	67	101.3	11.2	80	100.0	126	66	0.9	9.8	-30	0.0	20
		W8 <= 70 d	66	101.7	9.9	80	100.0	120	65	1.3	8.7	-19	0.0	20
		W12 <=105 d	67	101.7	11.6	80	100.0	145	66	1.1	9.0	-20	0.0	32
		M6 <=203 d	63	102.2	13.7	80	100.0	160	62	1.9	12.5	-20	0.0	60
		M9 <=294 d	59	102.7	11.2	80	100.0	121	58	2.7	10.4	-25	3.0	30
		M12 <=379 d	53	102.4	13.3	78	100.0	142	52	2.1	12.4	-25	0.0	30
		FU > 379 d	6	96.7	13.7	80	95.0	120	6	-0.8	14.3	-25	5.0	10
	Mel.250mg/kg	Baseline	73	102.7	10.9	80	100.0	130						
		W4 <= 42 d	71	104.3	13.4	80	103.0	149	71	1.5	10.5	-20	0.0	28
		W8 <= 70 d	67	103.0	13.0	80	100.0	144	67	-0.0	9.3	-17	0.0	24
		W12 <=105 d	64	102.7	13.1	80	100.5	137	64	-0.4	10.6	-35	0.0	25
		M6 <=203 d	66	103.6	12.9	80	102.0	136	66	0.6	11.0	-26	0.0	30
		M9 <=294 d	60	102.0	13.6	61	101.5	132	60	-0.8	13.0	-42	0.0	25
		M12 <=379 d	57	101.9	12.6	75	100.0	134	57	-1.1	10.2	-20	0.0	25
		FU > 379 d	8	104.9	14.4	88	102.0	127	8	3.9	9.9	-9	2.5	25
	Nap 10 mg/kg	Baseline	77	101.1	10.5	80	100.0	130						
		W4 <= 42 d	74	100.6	10.8	80	100.0	120	74	-0.6	8.7	-23	0.0	16
		W8 <= 70 d	66	100.4	11.6	79	100.0	125	66	-1.7	10.3	-30	0.0	18
		W12 <=105 d	69	100.7	11.3	79	100.0	134	69	-0.5	9.0	-26	0.0	17
		M6 <=203 d	70	100.3	11.5	80	100.0	125	70	-1.3	9.8	-20	0.0	17
		M9 <=294 d	65	101.9	11.9	80	100.0	129	65	0.4	9.4	-20	0.0	24
		M12 <=379 d	59	102.1	12.7	80	100.0	130	59	0.1	9.3	-20	0.0	25
		FU > 379 d	2	97.5	10.6	90	97.5	105	2	11.5	2.1	10	11.5	13

			Value at visit						Difference from baseline					
Endpoint	Treatment	Visit	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Diastolic BP (mmHg)	Mel.125mg/kg	Baseline	70	62.8	8.8	40	61.5	80						
		W4 <= 42 d	67	62.6	9.7	40	60.0	91	66	0.0	8.8	-26	0.0	20
		W8 <= 70 d	66	63.6	9.5	45	60.0	85	65	0.6	8.6	-22	0.0	20
		W12 <=105 d	67	63.1	9.5	40	61.0	92	66	0.5	9.4	-22	0.0	26
		M6 <=203 d	63	64.5	9.8	40	60.0	90	62	1.9	9.2	-20	0.0	30
		M9 <=294 d	59	63.1	10.2	41	60.0	90	58	0.2	9.3	-24	0.0	20
		M12 <=379 d	53	64.1	11.7	31	60.0	97	52	1.3	11.0	-24	0.0	26
		FU > 379 d	5	62.0	8.4	50	60.0	70	5	1.0	8.9	-10	0.0	10
	Mel.250mg/kg	Baseline	73	65.4	10.1	40	65.0	95						
		W4 <= 42 d	71	63.5	8.6	40	60.0	81	71	-2.1	10.5	-38	0.0	20
		W8 <= 70 d	67	64.2	8.4	43	61.0	80	67	-1.4	9.2	-29	0.0	20
		W12 <=105 d	64	65.1	9.9	48	63.5	90	64	-0.5	11.4	-32	0.0	38
		M6 <=203 d	66	63.4	9.9	49	60.0	82	66	-2.0	9.4	-32	0.0	20
		M9 <=294 d	59	63.7	9.6	40	65.0	85	59	-1.4	10.0	-30	0.0	20
		M12 <=379 d	57	62.4	9.5	45	60.0	90	57	-2.6	11.4	-30	-2.0	30
		FU > 379 d	8	62.8	10.5	48	60.0	80	8	-0.1	7.0	-13	0.0	10
	Nap 10 mg/kg	Baseline	77	61.6	7.9	50	60.0	90						
		W4 <= 42 d	74	61.5	7.9	40	60.0	85	74	-0.1	8.1	-20	0.0	27
		W8 <= 70 d	66	60.8	7.8	43	60.0	80	66	-1.3	8.2	-25	0.0	15
		W12 <=105 d	69	61.7	8.5	40	60.0	85	69	0.1	7.8	-21	0.0	16
		M6 <=203 d	70	61.5	8.7	40	60.0	80	70	-0.2	8.4	-20	0.0	26
		M9 <=294 d	65	62.9	8.4	45	60.0	80	65	1.1	9.8	-25	0.0	21
		M12 <=379 d	59	61.7	9.7	40	60.0	85	59	-0.9	8.3	-20	0.0	16
		FU > 379 d	2	67.5	3.5	65	67.5	70	2	11.5	12.0	3	11.5	20

Reviewer's comments:

- *Results are inconsistent in that there is a slight increase in mean SBP and DBP observed in meloxicam 0.125 mg group at different time points, at the same time meloxicam 0.25 mg and naproxen groups showed decreases and increases in mean BP at similar time points*

In Trial 107.235, mean differences from baseline for the vital signs were also small. There was a small increase relative to baseline of systolic blood pressure (mean = 1.7 mm Hg) observed in the higher meloxicam group (0.375 mg/kg/day) after Week 12 of the double-blind phase and after an additional 12 weeks of the open-label extension (meloxicam 0.375 mg/kg/day). However, for the other two treatment groups (meloxicam 0.250 mg/kg/day and naproxen 15 mg/kg/day during the double-blind phase), the mean difference relative to baseline of systolic blood pressure decreased after an additional 12 weeks of treatment with meloxicam 0.375 mg/kg/day (mean decreases of 2.1 mm Hg for both groups).

Table 43.

Vital Signs: Descriptive Statistics for Trial 107.235 over time (double-blind and open phase) including difference to baseline

			Value at visit						Difference from baseline					
Endpoint	Treatment[1]	Visit[2]	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Diastolic BP (mmHg)	Mel.250mg/kg	Baseline	61	60.3	8.8	40	60.0	80						
		Week 12	61	59.8	8.9	40	60.0	80	60	-0.1	8.7	-25	0.0	20
		Week 12 open	57	60.5	8.8	42	60.0	77	56	0.8	8.7	-25	0.0	18
	Mel.375mg/kg	Baseline	68	62.0	9.4	40	60.0	84						
		Week 12	67	62.1	9.1	40	60.0	80	65	0.7	11.2	-30	0.0	34
		Week 12 open	63	63.6	8.8	40	62.0	82	59	2.0	8.7	-20	0.0	24
	Nap 15 mg/kg	Baseline	71	61.8	9.6	40	60.0	80						
		Week 12	72	61.5	10.2	35	60.0	85	71	-0.4	7.7	-16	0.0	18
		Week 12 open	68	62.2	10.1	40	60.0	88	65	0.1	10.4	-24	0.0	25
Systolic BP (mmHg)	Mel.250mg/kg	Baseline	61	102.2	11.6	70	100.0	126						
		Week 12	61	98.2	13.5	70	100.0	123	60	-3.2	10.0	-20	0.0	24
		Week 12 open	57	98.7	12.6	70	98.0	123	56	-2.1	10.8	-30	0.0	28
	Mel.375mg/kg	Baseline	68	102.9	12.3	78	102.0	137						
		Week 12	67	103.5	12.0	80	100.0	132	65	1.7	11.6	-20	0.0	32
		Week 12 open	63	102.8	12.0	70	100.0	132	59	1.7	11.8	-28	0.0	36
	Nap 15 mg/kg	Baseline	71	103.9	15.5	76	100.0	177						
		Week 12	72	102.4	11.7	70	104.5	122	71	-1.5	12.0	-57	0.0	26
		Week 12 open	68	101.8	12.7	70	101.0	138	65	-2.1	13.6	-53	0.0	40
Pulse (bpm)	Mel.250mg/kg	Baseline	61	87.3	15.4	54	88.0	120						
		Week 12	61	84.6	10.4	64	82.0	115	60	-3.2	12.9	-39	-4.0	26
		Week 12 open	57	86.2	13.7	28	88.0	110	56	-1.8	18.2	-87	-2.5	38
	Mel.375mg/kg	Baseline	71	84.6	13.6	64	82.0	124						
		Week 12	69	86.8	14.2	60	84.0	132	68	1.5	9.8	-29	0.0	24
		Week 12 open	63	84.0	12.1	64	80.0	119	62	-0.6	12.6	-32	-1.0	28
	Nap 15 mg/kg	Baseline	73	85.1	15.3	55	80.0	120						
		Week 12	75	85.4	14.8	60	82.0	126	73	-0.1	9.9	-30	0.0	32
		Week 12 open	69	87.3	14.5	60	84.0	130	67	2.6	15.0	-25	4.0	50

[1] Treatment as randomized
[2] Visit Week 12 refers to end of double-blind phase, visit Week 12 open refers to end of open phase

Reviewer's comments:

- *Integrated data and data from trial 107.235 suggest that meloxicam 0.375 mg dose might increase both systolic and diastolic blood pressure.*

For the one-year, open-label (meloxicam 0.250 mg/kg/day) Trial 107.162 with limited numbers of patients (n = ≤35 patients at each time point), mean differences from baseline for vital signs were relatively small and variable and likely clinically inconsequential.

Table 44.

Vital Signs: Descriptive Statistics for Trial 107.162 over time (up to one year) including difference to baseline

			Value at visit					Difference from baseline				
Endpoint	Treatment	Visit	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Diastolic BP (mmHg)	Mel.250mg/kg	Baseline	35	64.0	9.6	50	60.0	90						
		W4 <= 42 d	34	63.2	5.5	50	60.0	75	33	1.2	9.6	-20	0.0	25
		W8 <= 70 d	34	63.5	10.1	40	60.0	80	33	1.1	10.5	-20	0.0	20
		W12 <=105 d	34	64.9	7.2	50	62.5	80	33	2.6	9.2	-20	0.0	20
		M6 <=203 d	35	65.7	10.4	40	70.0	80	34	3.2	12.0	-20	0.0	20
		M9 <=294 d	32	66.0	10.7	40	60.0	81	31	4.4	11.9	-20	0.0	26
		M12 <=379 d	31	64.5	8.1	50	60.0	80	30	2.8	10.6	-20	5.0	20
Systolic BP (mmHg)	Mel.250mg/kg	Baseline	35	99.7	10.0	80	100.0	130						
		W4 <= 42 d	34	95.1	9.1	80	90.0	130	33	-5.9	11.8	-30	-5.0	15
		W8 <= 70 d	34	96.6	9.7	80	92.5	120	33	-4.7	12.4	-30	-5.0	20
		W12 <=105 d	34	97.2	10.0	85	97.5	120	33	-3.8	13.1	-20	-5.0	30
		M6 <=203 d	35	98.0	11.1	80	100.0	120	34	-3.1	15.4	-30	0.0	40
		M9 <=294 d	32	101.4	13.1	80	100.0	146	31	1.1	13.1	-20	0.0	20
		M12 <=379 d	31	101.2	13.4	80	100.0	155	30	0.4	14.3	-30	2.5	25
Pulse (bpm)	Mel.250mg/kg	Baseline	35	84.0	10.7	60	80.0	108						
		W4 <= 42 d	34	81.8	10.6	60	82.0	104	33	-2.7	17.2	-32	-3.0	36
		W8 <= 70 d	33	88.0	13.5	64	86.0	134	32	2.8	15.5	-30	4.0	26
		W12 <=105 d	34	85.7	12.0	64	84.0	125	33	1.3	14.6	-40	1.0	24
		M6 <=203 d	35	83.2	8.6	66	84.0	104	34	-1.5	12.6	-26	-3.0	32
		M9 <=294 d	32	82.4	9.6	60	80.0	108	31	-2.4	13.0	-28	-4.0	26
		M12 <=379 d	30	84.9	9.6	70	82.5	115	29	1.7	11.3	-20	1.0	32

Reviewer's comments:

- *Again, there are inconsistent findings: increase in mean diastolic BP at all time points was observed with meloxicam 0.250 mg/kg dose and decrease in mean systolic BP*

APPEARS THIS WAY ON ORIGINAL

7.1.8.4 Additional analyses and explorations

None

Mean weight over time

A generic pediatric concern raised by the FDA Pediatric Written Request is the potential for a drug used in children to affect their growth and development.

Since NSAIDs have not been known to affect growth or development in children, this variable was not pre-specified as a safety endpoint for these clinical trials in JRA. The Sponsor performed a literature search to see if there have been any reports of an effect of NSAIDS on growth and development in children. The Medline, EMBASE+ and Derwent Drug File databases from 1986 to the present were searched for the combination terms of "NSAIDs and Growth Effects". The conclusion was that there was no evidence found from this search that NSAIDs have an effect on growth or development in children with JRA.

In the controlled and uncontrolled trials, the only growth and development measure that was followed over time was weight as this was used to adjust the NSAID dosing (on a mg/kg basis) of the JRA patients.

Table 45.

Weight over time: Integrated Trials 107.162, 107.208 and 107.235

			Value at visit						Difference from baseline					
Treatment	Visit		N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Melox. Total	Baseline		387	34.4	17.4	10	31.0	139.1						
	W12	<=105 d	379	35.5	17.7	10.3	32.0	139	379	1.0	1.8	-8.1	0.8	19
	W24/M6	<=203 d	288	34.4	15.9	10	31.7	97	288	1.9	2.2	-10.8	1.5	10.1
	M9	<=294 d	158	34.5	14.3	12	32.0	90.3	158	2.8	2.3	-3	2.6	11.5
	M12	<=379 d	64	36.4	16.6	12.8	32.9	99	64	4.2	3.0	-3.3	4.0	10.5
	FU	> 379 d	5	32.6	11.8	15.5	31.0	44.5	5	2.8	2.2	1.3	1.7	6.5
Naprox. Tota	Baseline		153	33.3	17.8	11.2	28.8	87						
	W12	<=105 d	152	34.2	18.0	11.5	28.6	89.6	152	0.8	1.5	-4	0.7	7.5
	W24/M6	<=203 d	72	32.0	16.2	14	26.5	83	72	1.7	1.5	-0.5	1.5	7.5
	M9	<=294 d	64	33.2	16.8	14.3	27.1	83	64	2.4	1.9	-0.9	2.2	7.8
	M12	<=379 d	17	31.6	13.7	14.5	28.0	53	17	3.2	2.3	-1	3.0	9.3
	FU	> 379 d	1	21.5		21.5	21.5	21.5	1	1.5		1.5	1.5	1.5

In the uncontrolled Trial 107.162 (meloxicam 0.250 mg/kg/day), weight was seen to increase steadily over the one year treatment period consistent with expected normal weight gain in a pediatric population . At baseline the average weight was 27.2 kilograms and by the end of 12 months of treatment the average weight was 31.3 kilograms (with a mean increase of 3.4 kilograms over one year).

Table 46.

Weight over time: trial 107.162

Treatment	Visit	Value at visit N	Mean	SD	Min	Median	Max	Difference from baseline N	Mean	SD	Min	Median	Max
Mel.250mg/kg	Baseline	36	27.2	11.7	13	24.3	64.5						
	W4 <= 42 d	34	28.1	11.9	13.4	24.7	66	34	0.3	0.8	-1.8	0.4	1.7
	W8 <= 70 d	34	28.5	12.2	13.5	24.9	66	34	0.8	1.0	-1	0.6	3.2
	W12 <=105 d	34	28.7	12.3	13.5	25.5	66	34	0.9	1.3	-1.1	0.6	4.5
	M6 <=203 d	34	29.5	12.6	13.7	26.4	68	34	1.7	1.4	-1	1.6	5.1
	M9 <=294 d	33	30.4	12.9	13.5	27.0	68.5	33	2.6	1.9	-0.8	2.9	7.3
	M12 <=379 d	31	31.3	13.5	14.1	28.8	63.5	31	3.4	2.9	-3.3	3.5	10

In pivotal controlled Trial 107.235, a similar degree of increase in weight was seen over time. During the controlled 12 week portion of the trial, the mean gain in weight observed for each of the assigned treatment groups was 1.4 kilogram (meloxicam 0.25 mg/kg), 1.2 kilogram (meloxicam 0.375 mg/kg) and 1.0 kilogram (naproxen 15 mg/kg). At 6 months, after all groups had been on meloxicam 0.375 mg/kg/d for an additional 12 weeks during the open-label extension phase, the final mean increase in weight from baseline was 1.9, 2.0, and 1.7 kilograms for the three assigned treatment groups, respectively (**Table 47**).

Table 47.

Weight over time: trial 107.235

Treatment[1]	Visit	Value at visit N	Mean	SD	Min	Median	Max	Difference from baseline N	Mean	SD	Min	Median	Max
Mel.250mg/kg	Baseline	62	33.9	16.4	10	32.4	74						
	W4 <= 56 d	62	34.4	16.4	10.1	33.6	74.5	62	0.4	0.9	-1.6	0.3	2.2
	W12 <=105 d	58	34.7	17.8	10.3	33.4	93	58	1.4	2.8	-3	1.0	19
	W18 <=147 d	57	34.7	17.4	10	33.2	78	57	1.4	2.2	-4.7	1.0	8.8
	W24 <=189 d	53	35.3	17.3	10	34.6	76	53	1.9	2.2	-2.6	1.3	9.4
	FU > 189 d	2	45.7	18.8	32.4	45.7	59	2	-0.7	1.3	-1.6	-0.7	0.2
Mel.375mg/kg	Baseline	72	37.0	21.6	11	32.6	139.1						
	W4 <= 56 d	71	37.2	21.6	10.7	32.7	139	71	0.3	1.5	-4.3	0.2	8
	W12 <=105 d	65	35.2	17.3	11.1	32.0	84.5	65	1.2	2.1	-8.1	0.9	9
	W18 <=147 d	63	36.0	17.0	11.9	32.1	81.8	63	1.6	2.4	-10.1	1.4	9.3
	W24 <=189 d	61	36.8	16.9	12.7	33.5	82.7	61	2.0	2.9	-10.8	1.5	10.1
	FU > 189 d	1	25.6		25.6	25.6	25.6	1	0.3		0.3	0.3	0.3
Nap 15 mg/kg	Baseline	75	37.5	19.1	11.2	34.5	87						
	W4 <= 56 d	75	38.0	19.2	11.3	35.0	88.3	75	0.5	1.1	-3.2	0.3	6
	W12 <=105 d	73	38.1	19.2	11.5	35.0	89.6	73	1.0	1.7	-3.5	0.7	7.5
	W18 <=147 d	69	38.5	19.8	11.8	34.0	89	69	1.5	2.2	-2.7	1.0	10.5
	W24 <=189 d	64	39.8	19.6	12	36.9	90.7	64	1.7	2.4	-2.7	1.2	11
	FU > 189 d	2	49.2	48.6	14.8	49.2	83.6	2	3.6	2.5	1.8	3.6	5.4

In the one year controlled Trial 107.208, a comparable degree of increase in weight was seen over time. During the controlled 12 week portion of the trial, the mean gain in weight observed for each of the assigned treatment groups was 1.0 kilogram (meloxicam 0.125 mg/kg), 1.1 kilogram (meloxicam 0.25 mg/kg) and 0.6 kilogram (naproxen 10 mg/kg). At 9 months, the final mean increase in weight from baseline was 3.0, 2.9, and 2.4 kilograms for the three assigned treatment groups, respectively (**Table 48**).

Table 48.

Weight over time: trial 107.208

Treatment	Visit	Value at visit N	Mean	SD	Min	Median	Max	Difference from baseline N	Mean	SD	Min	Median	Max
Mel.125mg/kg	Baseline	73	33.8	14.9	12	31.5	81						
	W4 <= 42 d	70	33.5	14.7	11	31.5	78.6	70	0.3	0.8	-2.4	0.0	2.7
	W8 <= 70 d	69	33.3	14.3	11	32.0	78	69	0.5	1.0	-3	0.3	3
	W12 <=105 d	70	33.8	14.3	13	31.6	79	70	1.0	1.3	-2	0.9	5
	M6 <=203 d	65	34.7	15.2	12	32.0	86	65	2.1	1.8	-1	2.0	7
	M9 <=294 d	62	36.2	15.2	12	33.5	90.3	62	3.0	2.5	-3	2.5	11.5
	FU > 294 d	15	41.5	18.9	12.8	43.5	90.1	15	5.0	3.1	0.8	5.7	10.5
Mel.250mg/kg	Baseline	74	32.9	15.1	12	29.2	92.5						
	W4 <= 42 d	71	33.5	15.4	11.5	29.7	94.6	71	0.3	0.9	-1.7	0.0	3.4
	W8 <= 70 d	68	34.1	15.7	11.7	30.8	98	68	0.8	1.3	-1.7	0.6	5.5
	W12 <=105 d	65	33.3	15.6	11.5	29.4	96.4	65	1.1	1.4	-1.3	0.9	5.4
	M6 <=203 d	67	34.4	15.8	12	31.0	97	67	2.0	1.9	-2.9	1.5	6.5
	M9 <=294 d	61	34.7	13.7	12.3	32.0	71.5	61	2.9	2.2	-1	2.6	9.5
	FU > 294 d	22	39.3	17.2	18.7	38.6	99	22	4.5	2.8	0	3.8	9.8
Nap 10 mg/kg	Baseline	78	29.2	15.5	12	23.6	81						
	W4 <= 42 d	76	29.8	15.6	13	24.2	81	76	0.3	0.7	-1.8	0.0	2.8
	W8 <= 70 d	71	30.9	16.0	13	25.0	83	71	0.6	0.9	-2.2	0.5	3.5
	W12 <=105 d	71	30.0	14.7	13	25.0	81	71	0.6	1.3	-4	0.5	4
	M6 <=203 d	71	31.8	16.3	14	26.5	83	71	1.6	1.5	-0.5	1.5	7.5
	M9 <=294 d	64	33.2	16.8	14.3	27.1	83	64	2.4	1.9	-0.9	2.2	7.8
	FU > 294 d	18	31.1	13.5	14.5	27.8	53	18	3.1	2.3	-1	3.0	9.3

The data on weight would suggest that use of either meloxicam or naproxen did not appear to have any appreciable negative effect on weight gain in the JRA pediatric population studied.

Table 49 displays the mean weight by treatment group over time. Data out to 9 months is displayed as beyond this time point the number of patients decreases markedly in both treatment groups. Noting that the patient number at each time point is decreasing with time, the mean weights remained approximately the same over 9 months for both patient groups. The mean differences (i.e., the mean of the differences in weight for the same individuals over time) between baseline and at 9 months [meloxicam (+ 2.8 kg, n=158) and naproxen (+2.4 kg, n=64)] and at 12 months [meloxicam (+ 4.2 kg, n=64) and naproxen (+3.2 kg, n=17)] suggested some increase in weight over time and were comparable between the 2 treatment groups even with the relatively small and unbalanced numbers at these time points.

Table 49. Weight (Kg) mean and standard deviation (SD) over time for Integrated Trials 107.162, 107.208, 107.235

	Meloxicam				Naproxen			
	Baseline (N=387)	24 Weeks (N= 288)	9 Months (N= 158)	12 Months (N =64)	Baseline (N= 153)	24 Weeks (N=72)	9 Months (N=64)	12 Months (N=17)
Weight (Kg)	34.4 ± 17.4	34.4 ± 15.9	34.5 ± 14.3	36.4 ± 16.6	33.3 ± 17.8	32.0 ± 16.2	33.2 ± 16.8	31.6 ± 13.7

Source: Table 2.7.4.8.10.2.1

Reviewer's comments:

- *Assessment for possible growth and development-related adverse events or weight change over time for up to 1 year of treatment does not suggest that meloxicam or naproxen has any significant negative effect on growth and development.*

- *Review of list –line listing of children who gained less than 2 kg over the course of each trial revealed that numerically more children on meloxicam 0.375 mg/kg/d and naproxen 15 mg/kg/d lost weight by the end of the study 107.235 (24 weeks) compared to meloxicam .250 mg/kg/d and naproxen 10 mg/kg/d groups at 12 months in study 107.208.*
- *It would be impossible to distinguish whether this is the effect of a study drug, or baseline treatment effect, or the effect of the disease itself.*

Uveitis

In Trial 107.235 patients underwent ophthalmologic examination (including slit lamp) during screening (before receiving study drug) and after approximately 12 weeks of double-blind treatment before the start of the open-label treatment phase. Whether patients had a history of uveitis was also captured for this trial. Based on the results of the ophthalmologic examination, uveitis was described as either present or not and if present as active, inactive or chronic. Investigators were instructed to select only one descriptor of uveitis. The definition of each descriptor of uveitis was not pre-specified and therefore was left up to the ophthalmologists' interpretation. Comparison of the ophthalmologists' exam reports and the descriptors selected provided insight into how the different terms to describe uveitis were being used. The term "active uveitis" was generally used to describe the presence of inflammatory cells in the anterior chamber of the eye. The term "inactive uveitis" was used to describe either very few inflammatory cells in the anterior chamber or the lack of inflammatory findings while under treatment or after recently completed treatment for active uveitis. The term "chronic uveitis" was used to describe either the presence of sequelae of chronic inflammation e.g., band keratopathy, synechiae, keratitic precipitates, without concomitant presence of inflammatory cells or simply that uveitis was longstanding.

Table 50 below summarizes the data on uveitis diagnosed by ophthalmologic examination in Trials 107.235 and 107.208. Assessment of the data from Trial 107.235 showed a total of 15 patients with evidence of uveitis (inactive, active and chronic) identified by exam at sometime during the trial (baseline and at the end of the 12 weeks of double-blind treatment). In the **Mel L** group, 1 patient with findings of active uveitis at baseline was found at 12 weeks to still have active uveitis, while the other 2 patients with active uveitis at baseline were found to have no findings of uveitis (1 patient) and findings of chronic uveitis (1 patient). Two patients with findings of chronic uveitis at baseline were found to have chronic uveitis (1 patient) and inactive uveitis (1 patient) after 12 weeks of treatment. One patient who did not have uveitis at baseline was found to have findings of inactive uveitis after 12 weeks of treatment. In the **Mel H** group, of the 4 patients with active uveitis at baseline, after 12 weeks of treatment 1 patient still had findings of active uveitis, 1 patient had findings of chronic uveitis, 1 patient had no findings of uveitis, and 1 patient did not have the follow-up exam performed. One patient who did not have findings of uveitis at baseline was described as having findings of inactive uveitis after treatment. In the **Nap** group, there were 2 patients with findings of active uveitis at baseline and after treatment these same 2 patients still had findings of active uveitis. Two (2) additional patients were found to have findings of active uveitis

after treatment (both patients did not have findings of uveitis at their baseline exams). Of the 20 patients with no exam performed after 12 weeks of treatment, 1 was noted to have findings of uveitis (active) at baseline and 2 did not have the exam performed at baseline as well. The other 17 patients were all found to have no evidence of uveitis at baseline. **Overall, 5 of these patients were assigned with a treatment-emergent AE (includes PT of uveitis and iritis) by the investigators**. In the other cases where an AE designation was not assigned, uveitis was either noted to be present prior to treatment and therefore could not be designated as a new untoward event or it was not felt to be worsening of an already existing condition.

In Trial 107.208 an ophthalmologic examination for uveitis was performed at the time of Visit 1 (screening) and at the end of treatment visit (for those patients who had received at least 8 weeks of study treatment). Previous findings from an ophthalmologic examination were acceptable if it had been performed within 8 weeks of the screening visit date. As in Trial 107.235, the CRFs asked if uveitis was present and if so, whether it was "active, inactive or chronic". The definition of each descriptor of uveitis was not pre-specified and so it was assumed that the ophthalmologists in Trial 107.208 used the same conventions as described above for the ophthalmologists in Trial 107.235.

In Trial 107.208 there were 24 patients with uveitis diagnosed at the baseline and/or end of treatment ophthalmologic examination. In the **Mel L** group, of the 4 patients with active uveitis at baseline, 3 were found to have no evidence of uveitis after treatment and 1 patient was described as having findings of chronic uveitis. Three (3) patients were found to have findings of inactive uveitis at baseline and after treatment 2 patients had no evidence of uveitis and 1 patient still had findings of inactive uveitis after treatment. Two (2) patients had chronic uveitis at baseline and after treatment one was described as still having findings of chronic uveitis and 1 patient had no evidence of uveitis. One (1) patient did not have evidence of uveitis at baseline but after treatment was described as chronic uveitis. In the **Mel H** group, 4 patients had active uveitis at baseline and after treatment 3 patients had findings of chronic uveitis and 1 patient did not have an end of treatment exam. There were 3 patients with inactive uveitis at baseline and after Treatment 2 of these patients did not have any evidence of uveitis and 1 patient still had findings of inactive uveitis. In the **Nap** treatment group there were 4 patients who had active uveitis at baseline. After Treatment, 1 of these patients had no evidence of uveitis, 2 patients had inactive uveitis and 1 patient still had findings of active uveitis. In this group there was 1 patient with findings described as inactive uveitis at baseline and after treatment there was no evidence of uveitis. One (1) patient had findings of chronic uveitis at baseline and after treatment still had findings of chronic uveitis. There was only 1 patient who did not findings of uveitis at baseline and after treatment was described as having chronic uveitis. **Overall, 10 of these patients were assigned with the treatment-emergent adverse event of Uveitis during this trial**.

In the 1 year, open-label (meloxicam 0.250 mg/kg/day) Trial 107.162 (n=36) there were 2 cases of uveitis (1 active, 1 chronic) at screening and 2 cases of uveitis (both active) at the end of treatment visit by ophthalmologic examination. **There were no patients assigned with the treatment-emergent adverse event, Uveitis.**

Table 50. **Number of Patients with Uveitis on Ophthalmologic Examination by Treatment Group in Trials 107.235 and 107.208**

Trial 107.235		
Treatment[+] (No.)	No. with Uveitis at Baseline/No. Examined Results	No. with Uveitis at 12 weeks/No. Examined Results
Mel L (62)	5/62 3 Active, 2 Chronic	5/58 (4 n.d.*) 1 Active, 1 Inactive, 2 Chronic
Mel H (72)	4/71 (1 n.d.) 4 Active	3/64 (8 n.d.) 1 Active, 1 Inactive, 1 Chronic
Nap (75)	2/74 (1 n.d.) 2 Active	4/67 (8 n.d.) 4 Active
Trial 107.208		
Treatment (No.)	No. with Uveitis at Screen/No. Examined Results	No. with Uveitis at End of Treatment/No. Examined Results
Mel L (73)	9/72 (1 missing) 4 Active, 3 Inactive, 2 Chronic	4/52 (2 missing) 1 Inactive, 3 Chronic
Mel H (74)	7/74 4 Active, 3 Inactive	4/51 (1 missing) 1 Inactive, 3 Chronic
Nap (78)	6/78 4 Active, 1 Inactive, 1 Chronic	5/58 1 Active, 2 Inactive, 2 Chronic

* = not done

[+] = Treatments in Trial 107.235: Mel L = meloxicam 0.125 increased to 0.250 mg/kg after 4 weeks; Mel H = meloxicam 0.250 increased to 0.375 mg/kg after 4 weeks; Nap = naproxen 10 increased to 15 mg/kg after 4 weeks. Treatments in Trial 107.208: Mel L = meloxicam 0.125 mg/kg; Mel H = meloxicam 0.250 mg/kg; Nap = 10 mg/kg.

Source Data: For Trial 107.235 Section 15, Table 15.3.5: 1 of U04-3227-01. For Trial 107.208 Appendix 16.2 Listing 9.2 of U03-1727.

Based on this analysis of ophthalmologic exam-documented uveitis in the trials, there is not adequate evidence to conclusively support that treatment with either meloxicam or naproxen prevents, successfully treats or induces/exacerbates uveitis.

7.1.9 Electrocardiograms (ECGs)

These data were not collected

7.1.10 Immunogenicity

Not submitted with this supplement application

7.1.11 Human Carcinogenicity

Not submitted with this supplement application

7.1.12 Special Safety Studies

Not performed

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The most relevant information is covered in the current approved package insert. This submission does not add any new information

7.1.14 Human Reproduction and Pregnancy Data

Not submitted with this supplement application

7.1.15 Assessment of Effect on Growth

In addition to a discussion of an analysis of the patients' weight gain during the trials in section 7.1.8.4 of this review, the Sponsor presented the results from a review of the treatment emergent adverse event databases from the clinical trials for terms suggestive of a possible effect on growth and development.

The adverse event preferred terms searched for in the databases included:

SOC: Investigations; PT: Body height above normal (tall stature), Body height below normal (short, petite stature), Body height abnormal, Body height decreased, Body height increased, Head circumference abnormal, Orthopedic examination abnormal, Physical breast examination abnormal, Physical testicle examination abnormal, Weight abnormal, Weight above normal, Weight below normal, Weight decreased, Weight increased, BMI, Blood growth hormone decreased, Blood growth hormone increased, Blood growth hormone abnormal.

SOC: Endocrine disorders; PT: Acromegaly, Gigantism, Growth accelerated, Growth hormone deficiency, Delayed puberty, Incomplete precocious puberty, True precocious puberty, Pseudoprecocious puberty, Precocious puberty, Ectopic growth hormone secretion, Hungry bone syndrome.

SOC: Skin disorders; PT: Nail growth cessation, Hair growth abnormal.

SOC: General disorders; PT: Growth retardation.

SOC: Musculoskeletal and connective tissue disorders; PT: Kyphosis, Lordosis, Hyphoscoliosis, Scoliosis, Spinal deformity, Bone metabolism disorder, Osteopenia, Limb reduction defect, Limb deformity, Slipped femoral epiphysis, Epiphyses premature fusion, Epiphyses delayed fusion.

Review of the treatment emergent adverse events occurring in Trials 107.208 and 107.162 (treatment for up to 1 year) and Trial 107.235 (treatment up to 24 weeks) did not reveal the presence of any of the possible growth and development-related adverse events listed above (except for 2 patients treated with meloxicam, one listed with the AE, Weight decreased and one with the AE, Weight increased).

In addition, a literature search was performed by the Sponsor to see if there have been any reports of an effect of NSAIDS on growth and development in children. The Medline, EMBASE+ and Derwent Drug File databases from 1986 to the present were searched for the combination terms of "NSAIDs and Growth Effects". There was no evidence found from this search that NSAIDs have an effect on growth or development in children with JRA.

These results and the results of the analysis of patient weight gain during the trials suggest that neither meloxicam nor the active comparator, naproxen had an appreciable clinically significant adverse effect on growth and development during the course of the clinical trials.

7.1.16 Overdose Experience

The most relevant information is covered in the current approved package insert. This submission does not add any new information.

7.1.17 Postmarketing Experience

There were two spontaneous reports of adverse events with meloxicam oral suspension.

- Case 2003-BP-03748MX: A 2 year-old girl with concurrent disease of bronchial asthma developed a mild face edema within 24 hours of the administration of 2 mL for upper respiratory tract inflammation. The event resolved spontaneously within 48 hours.
- Case 2001-BP-03683: A 6 year-old boy with concurrent disease of glomerulonephritis experienced hematuria following the administration of 9 mL (over the recommended dose of 4 mL for that age) for pharyngitis. It was unknown if treatment for the event was given or if meloxicam was discontinued. The patient recovered with no sequelae.

Face edema and allergic reactions in general, and hematuria are expected events with meloxicam; these cases do not change the understanding of the safety profile.

In addition, 18 patients in the pediatric population reported adverse events while using other meloxicam formulations. The average age of these patients is 13.6 years old (2-17), with a higher proportion of females (11 females, 6 males, 1 sex not reported). The majority of the reports were non-serious reports of stomatitis, nausea, rash and abdominal pain.

There was one serious case of facial palsy (2004-BP-01716BP) where a 15 year-old boy took one dose of Mobic 7.5 mg for contusion and pain secondary to sports and developed Bell's palsy on the left side of his face. He was treated with steroids and antivirals and underwent NCV and MRI. The results and outcome were unknown at the time of the report.

Other serious reports or cases of interest are overdose reports. In one accidental case (case 1996-BR-MOV01), a 2 year-old swallowed two tablets of Mobic and experienced non-serious events of drowsiness, abdominal cramp, vomiting and diarrhea. The four other cases were intentional overdoses in 14 and 15 year-old girls. In two cases, the patients experienced proteinuria, one was non-serious and asymptomatic (Case 2001-SW-00040), and one was accompanied with abdominal pain, gastritis, nausea and proteinuria (case 2001-SW-00039). The amount of the overdoses of meloxicam were 525 mg (35 tablets of meloxicam 15 mg) and 450 mg (30 tablets of meloxicam 15 mg), respectively. In the last two suicide attempts (Cases 1997-DE-04071 and 2004-DE-04294DE), the girls took several medications including meloxicam; 112.5 mg of Mobic in Case 1997-DE-04071 and 6 tablets of unknown strength in the other case. They were hospitalized and did not develop symptoms.

Reviewer's comments:

- *The post-marketing review in pediatric patients, knowing its limitations and with the exception of the Bell's palsy case that seemed coincidental to the use of meloxicam, reported no new events that change the understanding of meloxicam's safety profile.*

7.2 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The meloxicam JRA development program included an overall total of 470 patients with pauci- and polyarticular course JRA studied in 3 Trials: 107.235, 107.208 and 107.162.

Within these 3 trials there were a total of 387 patients with JRA who received meloxicam and a total of 153 patients who received naproxen. Among these patients there were 70 patients who received both naproxen and meloxicam because of the open-label extension design of Trial 107.235 where all patients were administered the highest dose of meloxicam.

There were several analyses performed on data available. Dataset was examined by treatment received (meloxicam vs. naproxen) regardless of dose, duration, or trial design (double-blind or open-label). In addition, integrated data from the 2 controlled trials (107.235 and 107.208) was analyzed by dose and after 4 and 12 weeks of data (short term data). Separate analysis of the data was performed from the 12 week open-label extension (meloxicam 0.375 mg/kg/day) from Trial 107.235 and the up to 1 year data from Trial 107.208 (double-blind) and Trial 107.162 (open-label; meloxicam 0.250 mg/kg/day).

Analysis by treatment showed that the 2 patient groups were reasonably balanced demographically with patients in both treatment groups (meloxicam and naproxen) fairly evenly distributed across the three age-specific (i.e., 2-6, 7-11 and 12-17 years of age) categories. Caucasians were the predominant race studied in the trials, comprising 88% of all of the patients (for whom racial information was available). As expected in a JRA population, females outnumbered males approximately 2:1 across all 3 trials. Disease course was approximately evenly divided between pauci- and polyarticular with the majority of patients having 4 or less actively inflamed joints.

Adverse events were representative of those expected in a pediatric population in general, or as part of the natural history of JRA, or with treatment with nonsteroidal anti-inflammatory agents. Serious AEs occurred with a frequency of 4.9% and 7.2% in patients treated with meloxicam or naproxen, respectively. The types of SAEs experienced were diverse with very few occurrences of any one preferred term (only "Juvenile Arthritis" in the naproxen-treated group appeared with a frequency equal to or greater than 1%). Overall, 4.9% of meloxicam-treated patients compared to 7.2% of naproxen-treated patients discontinued their participation in a trial due to adverse events. Analysis of AEs by subgroup including age, gender, concomitant use of methotrexate, race and disease course (pauci- and polyarticular), did not reveal any readily discernible differences between the meloxicam- and naproxen-treated groups. There were no appreciable differences observed between the 2 treatment groups in possible nonsteroidal anti-inflammatory drug (NSAID)-associated adverse events of interest (gastrointestinal, bleeding and skin-related). There were no appreciable clinically relevant differences noted among laboratory results, vital signs (with the exception of meloxicam dose 0.375 mg/kg/d that indicated a possible increase in systolic blood pressure), or weight gain in comparing the meloxicam- and naproxen-treated groups.

Analysis of the safety profile for those patients treated in the trials (either double-blinded or open-labelled) for the long term (up to 1 year) did not suggest any duration of treatment –associated qualitative differences in the AE profile (compared to the short term data). Assessment for possible growth and development-related adverse events or weight change over time for up to 1 year of treatment does not suggest that meloxicam or naproxen has any significant negative effect on growth and development.

Evaluation of the available post-marketing surveillance data of meloxicam oral suspension and meloxicam use in pediatric age-population in general, does not reveal any new events that would change currently known meloxicam's safety profile.

One of the biggest concerns with the use of NSAIDs in adults is their risk of cardio-vascular adverse events. However this does not seem to be an issue with the pediatric population.

In summary, based on this reviewer's assessment of the data presented with this application, the tolerability and safety profile of meloxicam (b) (4) 0.125 mg/kg (b) (4) once per day is **comparable** to that of naproxen (b) (4) for the treatment of the signs and symptoms of pauci- and polyarticular JRA for up to 1 year as studied in clinical trials (b) (4) .

However, review of data from adult RA and OA trials suggests a dose response from 15 mg to 22.5 mg in multiple adverse events categories including:
a. mortality
b. perforations, ulcers and bleeds
c. overall serious adverse events
d. overall adverse events leading to withdrawal as well as cardiovascular and gastrointestinal events leading to withdrawal
e. overall adverse events
f. laboratory adverse events: decreases in hematocrit, anemia, hepatic adverse events, renal dysfunction, hypertension

(b) (4)

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The meloxicam doses selected for study in the JRA clinical program were derived from experience with adult doses (7.5 mg, 15 mg and 22.5 mg per day) which had been shown to be effective in rheumatoid arthritis in two 12 week placebo controlled trials (U99-3147, U03-3586). In the pivotal adult RA trial, the 15 mg dose was more effective than the 7.5 mg dose, but no additional benefit was observed with the 22.5 mg dose (U03-3586). **Doses above 15 mg are not recommended because chronic use of meloxicam doses >15 mg per day are associated with an increase risk of overall adverse events and gastrointestinal bleeding events in adult RA and OA patients**. The initial assumption used for the meloxicam pediatric doses converted adult to pediatric doses based on a 60 kilogram adult. Review of currently approved NSAIDs with both adult RA and pediatric JRA indications revealed that the conversion factors used ranged from 50 to 60 kg for adult weights. Dividing the three adult doses (7.5, 15 and 22.5 mg), which have been established to be efficacious in RA, by 60 kilograms resulted in the three pediatric dose groups (01.25, 0.250 and 0.375 mg/kg/day) used in the meloxicam JRA clinical program.

Meloxicam oral suspension 7.5 mg/5 ml is the dosage form used in the JRA studies with meloxicam. The active comparator to meloxicam oral suspension is naproxen oral suspension 25 mg/ml. Bioavailability studies performed in adults with the meloxicam oral suspension demonstrated the bioequivalence of the meloxicam tablet with the oral suspension (Meloxicam Oral Suspension NDA 21-530), and established the dose proportionality of the oral suspension over the dose range of 7.5 to 22.5 mg. (U02-1641)

In the pediatric Trial 107.235, nine dosing weight categories were used to address patient weights from 9 to >57 kilograms. Pediatric patients weighing more than 57 kilograms were permitted to receive the maximum adult dose (corresponding to their pediatric dose group), i.e., 7.5 mg/day (0.125 mg/kg/day), 15 mg/day (0.25 mg/kg/day) and 22.5 mg/day (0.375 mg/kg/day). The active comparator, naproxen had eight dosing weight categories from 9 to >51 kilograms with pediatric patients above 51 kilograms receiving the maximum adult dose of 500 mg/day or 750 mg/day (corresponding to 10 mg/day or 15 mg/day, respectively).

Based on the FDA pediatric use section in labelling regulations [21 CFR 201.57(f)(9)] a drug may be labelled for the signs and symptoms of JRA if it has been established to be safe and effective for the adult population and the mechanism of the drug is sufficiently similar in children as is the case with NSAIDs. Meloxicam has a mechanism of action similar to other approved NSAIDs, and this along with the exposure bridge from the pediatric to the adult doses allows one to extrapolate efficacy from the adult RA to pediatric JRA.

The initial JRA Phase 2 open label study (107.162), (b) (4)

In this Phase 2 study, pharmacokinetic data were available for 18 children, 13 females and 5 males. Seven children were aged 2–6 years (mean 3.4 years) and 11 children were aged 7–14 years (mean 10.8 years). Meloxicam plasma concentrations increased rapidly after oral administration, peaking on average 2 hours (median) after intake. Maximum concentrations (C_{max}) values obtained after initial (single) dosing was approximately 34% lower in the younger age group than in the older age group (1.20 µg/mL and 1.82 µg/mL, respectively). $AUC_{0-\infty}$ was also 28% lower in the younger age group than in the older age group (24.8 µg·h/mL and 34.4 µg·h/mL, respectively). A retrospective comparison of these findings with historic adult data (U97-2327) revealed the pharmacokinetic properties of meloxicam in children to be generally comparable to those seen in adults. Despite a trend towards higher meloxicam concentrations in the older children in this study, drug plasma concentrations achieved in children are typically within the range seen in adults. Meloxicam elimination half-life was found to be shorter in children (13 hours in both age groups in this study versus 19 hours in adults). A trend towards increased body weight adjusted clearance, particularly in children of the younger

age group, was also apparent (NCL/F: 0.162 mL/min/kg for 2–6 year olds compared with 0.111 and 0.102 mL/min/kg in older children and adults, respectively).

The pivotal Phase 3 JRA double-blind, dose-escalation, active controlled study (107.235) was then conducted to establish the efficacy and safety of meloxicam oral suspension at doses of 0.125 to 0.25 mg/kg/d (n=62) and 0.25 to 0.375 mg/k/d (n=72) versus naproxen oral suspension (10 to 15mg/kg/d) administered bid (n=75) in 209 pauci- and polyarticular JRA patients (U04-3227). This study also obtained steady-state pharmacokinetic data for the meloxicam oral suspension 0.375 mg/kg/d dose. (b) (4)

The efficacy and safety of the meloxicam oral suspension is further supported by a Phase 3 one year, double-blind, active controlled JRA study (107.208) conducted in Europe that showed meloxicam oral suspension administered in doses of 0.125 mg/kg/day (n=73) (b) (4) once daily over one year was comparable to naproxen oral suspension (n=78) at a standard dose of 10 mg/kg daily divided in two doses.

Exposures at 0.125 mg/kg to 0.375 mg/kg in children are comparable to the exposures seen in adults dosed with 7.5mg to 22.5 mg meloxicam. (b) (4) .

9 OVERALL ASSESSMENT

9.1 Conclusions

The purpose of the trials in the JRA program (107.235, 107.208 and 107.162) was to evaluate the efficacy and safety of meloxicam oral suspension compared to naproxen oral suspension in patients with juvenile rheumatoid arthritis after the safety and efficacy of meloxicam have been established in adult RA trials. Pharmacokinetic data from Trials 107.162 and 107.235 established that exposure and pharmacokinetics of pediatric meloxicam doses used in all three trials are comparable to the adult RA efficacious doses. The primary efficacy endpoint for two efficacy trials 107.235 and 107.208 was the response rate by ACR pediatric30 at the end of the 12-week double-blind phase. Secondary efficacy endpoints included individual JRA core set outcome criteria, patient's discomfort, parent's global assessment of arthritis and acetaminophen consumption, among others. All comparisons of meloxicam oral suspension versus naproxen oral suspension were not statistically significant. A subgroup analysis showed consistent ACR Pediatric 30 response rates across disease subtypes (pauci- and polyarticular), age groups (2-6, 7-11 and 12-17 years of age), gender and methotrexate use. (b) (4)

(b) (4) Of note, the effect size of meloxicam observed in JRA trials is similar to that observed in adult RA trials. Treatment was generally well tolerated. Discontinuations due to adverse events occurred in 4.9% of meloxicam-treated patients compared to 7.2% of naproxen-treated patients and 3 patients discontinued the trials due to adverse laboratory event (2-in meloxicam groups and one in naproxen group). There were no cases of gastrointestinal perforation, obstruction/ulceration, or haemorrhage reported in the trials and there were no cases of cardio-vascular adverse events reported.

However, there were safety concerns raised in adult RA and OA studies with 22.5 mg dose that translates to 0.375 mg/kg/day pediatric dose. In addition, there was an indication that daily dose 0.375 mg/kg might increase systolic blood pressure in pediatric patients. (b) (4)

Therefore, it is concluded that efficacy and safety of meloxicam oral suspension were comparable to naproxen oral suspension in the treatment of patients with pauci- and polyarticular juvenile rheumatoid arthritis. Meloxicam oral suspension with once daily dosing may provide an important addition to the treatment of juvenile rheumatoid arthritis. The recommended (b) (4) dose for meloxicam oral suspension in JRA is 0.125 mg/kg up to 7.5 mg administered once daily. (b) (4)

9.2 Recommendation on Regulatory Action

This reviewer recommends an approval for meloxicam oral suspension (b) (4) 0.125 mg/kg (b) (4) for the treatment of the signs and symptoms of juvenile rheumatoid arthritis (JRA)

9.3 Recommendation on Postmarketing Actions

None
The Sponsor needs to continue to monitor safety data of the product including use in the pediatric population.

9.4 Labeling Review

Pediatric data was included into the label in Pharmacokinetics, Clinical Trials, Adverse Reactions, Indications and Usage, Dosage and Administration sections (see label below)

This Medication Guide has been approved by the US Food and Drug Administration

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

/s/

Tatiana Oussova
8/10/05 02:04:41 PM
MEDICAL OFFICER

Sharon Hertz
8/10/05 02:21:59 PM
MEDICAL OFFICER
I concur with Dr. Oussova's conclusions about efficacy and safety, (b) (4) . Refer to the Deputy Division Memo for more information on the recommended dosing of meloxicam in JRA.