

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207233Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Application Numbers NDA 207233; IND 114045  
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Reviewer Name Amelia Lockett, M.D.  
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Established Name (b) (4) meloxicam  
(Proposed) Trade Name Vivlodex™  
Therapeutic Class NSAID  
Applicant Iroko Pharmaceuticals

Formulations 5 mg and 10 mg capsules  
Dosing Regimen 5 mg or 10 mg orally once daily  
Indication Management of osteoarthritis pain  
Intended Population Adults

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval of Vivlodex™ 5 mg with revisions to the proposed labeling. Despite Vivlodex 5 mg and 10 mg demonstrating similar benefit in treating osteoarthritis pain when compared to placebo on the primary efficacy endpoint, I also recommend approval of Vivlodex 10 mg.

### 1.2 Risk Benefit Assessment

To support approval of Vivlodex for the indication of management of osteoarthritis pain, the Applicant, Iroko Pharmaceuticals, submitted one Phase 1 and two Phase 3 clinical trials. It appears that all clinical trials submitted for this NDA were conducted with acceptable ethical standards. The Applicant also relied in part on the safety and efficacy of Mobic (NDA 020938), for this 505(b)(2) application.

One Phase 3 trial, MEL3-12-02, was meant to establish the efficacy of Vivlodex in those with osteoarthritis pain of the knee or hip. The primary efficacy endpoint of this trial was the change from baseline to Week 12 in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Pain Subscale Score. By this measure, both Vivlodex 5 mg and 10 mg demonstrated similar benefit in treating osteoarthritis pain when compared to placebo. Although the difference between the Vivlodex 5 mg and Vivlodex 10 mg treatment groups was small, a trend exists in which less rescue medication use correlated with the higher dose of Vivlodex. The fraction of subjects requiring acetaminophen rescue medication, the mean number of rescue medication doses, and the mean number of days rescue medication was taken were all lower in the Vivlodex 10 mg treatment group than in the Vivlodex 5 mg treatment group.

The safety profile for Vivlodex that has emerged from this examination is similar to the safety profile of meloxicam's already-approved formulations. Overall, no new safety concerns have been identified. However, that rate of hypertension in the open-label study in patients taking Vivlodex 10 mg appeared higher than the rate of hypertension reported in the Mobic label as well as higher than the rate in study subjects taking Vivlodex 5 or 10 mg in the double-blind study. Factors that support that this finding is not of concern are that there is a lower systemic exposure to meloxicam with Vivlodex compared to Mobic, the higher rate of hypertension occurred in the open-label study without a placebo or other comparator, and there is a high lifetime risk of developing hypertension. The Vivlodex label, like all NSAIDs, will include warnings for hypertension.

Vivlodex is available in 5 mg and 10 mg capsules, doses that are numerically lower than the available formulations of meloxicam as Mobic (7.5 mg and 15 mg tablets). When taken under fasted conditions, Vivlodex 10 mg has a 33% lower systemic exposure when compared to Mobic 15 mg tablets. The lifetime risk of developing hypertension in the trial population is high. According to one publication, the “residual lifetime risk for hypertension for middle-aged and elderly individuals is 90%.” (Vasan et al., 2002) The mean age of subjects in trial MEL3-12-03 was 61.7 years.

In general, the risk-benefit profile of Vivlodex is favorable for the management of pain from osteoarthritis.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No safety issues identified in the review of this application require postmarket risk evaluation and mitigation strategies.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

No requirement for pediatric studies exists under the Pediatric Research Equity Act (PREA) because the indication for Vivlodex is management of osteoarthritis pain, a condition mostly present in adults.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Vivlodex Capsules (meloxicam) represent a modified presentation of meloxicam, a previously approved drug product. Vivlodex Capsules use SoluMatrix Fine Particle Technology™ to reduce drug particle size with the theoretical advantage of encouraging enhanced meloxicam absorption in the gastrointestinal tract. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) and the indication sought for Vivlodex is for the management of osteoarthritis pain in adults. Vivlodex Capsules contain either 5 mg or 10 mg of meloxicam, a difference in dosage compared with currently marketed oral meloxicam tablets that are available in 7.5 mg and 15 mg doses. The dosing schedule sought for Vivlodex Capsules is orally administered 5 mg or 10 mg once daily.

### **2.2 Currently Available Treatments for Proposed Indication**

Numerous products in the NSAID class are currently available with a similar indication. Cymbalta (duloxetine) is approved for the treatment of chronic musculoskeletal pain, which includes the treatment of osteoarthritis.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Meloxicam was first approved for use in the United States as the drug Mobic on April 14, 2000. It is available as an oral tablet and oral suspension under the Mobic trade name, and as multiple generic tablet formulations.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Meloxicam is a member of the NSAID class of drugs and has risks common to the class, including risks of cardiovascular thrombotic and gastrointestinal events. The Mobic labeling includes NSAID class language, including a Boxed Warning for cardiovascular and gastrointestinal risks. The following information is derived from the Boxed Warning, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections of the Mobic package insert (Mobic US labeling 2012), on which Iroko intends to rely for safety and efficacy:

The following are contraindications to Mobic:

- Hypersensitivity to meloxicam
- Asthma, urticaria, or allergic-type reactions to aspirin or NSAIDS
- Treatment of peri-operative pain for CABG surgery

The following are adverse events that may be observed with Mobic and are derived from the WARNINGS AND PRECAUTIONS section of the Mobic labeling:

- Cardiovascular thrombotic events
- Myocardial infarction
- Stroke
- Gastrointestinal inflammation, bleeding, ulceration, perforation of the stomach, or small or large intestine
- Increased risk of gastrointestinal events with use of aspirin and an NSAID
- Borderline elevation of liver tests
- Fulminant hepatitis, liver necrosis, and hepatic failure are rare, but have been reported
- Hypertension
- Decreased effectiveness of ACE inhibitors, thiazides, or loop diuretics
- Fluid retention and edema
- Renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury
- Exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis
- Anemia and inhibited platelet aggregation

The following recommendations are derived from the WARNINGS AND PRECAUTIONS section of the Mobic labeling:

- Mobic is not recommended for those with creatinine clearance less than 20 mL/min or those who are very dehydrated
- Use Mobic cautiously in those with pre-existing renal disease
- Do not give Mobic to those with the “aspirin triad:” asthma, rhinitis, possible nasal polyps
- Do not use Mobic after 30 weeks gestation in pregnancy

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The US clinical trials for this NDA were conducted under IND 114045.

**Table 1 Presubmission Regulatory Activity**

Meeting Date/Type	Key Points
13 November 2012 Type B End-of-Phase 2	<ol style="list-style-type: none"> <li>1. The Division agrees that a 505(b)(2) NDA is appropriate for Meloxicam (b) (4) Capsules.</li> <li>2. A Phase 2 dose-ranging study is not required.</li> <li>3. The Division requires a safety database of at least 600 subjects. At least 300 subjects must be exposed for 6 months and at least 100 patients must be exposed for 12 months to Meloxicam (b) (4) 10 mg once a day.</li> <li>4. The Division agrees to the proposed indication of (b) (4) of osteoarthritis pain.”</li> <li>5. The Division agrees with the primary endpoint for the pivotal Phase 3 trial: mean change from baseline for WOMAC pain subscale score. However, the WOMAC subscale must be used as a complete set.</li> <li>6. The Division agrees that a waiver request for pediatric studies is acceptable, but that the Pediatric Research Committee (PeRC) makes the final determination of this waiver.</li> <li>7. The Division told Iroko to provide rationale for the indication “OA pain.”</li> </ol>
16 July 2014 Pre-NDA Preliminary Meeting Comments	<ol style="list-style-type: none"> <li>1. The to-be-marketed formulation must be used in the studies to support the NDA submission or bridging rationale must be made.</li> <li>2. The Division reports it appears acceptable if integrated safety analysis are comprised of pooled data from the Phase 3 trials.</li> <li>3. The Division expressed concerns about the proposed analysis approach.</li> <li>4. The Division indicates that any reference article essential to support approval of the NDA must be submitted with the application.</li> <li>5. The Division indicates a plan should be in place to minimize medication error and confusion with other meloxicam products.</li> </ol>

## 2.6 Other Relevant Background Information

Not applicable.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

NDA 207233 was submitted in eCTD format. Overall, it was well-organized and information was easy to find. Over the course of the review of this NDA, clinically-related Information Requests were sent to Iroko with the following subjects:

- Request for a tabular list of study sites with number of subjects screened, randomized, with protocol violations, and prematurely discontinued
- Request for a safety assessment of meloxicam based on all current worldwide knowledge regarding meloxicam (This was already located within the NDA submission, but it was not found initially.)
- Request for normal lab values for all laboratories studied in the units in which they were reported in the NDA and a conversion table for the laboratories in the “Criteria for Laboratory Values of Potential Clinical Concern” as converted into the units in which they were reported in the NDA
- Request for blood pressure “shift” tables
- Request for additional subject narratives and table of hepatic-related adverse events for trial MEL3-12-03
- Request for list of clinical investigators who are full-time and part-time employees of Iroko Properties, Inc.
- Request for explanation of discrepancy between MEL3-12-03 subjects with the reported adverse event of hypertension and the percentage of subjects who had a shift in systolic blood pressure from normal too high from Baseline to Week 52
- Request for explanation of incidence of hypertension with Vivlodex 10 mg in clinical trials and request for explanation of why Vivlodex 10 mg did not display increased efficacy over Vivlodex 5 mg for the primary endpoint
- Request for a reference and citation

#### 3.2 Compliance with Good Clinical Practices

It appears that all clinical trials submitted to this NDA were conducted with acceptable ethical standards. Protocol violations were numerous, but likely did not influence the trial results. For further detail on protocol violations, see Section 5.3 of this review.

The Office of Scientific Investigations (OSI) inspected the following sites:

Site #102:  
Enrico Guy Jones, MD  
Richard Montgomery, MD  
Triad Clinical Trials, LLC  
515 College Road, Suite 15

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Greensboro, NC 27410, US  
MEL3-12-02 randomized: 32

Site #124:  
David William Bouda, MD  
Heartland Clinical Research, Inc.  
2201 North 90th Street, Suite  
125-126  
Omaha, NE 68134, US  
MEL3-12-02 randomized: 26  
MEL3-12-03 randomized: 50

These sites were selected because they randomized a large number of subjects in Phase 3 efficacy trial MEL3-12-02. The site inspection was conducted in June 2015. The Clinical Inspection Summary from the Office of Scientific Investigations concluded that data from audited sites appear reliable.

### **3.3 Financial Disclosures**

Iroko provided financial information for the principal and sub-investigators who conducted the following clinical trials: MEL1-11-01, MEL1-12-04, MEL3-12-02, and MEL3-12-03. No financial incentives that might adversely affect data integrity were identified.

For further information, see Section 9.8 of this review.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

(b) (4) manufactured the supplies for relevant clinical trials: MEL1-12-04, MEL3-12-02, and MEL3-12-03 and will also be responsible for the commercial batches of Vivlodex. Per the CMC reviewer for this submission, some outstanding CMC issues persist. For further information see the CMC review of this submission.

### **4.2 Clinical Microbiology**

Not Applicable.

### 4.3 Preclinical Pharmacology/Toxicology

This Vivlodex NDA has been filed as a 505(b)(2) application, relying in part on the previous findings of safety and efficacy of previously-approved Mobic as well as nonclinical pharmacologic, pharmacokinetic, and toxicology literature from 1990 to 2014. No nonclinical studies of Vivlodex were conducted for this NDA.

An in silico computational genotoxicity evaluation of three meloxicam-related impurities was performed by the Applicant: (b) (4)

(b) (4) The first two listed impurities showed no evidence of genetic toxicity to humans. However, (b) (4) (b) (4) showed evidence of potential genotoxicity. This will be mitigated by keeping the level below 1.5 µg/day in accordance with ICH M7.

### 4.4 Clinical Pharmacology

MEL1-12-04 was a Phase 1 randomized single-center, single-dose, crossover bioavailability trial in fed and fasted healthy subjects comparing Vivlodex 5 mg, Vivlodex 10 mg, and Mobic 15 mg tablets. Among the pharmacokinetic parameters analyzed in this trial were  $C_{max}$  (maximum plasma concentration),  $T_{max}$  (time to achieve maximum plasma concentration), and  $AUC_{0-infinity}$  (area under the concentration-time curve from time 0 extrapolated to infinity).

#### 4.4.1 Mechanism of Action

The exact mechanism of action of meloxicam is unknown, but it may function by competitive, (b) (4) inhibition of cyclooxygenase-1 and cyclooxygenase-2 in prostaglandin synthesis.

#### 4.4.2 Pharmacodynamics

The pharmacodynamic characteristics of meloxicam apply to Vivlodex. According to the Mobic labeling, these include analgesic, anti-inflammation, and antipyretic actions. (Mobic US labeling, 2012)

#### 4.4.3 Pharmacokinetics

The pharmacokinetic characteristics of meloxicam (distribution, metabolism, excretion) can be applied to Vivlodex. The following information is from the Mobic US labeling, 2012 and pertains generally to meloxicam in the form of Mobic, but this information can be extrapolated to Vivlodex:

Distribution (b) (6)

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Lockett  
NDA 207233  
Vivlodex ( (b) (4) meloxicam)

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Meloxicam (b) (6) bound to plasma proteins (b) (6) the (b) (6) therapeutic (b) (6)

### Metabolism

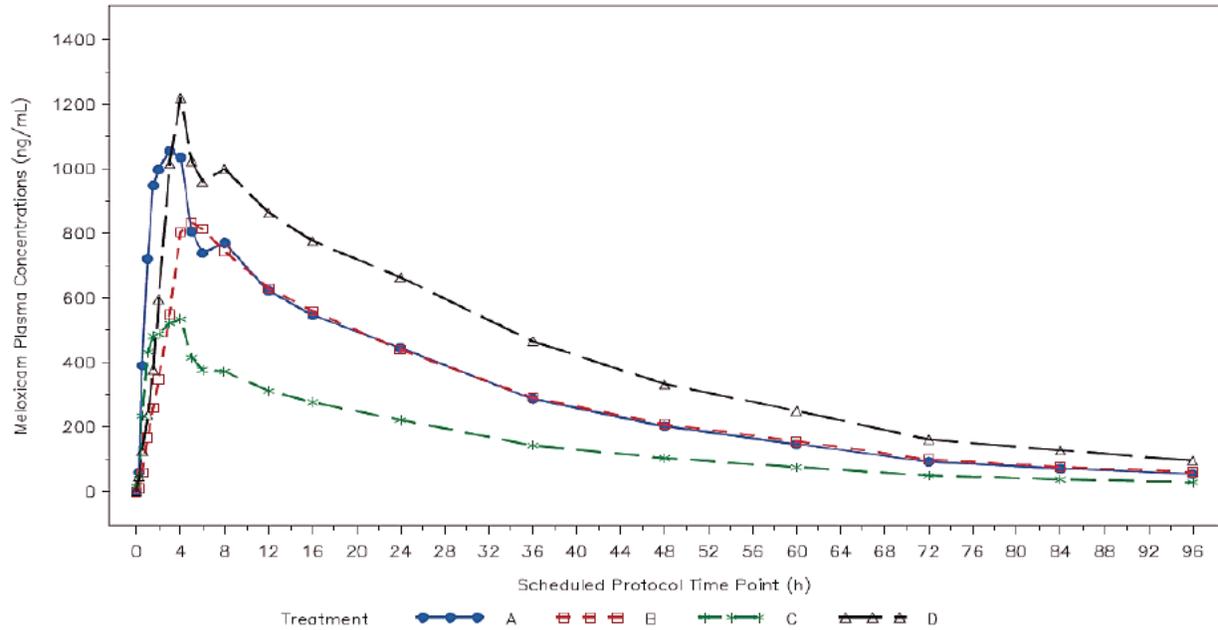
Metabolism of meloxicam occurs in the liver, (b) (6)

### Excretion

Meloxicam, (b) (6) in the form of (b) (6) metabolites, (b) (6)

In MEL1-12-04, Vivlodex in single oral dose displayed dose-proportional pharmacokinetics with mean  $C_{max}$  under fasted conditions for Vivlodex 5 mg and 10 mg attained within 2 hours. A decrease in the rate of systemic absorption of Vivlodex occurred when taken with food, but not the extent of absorption. Vivlodex 10 mg has a 33% lower systemic exposure when compared to Mobic 15 mg tablets when taken under fasted conditions. Below is a figure from the results of trial MEL1-12-04 in which Vivlodex is compared to Mobic followed by a table of more detailed pharmacokinetic information.

**Figure 1 Arithmetic Mean Meloxicam Concentrations Versus Nominal Time Overlaid by Treatment Linear Scale; Mean Meloxicam Plasma Concentration Time Data Treatments A, B, C, and D**



Treatment A: Meloxicam (b) (4) Capsules 10 mg (Test) (Fasting)  
Treatment B: Meloxicam (b) (4) Capsules 10 mg (Test) (Fed)  
Treatment C: Meloxicam (b) (4) Capsules 5 mg (Test) (Fasting)  
Treatment D: Mobic tablet 15 mg (Reference) (Fasting)

(Source: NDA 207233 Applicant's figure page 51 of MEL1-12-04 Clinical Trial Report)

**Table 2 Summary of Meloxicam Pharmacokinetic Parameters**

Parameter (unit)	Mean ± SD (N)			
	Meloxicam Capsules 10 mg (Fasted)	Meloxicam Capsules 10 mg (Fed)	Meloxicam (b) (4) Capsules 5 mg (Fasted)	Mobic 15 mg Tablet (Fasted)
C <sub>max</sub> (ng/mL)	1252.78 ± 254.22 (27)	973.88 ± 165.36 (26)	642.39 ± 138.49 (26)	1288.81 ± 424.40 (27)
t <sub>max</sub> * (h)	2.00 (1.00, 5.00) (27)	5.00 (1.50, 16.02) (26)	2.00 (0.50, 4.07) (26)	4.00 (2.02, 8.00) (27)
AUC <sub>0-t</sub> (ng*h/mL)	28190.52 ± 9264.72 (27)	26681.19 ± 9748.03 (26)	14206.47 ± 5415.31 (26)	39093.82 ± 16500.17 (27)
AUC <sub>0-∞</sub> (ng*h/mL)	29173.01 ± 11042.09 (26)	27145.85 ± 11469.51 (24)	13610.54 ± 3342.69 (24)	40875.58 ± 11733.47 (23)
t <sub>1/2</sub> (h)	22.04 ± 10.08 (27)	22.27 ± 9.88 (26)	22.32 ± 10.91 (26)	23.64 ± 10.04 (27)

N = number of subjects randomized

\*t<sub>max</sub> is presented as median (min, max)

(Source: NDA 207233 Applicant's table page 52 of MEL1-12-04 Clinical Trial Report)

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The clinical development program supporting the 505(b)(2) NDA submission for Vivlodex Capsules 5 mg and 10 mg for management of osteoarthritis pain consists of three clinical trials in which the commercial formulation of Vivlodex was used:

**Table 3 Clinical trials to support NDA 207233**

Trial	Dates	Phase/ Trial Design	No. of Sites	Treatment Groups	N Enrolled/ completed
MEL1-12-04	21May2013 to 23Aug2013	Phase 1; bioavailability; single-dose crossover trial; healthy subjects fed and fasted	1	1. Vivlodex 5mg 2. Vivlodex 10mg 3. Mobic 15mg	28/25
MEL3-12-02	1Mar2013 to 22Oct2013	Phase 3; efficacy and safety; double-blind; subjects with pain due to osteoarthritis of the knee or hip	40	1. Vivlodex 5mg 2. Vivlodex 10mg 3. Placebo	403/350
MEL3-12-03	13Mar2013 to 24Jun2014	Phase 3; safety; open-label; subjects with pain due to OA of the knee or hip	41	1. Vivlodex 10mg	600/390

Two additional Phase 1 pharmacokinetic trials (QP09C03 and MEL1-11-01) were performed with formulations of Vivlodex that differ from the commercial formulation for which this NDA was submitted.

## 5.2 Review Strategy

The focus of this review is on MEL3-12-02 for evaluating the efficacy of Vivlodex and on MEL3-12-02 and MEL3-12-03 for evaluating the safety of Vivlodex. Some exploration of MEL1-12-04 for additional safety findings has also been performed.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Protocol MEL3-12-02

#### 5.3.1.1 Title:

A Phase 3, Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Fixed-Dose, Parallel-Group, Efficacy, and Safety Trial of Meloxicam SoluMatrix™ Capsules in Patients with Pain Due to Osteoarthritis of the Knee or Hip

#### 5.3.1.2 Objective:

Compare efficacy and safety of Vivlodex to placebo once daily in those with osteoarthritis pain of the knee or hip

#### 5.3.1.3 Trial Design:

This trial, conducted at forty sites in the United States, was to have been a randomized, double-blind, and double-dummy trial comparing Vivlodex 5 mg and 10 mg with placebo in those with osteoarthritis pain of the knee or hip. The trial was to have been 12 weeks long during which subjects took study medication once daily.

#### Screening period (Visit 1)

The following assessments and procedures were to have been performed within 14 days of first dosing with study drug:

- History and physical exam including vital signs
- 12-lead ECG
- Hematology, chemistry, urinalysis, urine drug screen, and alcohol breathalyzer test, as well as serum pregnancy test for females of childbearing potential
- Radiographs of target joint
- WOMAC pain subscale assessment
- Dispense rescue medication (acetaminophen)

- 5 day washout period during which subjects are only allowed to take acetaminophen as rescue medication. Acetaminophen is prohibited within 6 hours of starting study drug.

#### Treatment period

This period was to have taken place over 12 weeks. Acetaminophen was to have been the allowed rescue medication and could be taken 500 mg every 4 to 6 hours to a maximum of 3000 mg per day. Acetaminophen was to have only been prohibited before study Visits 2, 3, 4, and 5. Visit 5 was to have represented the end of the study after 12 weeks of daily treatment with study drug.

#### Visit 2 (Day 0)(Baseline)

Visit 2 was to have represented the first day of treatment with study drug. On this day, the WOMAC pain, stiffness, and function subscale assessments were to have been administered. Rescue medication and study drug were to have been dispensed. Subjects were to have been randomized 1:1:1 to placebo, Vivlodex 5 mg, or Vivlodex 10 mg. Subjects were to have taken study drug one time daily in the morning.

#### Visit 3 (~Day 14)

At Visit 3, the WOMAC pain, stiffness, and function subscale assessments were to have been administered.

#### Telephone Assessments (within 7 days of Visit 3)

These telephone assessments were to have occurred before and 2 hours after daily study drug administration. A pre-dose Numerical Rating Scale was to have been recorded. Two hours after dosing, another Numerical Rating Scale was to have been recorded.

#### Visit 4 (~Day 42)

At Visit 4, the WOMAC pain, stiffness, and function subscale assessments were to have been administered.

#### Visit 5 (~Day 84 or Early Termination Visit)

At Visit 5, the WOMAC pain, stiffness, and function subscale assessments were to have been administered. Additionally, the Patient Global Impression of Change and Clinical Global Impression of Change tests were to have been administered. If a subject terminated study drug early, this visit was to have occurred as soon as possible instead of at Day 84.

#### Visit 6 (~Day 84)

Visit 6 was to have been only for subjects who terminated the study early. At this visit, subjects who terminated the study early were to have taken WOMAC pain, stiffness, and function subscales.

Post-treatment follow-up

The follow-up visit was to have been within approximately 7 days of Visit 5 or the Early Termination Visit. At this visit, vital signs and adverse events were to have been recorded.

Below is the Schedule of Events table for MEL3-12-02.

**Table 4 Schedule of Events for MEL3-12-02**

	Screening	Treatment Period					Follow-up	
	V1 Screening Visit (Days -14 to -4)	V2 Baseline Day 0	V3 Week 2 Day 14 ± 2 days	Telephone Assessments Within 7 days of V3	V4 Week 6 Day 42 ± 3 days	V5 Week 12 Day 84 ± 3 days (or ET)	V6 (Day 84 ± 3 days) Abbreviated Week 12 Visit <sup>k</sup>	About 1 week after last dose of study drug
Written informed consent	X							
Inclusion/exclusion criteria	X	X <sup>a</sup>						
Demographics	X							
Medical history	X	X <sup>a,b</sup>						
Physical examination	X <sup>c</sup>	X <sup>a</sup>			X	X		
Vital signs <sup>d</sup>	X	X <sup>a</sup>	X		X	X <sup>c</sup>		X
Height, weight, and BMI	X					X		
12-lead electrocardiogram	X				X	X		
Clinical laboratory tests (hematology, chemistry, and urinalysis)	X							
Pregnancy test for female subjects of childbearing potential <sup>f</sup>	X	X <sup>a</sup>				X		
Urine drug screen	X	X <sup>a</sup>						
Alcohol breathalyzer test	X	X <sup>a</sup>						
Target joint radiographs <sup>g</sup>	X							
WOMAC pain, stiffness, and function subscales	X <sup>h</sup>	X <sup>h</sup>	X <sup>i</sup>		X <sup>i</sup>	X <sup>i</sup>	X	
Randomization		X <sup>a</sup>						
Patient Global Impression of Change						X		
Clinical Global Impression of Change						X		
Dispense rescue medication/study drug	X	X	X		X	X		
Collect rescue medication/study drug and perform accountability		X <sup>i</sup>	X		X	X		
Download rescue medication dosing history from MEMS monitor			X		X	X		
Concomitant medications	X	X <sup>a</sup>	X		X	X	X	X
Adverse events		X <sup>a</sup>	X		X	X	X	X
Collect time of study drug dosing				X				

	Treatment Period					Follow-up	
	Screening	V2	V3	Telephone Assessments Within 7 days of V3	V4		V5
V1 Screening Visit (Days -14 to -4)	X						About 1 week after last dose of study drug
Assessment of pain intensity <sup>m</sup>	X	X	X <sup>l</sup>	X	X		
Review procedures/schedule visit					X		

Abbreviations: BMI = body mass index; ET = early termination; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; MEMS = Medication Event Monitoring System.

- a. Must be performed before the first dose of study drug is administered.
- b. Medical history since Screening will be updated.
- c. A complete physical examination (excluding genitourinary, rectal, and breast examinations) will be performed at Screening. Subjects will be asked to identify their most painful joint. To be eligible for study participation, the subject's most painful joint must be the target joint (knee or hip). An abbreviated physical examination (excluding genitourinary, rectal, and breast examinations) assessing changes from the initial physical examination will be performed at V2 and V5 or ETV.
- d. Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a sitting position for at least 5 minutes.
- e. Only the weight measurement is required at V5.
- f. Serum pregnancy test at Screening and urine pregnancy test at Day 0 (Baseline) and Day 84 (V5/ETV). Test results must be negative for the subject to continue in the study.
- g. Determine Kellgren-Lawrence grade.
- h. At Screening, only the WOMAC pain subscale assessments will be completed. At Baseline, the WOMAC pain subscale assessments will be completed before randomization. Randomized subjects will be administered the WOMAC (including the pain, stiffness, and function subscales).
- i. Must be performed at V2 after randomization but before study drug is dispensed and at V3, V4, and V5 at approximately the same time relative to study drug dosing, preferably at a constant 2 to 4 hours after the morning study drug dose.
- j. Only rescue medication accountability will be performed. Study drug will not be dispensed until the end of this visit.
- k. For Early Termination subjects only.
- l. Schedule phone assessments and Visit 4.
- m. Collected at time 0 (just prior to daily dose) and again at 2 hours (+/- 15 minutes) after dosing with study medication

(Source: NDA 207233 Applicant's table pages 51-52 of MEL3-12-02 Protocol)

#### 5.3.1.4 Trial Population:

##### Inclusion Criteria (verbatim from NDA 207233 pages 20-21 of MEL3-12-02 Protocol)

1. Is male or female 40 years of age or older.
2. Is able to provide written informed consent to participate in the study, and must voluntarily sign and date an informed consent form (ICF) that is approved by an institutional review board (IRB) before the conduct of any study procedure.
3. Is willing and able to understand and comply with study procedures and requirements.
4. Has a primary diagnosis of American College of Rheumatology Functional Class I-III OA of the hip or knee, defined by the following:
  1. In the case of documented hip OA:
    - Articular hip pain and
    - Radiographic Severity Grade II-III (Kellgren-Lawrence).
  - In the case of documented knee OA:
    - Knee pain and
    - Radiographic Severity Grade II-III (Kellgren-Lawrence) and
    - At least 1 of the following 3 criteria: 1) age at least 50 years; 2) morning stiffness less than 30 minutes in duration; 3) crepitus.
5. Is a current chronic user of NSAIDs and/or acetaminophen for his/her OA pain and is anticipated to benefit from continuous treatment with therapeutic doses of NSAIDs. A current chronic user is defined as a subject who has used these treatments for  $\geq 20$  days of the last 30 days before Screening.
6. Has discontinued all analgesic therapy at Screening (except study-specified rescue medication) and refrained from taking study-specified rescue medication for 6 hours before the Baseline assessment.
7. Has a valid WOMAC pain subscale mean VAS score that is  $\geq 40$  mm at Baseline AND has a  $\geq 15$  mm increase (OA pain flare) in the valid WOMAC pain subscale mean score from Screening at Baseline. (NOTE: For a “valid” score, the subject must answer at least 4 of the 5 questions on the pain subscale.)
8. Has a body weight of  $\geq 45$  kg and a body mass index (BMI) of  $\leq 40$  kg/m<sup>2</sup>.
9. If female and of childbearing potential, is nonlactating and nonpregnant (has negative pregnancy test results at Screening [serum] and Baseline [urine]).
10. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following medically acceptable methods of birth control and agrees to continue with the regimen throughout the study:
  - Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject’s usual menstrual cycle period) before study drug administration.
  - Total abstinence from sexual intercourse since the last menses before study drug administration.
  - Intrauterine device
  - Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream).
11. Is able to ambulate.

##### Exclusion criteria (verbatim from NDA 207233 pages 21-23 of MEL3-12-02 Protocol)

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, or any NSAIDs, including meloxicam; history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to any ingredients of the study drug.
2. Requires regular use of opioid or opioid combination products to control OA pain of the knee or hip.
3. Has a history or current diagnosis of any clinically significant cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition which, in the opinion of the investigator, could compromise the subject’s welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.

4. Has a history or current diagnosis of a significant psychiatric disorder which, in the opinion of the investigator, would affect the subject's ability to comply with the study requirements.
5. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding squamous or basal cell carcinoma of the skin).
6. Has a known or suspected history of alcoholism or drug abuse or misuse within 2 years before Screening or evidence of tolerance or physical dependence before study drug administration.
7. Has a history or current diagnosis of any clinically significant gastrointestinal (GI) disorder, including any history of peptic or gastric ulcers or GI bleeding.
8. Has a surgical or medical condition of the GI or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance.
9. Has a history of major surgery on the target hip or knee joint at any time or a history of minor surgery (arthroscopy) on the target hip or knee joint within 1 year before Screening.
10. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the investigator's brochure for Meloxicam SoluMatrix Capsules), to be an unsuitable candidate to receive the study drug.
11. Has received hyaluronic acid injections in the target joint in the 6 months before Screening or between Screening and Baseline.
12. Has received systemic corticosteroids (either oral or parenteral) for treatment of OA or intra-articular corticosteroids administered in the target joint within 3 months before Screening. (Inhaled nasal steroids and topical corticosteroids will be allowed).
13. Expects to use concurrent analgesic, anti-inflammatory therapy, including aspirin (allowed only if administered at a morning dose  $\leq$  325 mg daily) at Baseline.
14. Is currently receiving or expects to use anticoagulants (eg, heparin or warfarin).
15. Has been treated with agents that could affect the analgesic response (such as central alpha agents adrenergic [clonidine and tizanidine], neuroleptic agents, and other antipsychotic agents) within 2 weeks before dosing with study drug or expects to use such agents during the treatment period.
16. Has started physical therapy within 4 weeks before Screening. Subjects who have had at least 4 weeks of physical therapy (allowing time to stabilize on treatment) and are planning to remain on a stable regimen throughout the treatment are not excluded.
17. Has a current medical or arthritic disease that could confound or interfere with the evaluation of efficacy, including but not limited to: rheumatoid arthritis, septic arthritis, systemic lupus erythematosus, spondyloarthritis, Paget's disease affecting the study joint, osteochondritis dessicans or osteonecrosis of the study joint, primary osteochondromatosis, Wilson's disease, fibromyalgia, uncontrolled gout, acromegaly, hemochromatosis, ochronotic arthritis, heritable disorders (eg, hypermobility) and collagen gene mutations, or articular fracture.
18. Is a candidate for imminent (ie, during the 5 months after Screening) joint replacement of any joint.
19. Has tested positive either on the urine drug screen or on the alcohol breathalyzer test. Subjects who test positive at Screening only and can produce a prescription for the medication from their physician may be considered for study enrollment at the discretion of the investigator.
20. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results  $\geq$  3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], or creatinine  $\geq$  1.5 times the ULN) or has any clinically significant laboratory finding at Screening that in the investigator's opinion contraindicates study participation.
21. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.
22. Previously participated in another clinical study of Meloxicam SoluMatrix Capsules or received any investigational drug or device or investigational therapy within 30 days before Screening.

#### 5.3.1.5 Trial Medications and Treatment Groups:

403 subjects were to have been randomized 1:1:1 to one of three treatment groups that would receive one of the following treatments every morning for 12 weeks:

1. 5 mg Vivlodex capsule and 10 mg placebo

2. 10 mg Vivlodex capsule and 5 mg placebo
3. 10 mg placebo and 5 mg placebo

A 10 mg placebo and 5 mg placebo were necessary because the Vivlodex capsules of differing strengths are of differing sizes.

#### 5.3.1.6 Trial Conduct:

Subjects were randomized via a computer-generated schedule and given trial drug in blister packs. The first dose of trial drug was taken with the subject in the clinic at Visit 2. If a dose was not taken in the morning, it could be taken later that day. However, a missed dose could not be taken the next day.

#### 5.3.1.7 Rescue Medications:

A washout period of at least 5 days was mandatory in between study Visits 1 and 2. The following concomitant medications were prohibited during the washout period and at any time during the study:

- Pain medication
- Anti-inflammatory therapy
- Aspirin  $\geq$ 325 mg daily
- Anticoagulants
- Hyaluronic acid treatments in target joint
- Systemic corticosteroids for osteoarthritis
- Intra-articular corticosteroids in target joint
- Drugs that could affect analgesic response (centrally-acting alpha agents, clonidine, tizanidine)
- Neuroleptics
- Antipsychotics

Acetaminophen 500 mg every 4 to 6 hours, up to 3000 mg daily was allowed as a rescue medication during the washout period and treatment period.

#### 5.3.1.8 Efficacy Assessments:

Four scales were to have been used to measure efficacy:

1. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): The 100 mm WOMAC pain subscale assessment was to have been completed at Visits 1 and 2 (before randomization). WOMAC pain, stiffness, and function subscales were to have been completed at Visit 2 after randomization but before study drug, and at Visits 3, 4, and 5 (or Early Termination Visit) after trial drug dosing. The Applicant has noted that the recall period will be 24 hours instead of 48 hours.

2. 11- point Numerical Pain Rating Scale (NPRS): Subjects were to have been given this assessment via telephone within 7 days of Visit 3 just before the daily dose of the trial medication and approximately 2 hours after the dose of trial medication. In this scale, “0” represents “no pain” and “10” represents “the Worst Pain Imaginable.”

3. Clinical Global Impression of Change: At the Week 12 or Early Termination Visit, the Investigator was to have answered the following question: “How do you rate the subject’s change in overall status since beginning treatment with trial drug?”

4. Patient Global Impression of Change: The subject was to have answered this question: “How would you rate your change in overall status since beginning treatment with trial drug?”

The questions in 3 and 4, above, were to have been answered with one of the following responses:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

#### 5.3.1.9 Efficacy Endpoints:

Primary Efficacy Endpoint: mean change between Baseline (Visit 2) and Week 12 WOMAC pain subscale scores

Secondary Efficacy Endpoints (verbatim from NDA 207233 pages 31-32 of MEL3-12-02 protocol)

- Mean change from Baseline in the WOMAC pain subscale score (difference between baseline score and each scheduled visit score for Week 2 [V3] and Week 6 [V4])
- Mean change from Baseline in the WOMAC pain subscale score (difference between baseline score and the average WOMAC pain subscale score over the 12-week period)
- Mean change from Baseline in the WOMAC function subscale score (difference between baseline score and each scheduled visit score for Week 2 [V3], Week 6 [V4] and Week 12[V5]).
- Mean change from Baseline in the WOMAC function subscale score (difference between baseline score and the average WOMAC function subscale score over the 12-week period)
- Mean change from Baseline in the Total WOMAC score (the total score is obtained by calculating the means of the VAS scores for the questions in the pain, stiffness, and physical function subscales; the mean change from Baseline is computed as the difference between baseline score for Week 2 [V3], Week 6 [V4], and Week 12 [V5]) and the average Total WOMAC score over the 12-week period)
- Patient Global Impression of Change at Week 12 (V5) or Early Termination
- Clinical Global Impression of Change at Week 12 (V5) or Early Termination
- Amount and timing of rescue medication taken by each subject
- Cumulative discontinuations due to lack of efficacy at Week 12

- Responder rates for subjects with at least 30% and for subjects with at least 50% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12, respectively), as assessed on the basis of WOMAC pain subscale scores
- Responder rates for subjects who achieve a reduction in pain, evaluated at a continuous cutoff ranging from 0% to 100% reduction in pain intensity from Baseline to each scheduled visit (Weeks 2, 6, and 12, respectively), as assessed on the basis of WOMAC pain subscale scores (NOTE: all subjects who withdraw early from the study will be considered non-responders.)
- Responder analysis using the OMERACT-OARSI responder criteria at Weeks 2, 6, and 12
- Responders with > 10-mm improvement in mean WOMAC pain subscale score at Week 12

#### 5.3.1.10 Safety Assessments:

The following safety assessments were to have been performed. They are discussed in more detail in Section 7 of this review.

- Physical exams
- Labs
- Vital Signs
- Electrocardiograms
- Incidence of treatment-emergent adverse events

#### 5.3.1.11 Statistical Analysis:

*Primary efficacy variable:* The primary efficacy variable is defined as the mean difference in WOMAC pain subscale score from Visit 2 before study drug and Visit 5 at Week 12. The intent-to-treat population is the population used for efficacy analysis, defined as those who received  $\geq 1$  dose of study drug.

*Secondary efficacy variables:* The secondary efficacy variables are numerous and roughly correspond with the secondary endpoints listed in Section 5.3.1.9 of this review.

*Safety Variables:*

- Changes in physical exams, labs, vital signs, and electrocardiograms
- Incidence of treatment-emergent adverse events

*Statistical analysis methods:*

The analysis populations were to have been:

1. The intent-to-treat (ITT) population, defined as those who received  $\geq 1$  dose of study drug.
2. The per-protocol (PP) population, defined as those who completed all 12 weeks of the trial.
3. The safety population is defined as all subjects who received trial drug.

The primary efficacy analysis, based on the ITT population, compares Vivlodex with placebo after 12 weeks of treatment with mean change from baseline in WOMAC pain subscale scores. A restricted maximum likelihood-based mixed model repeated

measures (REML-based MMRM) analysis was used. Sequential testing was used for Vivlodex 5 mg and Vivlodex 10 mg compared to placebo.

Statistics were to have been given for the amount of rescue medication used.

*Sample size calculation:*

The applicant calculated that a sample size of 134 subjects in each treatment group would yield a  $\geq 90\%$  study power to identify a minimal difference of 10.75 millimeters among the treatment groups with a 2-sided, 2-sample *t*-test with a 0.05 significance level. 403 subjects were enrolled in this study and 350 subjects completed this study.

5.3.1.12 Trial Results:

*Protocol Violations:*

56 major protocol deviations occurred during the trial. 18 of these occurred in the placebo group, 22 of these occurred in the Vivlodex 5 mg group, and 16 of these occurred in the Vivlodex 10 mg group. Most sites with protocol violations had two or fewer major protocol violations with the exception of:

**Table 5 Protocol Violations in MEL3-12-02**

Site	No. Major Protocol Violations	No. Total Subjects Randomized at Site
103	6	5
108	6	12
109	3	2
111	4	7
114	3	12
116	5	14
120	11	15
125	8	20
127	4	4
131	3	11
135	3	23

**Table 6 Protocol Deviations and Violations for MEL3-12-02**

Deviation	Placebo (N=133)	Vivlodex 5 mg (N=138)	Vivlodex 10 mg (N=131)
Major	18	22	16
Inclusion criteria	2	2	2
Exclusion criteria	5	9	6
Visit out of window	0	1	2
Missed visit	1	0	0
Assessment not done	2	1	1
IP compliance	0	1	1
Rescue medication compliance	3	6	1
Other	6	7	6
Minor	95	101	98
Inclusion criteria	0	1	0

Deviation	Placebo (N=133)	Vivlodex 5 mg (N=138)	Vivlodex 10 mg (N=131)
Visit out of window	35	17	20
Missed visit	6	9	11
Assessment not done	12	15	13
IP compliance	61	58	64
GCP compliance	7	6	7
Rescue medication compliance	24	17	21
Assessment out of window	0	1	2
Other	24	22	28

IP Compliance: Investigational Product Compliance

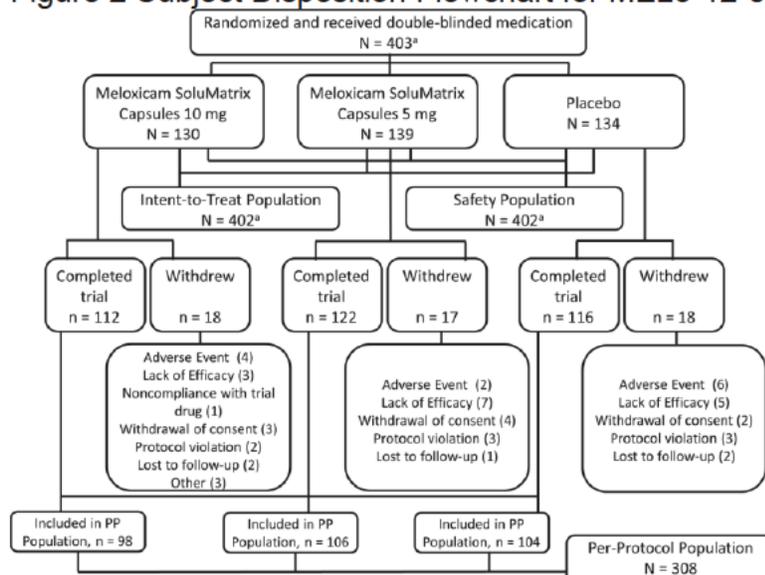
(Source: Reviewer generated table based on NDA 207233 Applicant's table page 171 of MEL3-12-02 Clinical Study Report)

Major protocol violations most likely to affect the efficacy analysis were rescue medication compliance and the use of prohibited medications. After review of the major protocol violations for use of prohibited medications, I conclude that the deviations and violations are not expected to artificially bolster the efficacy of Vivlodex.

*Enrollment/Subject Disposition:*

403 subjects were randomized and 350 subjects completed the trial. 53 subjects were discontinued from the trial. A flowchart of randomized subjects is below:

Figure 2 Subject Disposition Flowchart for MEL3-12-02



Source: Section 14.1, Table 14.1.1 and Appendix 16.2.1, Listing 16.2.1.1

Abbreviations: PP =Per-Protocol

<sup>a</sup> One subject was randomized but withdrew prior to administration of trial drug; therefore, the Intent-to-Treat Population and Safety Population had 402 subjects. One subject was assigned to the Meloxicam SoluMatrix Capsules 5 mg group, but actually received Meloxicam SoluMatrix Capsules 10 mg.

(Source: NDA 207233 Applicant's figure page 59 of MEL3-12-02 Clinical Study Report)

*Extent of Exposure:*

Because one subject withdrew prior to receiving study drug, 402 subjects received trial drug and were therefore included in the safety population.

*Demographics:*

Subject characteristics across the placebo, Vivlodex 5 mg, and Vivlodex 10 mg treatment groups were similar. The mean age of subjects was 60.7-years-old, with the youngest subject being 40-years-old and the oldest subject 87-years-old. Mean (SD) baseline WOMAC pain subscale score was 72.64 (14.922) and was comparable in the three treatment groups. Below is a table of demographic characteristics of subjects in MEL3-12-02.

**Table 7 Demographic characteristics of all subjects in MEL3-12-02**

Mean age (years)	60.7
Percentage of females	65.9%
Percentage of males	34.1%
Percentage White	78.6%
Percentage African American or Black	19.7%
Mean BMI (kg/m <sup>2</sup> )	30.9
Mean weight (kg)	88.1

*Baseline therapy for osteoarthritis:*

Medications commonly taken prior to starting the trial to treat osteoarthritis included: ibuprofen (49.8%), naproxen sodium (25.9%), meloxicam (7.0%) and naproxen (5.0%).

For information on the analysis of efficacy, see section 6.0 of this review.

5.3.2 Protocol MEL3-12-03

5.3.2.1 Title:

A Multicenter, Open-Label, Safety Study of Meloxicam SoluMatrix™ Capsules in Subjects with Osteoarthritis of the Knee or Hip

5.3.2.2 Objective:

Safety evaluation of 10 mg Meloxicam SoluMatrix daily for 52 weeks in those with osteoarthritis pain of the knee or hip

### 5.3.2.3 Trial Design and Procedures:

This trial was to have been a Phase 3, open-label, multi-center trial in the United States in which subjects with pain from osteoarthritis of the knee or hip were administered 10 mg Vivlodex once daily for up to 52 weeks.

#### Screening Visit

This visit was to have taken place within 14 days of the Baseline Visit. The following assessments and procedures were to have taken place at the Screening Visit:

- History and physical exam including vital signs
- 12-lead ECG
- Hematology, chemistry, urinalysis, urine drug screen, and alcohol breathalyzer test, as well as serum pregnancy test for females of childbearing potential

#### Treatment period

##### Baseline Visit (Day 1)

This was to have been the first day that trial drug was taken. The following assessments and procedures were to have taken place at this Visit:

- Abbreviated physical exam
- Vital signs
- Urine drug screen and alcohol breathalyzer test
- Urine pregnancy test for females of childbearing potential

##### Week 1, 4, and 8 Visits

The following assessments and procedures were to have taken place at these Visits:

- Vital signs
- 12-lead ECG (Week 4 only)
- Hematology, chemistry, and urinalysis (at Weeks 4 and 8 only)

##### Week 12, 16, 20, 24, 32, 40, and 48 Visits

The following assessments and procedures were to have taken place at these Visits:

- Vital signs
- Hematology, chemistry, and urinalysis (at Weeks 12, 24, 32, 40, and 48 only)
- Urine pregnancy test for females of childbearing potential at Weeks 12, 24, 32, 40, and 48

##### Week 52 (or Early Termination Visit)

The following assessments and procedures were to have taken place at this Visit:

- Abbreviated physical exam
- Vital signs

- Hematology, chemistry, and urinalysis
- Urine pregnancy test for females of childbearing potential

Post-treatment follow-up (Week 53)

This Visit was to have taken place 7 +/- 3 days following the Week 52 or Early Termination Visit. Vital Signs were to have been recorded at this Visit.

For more detail of trial procedures, see the Schedule of Events below.

**Table 8 Schedule of Events for MEL3-12-03**

	Screening Visit <sup>a</sup>	Treatment Period					Follow-up
		Baseline Visit Day 1	Week 1	Week 4	Week 8	Weeks 12, 16, 20, 24, 32, 40, and 48	
Written informed consent	X						
Inclusion/exclusion criteria	X	X <sup>b</sup>					
Demographics	X						
Medical history	X	X <sup>b,c</sup>					
Physical examination <sup>d</sup>	X	X <sup>b</sup>				X	
Vital signs <sup>e</sup>	X	X <sup>b</sup>	X	X	X	X	X
Height, weight, and BMI	X						
12-lead electrocardiogram	X		X				
Clinical laboratory tests (hematology, chemistry, urinalysis)	X		X	X	X	X <sup>f</sup>	X
Pregnancy test for female subjects of childbearing potential <sup>g</sup>	X	X <sup>b</sup>				X <sup>h</sup>	X
Urine drug screen	X	X <sup>b</sup>					
Alcohol breathalyzer test	X	X <sup>b</sup>					
Dispense study drug <sup>i</sup>	X	X	X	X	X	X	
Collect study drug and perform accountability			X	X	X	X	X
Concomitant medications	X	X <sup>b</sup>	X	X	X	X	X
Adverse events		X <sup>b</sup>	X	X	X	X	X
Review procedures/schedule visit	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; EIV = Early Termination Visit.

a. For subjects who rollover from the MEL3-12-02 study, applicable demographic and medical history data and Week 12 assessments from that study will be used in lieu of Screening Visit.

b. Must be performed before the first dose of study drug is administered.

c. Medical history since Screening will be updated.

d. A complete physical examination (excluding the genitourinary, rectal, and breast examinations) will be performed at Screening. Subjects will be asked to identify their most painful joint. To be eligible for study participation, the subject's most painful joint must be the target joint (knee or hip). An abbreviated physical examination (excluding the genitourinary, rectal, and breast examinations) assessing changes from the initial physical examination will be performed at Baseline and Week 52 or Early Termination Visit (whichever occurs first).

e. Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a sitting position for 5 minutes.

f. Clinical laboratory tests will be performed at Weeks 12, 24, 32, 40, and 48 only.

g. A serum pregnancy test is performed at Screening and a urine pregnancy test is performed at all other specified time points. Results must be negative for the subject to continue in the study.

- h. Perform a urine pregnancy test at Weeks 12, 24, 32, 40, and 48 only. Results must be negative for the subject to continue in the study.  
i. Study drug is dispensed as a 90-count bottle (approximately a 3-month supply).

(Source: NDA 207233 Applicant's table page 38-39 of MEL3-12-03 protocol)

### 5.3.2.4 Trial Population:

**Inclusion Criteria:** (verbatim from NDA 207233 pages 17-18 of MEL3-12-03 Protocol)

1. Is male or female  $\geq 40$  years of age.
2. If a participant in the previous MEL3-12-02 study, completed the study and did not discontinue for lack of efficacy or safety.
3. Has a diagnosis of OA of the hip or knee with ongoing knee and/or articular hip pain.
4. Is a current chronic user of NSAIDs and/or acetaminophen for his/her OA pain and is anticipated to benefit from continuous treatment with therapeutic doses of NSAIDs. A current chronic user is defined as a subject who has used these treatments for  $\geq 20$  days of the last 30 days before Screening.
5. Has a body weight  $\geq 45$  kg and a body mass index (BMI)  $\leq 40$  kg/m<sup>2</sup>.
6. If female and of childbearing potential, is nonlactating and nonpregnant (has a negative serum pregnancy test result at Screening and a negative urine pregnancy test result at Baseline).
7. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following medically acceptable methods of birth control and agrees to continue with the regimen throughout the study:
  - Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before study drug administration.
  - Total abstinence from sexual intercourse since the last menses before study drug administration.
  - Intrauterine device.
  - Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream).
8. Is able to ambulate.
9. Is able to provide written informed consent to participate in the study and able to understand the procedures and study requirements.
10. Must voluntarily sign and date an informed consent form (ICF) that is approved by an IRB before the conduct of any study procedure.
11. Is willing and able to comply with study requirements.

**Exclusion Criteria:** (verbatim from NDA 207233 page 18-19 of MEL3-12-03 protocol)

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, or any NSAIDs, including meloxicam; history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to any ingredients of the study drug.
2. Requires continuous use of opioid or opioid combination products to control OA pain of the knee or hip.
3. Has any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the investigator, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.
4. Has a history or current diagnosis of a significant psychiatric disorder that, in the opinion of the investigator, would affect the subject's ability to comply with the study requirements.
5. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding squamous or basal cell carcinoma of the skin).
6. Has known or suspected history of alcoholism or drug abuse or misuse within 2 years before Screening or evidence of tolerance or physical dependence before study drug administration.
7. Has a history of a clinically significant GI event within the 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding.

8. Has a surgical or medical condition of the GI or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance.
9. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the IB for Meloxicam SoluMatrix Capsules), to be an unsuitable candidate to receive the study drug.
10. Has received hyaluronic acid injections in the target joint in the 6 months before Screening or between Screening and Baseline.
11. Has received systemic corticosteroids (either oral or parenteral) within 3 months before Screening (inhaled nasal steroids and topical corticosteroids are allowed).
12. Has used aspirin or aspirin-containing products within 7 days before study drug administration. Aspirin at a daily dose of  $\leq 325$  mg/day is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for  $\geq 30$  days before Screening and has not experienced any relevant medical problem.
13. Is currently receiving or expects to use anticoagulants (eg, heparin or warfarin).
14. Is a candidate for imminent (ie, during the 5 months after Screening) joint replacement of any joint.
15. Has tested positive either on the urine drug screen or on the alcohol breathalyzer test. Subjects who test positive at Screening only and can produce a prescription for the medication from their physician may be considered for study enrollment at the discretion of the investigator.
16. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results  $\geq 3$  times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase, and alanine aminotransferase [ALT], or bilirubin and creatinine  $> 1.5$  times the ULN) or has any clinically significant laboratory finding that in the investigator's opinion contraindicates study participation.
17. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.
18. Has received any investigational drug (except Meloxicam SoluMatrix Capsules), device, or therapy within 30 days before Screening.

#### 5.3.2.5 Trial Medications:

Subjects were to have taken Vivlodex 10 mg once daily.

#### 5.3.2.6 Trial Conduct:

The first dose of trial drug was to have been taken at the Baseline Visit on Day 1. Trial drug was to have been taken in the morning. If a dose of trial drug was missed, it could be taken later that day. However, a missed dose could not be taken the next day.

#### 5.3.2.7 Rescue Medications:

Acetaminophen up to 500 mg every 4 to 6 hours to a maximum of 3000 mg per day was to be allowed as a rescue medication.

#### 5.3.2.8 Safety Assessments:

Safety endpoints in this trial were to have included:

- Incidence of adverse events
- Change in physical exam findings, labs, and electrocardiograms
- Vital signs

### 5.3.2.9 Statistical Analysis:

*Statistical analysis methods:* Data for this trial was to have been summarized using descriptive statistics.

*Sample size calculation:* The Applicant’s goal was to enroll 600 subjects such that at least 300 subjects were to have 6 months of exposure to Vivlodex and at least 100 subjects were to have 12 months of exposure to Vivlodex.

### 5.3.2.10 Trial Results:

*Protocol Violations:*

251 subjects had major protocol violations that occurred during the trial. 46 of these subjects had major protocol violations associated with compliance with Vivlodex. Below is a table of protocol deviations and violations:

**Table 9 Summary of Protocol Deviations and Violations; Trial MEL3-12-03; Vivlodex 10 mg; N=600**

	n	(%)
Subjects with any inclusion/exclusion criteria deviations	20	(3.3%)
Major	251	(41.8%)
Inclusion Criteria	3	(0.5%)
Exclusion Criteria	17	(2.8%)
Missed Visit	42	(7.0%)
Assessment Not Done	42	(7.0%)
IP Compliance	46	(7.7%)
Other	163	(27.2%)
Minor	526	(87.7%)
Visit out of window	259	(43.2%)
Assessment Not Done	10	(1.7%)
IP Compliance	474	(79.0%)
GCP Compliance	26	(4.3%)
Rescue Medication Compliance	6	(1.0%)
Assessment out of window	5	(0.8%)
Other	43	(7.2%)

(Source: NDA 207233 Applicant’s table page 115 of MEL3-12-03 Clinical Study Report)

As demonstrated in the table above, numerous protocol violations and deviations occurred during this trial. Major protocol violations have been reviewed and are not expected to substantially affect the results of the trial. If anything, the protocol violations may provide more realistic conditions under which Vivlodex will be taken.

*Enrollment/Subject Disposition:*

600 subjects were enrolled in the trial. Two of these subjects were also enrolled in MEL3-12-02. 390 subjects completed the trial. Below is a table that details subject disposition.

**Table 10 Subject Disposition (All Subjects) for MEL3-12-03**

Category	Meloxicam SoluMatrix Capsules 10 mg N=600
Safety Population	600 (100%)
Completed trial	390 (65.0%)
Withdrew from trial	210 (35.0%)
Reason for withdrawal	
Adverse event	79 (13.2%)
Lack of efficacy	28 (4.7%)
Noncompliance with trial drug	13 (2.2%)
Subject withdrew consent	27 (4.5%)
Investigator decision	3 (0.5%)
Protocol violation	25 (4.2%)
Lost to follow-up	15 (2.5%)
Death <sup>a</sup>	1 (0.2%)
Other <sup>b</sup>	19 (3.2%)
Participated in MEL3-12-02 Trial	2 (0.3%)

Source: Section 14.1, Table 14.1.1

<sup>a</sup> Two subjects who participated in this trial died; however, only one subject (Subject 142-001) died during the trial. The other subject (Subject 125-009) died approximately (b) (4) withdrawing from the trial due to an AE.

<sup>b</sup> The reason for withdrawal of 18 of the 19 subjects listed as “other” was because Site 104 closed its business operations unexpectedly during the trial. The additional 1 subject who withdrew due to “other” reasons was withdrawn by the Sponsor because the subject was human immunodeficiency virus (HIV)-positive.

Note: The denominator for the percentages is the number of subjects in the Safety Population.

(Source: NDA 207233 Applicant’s table page 42 of MEL3-12-03 Clinical Study Report)

**Extent of Exposure:**

600 subjects began this trial, received at least one dose of Vivlodex 10 mg, and are considered to be in the safety population. 446 of 600 subjects received Vivlodex 10 mg for greater than 6 months and 391 of 600 subjects received Vivlodex 10 mg for 52 weeks.

**Demographics:** Subjects in this trial had a mean age of 61.7 years with an age range of 40 to 86 years. Subjects in the trial were mostly White (86.7%) and female (59.7%). The demographic characteristics of subjects in this trial are in the table below.

**Table 11 Demographic Characteristics (Safety Population) for MEL3-12-03**

Variable	Meloxicam SoluMatrix Capsules 10 mg N=600
Age (years)	
Mean (SD)	61.7 (8.68)
Median	61.0
Minimum, maximum	(40, 86)

Variable	Meloxicam SoluMatrix Capsules 10 mg N=600
Gender, n (%)	
Male	242 (40.3%)
Female	358 (59.7%)
Ethnicity, n (%)	
Hispanic or Latino	33 (5.5%)
Not Hispanic or Latino	567 (94.5%)
Race, n (%)	
American Indian or Alaska Native	2 (0.3%)
Asian	6 (1.0%)
Black or African American	73 (12.2%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)
White	520 (86.7%)
Weight, kg	
Mean (SD)	88.50 (18.28)
Median	87.54
Minimum, maximum	(47.9, 154.7)
Height (cm)	
Mean (SD)	169.56 (10.17)
Median	167.64
Minimum, maximum	(144.8, 203.2)
Body mass index, kg/m <sup>2</sup>	
Mean (SD)	30.65 (5.02)
Median	30.50
Minimum, maximum	(17.0, 40.2)

Source: Section 14.1, Table 14.1.2

Abbreviation: SD = standard deviation.

Note: The denominator for percentages is the number of subjects in the Safety population.

(Source: NDA 207233 Applicant's table page 45 of MEL3-12-03 Clinical Study Report)

***Baseline therapy for osteoarthritis:***

Medications commonly taken prior to starting the trial to treat osteoarthritis included, but were not limited to: acetaminophen (46.5%), ibuprofen (39.7%), naproxen sodium (22%), naproxen (13.7%), and meloxicam (9.7%).

For analysis of safety, see section 7 of this review

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

Iroko seeks approval of Vivlodex for management of osteoarthritis pain in adults.

##### 6.1.1 Methods

One Phase 3 clinical trial was conducted to support the efficacy of Vivlodex capsules: MEL3-12-02. In this trial, performed under IND 114045, subjects received placebo, Vivlodex 5 mg, or Vivlodex 10 mg.

##### 6.1.2 Demographics

For subject demographics for MEL3-12-02, see section 5.3.1.12 of this review

##### 6.1.3 Subject Disposition

For subject disposition for MEL3-12-02, see section 5.3.1.12 of this review.

##### 6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was the mean change in the WOMAC pain subscale score from Visit 2 (Baseline) to Visit 5 (Week 12). The WOMAC pain subscale score was obtained from the means of the completed visual analog scale scores on a 0 to 100 millimeter scale.

This endpoint was analyzed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) method. This model only includes observed data and does not impute missing data. Week 2 and Week 6 Visit data values were included in estimation. This approach is not what the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) recommends for the handling of missing data.

The Applicant used a hierarchical testing plan in which the Vivlodex 10 mg treatment group was compared to placebo, and if this treatment group is significantly different from placebo, then the Vivlodex 5 mg treatment group is compared to placebo. The biostatistics reviewer for this submission found this to be an acceptable method to control for multiplicity.

MMRM analysis showed differences compared with the placebo in the two Vivlodex treatment groups ( $P < 0.05$ ), with the Vivlodex 5 mg treatment group displaying a slight, but not meaningful, increase in efficacy over the Vivlodex 10 mg treatment group. MMRM analysis results are displayed in the table below:

**Table 12 Primary Efficacy Analysis (MMRM Analysis) change from Baseline to Week 12 in WOMAC Pain Subscale Scores—(ITT population)**

Visit Statistics	Placebo N=133	Meloxicam SoluMatrix Capsules	
		5 mg N=139	10 mg N=130
Baseline, n	133	139	130
Mean (SD)	73.20 (15.472)	72.51 (15.360)	72.19 (13.938)
Median	75.20	73.20	72.10
Week 12, n	127	131	119
Mean (SD)	44.64 (27.917)	32.91 (26.212)	34.74 (26.709)
Median	44.60	25.00	32.20
Change from Baseline to Week 12, n	127	131	119
LS mean (SE) <sup>a</sup>	-25.68 (2.636)	-36.52 (2.485)	-34.41 (2.678)
95% CI <sup>a</sup>	(-30.86, -20.50)	(-41.40, -31.63)	(-39.68, -29.15)
Comparison vs placebo <sup>a</sup>			
Difference in LS mean (SE)	--	-10.84 (3.097)	-8.74 (3.154)
95% CI for difference	--	(-16.93, -4.75)	(-14.94, -2.53)
P value for difference	--	0.0005	0.0059

Source: Section 14.2, Table 14.2.1.1

Abbreviations: CI = confidence interval; ET = early termination; ITT = intent-to-treat; LS = least squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities OA Index.

<sup>a</sup> LS mean, LS mean differences (treatment - placebo), 95% confidence intervals, and P values were obtained from the MMRM model with treatment as the main effect, investigative site and gender as blocking factors, and the baseline WOMAC pain subscale score as a covariate. Week was included in the model as a categorical variable (Week 2, 6, and 12 respectively) along with the treatment-by-week interaction. An unstructured covariance matrix was used to model the within-subject correlation.

Note: WOMAC pain data from ET Visits were assigned (windowed) to the closest visit with missing data (Week 2, 6 or 12). With the exception of WOMAC data obtained from the incorrect version of the questionnaire, all available observed data was included in the analysis, including efficacy results after early termination and after rescue medication use.

(Source: NDA 207233 Applicant's table page 68-69 of MEL3-12-02 Clinical Study Report)

Iroko was again contacted via email on August 26, 2015 with the following Information Request:

In MEL3-12-02, Vivlodex 5 mg appears to have performed similarly to Vivlodex 10 mg for the primary endpoint. Why do you think Vivlodex 10 mg did not display increased efficacy over Vivlodex 5 mg for the primary endpoint?

Iroko replied with the following response on September 16, 2015:

In a randomized, double-blind clinical trial of 774 adults with OA of the hip or knee, a consistent dose response for meloxicam was not demonstrated for all efficacy endpoints (Yocum 2000).

A randomized, double-blind clinical trial of meloxicam in children with juvenile idiopathic arthritis found no statistically significant differences in meloxicam efficacy response rates based on ACR Pediatric 30 criteria at a low dose of 0.125 mg/kg (63% to 77%) and a higher 0.25 mg/kg dose (58% to 76%) (Ruperto 2005). In a randomized, double-blind trial of 423 adults with rheumatoid arthritis, no differences were observed in magnitude of efficacy results based on the mean [SD] Ritchie Joint Index rating on Day 21 in patients treated with meloxicam at doses of 7.5 mg (6 [8]) and 15 mg (4 [7]). In an analysis of mean (SD) morning pain intensity, measured on a 10 cm VAS, meloxicam 7.5 mg (4.0 [2.9]) and 15 mg (4.1 [2.9]) also performed comparably. Similar trends were seen in analyses of pain at night and patient global efficacy assessment (Reginster1996).

Clinical trial MEL3-12-02 was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of Vivlodex™ Capsules at doses of 5 mg and 10 mg once daily for up to 12 weeks in subjects with pain due to osteoarthritis of the hip or knee. As described in other meloxicam trials in the published literature, results for the primary efficacy parameter, change from baseline to Week 12 in the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) pain subscale score, were similarly positive compared to placebo for Vivlodex™ Capsules at both 5 mg (P=0.0005) and 10 mg (P=0.0059) doses. A similar trend was observed for other endpoints based on the WOMAC including subscale assessments and responder analyses.

In contrast, dose-related differences were demonstrated for multiple secondary efficacy parameters favoring Vivlodex™ Capsules 10 mg over the 5 mg dose. No formal statistical comparison of Vivlodex™ Capsules 5 mg and 10 mg was performed. Rescue medication usage in MEL3-12-02 was lowest among subjects receiving Vivlodex™ Capsules 10 mg once daily as measured by proportion of subjects requiring rescue medication, total cumulative rescue medication dosage, daily rescue medication dosage and average number of days of rescue medication use (see Section 5.3.5.1 MEL3-12-02, Section 11.4.3.5).

Subjects receiving Vivlodex™ Capsules 10 mg in this study also reported more positive results overall as measured by the Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) assessments. Both doses of Vivlodex™ Capsules resulted in more positive overall PGIC responses compared to placebo (P=0.0049 for 5 mg, P=0.0012 for 10 mg); the odds ratio for subjects rating their condition as “much improved” or “very much improved” compared to “much worse” or “very much worse” was statistically superior to placebo only for Vivlodex™ 10 mg (P=0.0416). A higher percentage of responders were noted in the Vivlodex™ 10 mg once daily group compared with the Vivlodex™ 5 mg and placebo groups in a modified Outcome Measures in Rheumatology-Osteoarthritis Research Society (OMERACT/OARSI) analysis (see Section 5.3.5.1 MEL3-12-02, Section 11.4.3.6.4). Fewer subjects in the Vivlodex 10 mg once daily treatment group withdrew from the study due to lack of efficacy (see Section 5.3.5.1 MEL3-12-02, Section 11.4.4.2).

Formal statistical testing between Vivlodex™ Capsules doses was not performed in trial MEL3-12-02. Both Vivlodex™ doses demonstrated efficacy compared to placebo for the multiple primary and secondary endpoints, as has been described in other meloxicam trials in the published literature. Although a lack of dose response between Vivlodex™ Capsules 5 mg and 10 mg doses was generally observed in efficacy analyses based on the WOMAC assessments, an apparent dose response was observed for multiple other secondary efficacy analyses.

### 6.1.5 Analysis of Secondary Endpoints

Numerous secondary endpoints were assessed in Study MEL3-12-02. (See section 5.3.1.9 of this review for a list of secondary endpoints.) Results suggest that Vivlodex 10 mg performed numerically better than Vivlodex 5 mg on some secondary endpoints, including:

1. Rescue medication usage
2. Patient and Clinical Global Impressions of Change
3. Modified Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder analysis
4. Rates of discontinuation for lack of efficacy

The following is an exploration of these secondary endpoints:

#### 1. Rescue medication usage:

The fraction of subjects requiring acetaminophen rescue medication was lower in the Vivlodex 5 mg and 10 mg treatment groups than in the placebo group. Additionally, the mean number of rescue medication doses and mean number of days rescue medication was used was lower in the Vivlodex 5 mg and 10 mg treatment group. Overall, a trend exists in which less rescue medication use correlated with higher dose of Vivlodex. The table below describes acetaminophen rescue medication use by treatment group.

**Table 13 Summary of Rescue Medication Usage (ITT Population)**

Rescue Medication Usage	Placebo N=133	Meloxicam SoluMatrix Capsules	
		5 mg N=139	10 mg N=130
Subjects (%) who took any rescue medication	114 (86.4%)	116 (84.1%)	101 (80.2%)
Subjects (%) who did not take rescue medication	18 (13.6%)	22 (15.9%)	25 (19.8%)
Comparison vs placebo <sup>a</sup>	--	0.5940	0.1813
Daily rescue medication usage (mg) <sup>b</sup> , n	104	108	94
Mean (SD)	448.0 (395.76)	306.2 (333.44)	281.6 (313.09)
Median	318.7	196.5	153.4
LS Mean (SE) <sup>c</sup>	464.1 (43.73)	326.2 (41.36)	313.6 (45.50)
95% CI	(378.0, 550.3)	(244.8, 407.7)	(224.0, 403.1)
Comparison vs. placebo	--	0.0046	0.0024
Rescue medication usage (number of doses), n	122	130	119
Mean (SD)	67.7 (72.60)	46.2 (60.03)	40.0 (53.83)
Median	40.5	24.0	16.0
LS Mean (SE) <sup>c</sup>	73.2 (7.03)	52.4 (6.61)	48.4 (7.13)
95% CI	(59.4, 87.1)	(39.4, 65.4)	(34.4, 62.4)
Comparison vs. placebo	--	0.0060	0.0013

Rescue Medication Usage	Placebo N=133	Meloxicam SoluMatrix Capsules	
		5 mg N=139	10 mg N=130
Rescue medication usage (number of days), n	130	138	128
Mean (SD)	30.6 (26.09)	22.2 (21.50)	19.4 (20.37)
Median	24.0	17.0	12.5
LS Mean (SE) <sup>c</sup>	33.9 (2.36)	25.3 (2.16)	23.5 (2.34)
95% CI	(29.3, 38.6)	(21.0, 29.5)	(18.8, 28.1)
Comparison vs. placebo	--	0.0007	<0.0001

Source: Section 14.2, Table 14.2.6.1, Table 14.2.6.2, Table 14.2.6.3, and Table 14.2.6.4

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat;

LS = least squares; SD = standard deviation; SE = standard error

<sup>a</sup> P value was obtained from the Fisher's exact test (or chi-square test, as appropriate) for comparing active treatment groups and the placebo group.

<sup>b</sup> Mean rescue usage (mg) was defined as the total amount of rescue (mg) divided by the number of days between when subject completed or discontinued treatment and when the first trial drug dose was used +1. Subjects who did not receive any rescue medication are not included in this analysis.

<sup>c</sup> The LS mean, LS mean differences (treatment-placebo), 95% confidence intervals, and P values were obtained from the ANCOVA model with treatment as the main effect, investigative site and gender as blocking factors.

Note: Amount of rescue medication is equal to the number of pills returned subtracted from the number of pills dispensed that is recorded on the drug accountability log. Rescue medication received prior to the first dose of trial drug was not included. Subjects were counted as receiving rescue medication if they had at least one dose of rescue medication according to the rescue drug accountability log after the first dose of the trial drug.

(Source: NDA 207233 Applicant's table page 85-86 of MEL3-12-02 Clinical Study Report)

## 2. Patient and Clinical Global Impressions of Change:

For Patient Global Impressions of Changes and Clinical Global Impressions of Change, a higher fraction of subjects in the Vivlodex 10 mg treatment group were "Very much improved or much improved" compared to subjects in the Vivlodex 5 mg group. See the table below for more detail:

**Table 14 Patient Global Impression of Change and Clinical Global Impression of Change Score at Week 12 (Intent-to-Treat Population)**

Number of Subjects (%)	Placebo N=133	Meloxicam SoluMatrix Capsules	
		5 mg N=139	10 mg N=130
<b>Patient Global Impression of Change</b>			
Very much improved or much improved	52 (40.0%)	68 (50.0%)	66 (52.8%)
Much worse or very much worse	9 (6.9%)	5 (3.7%)	3 (2.4%)
Odds ratio for being very much improved or much improved vs much worse or very much worse (95% CI)	--	2.35 (0.74, 7.44)	3.81 (0.98, 14.78)
P value <sup>a</sup>	--	0.1378	0.0416
Very much improved	19 (14.6%)	28 (20.6%)	28 (22.4%)
Much improved	33 (25.4%)	40 (29.4%)	38 (30.4%)
Minimally improved	32 (24.6%)	41 (30.1%)	39 (31.2%)

Number of Subjects (%)	Placebo N=133	Meloxicam SoluMatrix Capsules	
		5 mg N=139	10 mg N=130
No change	23 (17.7%)	20 (14.7%)	12 (9.6%)
Minimally worse	14 (10.8%)	2 (1.5%)	5 (4.0%)
Much worse	8 (6.2%)	4 (2.9%)	2 (1.6%)
Very much worse	1 (0.8%)	1 (0.7%)	1 (0.8%)
<i>P</i> value <sup>b</sup>	--	0.0049	0.0012
<b>Clinical Global Impression of Change</b>			
Very much improved or much improved	50 (38.5%)	70 (51.1%)	66 (52.8%)
Much worse or very much worse	7 (5.4%)	5 (3.6%)	1 (0.8%)
Odds ratio for being very much improved or much improved vs much worse or very much worse (95% CI)	--	1.96 (0.59, 6.53)	9.24 (1.10, 77.54)
<i>P</i> value <sup>a</sup>	--	0.2682	0.0152
Very much improved	17 (13.1%)	22 (16.1%)	25 (20.0%)
Much improved	33 (25.4%)	48 (35.0%)	41 (32.8%)
Minimally improved	34 (26.2%)	39 (28.5%)	35 (28.0%)
No change	28 (21.5%)	22 (16.1%)	18 (14.4%)
Minimally worse	11 (8.5%)	1 (0.7%)	5 (4.0%)
Much worse	6 (4.6%)	5 (3.6%)	1 (0.8%)
Very much worse	1 (0.8%)	0	0
<i>P</i> value <sup>b</sup>	--	0.0070	0.0013

Source: Section 14.2, Table 14.2.8.1 and Table 14.2.8.2

Abbreviations: CI = confidence interval

<sup>a</sup> *P* values were obtained from odds ratio tests for comparing odds in active treatment groups and the placebo group.

<sup>b</sup> *P* values were obtained from the Cochran-Mantel-Haenszel row means score tests for comparing the 2 active treatment groups and the placebo group.

(Source: NDA 207233 Applicant's table page 101 of MEL3-12-02 Clinical Study Report)

### 3. Modified OMERACT-OARSI responder analysis:

OMERACT-OARSI criteria were used to define "responders" to Vivlodex. Responders were defined as: (verbatim from NDA 207233 page 52 of MEL3-12-02 Clinical Study Report)

- Improved pain or function subscale score  $\geq 50\%$  and absolute change  $\geq 20$  mm
- Met 2 of the 3 following criteria:
  - Pain improvement  $\geq 20\%$  from Baseline and absolute change  $\geq 10$  mm,
  - Function improvement  $\geq 20\%$  from Baseline and absolute change  $\geq 10$  mm,
  - Patient's global impression of change, rated as either "improved," "much improved," or "very much improved."

If neither of the 2 major criteria were met, then the subject was considered a non-responder.

It appears that all subjects who discontinued the study before completion, regardless of the cause, were considered non-responders.

More “responders” by the above criteria were present in the Vivlodex 10 mg treatment group compared to the Vivlodex 5 mg and placebo treatment groups as demonstrated in the table below.

**Table 15 Percentage of subjects who met criteria for Modified OMERACT-OARSI**

Treatment group	% of subjects who met Modified OMERACT-OARSI criteria
Placebo	63.8%
Vivlodex 5 mg	75.9%
Vivlodex 10 mg	79%

#### 4. Rates of discontinuation for lack of efficacy in MEL3-12-02

The following table demonstrates that more subjects in the placebo and Vivlodex 5 mg treatment group discontinued the trial for lack of efficacy than those in the Vivlodex 10 mg treatment group.

**Table 16 Rates of discontinuation for lack of efficacy in MEL3-12-02**

Treatment Group	No. of subjects who discontinued for lack of efficacy
Placebo	5
Vivlodex 5 mg	7
Vivlodex 10 mg	3

At Week 2, subjects in the 5 mg treatment group showed mildly better improvement in pain with some aspects of some secondary endpoints. These differences were relatively small and of unclear clinical significance

#### 6.1.6 Other Endpoints

One exploratory analysis was performed in which pain intensity was measured by Numerical Pain Rating Scale (NPRS) before and 2 hours after drug dosing. This was performed within one week of Visit 3. Versus placebo, those taking Vivlodex 5 mg and 10 mg showed a larger least squares mean percentage reduction in NPRS score.

#### 6.1.7 Subpopulations

The Applicant provided subgroup analyses of the primary endpoint by age < 65 years, age ≥ 65 years, sex, and race, including African American or Black and White. The results are displayed in the table below. These subgroups consistently trend to demonstrate supportive efficacy. An important caveat of these findings is that this trial was not powered to assess the primary endpoint in these subgroups.

Table 17 Subgroup Analyses of Primary Efficacy Parameter- Trial MEL3-12-02- ITT Population

Subgroup Statistics	Placebo N=133	Vivlodex Capsules		Placebo N=133	Vivlodex Capsules	
		5 mg N=139	10 mg N=130		5 mg N=139	10 mg N=130
<b>Age group</b>		<65 years of age			>=65 years of age	
n	85	91	82	42	40	37
LS Mean (SE) <sup>a</sup>	-25.74 (3.253)	-37.84 (2.981)	-36.90 (3.225)	-26.71 (4.167)	-34.70 (4.170)	-32.92 (4.314)
95% CI	(-32.14, -19.34)	(-43.71, -31.97)	(-43.25, -30.55)	(-34.97, -18.45)	(-42.96, -26.43)	(-41.47, -24.38)
Comparison vs placebo	--	0.0021	0.0056	--	0.1561	0.2759
<b>Gender</b>		<b>Male</b>			<b>Female</b>	
N	39	46	43	88	85	76
LS Mean (SE) <sup>a</sup>	-30.25 (4.844)	-36.29 (4.356)	-29.61 (4.683)	-23.73 (2.904)	-37.04 (2.855)	-36.87 (3.068)
95% CI	(-39.85, -20.66)	(-44.92, -27.66)	(-38.88, -20.34)	(-29.45, -18.01)	(-42.66, -31.41)	(-42.91, -30.82)
Comparison vs placebo	--	0.3270	0.9167	--	0.0003	0.0005
<b>Race<sup>b</sup></b>		<b>Black or African American</b>			<b>White</b>	
N	21	26	26	106	102	89
LS Mean (SE) <sup>a</sup>	-31.21 (8.187)	-40.61 (7.167)	-38.22 (7.087)	-24.59 (2.762)	-36.02 (2.637)	-33.51 (2.973)
95% CI	(-47.57, -14.85)	(-54.93, -26.28)	(-52.40, -24.05)	(-30.03, -19.16)	(-41.20, -30.83)	(-39.35, -27.66)
Comparison vs placebo	--	0.3246	0.4447	--	0.0007	0.0095
<b>OA location</b>		<b>Knee</b>			<b>Hip</b>	
n	108	116	107	19	15	12
LS Mean (SE)	-24.93 (2.773)	-35.75 (2.582)	-32.25 (2.770)	-28.42 (7.367)	-41.43 (8.150)	-52.78 (8.601)
95% CI	(-30.38, -19.48)	(-40.83, -30.68)	(-37.70, -26.81)	(-43.37, -13.48)	(-57.99, -24.86)	(-70.26, -35.30)
Comparison vs placebo	--	0.0011	0.0284	--	0.2332	0.0273

Source: 5.3.5.1 MEL3-12-02 CSR Section 14.2, Table 14.2.13.1, Table 14.2.13.2, Table 14.2.13.3, and Table 14.2.13.5

Abbreviations: CI = confidence interval; ET = early termination; ITT = intent-to-treat; LS = least squares; MMRM = mixed model for repeated measures; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

<sup>a</sup> LS mean, LS mean differences (treatment - placebo), 95% CIs, and P values were obtained from the MMRM model with treatment as the main effect, investigative site and gender as blocking factors, and the baseline WOMAC pain subscale score as a covariate. For the gender subgroup analysis, gender was not included as a blocking factor.

<sup>b</sup> Due to small sample sizes, subgroup analyses by race for the following groups are not presented in this table: American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander. Data for these subgroups are provided in Section 14.2, Table 14.2.13.3.

(Source: NDA 207233 Applicant's table page 61 of Summary of Clinical Efficacy)

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Vivlodex 5 mg and 10 mg are endorsed by the Applicant for management of osteoarthritis pain. The amount of meloxicam in Vivlodex is numerically smaller than in the already-approved meloxicam tablet, Mobic (7.5 mg and 15 mg).

The primary endpoint was met for the Phase 3 efficacy trial, MEL3-12-02. Vivlodex 5 mg and 10 mg demonstrated efficacy compared to placebo. Vivlodex 10 mg did not have advantage over Vivlodex 5 mg for the primary endpoint, but some of the secondary endpoints did suggest benefit of the 10 mg over the 5 mg dose.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The indication for Vivlodex is for a chronic pain condition. Tolerance is not known to develop to meloxicam or NSAIDs. This section is not relevant to this drug product. Efficacy was evaluated over a 12-week double-blind period and was demonstrated for both doses of Vivlodex.

### 6.1.10 Additional Efficacy Issues/Analyses

Comparative claims cannot be made between Vivlodex and other meloxicam preparations because Phase 3 trial MEL3-12-02 was not designed to compare the efficacy of the two drug formulations.

## 7 Review of Safety

### Safety Summary

The primary purpose of this safety review is to determine if the safety of Vivlodex is different than the safety profile of previously approved meloxicam. Eight-hundred sixty-eight subjects received at least one dose of Vivlodex 5 mg or Vivlodex 10 mg in Phase 3 clinical trials conducted for this NDA. The safety profile for Vivlodex that has emerged from this examination is similar to the safety profile of meloxicam's already-approved formulations. However, there is the possibility that Vivlodex 10 mg may cause more hypertension than Mobic did in previous clinical trials. This potential risk is mitigated by the pharmacokinetic properties of Vivlodex, the presence of hypertension in the meloxicam and Vivlodex labeling, and the high lifetime risk of developing hypertension. Overall, no new safety concerns have been identified.

### 7.1 Methods

In support of this NDA, the Applicant provided safety data for Vivlodex from two Phase 3 trials (MEL3-12-02 and MEL3-12-03) in subjects with osteoarthritis pain of the hip or knee. MEL3-12-02 was conducted for the purpose of obtaining efficacy and safety data.

MEL3-12-03 was conducted solely for the purpose of collecting safety data. The Safety Population for each trial is defined as all subjects who received one or more doses of trial medication.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Trials conducted to evaluate the safety of Vivlodex are summarized in Section 5.1 of this review.

#### 7.1.2 Categorization of Adverse Events

The Applicant defines treatment-emergent adverse events (TEAEs) as adverse events that began with trial drug treatment or that were present before trial drug administration and increased in severity with the start of trial drug and up to 30 days after discontinuing trial drug (NDA 207233 page 15 of the Applicant's Summary of Clinical Safety). TEAEs were coded and assembled by System Organ Class or preferred term using version 15.0 of the Medical Dictionary for Regulatory Activities.

A comparison of preferred terms to verbatim terms used by investigators and patients revealed that the coding of adverse events was performed correctly.

#### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data was pooled for the two Phase 3 (MEL3-12-02 and MEL3-12-03) trials, presumably to create a larger safety population. Safety analysis was performed on this unified population. Safety data was also collected from Phase 1 trial MEL1-12-04 and presented separately from the Phase 3 trials.

Two additional Phase 1 pharmacokinetic trials (QP09C03 and MEL1-11-01) were performed with formulations of Vivlodex that differ from the commercial formulation for which this NDA was submitted. Safety data was presented separately for these trials.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### *Exposure to Drug*

In Phase 1 trial MEL1-12-04, 28 healthy subjects received at least one dose of Vivlodex capsules. According to the Applicant, 868 subjects in Phase 3 trials received at least one dose of Vivlodex capsules 5 mg or 10 mg. In MEL3-12-02, 138 subjects received at

least one dose of Vivlodex 5 mg and 131 subjects received at least one dose of Vivlodex 10 mg. In MEL3-12-03, 600 subjects received at least one dose of Vivlodex 10 mg. Two subjects participated in both MEL3-12-02 and MEL3-12-03. It is unclear why the Applicant asserts that 868 subjects received one dose of Vivlodex capsules in Phase 3 trials when 867 individuals participated in Phase 3 trials with Vivlodex.

MEL1-12-04 is a Phase 1 cross-over study evaluating Vivlodex in healthy subjects under fed and fasted conditions. 25/28 subjects completed this study. Below is a table summarizing exposure to Vivlodex Capsules in MEL1-12-04.

**Table 18 Exposure to a Single Dose of Vivlodex in MEL1-12-04**

Dose Group	N
Vivlodex 10 mg-fasted	27
Vivlodex 10 mg-fed	26
Vivlodex 5 mg-fasted	26
Mobic 15 mg-fasted	27

Demographic characteristics of the Integrated Safety Population (subjects from MEL3-12-02 and MEL3-12-03) were mostly balanced across all treatment groups. More female subjects (62.2%) were in the population than male subjects (37.8%). The mean body weight was 88.31 kg. The majority of the population (83.5%) was White, and the age range of the population was 40 to 87 years (mean age at screening was 61.3 years). 15.1% were Black, and 93.4% were not Hispanic or Latino.

Medications received at any time during the trial by greater than 10% of those subjects who took Vivlodex 5 mg or 10 mg in MEL3-12-02 or MEL3-12-03 included:

- paracetamol (38.1%)
- multivitamins (26.3%)
- acetylsalicylic acid (25.2%)
- lisinopril (15.6%)
- fish oil (15.2%)
- simvastatin (12.1%)
- vitamin D (11.5%).

## 7.2.2 Explorations for Dose Response

Meloxicam was first approved for use in the United States April 14, 2000 as the drug Mobic. Mobic is available in 7.5 mg and 15 mg tablets. Vivlodex capsules are available in 5 mg and 10 mg formulations. In MEL3-12-02, placebo, Vivlodex 5 mg, and Vivlodex 10 mg were studied for a determination of efficacy. For a discussion of efficacy, see section 6 of this review. For additional information on adverse events as they pertain to dose, see section 7.5.1 of this review.

### 7.2.3 Special Animal and/or In Vitro Testing

No nonclinical studies of Vivlodex were conducted for this NDA. See section 4.3 of this review.

### 7.2.4 Routine Clinical Testing

Safety testing in Phase 3 trials was adequate and included physical examination, vital sign measurements, hematology, serum chemistry, urinalysis, urine drug screen, alcohol breathalyzer test, 12-lead electrocardiograms, and serum and urine pregnancy tests for females of childbearing potential at specified time points with acceptable frequency. Specific safety concerns with meloxicam, including gastrointestinal and cardio-embolic events were suitably monitored.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Clinical trial MEL1-12-04 determined the relative bioavailability of meloxicam formulations Vivlodex 10 mg capsules and Mobic 15 mg tablets. For more details, see section 4.4 of this review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 2.4 of this Review.

## 7.3 Major Safety Results

### 7.3.1 Deaths

Phase 1 clinical trials QP09C03 and MEL1-12-04 and Phase 3 clinical trial MEL3-12-02 did not report any deaths.

Deaths are preliminarily described in the table below. A more detailed description of these deaths follows the table.

**Table 19 Deaths in trials evaluating Vivlodex**

Trial	Study Phase	Subject
MEL1-11-01	1	Signed informed consent, but was not enrolled in trial
MEL3-12-03	3	142-001
MEL3-12-03	3	125-009

MEL1-11-01 reported one death in a 28-year-old male. His death was attributed to suicide from asphyxiation by hanging. This subject signed the informed consent, but was never enrolled in the trial, nor did he receive trial drug.

MEL3-12-03 reported one subject death (Subject 142-001) during the trial and another subject death (Subject 125-009) after withdrawal from the trial. These two deaths are explained in detail below.

#### Subject 142-001

This 69-year-old male with a medical history significant for tobacco use (quit smoking 1974), hypertension, and hyperlipidemia was on Vivlodex 10 mg daily for approximately 142 days when he experienced a ruptured infrarenal abdominal aortic aneurysm. He presented to medical care and the aneurysm was repaired with Endoluminal stent graft placement. His post-operative course was complicated by a decompression laparotomy with retroperitoneal hematoma evacuation marked by three liters of blood loss. The patient's heart rate and blood pressure decreased and chest compressions were begun. Despite additional resuscitative efforts, the subject expired on the same day that he presented to medical care for his ruptured aortic aneurysm. The subject had no history of abdominal aneurysm before presentation with rupture.

The investigator considers his aortic aneurysm rupture to be unrelated to Vivlodex.

Meloxicam can worsen hypertension and can contribute to aortic aneurysm formation and rupture. However, a review of the case report forms for this subject do not indicate worsening hypertension with the study drug for subject. Therefore, I agree that this subject's aortic aneurysm rupture is unrelated to Vivlodex.

#### Subject 125-009

This 62-year-old male with hypertension, hyperlipidemia, obesity, and hypothyroidism was on Vivlodex 10 mg for 282 days when he was hospitalized on (b) (6) for shortness of breath.

He was hospitalized again on (b) (6) with community acquired pneumonia and the same day was found to have bilateral pulmonary embolism and acute systolic heart failure. The investigator considered his pulmonary embolism and cardiac failure to be unrelated to trial drug. Of note, he was found to have an additional risk factor for venous thrombosis: heterozygous for the G20210A mutation in the prothrombin/factor II gene. He was discharged from this hospitalization on (b) (6)

Although the investigator considered none of the adverse events described above to be related to Vivlodex, the subject was taken off study drug due to the events. His last dose of Vivlodex 10 mg was (b) (6)

The patient expired on (b) (6), at which time it was conveyed that he had metastatic mucinous adenocarcinoma.

The investigator determined his death to be unrelated to study drug. However, the investigator was unable to state the cause of death. Insufficient detail has been included

to definitively determine if the subject's death was related to Vivlodex, although, his diagnosis of metastatic mucinous adenocarcinoma encourages concurrence with the investigator's determination that death was unrelated to trial drug.

### 7.3.2 Nonfatal Serious Adverse Events

Subjects in clinical trials QP09C03, MEL1-11-01, MEL1-12-04, and MEL3-12-02 experienced no serious adverse events. 35 subjects in MEL3-12-03 experienced at least one serious adverse event. These are summarized in the table below as well as in section 9.4 of this review. All of the Serious Adverse Events were treatment-emergent adverse events except for right breast cancer in Subject 120-006. As noted in more detail section 9.4 of this review, it has been concluded that 12 of the 35 serious adverse events were potentially related to trial drug.

**Table 20 Non-Fatal Serious Adverse Events in MEL3-12-03 (N=600)**

System Organ Class	Preferred Term	No. of times SAE experienced
<b>Blood and lymphatic system disorders</b>		
	Anaemia	1
<b>Cardiac disorders</b>		
	Angina pectoris	2
	Cardiac failure congestive	1
	Coronary artery disease	1
	Coronary artery stenosis	1
<b>Gastrointestinal disorders</b>		
	Gastroesophageal reflux disease	1
	Diverticulum intestinal haemorrhagic	1
	Duodenal ulcer haemorrhage	1
	Gastric ulcer haemorrhage	1
<b>General disorders and administration site conditions</b>		
	Chest pain	1
	Non-cardiac chest pain	2
<b>Hepatobiliary disorders</b>		
	Drug-induced liver injury	1
<b>Infections and infestations</b>		
	Appendicitis perforated	1
	Bronchitis	1
	Diverticulitis	2
	Staphylococcal sepsis	1
	Lobar pneumonia	1
	Meningitis bacterial	1
	Sepsis	1
<b>Injury, poisoning and procedural complications</b>		
	Post procedural complication	1
	Road traffic accident	1
	Spinal compression fracture	1
<b>Musculoskeletal and Connective Tissue Disorders</b>		
	Costochondritis	1
<b>Neoplasms benign, malignant, and unspecified</b>		
	Breast cancer	3
	Lung squamous cell carcinoma stage unspecified	1
	Transitional cell carcinoma	1

System Organ Class	Preferred Term	No. of times SAE experienced
Nervous system disorders		
	Carotid artery stenosis	1
	Haemorrhagic cerebral infarction	1
	IVth nerve paralysis	1
Renal and urinary disorders		
	Renal failure acute	2
Respiratory, thoracic, and mediastinal disorders		
	Acute respiratory distress syndrome	1
	Acute respiratory failure	1
	Chronic obstructive pulmonary disease	1
	Pulmonary embolism	1
Surgical and medical procedures		
	Medical device removal	1
Vascular disorders		
	Hypertensive crisis	1

Adverse Events in subjects who experienced death were not included in this table (Subjects 125-009 and 142-001)

### 7.3.3 Dropouts and/or Discontinuations

#### MEL1-12-04

MEL1-12-04 had one subject (Subject 19) who experienced an adverse event leading to trial withdrawal. His case is detailed in the paragraph below.

Subject 19 is a 26-year-old male with history of intergluteal pilonidal disease who, after receiving one dose of Vivlodex 10 mg, experienced a pilonidal abscess. He continued the trial, receiving a Mobic 15 mg tablet, after which it became medically necessary to treat the abscess with surgical drainage and concomitant medication therapy. The subject continued to be followed for the purpose clinical research, but was subsequently withdrawn from the trial.

#### MEL3-12-02

12 subjects discontinued MEL3-12-02 because of treatment-emergent adverse events (TEAEs). Of those, six were in the placebo group, two were in the Vivlodex 5 mg treatment group, and four were in the Vivlodex 10 mg treatment group. Of the subjects on Vivlodex 5 mg with TEAEs leading to study discontinuation, one had stomach pain and the other had worsening osteoarthritis of the right knee. The following TEAEs led to study discontinuation in those on Vivlodex 10 mg:

- Worsening of hypertension
- Elevated LFTs
- Low potassium; worsening of hypertension
- Shortness of breath

For more information on treatment-emergent adverse events leading to study discontinuation in MEL3-12-02, see section 9.5 of this review.

#### MEL3-12-03

77 subjects discontinued MEL3-12-03 because of TEAEs. A table detailing TEAEs leading to study discontinuation by preferred term and system organ class for MEL3-12-03 is below:

**Table 21 Non-fatal TEAEs (including SAEs) leading to study discontinuation in MEL3-12-03 N=600**

System Organ Class	Preferred Term	No. of times TEAE experienced
<b>Blood and lymphatic system disorders</b>		
	Anaemia	2
<b>Cardiac disorders</b>		
	Angina pectoris	1
	Cardiac failure congestive	1
	Coronary artery disease	1
	Myocardial ischaemia	1
	Tricuspid valve incompetence	1
<b>Gastrointestinal disorders</b>		
	Abdominal discomfort	3
	Abdominal pain	2
	Abdominal pain upper	2
	Acquired oesophageal web	1
	Diarrhoea	3
	Diverticulum intestinal haemorrhagic	1
	Duodenal ulcer haemorrhage	1
	Dry mouth	1
	Dyspepsia	1
	Gastric ulcer	3
	Gastric ulcer haemorrhage	1
	Gastritis erosive	1
	Gastroesophageal reflux disease	4
	Hematochezia	1
	Nausea	2
<b>General disorders and administration site conditions</b>		
	Chest pain	1
	Oedema peripheral	2
<b>Hepatobiliary disorders</b>		
	Drug-induced liver injury	1
	Hepatic function abnormal	1
	Hyperbilirubinaemia	1
<b>Infections and infestations</b>		
	Bronchitis	1
	Diverticulitis	1
	Lobar pneumonia	1
	Meningitis bacterial	1
	Sepsis	1
	Staphylococcal sepsis	1
<b>Injury, poisoning, and procedural complication</b>		
	Overdose	1
<b>Investigations</b>		
	Blood creatinine increased	2
	Blood potassium increased	1
	Blood pressure increased	1
	Blood urea increased	1
	Electrocardiogram T wave inversion	1
	Hepatic enzyme increased	2
	Liver function test abnormal	3

System Organ Class	Preferred Term	No. of times TEAE experienced
Metabolism and nutrition disorders		
	Fluid retention	1
Musculoskeletal and connective tissue disorders		
	Arthralgia	3
	Osteoarthritis	5
	Pain in extremity	1
	Tendonitis	1
Neoplasms benign, malignant, and unspecified		
	Breast cancer	2
	Transitional cell carcinoma	1
Nervous system disorders		
	Aphasia	1
	Headache	1
	Hypoaesthesia	1
	IVth cranial nerve paralysis	1
	Somnolence	1
Psychiatric disorders		
	Nervousness	1
Renal and urinary disorders		
	Renal mass	1
	Urinary retention	1
Respiratory, thoracic, and mediastinal disorders		
	Pulmonary embolism	1
	Chronic Obstructive Pulmonary Disease	1
	Dyspnoea exertional	1
Skin and subcutaneous tissue disorders		
	Rash	2
	Skin irritation	1
Vascular disorders		
	Hypertension	3
	Phlebitis superficial	1

Additional details of TEAEs in Phase 3 trial MEL3-12-03 are in section 9.6 of this review.

### 7.3.4 Significant Adverse Events

The following are considered significant adverse events:

1. Severe adverse events
2. Adverse events leading to trial withdrawal (described in section 7.3.3 of this review)

#### 7.3.4.1 Severe Adverse Events

The following adverse events were described as severe:

##### For MEL3-12-02:

Three subjects had severe TEAEs in MEL3-12-02. In the placebo group, one subject had gastroenteritis and one subject had migraine. In the Vivlodex 10 mg group, Subject 108-007 had increased hepatic enzymes.

Subject 108-007 was a 75-year-old female. Her first day of Vivlodex 10 mg was on April 10, 2013. Her last day of Vivlodex was July 1, 2013. Hepatic enzymes were trending downward, but had not returned to normal when they were last checked on July 25, 2013. Bilirubin was not elevated in this subject. The investigator considered the increase in hepatic enzymes to be not related to Vivlodex. The investigator's reasoning for this judgment is not documented. The increase in hepatic enzymes is potentially related to Vivlodex.

The following table displays lab values for Subject 108-007:

**Table 22 Lab values for Subject 108-007**

Date	Alkaline Phosphatase (U/L)	ALT (U/L)	AST (U/L)
3/28/2013	113	21	26
5/20/2013	119	23	28
7/01/2013	218	175 (> 5 x ULN)	128
7/08/2013	214	100	71
7/25/2013	144	36	30

Note: ref range high in females are the following: alk phos 98; ALT 33; AST 34

For MEL3-12-03:

23 subjects had at least one severe TEAE in MEL3-12-03. These are displayed by system organ class and preferred term in the table below:

**Table 23 Severe TEAEs in MEL3-12-03**

System Organ Class	Preferred Term	No. of times AE experienced
Any Treatment Emergent Adverse Events		
Cardiac disorders		
	Angina pectoris	1
	Cardiac failure congestive	1
	Coronary artery disease	1
Gastrointestinal disorders		
	Duodenal ulcer hemorrhage	1
	Gastric ulcer hemorrhage	1
	Gastroesophageal reflux disease	1
Hepatobiliary disorders		
	Drug-induced liver injury*	1
Infections and infestations		
	Appendicitis perforated	1
	Diverticulitis	1
	Lobar pneumonia	1
	Meningitis bacterial	1
	Sepsis	1
	Staphylococcal sepsis	1
Injury, poisoning, and procedural complications		
	Meniscus lesion	1
	Road traffic accident	1

System Organ Class	Preferred Term	No. of times AE experienced
	Spinal compression fracture	1
Musculoskeletal and connective tissue disorders		
	Arthralgia	2
	Osteoarthritis	1
Neoplasms benign, malignant, and unspecified		
	Lung squamous cell carcinoma stage unspecified	1
	Transitional cell carcinoma	1
Nervous system disorders		
	Carotid artery stenosis	1
	Hemorrhagic cerebral infarction	1
	Headache	1
Renal and urinary disorders		
	Renal cyst	1
Respiratory, thoracic, and mediastinal disorders		
	Acute respiratory distress syndrome	1
	Acute respiratory failure	1
	Dyspnea	1
Surgical and medical procedures		
	Explorative laparotomy	1
Vascular disorders		
	Aortic aneurysm rupture	1

\*One subject in the clinical trials conducted experienced drug-induced liver injury. This was subject 134-014 in MEL3-12-03 and is discussed in more detail in section 7.3.5.3.3 Hepatic of this review.

### 7.3.5 Submission-Specific Primary Safety Concerns

Events of clinical concern in subjects receiving Vivlodex are cardio-embolic, gastrointestinal bleeding, hepatic, and renal in nature.

#### 7.3.5.1 MEL1-12-04 events of clinical concern:

No TEAEs of clinical concern were reported for trial MEL1-12-04.

#### 7.3.5.2 MEL3-12-02 events of clinical concern:

Below is a summary table of TEAEs of clinical concern in MEL3-12-02. No subjects with hepatic events of clinical concern had an elevation of bilirubin exceeding the reference range to accompany the hepatic event of clinical concern. Subject narratives are present in section 9.7 of this review.

**Table 24 TEAEs of Clinical Concern in MEL3-12-02**

Area of Clinical Concern	Subject	Preferred Term	Treatment Group	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
Cardio-embolic	123-007	Chest Pain/ Palpitations	Vivlodex 5 mg	Not related/ Unlikely related	Unable to determine

Hepatic	108-007	Hepatic enzyme increased	Vivlodex 10 mg	Not related	Potentially related
	112-014	Liver function test abnormal	Vivlodex 5 mg	Possibly related	Potentially related
	131-002	Liver function test abnormal	Vivlodex 10 mg	Possibly related	Potentially related
Renal	108-013	Blood urea increased	Vivlodex 10 mg	Not related	Potentially related

7.3.5.3 MEL3-12-03 events of clinical concern:

The following were TEAEs of clinical concern in MEL3-12-03:

7.3.5.3.1 Cardio-embolic:

Below is a table of cardio-embolic events

**Table 25 Cardio-embolic TEAEs in MEL3-12-03**

System Organ Class	Preferred Term	No. of times AE experienced
<b>Cardiac disorders</b>		
	Angina pectoris	2
	Cardiac failure acute	1
	Cardiac failure congestive	1
	Coronary artery disease	5
	Coronary artery stenosis	1
	Supraventricular extrasystoles	1
<b>General disorders and administration site conditions</b>		
	Chest pain	1
<b>Nervous system disorders</b>		
	Aphasia	1
	Carotid artery stenosis	1
	Electrocardiogram T wave inversion	1
	Myocardial ischaemia	1
	Transient ischaemic attack	1
<b>Respiratory, thoracic, and mediastinal disorders</b>		
	Pulmonary embolism	2
<b>Vascular disorders</b>		
	Deep vein thrombosis	1

Below is a summary table of subjects with cardio-embolic TEAEs of clinical concern in MEL3-12-03. Subject narratives are present in section 9.7 of this review.

**Table 26 Summary of subjects with cardio-embolic TEAEs in MEL3-12-03**

Subject	Preferred Term(s)	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
101-004	Coronary artery stenosis/ coronary artery disease	Not related	Potentially related
109-006	Coronary artery disease	Not related	Potentially related
112-023	Aphasia	Possibly related	Potentially related

Subject	Preferred Term(s)	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
118-015	Coronary artery disease	Unlikely related	Potentially related
118-027	Transient ischemic attack/Carotid artery stenosis	Unlikely related/ Not related	Potentially related/ Not related
120-041	Electrocardiogram T wave inversion/ myocardial ischaemia/ coronary artery disease	Possibly related	Potentially related
123-011	Cardiac failure congestive	Not related	Potentially related
124-023	Angina pectoris	Not related	Potentially related
124-051	Chest pain/ coronary artery disease/ supraventricular extrasystoles	Not related/ Unlikely related/ Not related/	Not related/ Potentially related/ Not related
125-009	Cardiac failure acute/ pulmonary embolism	Not related/ Not related	Unable to determine, but unlikely related
131-006	Angina Pectoris	Not related	Potentially related
137-010	Pulmonary embolism/ deep vein thrombosis	Not related/ Unlikely related	Potentially related

#### 7.3.5.3.2 GI bleeding:

Gastrointestinal bleeding events are described in the table below:

**Table 27 GI bleeding TEAEs in MEL3-12-03**

System Organ Class	Preferred Term	No. of times AE experienced
Gastrointestinal disorders		
	Diverticulum intestinal haemorrhagic	1
	Duodenal ulcer haemorrhage	1
	Gastric ulcer haemorrhage	1
	Rectal haemorrhage	2

Below is a summary table of subjects with GI bleeding TEAEs of clinical concern in MEL3-12-03. Subject narratives are present in section 9.7 of this review.

**Table 28 Summary of subjects with GI bleeding TEAEs in MEL3-12-03**

Subject	Preferred Term(s)	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
108-001	Rectal haemorrhage	Not related	Not related
120-020	Diverticulum intestinal haemorrhagic	Probably related	Potentially related
138-010	Duodenal ulcer haemorrhage/ Gastric ulcer haemorrhage	Probably related	Potentially related
142-019	Rectal haemorrhage	Not related	Not related

#### 7.3.5.3.3 Hepatic:

In MEL3-12-03, fifteen subjects had hepatic-related TEAEs. These subjects are detailed in the table below.

(b) (4)

**Table 29 S Maximum Liver Function Test Measurements in Subjects Treated with Vivlodex Capsules 10 mg with Hepatic Laboratory-Related Treatment Emergent Adverse Events**

Subject	Days of Treatment to Adverse Event	Adverse Event: Preferred Term	Resolved	Maximum Measured Values and Magnitude of Change from ULN (1x, 2x, 3x, etc.)			
				ALP U/L (xULN)	AST U/L (xULN)	ALT U/L (xULN)	Bilirubin umol/L (xULN)
104-025	84	Hyperbilirubinaemia	No	99 (≤1x)	24 (≤1x)	28 (≤1x)	42.8 (2x)
106-002	15	Hepatic function abnormal	No	87 (≤1x)	80 (2x)	133 (3x)	10.3 (≤1x)
114-002	340	Hepatic enzyme increased	No	90 (≤1x)	63 (2x)	99 (2x)	15.4 (≤1x)
115-009	336	Liver function test abnormal	No	68 (≤1x)	149 (4x)	140 (4x)	30.8 (2x)
118-030	174	Liver function test abnormal	No	89 (≤1x)	86 (2x)	41 (≤1x)	10.6 (≤1x)
123-001	57	Alanine aminotransferase increased	Yes	209 (2x)	130 (3x)	253 (6x)	6.8 (≤1x)
		Aspartate aminotransferase	Yes				
		Liver function test abnormal	Yes				
123-012	29	Alanine aminotransferase increased	No	81 (≤1x)	76 (2x)	112 (3x)	18.8 (≤1x)
123-013	282	Liver function test abnormal	Yes	94 (≤1x)	216 (6X)	151 (5x)	18.8 (≤1x)
124-051	63	Blood alkaline phosphatase increased	No	171 (2x)	36 (≤1x)	44 (≤1x)	10.3 (≤1x)
128-002	28	Hepatic enzyme increased	Yes	192 (2x)	71 (2x)	101 (3x)	12(≤1x)
131-005	29	Liver function test abnormal	Yes	76 (≤1x)	130 (4x)	84 (3x)	10.3 (≤1x)

Subject	Days of Treatment to Adverse Event	Adverse Event: Preferred Term	Resolved	Maximum Measured Values and Magnitude of Change from ULN (1x, 2x, 3x, etc.)			
				ALP U/L (xULN)	AST U/L (xULN)	ALT U/L (xULN)	Bilirubin umol/L (xULN)
134-014 <sup>a</sup>	224	Drug-induced liver injury	Yes	180 (2x)	30 (≤1x)	57 (2x)	183 (9x)
133-006 <sup>a</sup>	313	Hepatic function abnormal	Yes	83 (≤1x)	37 (≤1x)	38 (≤1x)	13.7 (≤1x)
106-070 <sup>a</sup>	59	Hepatic enzyme increased	Yes	107 (≤1x)	104 (3x)	137 (3x)	34.2(2x)
107-021 <sup>a</sup>	340	Liver function test abnormal	No	141 (≤1x)	85 (3x)	50 (2x)	15.4 (≤1x)

<sup>a</sup>Additional subjects included. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase. For the definitions of the ULN of normal for each analyte please see MEL3-12-03 CSR, Table 12-13. #xULN for ALT, AST, ALP and Bilirubin are rounded to the nearest whole number. ≤1x ULN indicates that the maximum result was within normal range.

(Source: NDA 207233 Applicants table pages 4-5 of Clinical Information Amendment 0009)

Note: Ref range high for bilirubin is 20.5 µmol/L. In males, ref range highs for ALT=44, AST=39, ALP=129. In females, ref range highs for ALT=33, AST=34, ALP=98.

Of particular interest is Subject 134-014. She is a 55-year-old female who experienced probable drug induced hepatitis. She began Vivlodex 10 mg daily on April 23, 2013. At the time, she was also taking the following medications: multivitamin, silybum marianum, olea europaea leaf extract, cyanocobalamin, Vitamin D NOS, magnesium, chondroitin sodium sulfate with glucosamine hydrochloride.

On approximately (b) (6), she experienced right breast implant rupture. Her breast implants were removed on (b) (6).

In the perioperative period, she received the following medications in addition to Vivlodex 10 mg daily:

- (b) (6): lorazepam, pregabalin, oxycodone/acetaminophen
- (b) (6): cefadroxil
- (b) (6): tramadol and Vicodin

On (b) (6), she began to experience pruritus, pale stool, and dark urine. On November 27, 2013, she began taking hydroxyzine 100 mg three times daily for the pruritus. On November 28, 2013, she had symptoms consistent with jaundice. The last dose of Vivlodex was on December 1, 2013. Labs were drawn on December 2, 2013, revealing alkaline phosphatase of 190 U/L (nl 42-98 U/L), ALT 80 U/L (nl 0-33), bilirubin 171 µmol/L (nl 5.1-20.5). On (b) (6), after being on Vivlodex 10 mg daily for 224 days, she had severe drug-induced liver injury.

On (b) (6), MRI revealed hepatomegaly. (b) (6), a liver biopsy was performed, revealing changes consistent with drug-induced hepatitis. Drug-induced liver injury was considered by the investigator to be likely related to Vivlodex. Despite her greatly elevated bilirubin, her ALT never exceeded 3 times the upper limit of normal and she never technically met the definition of Hy's Law. Her drug-induced liver injury may be related to Vivlodex, but the timing of the liver injury—after a surgical procedure in which she received other medications—indicates that her DILI may be related to another medication or may be related to the combination of Vivlodex and another medication. More detail of her case is in section 9.4 of this review.

#### 7.3.5.3.4 Renal:

Renal events are described in the table below:

**Table 30 Renal TEAEs in MEL3-12-03**

System Organ Class	Preferred Term	Vivlodex 10 mg
Investigations		
	Blood creatinine increased	5
	Blood urea increased	2
Renal and urinary disorders		
	Renal failure	1
	Renal failure acute	2

Below is a summary table of subjects with renal TEAEs of clinical concern in MEL3-12-03. Subject narratives are present in section 9.7 of this review.

**Table 31 Summary of subjects with renal TEAEs in MEL3-12-03**

Subject	Preferred Term(s)	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
107-006	Renal failure	Possibly related	Potentially related
109-004	Blood creatinine increased	Possibly related	Potentially related
118-018	Blood creatinine increased	Probably related	Potentially related
127-004	Blood creatinine increased	Not related	Not related
131-009	Renal failure acute	Unlikely related	Potentially related, but unlikely related
133-006	Renal failure acute	Not related	Not related
138-018	Blood creatinine increased/ Blood urea increased	Probably related	Potentially related
138-033	Blood creatinine increased/ Blood urea increased	Probably related	Potentially related

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Subjects in MEL1-12-04 had no treatment-emergent adverse events of clinical concern.

#### Integrated Safety Population (Phase 3 trials)

868 subjects received either Vivlodex 5 mg or Vivlodex 10 mg in Phase 3 clinical trials. The most frequent treatment-emergent adverse events are organized by preferred term in the tables below and presented separately for trials MEL3-12-02 and MEL3-12-03.

**Table 32 For MEL3-12-02: Summary of Most Frequent (greater than or equal to 1% of Subjects in any Group) Treatment-Emergent Adverse Events by Preferred Term (Safety Population)**

Preferred Term, n (%)	Placebo N=133	Meloxicam SoluMatrix Capsules			Total N=402
		5 mg N=138	10 mg N=131	Combined N=269	
Diarrhoea	1 (0.8%)	4 (2.9%)	3 (2.3%)	7 (2.6%)	8 (2.0%)
Headache	4 (3.0%)	2 (1.4%)	5 (3.8%)	7 (2.6%)	11 (2.7%)
Nausea	0	3 (2.2%)	3 (2.3%)	6 (2.2%)	6 (1.5%)
Osteoarthritis	3 (2.3%)	4 (2.9%)	1 (0.8%)	5 (1.9%)	8 (2.0%)
Urinary tract infection	3 (2.3%)	3 (2.2%)	2 (1.5%)	5 (1.9%)	8 (2.0%)
Abdominal Discomfort	0	1 (0.7%)	3 (2.3%)	4 (1.5%)	4 (1.0%)
Constipation	2 (1.5%)	2 (1.4%)	2 (1.5%)	4 (1.5%)	6 (1.5%)
Upper respiratory tract infection	2 (1.5%)	2 (1.4%)	2 (1.5%)	4 (1.5%)	6 (1.5%)

Preferred Term, n (%)	Placebo N=133	Meloxicam SoluMatrix Capsules			Total N=402
		5 mg N=138	10 mg N=131	Combined N=269	
Nasopharyngitis	0	1 (0.7%)	2 (1.5%)	3 (1.1%)	3 (0.7%)
Dry mouth	0	2 (1.4%)	0	2 (0.7%)	2 (0.5%)
Hypertension	1 (0.8%)	0	2 (1.5%)	2 (0.7%)	3 (0.7%)
Toothache	1 (0.8%)	0	2 (1.5%)	2 (0.7%)	3 (0.7%)
Oedema peripheral	2 (1.5%)	0	1 (0.8%)	1 (0.4%)	3 (0.7%)
Pain in extremity	2 (1.5%)	1 (0.7%)	0	1 (0.4%)	3 (0.7%)
Epicondylitis	2 (1.5%)	0	0	0	2 (0.5%)

Source: Section 14.3.1, Table 14.3.1.8

Abbreviations: TEAE = treatment-emergent adverse event

Note: The denominator for the percentages was the number of subjects in each treatment group. At each level of summarization (preferred term) subjects who experienced more than 1 treatment-emergent adverse event (TEAE) were counted only once. Preferred terms were sorted in descending order of frequency within the Combined Meloxicam SoluMatrix Capsules group. All TEAEs were coded by using the MedDRA, Version 15.0.

(Source: NDA 207233 Applicant's table page 114 of MEL3-12-02 Clinical Study Report)

**Table 33 For MEL3-12-03: Summary of Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects by Preferred Term (Safety Population)**

Preferred Term, n (%)	Meloxicam SoluMatrix Capsules 10 mg N=600
Any TEAE	406 (67.7%)
Arthralgia	33 (5.5%)
Urinary tract infection	33 (5.5%)
Osteoarthritis	30 (5.0%)
Hypertension	25 (4.2%)
Diarrhea	24 (4.0%)
Headache	24 (4.0%)
Upper respiratory tract infection	24 (4.0%)
Back pain	21 (3.5%)
Nasopharyngitis	21 (3.5%)
Bronchitis	18 (3.0%)
Sinusitis	17 (2.8%)
Constipation	15 (2.5%)
Dyspepsia	15 (2.5%)

<b>Preferred Term, n (%)</b>	<b>Meloxicam SoluMatrix Capsules 10 mg N=600</b>
Edema peripheral	13 (2.2%)
Nausea	13 (2.2%)
Pain in extremity	12 (2.0%)
Abdominal discomfort	10 (1.7%)
Dizziness	10 (1.7%)
Muscle strain	10 (1.7%)
Contusion	9 (1.5%)
Fall	9 (1.5%)
Rash	9 (1.5%)
Type 2 diabetes mellitus	9 (1.5%)
Depression	8 (1.3%)
Insomnia	8 (1.3%)
Musculoskeletal pain	8 (1.3%)
Sinus congestion	8 (1.3%)
Cough	7 (1.2%)
Fatigue	7 (1.2%)
Gastroesophageal reflux disease	7 (1.2%)
Abdominal distension	6 (1.0%)
Abdominal pain	6 (1.0%)
Arthropod bite	6 (1.0%)
Basal cell carcinoma	6 (1.0%)
Blood potassium increased	6 (1.0%)
Dermatitis	6 (1.0%)
Gastroenteritis viral	6 (1.0%)
Hematuria	6 (1.0%)
Liver function test abnormal	6 (1.0%)
Pain	6 (1.0%)
Sciatica	6 (1.0%)
Tooth abscess	6 (1.0%)
Toothache	6 (1.0%)

Source: Section 14.3.1, Table 14.3.1.3

Abbreviations: TEAE = treatment-emergent adverse event

Note: The denominator for the percentages is the number of subjects in the Safety population. At each level of summarization (preferred term), subjects experiencing more than one TEAE were counted only once. All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 15.0.

(Source: NDA 207233 Applicant's table page 56 of MEL3-12-03 Clinical Study Report)

## 7.4.2 Laboratory Findings

### 7.4.2.1 Laboratory findings in Phase 3 trials (MEL3-12-02 and MEL3-12-03)

Laboratory values of potential clinical concern for MEL3-12-03 are defined in the table below. Criteria for Laboratory Values of Potential Clinical Concern are identical for MEL3-12-02 with the exception of BUN. For MEL3-12-02, BUN  $\geq 24$  mg/dl is the High value that has reached a Potentially Clinically Significant Abnormal Level.

**Table 34 Criteria for Laboratory Values of Potential Clinical Concern**

Test (Unit)	Subject Gender	Lower Limit of Normal	Upper Limit of Normal	Potentially Clinically Significant Abnormal Level	
				Low	High
Hb (g/dL)	Female	11.5	16.0	$\leq 8.0$	$\geq 19.0$
	Male	13.0	17.5	$\leq 8.0$	$\geq 19.0$
Hct (%)	Female	36.4	48.9	$\leq 24$	$\geq 60$
	Male	41.6	54.1	$\leq 24$	$\geq 60$
WBC ( $10^3/\mu\text{L}$ )	Both	4.5	11.0	$\leq 2.0$	$\geq 22$
Absolute neutrophils ( $10^3/\mu\text{L}$ )	Both	1.8	7.7	$\leq 0.5$	$\geq 15.4$
Platelets ( $10^3/\mu\text{L}$ )	Both	130	400	-	$> 1000$
ALT (U/L)	Female	0	33	-	$> 3 \times \text{ULN}$
	Male	0	44	-	$> 3 \times \text{ULN}$
AST (U/L)	Female	14	34	-	$> 3 \times \text{ULN}$
	Male	14	39	-	$> 3 \times \text{ULN}$
Albumin (g/dL)	Both	3.5	5.2	$< 2.0$	-
Alk Phos (U/L)	Female	42	98	-	$> 1.5 \times \text{ULN}$
	Male	53	129	-	$> 1.5 \times \text{ULN}$
Bilirubin (total) mg/dL	Both	0.3	1.2	-	$> 2 \times \text{ULN}$
BUN mg/dL	Both	9	23	-	$\geq 31$
Creatinine (mg/dL)	Female	0.49	1.11	-	$\geq 1.5 \times \text{ULN}$
	Male	0.69	1.31	-	$\geq 1.5 \times \text{ULN}$
Potassium (mmol/L)	Both	3.5	5.1	$\leq 3.0$	$\geq 5.5$
Sodium (mmol/L)	Both	136	145	$\leq 120$	$\geq 155$
Bicarbonate (mmol/L)	Both	20	31	$\leq 15$	$\geq 40$
LDH (U/L)	Both	120	246	-	$> 2 \times \text{ULN}$
Glucose (random) mg/dL	Both	60	140	$\leq 55$	$\geq 200$

Source: MEL3-12-03 Final SAP v1.0, Table 1.

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Hb = hemoglobin; Hct = hematocrit; LDH = lactate dehydrogenase; ULN = upper limit of normal; WBC = white blood cells  
 (Source: NDA 207233 Applicant's table page 76 of MEL3-12-03 Clinical Study Report)

#### 7.4.2.1.1 In MEL3-12-02:

Labs were performed in MEL3-12-02 at the following times:

- Hematology, chemistry, and urinalysis obtained at Visits 1, 4, and 5(or early termination).
- Urine drug screen at Visits 1 and 2

Laboratory values identified as being of potential clinical concern based on the criteria in the table above were reported in the clinical study report and were reviewed. Most of the subjects with laboratory values of potential clinical concern are described in other sections of this NDA review. Subjects with labs of potential clinical concern who are not described elsewhere in this review are described in the table below:

**Table 35 Further detail of subjects with laboratories of clinical concern in MEL3-12-02 not described in other parts of this NDA review**

Subject	Treatment group	Lab values of concern		Further details
		Date	Value	
118-003	Vivlodex 5 mg	2/27/2013	K 4.8 mmol/L	49-year-old male
		4/18/2013	K 4.7 mmol/L	
		5/28/2013	K 6.1 mmol/L	
		6/10/2013	K 4.5 mmol/L	
122-017	Vivlodex 5 mg	5/22/2013	BUN 6.8 mmol/L	53-year-old female; discontinued trial prior to completing treatment
		7/16/2013	BUN 9.6 mmol/L	
		9/20/2013	BUN 5.7 mmol/L	

No subjects met the criteria for Hy's Law.

ALT, AST, alkaline phosphatase, and BUN had some changes from baseline at weeks 6 and 12 in the Vivlodex treatment group versus placebo. These changes are detailed in the table below:

**Table 36 Changes from Baseline to Weeks 6 and 12 for ALT, AST, alkaline phosphatase and BUN**

Mean change from baseline	Vivlodex 10 mg	Vivlodex 5 mg	Placebo
To week 6 in ALT (U/L)	+3.3	+1.5	-0.9
To week 12 in ALT (U/L)	+1.5	+2.2	0.0
To week 6 in AST (U/L)	+3.0	+ 1.2	-0.6
To week 12 in AST (U/L)	+0.6	+0.9	
To week 12 in Alk Phos (U/L)	-1.6	-0.8	-0.4
To week 6 in BUN (mmol/L)	+0.29	+0.11	decrease
To week 12 in BUN (mmol/L)	+0.5	+0.05	decrease

Shifts in clinical chemistry values from baseline to week 12 that occurred in  $\geq 5\%$  of subjects are described in the table below:

**Table 37 Summary of Shifts in Chemistry Parameters From Normal Baseline Values to Low or High Values at the Week 12 Evaluation in at Least 5% of Subjects in any Treatment Group (Safety Population)**

Analyte (Unit); n (%)	Placebo N=133		Meloxicam SoluMatrix Capsules			
			5 mg N=138		10 mg N=131	
	N to L	N to H	N to L	N to H	N to L	N to H
Alk Phos (U/L)	1 (0.8%)	6 (5.1%)	2 (1.6%)	5 (3.9%)	4 (3.4%)	1 (0.9%)
ALT (U/L)	0	6 (5.1%)	0	8 (6.3%)	0	11 (9.4%)
AST (U/L)	3 (2.5%)	5 (4.2%)	2 (1.6%)	8 (6.3%)	1 (0.9%)	5 (4.3%)
Bilirubin (µmol/L)	7 (5.9%)	0	5 (3.9%)	0	2 (1.7%)	4 (3.4%)
BUN (mmol/L)	0	1 (0.8%)	2 (1.6%)	10 (7.8%)	0	13 (11.1%)
Glucose (mmol/L)	0	8 (6.8%)	0	8 (6.4%)	1 (0.9%)	7 (6.0%)
LDH (U/L)	0	3 (2.5%)	1 (0.8%)	7 (5.5%)	0	7 (6.0%)
Potassium (mmol/L)	0	3 (2.5%)	1 (0.8%)	8 (6.4%)	1 (0.9%)	4 (3.4%)

Source: Section 14.3.1, Table 14.3.10.2.2

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; N to L = normal to low; N to H = normal to high

Note: Baseline was the last measurement prior to the first dose of trial drug. Percentages are based on the number of subjects with nonmissing values at both Baseline and the scheduled visit.

(Source: NDA 207233 Applicant's table page 123 of MEL3-12-02 Clinical Study Report)

For hematology labs, there were no significant mean changes from baseline for any visit or treatment group. Some subjects in the Vivlodex treatment groups had changes in hematology labs from Baseline to Week 12. These changes are described in the table below:

**Table 38 Changes in hematology labs from Baseline to Week 12**

Shift in lab value	Number of subjects (%)		
	In Vivlodex 10 mg group	In Vivlodex 5 mg group	In placebo group
Leukocyte count from nl to low	9 (7.7)	14 (10.9)	-
Erythrocyte count from nl to low	6 (5.1)	-	-
Eosinophil/leukocyte % from nl to high	12 (10.3)	8 (6.3)	6 (5.1)

For urinalysis labs, mean changes were comparable in Vivlodex and placebo treatment groups. Shifts in urinalysis values from baseline to week 12 that occurred in ≥ 5% of subjects are described in the table below:

**Table 39 Summary of Shifts in Urinalysis Parameters from Normal Baseline Values to Low or High Values at the Week 12 Evaluation in at Least 5% of Subjects in any Treatment Group (Safety Population)**

Analyte (Unit); n (%)	Placebo N=133		Meloxicam SoluMatrix Capsules			
			5 mg N=138		10 mg N=131	
	N to L	N to H	N to L	N to H	N to L	N to H
Hyaline casts (/lpf)	0	1 (4.0%)	0	2 (9.1%)	0	0
Specific gravity	10 (8.5%)	4 (3.4%)	11 (8.8%)	6 (4.8%)	8 (6.8%)	6 (5.1%)
Urine erythrocytes (/hpf)	0	2 (8.0%)	0	0	0	1 (3.3%)
Urine leukocytes (/hpf)	0	4 (16.0%)	0	4 (18.2%)	0	2 (6.7%)

Source: Section 14.3.1, Table 14.3.10.3.2

Abbreviations: hpf = high powered field; lpf = low powered field; N to L = normal to low; N to H = normal to high

Note: Baseline was the last measurement prior to the first dose of trial drug. Reflex microscopic testing (eg, hyaline casts, urine erythrocytes, and urine leukocytes) was performed only for abnormal urinalysis findings. Percentages are based on the number of subjects with nonmissing values for both the Baseline and the individual Week 12 assessments.

(Source: NDA 207233 Applicant's table page 124 of MEL3-12-02 Clinical Study Report)

Two laboratory-related treatment-emergent adverse events led to trial discontinuation for MEL3-12-02.

**Table 40 Laboratory-related TEAEs leading to trial discontinuation for MEL3-12-02**

Subject	Treatment-Emergent Adverse Event	Summary
131-002	Elevated LFTs	72-year-old male in Vivlodex 10 mg treatment group
132-012	Low potassium	84-year-old male in Vivlodex 10 mg treatment group

#### 7.4.2.2. In MEL3-12-03:

Labs were performed in MEL3-12-03 at the following times:

- Hematology, chemistry, and urinalysis obtained at the screening visit and Weeks 4, 8, 12, 24, 32, 40, 48, and 52 (or early termination visit).
- Urine drug screen at screening and baseline

Laboratory values identified as being of potential clinical concern based on the criteria in the table in 7.4.2.1 were reported in the clinical study report and were reviewed. After review of these labs, laboratory values that continued to be of clinical concern are described in the table below. One subject, Subject 138-018, was excluded from this table because she is described elsewhere in this NDA.

**Table 41 Further detail of selected subjects with laboratories of clinical concern in MEL3-12-03**

Subject	Lab values of concern	Further details
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	Date	Week or Visit	Value		
102-007	4/11/2013	Screen	BUN 6.8 mmol/L		66-year-old male
	5/16/2013	4	BUN 7.1 mmol/L		
	6/13/2013	8	BUN 7.9 mmol/L		
	7/08/2013	12	BUN 8.6 mmol/L		
	10/04/2013	24	BUN 6.8 mmol/L		
	11/25/2013	32	BUN 7.9 mmol/L		
	1/21/2014	40	BUN 7.9 mmol/L		
	3/26/2014	48	BUN 10 mmol/L		
	4/17/2014	52/ET	BUN 12.9 mmol/L		
112-020	5/07/2013	Screen	Alk Phos 159 U/L		Subject had SAE of perforated appendicitis (b) (6)
	6/13/2013	4	Alk Phos 138 U/L		
	7/10/2013	8	Alk Phos 118 U/L		
	8/7/2013	12	Alk Phos 118 U/L		
	10/30/2013	24	Alk Phos 120 U/L		
	12/23/2013	32	Alk Phos 122 U/L		
	2/19/2014	40	Alk Phos 142 U/L		
	4/16/2014	48	Alk Phos 518 U/L		
	5/14/2014	52/ET	Alk Phos 161 U/L		
115-011	5/20/2013	Screen	BUN 6.8 mmol/L		69-year-old male
	6/24/2013	4	BUN 11.4 mmol/L		
	7/22/2013	8	BUN 9.3 mmol/L		
	8/16/2013	12	BUN 13.2 mmol/L		
	11/11/2013	24	BUN 8.9 mmol/L		
	1/6/2014	32	BUN 9.3mmol/L		
	3/3/2014	40	BUN 10 mmol/L		
	4/28/2014	48	BUN 11.1 mmol/L		
	5/29/2014	52/ET	BUN 10 mmol/L		
118-004	3/21/2013	Screen	BUN 6.4 mmol/L		51-year-old male discontinued for lack of efficacy
	4/24/2013	4	BUN 11.1 mmol/L		
	6/5/2013	ET	BUN 8.2 mmol/L		
118-014	4/2/2013	Screen	Alk Phos 79 U/L		Last dose of study drug received 9/4/2013. Study discontinued for protocol violation—newly discovered past medical history of gastric sleeve surgery
	5/7/2013	4	Alk Phos 73 U/L		
	6/4/2013	8	Alk Phos 66 U/L		
	7/2/2013	12	Alk Phos 85 U/L		
	9/4/2013	ET	Alk Phos 156 U/L		
119-009	4/4/2013	Screen	ALT 101 U/L	AST 110 U/L	52-year-old male discontinued June 9, 2013 for “noncompliance” with study drug
	5/6/2013	4	ALT 105 U/L	AST 108 U/L	
	6/5/2013	8	ALT 146 U/L	AST 150 U/L	
	6/14/2013	ET	ALT 108 U/L	AST 96 U/L	
	6/20/2013		ALT 121 U/L	AST 147 U/L	
120-032	4/29/2013	Screen	K 4.7 mmol/L		59-year-old female discontinued from study 5/24/2013 because had not previously disclosed NSAID allergy
	5/29/2013	ET	K 6.2 mmol/L		
128-002	4/9/2013	Screen	ALT 54 U/L	Alk Phos 169 U/L	59-year-old female had last dose of study drug 5/13/2013. Discontinued trial for lack of efficacy and hepatic enzyme increased.
	5/13/2013	ET	ALT 101 U/L	Alk Phos 192 U/L	

No subjects met the criteria for Hy’s Law. Subject 134-014 (further described in section 9.4 of this review) experienced severe drug-induced liver-injury, but this may have been precipitated by other medications the subject received. At the peak of her bilirubin elevation, her ALT was 80 U/L (nl 0-33) and bilirubin was 171 µmol/L (nl 5.1-20.5). Despite her greatly elevated bilirubin, her ALT never exceeded 3 times the upper limit of normal and she never technically met the definition of Hy’s Law. Her drug-induced liver injury may be related to Vivlodex, but the timing of the liver injury—after a surgical procedure in which she received other medications—indicates that her DILI may be related to another medication or may be related to the combination of Vivlodex and another medication.

ALT, alkaline phosphatase, and creatinine had some changes from baseline. These changes are detailed in the table below:

**Table 42 Changes from Baseline in ALT, alkaline phosphatase, and creatinine in MEL3-12-03**

Mean change from baseline	Vivlodex 10 mg
To week 40 in ALT (U/L)	+2.2
To week 4 in Alk Phos (U/L)	-2.1
To week 12 in creatinine (µmol/L)	+4.2
To week 48 in creatinine (µmol/L)	-5.9
To week 52 in creatinine (µmol/L)	-4.4

Shifts in clinical chemistry values from baseline to week 52 that occurred in ≥ 5% of subjects are described in the table below:

**Table 43 Summary of Shifts in Chemistry Parameters from Normal Baseline Values to Low or High Values at Week 52 Occurring in at Least 5% of Subjects (Safety Population)**

Analyte (Unit); n (%)	Meloxicam SoluMatrix Capsules 10 mg N=600		
	n <sup>a</sup>	Normal to Low	Normal to High
ALT (U/L)	393	0	23 (5.9%)
AST (U/L)	393	1 (0.3%)	24 (6.1%)
BUN (mmol/L)	393	5 (1.3%)	38 (9.7%)
Glucose (mmol/L)	388	0	24 (6.2%)

Source: Section 14.3.1, Table 14.3.10.2.2

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen

<sup>a</sup>Number of subjects with non-missing values at both Baseline and the Week 52 visit.

Note: Baseline was the last measurement prior to the first dose of trial drug. Percentages are based on the number of subjects with nonmissing values at both Baseline and the scheduled visit.

(Source: NDA 207233 Applicant’s table page 74 of MEL3-12-03 Clinical Study Report)

In hematology labs, hematocrit and hemoglobin shifted from normal to low from baseline to week 52 in less than 5% of subjects and from normal to low in less than 7%

of subjects for any scheduled visit. Some subjects had changes in hematology labs from baseline to week 52. These changes are described in the table below:

**Table 44 Shift in lab values from baseline to week 52 in those with non-missing lab values for baseline and week 52**

Shift in lab value	Number of subjects (%)
Leukocyte % from normal to low	21 (5.3)
Lymphocyte/leukocyte % from normal to low	27 (6.9)
Eosinophil/leukocyte % from normal to high	42 (10.7)
Neutrophil/leukocyte % from normal to high	20 (5.1)

In urinalysis labs, 5.8% to 11.5 % of subjects had urine erythrocyte increase from normal to high between weeks 4 and 40. At week 24, 14% of subjects had urine leukocyte values that had shifted from normal to high. Shifts in urinalysis values from baseline to week 52 that occurred in  $\geq 5\%$  of subjects are described in the table below:

**Table 45 Summary of Shifts in Urinalysis Parameters From Normal Baseline Values to Low or High Values at Week 52 Occurring in at Least 5% of Subjects (Safety Population)**

Analyte (Unit); n (%)	Meloxicam SoluMatrix Capsules 10 mg N=600		
	n <sup>a</sup>	Normal to Low	Normal to High
Hyaline casts (/lpf)	106	0	8 (7.5%)
Specific gravity	394	39 (9.9%)	8 (2.0%)
Urine leukocytes (/hpf)	102	0	7 (6.9%)

Source: Section 14.3.1, Table 14.3.10.3.2

Abbreviations: hpf = high-powered field; lpf = low-powered field;

<sup>a</sup>Number of subjects with nonmissing values at both Baseline and the scheduled visit.

Note: Baseline was the last measurement prior to the first dose of trial drug. Percentages are based on the number of subjects with nonmissing values at both Baseline and the scheduled visit.

(Source: NDA 207233 Applicant's table page 75 of MEL3-12-03 Clinical Study Report)

12 laboratory-related treatment-emergent adverse events led to trial discontinuation for MEL3-12-03

**Table 46 Laboratory-related TEAEs leading to trial discontinuation in MEL3-12-03**

Subject	Treatment-Emergent Adverse Event	Age/sex
104-025	Hyperbilirubinemia	84-year-old male
106-002	Worsening liver functions	63-year-old male
106-070	Elevated liver enzymes	44-year-old male
114-002	Elevated liver enzymes	57-year-old male
115-009	Elevated liver function tests	61-year-old female
118-018	Elevated serum creatinine	64-year-old male
120-017	Anemia	59-year-old female
123-001	Elevated LFT values	56-year-old male
123-013	Elevated liver function test	61-year-old female

Subject	Treatment-Emergent Adverse Event	Age/sex
134-014*	Probable drug-induced hepatitis	55-year-old female
137-036	Elevated potassium	65-year-old male
138-018	Elevation in creatinine levels	77-year-old female

For more detail of these cases, see section 9.6 of this review.

\*For more detail of this case, see section 9.4 of this review.

### 7.4.3 Vital Signs

#### 7.4.3.1 MEL1-12-04

There were no vital sign-related adverse events in Phase 1 trial MEL1-12-04.

#### 7.4.3.2 MEL3-12-02

In MEL3-12-02, there were three vital sign-related TEAEs leading to trial discontinuation, including two subjects with hypertension and one subject with dyspnea.

**Table 47 Vital sign-related TEAEs leading to trial discontinuation in MEL3-12-02**

Subject	Treatment	Summary
124-033	Vivlodex 10 mg	66-year-old female with worsening hypertension
132-012	Vivlodex 10 mg	84-year-old male with worsening hypertension
132-014	Vivlodex 10 mg	78-year-old female with shortness of breath

#### 7.4.3.3 MEL3-12-03

In MEL3-12-03, there were four vital sign-related TEAEs leading to trial discontinuation and three vital sign-related SAEs. These are described in the tables below.

**Table 48 Vital sign-related TEAEs leading to trial discontinuation in MEL3-12-03**

Subject	Event	Relatedness to study drug per investigator	Relatedness to study drug per reviewer
111-010	Worsening of hypertension	Possibly related	Potentially related
126-003	Increased blood pressure	Possibly related	Potentially related
126-004	Hypertension	Possibly related	Potentially related
126-006	Increased hypertension	Probably related	Potentially related

**Table 49 Vital sign-related SAEs for MEL3-12-03**

Subject	Event	Summary	Relatedness to study drug per investigator	Relatedness to study drug per reviewer	Location of subject narrative in this review
107-005	Hypertensive crisis		Not related	Potentially related	Section 9.4
119-004	Increased respiratory rate	COPD	Not related	Not related	
125-009	Increased respiratory rate	Pulmonary embolism	Not related	Not related	Section 7.3.1

In this trial, a pulse rate of clinical concern was defined as heart rate less than 50 or greater than 90 beats per minute. 120 subjects (20.1%) had elevated heart rate of potential clinical concern at least once in the trial. Two of these subjects had the treatment-emergent adverse event of mild tachycardia.

A respiratory rate of clinical concern was defined as a respiratory rate of less than 12 or greater than 16 breathes per minute. 315 subjects (52.7%) had at least one respiratory rate of clinical concern at some point in the trial.

#### 7.4.3.4 Hypertension with Vivlodex

Of the 600 subjects who received Vivlodex 10 mg in MEL3-12-03, 25 (4.2%) experienced the TEAE of hypertension.

Four subjects discontinued MEL3-12-03 for TEAEs related to increased blood pressure. Discontinued subjects 111-010, 126-003, 126-004, and 126-006 experienced worsening of hypertension, elevated blood pressure, hypertension, and increased hypertension, respectively. All four of these TEAEs were judged to be possibly or probably related to Vivlodex by their respective trial investigators.

Subject 107-005 in MEL3-12-03 had the SAE of hypertension urgency. More information on his case is presented in section 9.4 of this review.

Two subjects discontinued MEL3-12-02 for TEAEs of worsening hypertension: Subjects 124-033 and 132-012. Both of these subjects were in the Vivlodex 10 mg treatment group.

The following tables were provided by the Applicant and summarize changes to blood pressure that occurred during MEL3-12-02 and MEL3-12-03.

**Table 50 Summary of Shifts in Blood Pressure Values from Normal Values to Low or High Values (Safety Population MEL3-12-02)**

Analyte Visit Comparison	Placebo (N=133)		Meloxicam SoluMatrix Capsules						
			5 mg (N=138)			10 mg (N=131)			
			n <sup>a</sup>	Normal to Low n (%)	Normal to High n (%)	n <sup>a</sup>	Normal to Low n (%)	Normal to High n (%)	
<b>Systolic Blood Pressure</b>									
<b>Baseline to Week 2</b>	133	0	6 (4.5)	137	0	6 (4.4)	127	0	12 (9.4)
<b>Week 2 to Week 6</b>	127	0	13 (10.2)	134	0	11 (8.2)	126	0	9 (7.1)
<b>Week 6 to Week 12</b>	119	0	13 (10.9)	128	0	10 (7.8)	119	0	8 (6.7)
<b>Baseline to Week 12</b>	119	0	10 (8.4)	128	0	9 (7.0)	119	0	8 (6.7)
<b>Diastolic Blood Pressure</b>									
<b>Baseline to Week 2</b>	133	2 (1.5)	2 (1.5)	137	3 (2.2)	5 (3.6)	127	3 (2.4)	2 (1.6)
<b>Week 2 to Week 6</b>	127	2 (1.6)	7 (5.5)	134	1 (0.7)	6 (4.5)	126	1 (0.8)	4 (3.2)
<b>Week 6 to Week 12</b>	119	2 (1.7)	2 (1.7)	128	3 (2.3)	4 (3.1)	119	1 (0.8)	5 (4.2)
<b>Baseline to Week 12</b>	119	1 (0.8)	4 (3.4)	128	3 (2.3)	6 (4.7)	119	1 (0.8)	5 (4.2)

<sup>a</sup> Number of subjects with non-missing values at both visits in the Visit Comparison.

Note: Percentages are based on the number of subject with non-missing values at both visits in the Visit Comparison.

Baseline is the last measurement prior to the first dose of study drug.

For systolic blood pressure: Low is < 90 mmHg, Normal is ≥90 mmHg to ≤140 mmHg, High is > 140 mmHg.

For diastolic blood pressure: Low is < 60 mmHg, Normal is ≥60 mmHg to ≤90 mmHg, High is > 90 mmHg.

(Source: NDA 207233 Applicant's table page 4 of Clinical Information Amendment 0007)

As demonstrated in the table above, when comparing systolic blood pressure at Baseline to systolic blood pressure at Week 12, 8.4% (10 of 119) of those in the placebo group had a shift in systolic blood pressure from normal to high during the trial compared to 7% (9 of 128) in the Vivlodex 5 mg group and 6.7% (8 of 119) in the Vivlodex 10 mg group.

**Table 51 Summary of Shifts in Blood Pressure Values from Normal Values to Low or High Values (Safety Population MEL3-12-03)**

Analyte Visit Comparison	Meloxicam SolutiMatrix Capsules 10 mg (N=600)		
	n <sup>a</sup>	Normal to Low n (%)	Normal to High n (%)
<b>Systolic Blood Pressure</b>			
Baseline to Week 1	598	0	59 (9.9)
Week 1 to Week 4	590	0	54 (9.2)
Week 4 to Week 8	565	1 (0.2)	42 (7.4)
Week 8 to Week 12	534	0	35 (6.6)
Week 12 to Week 16	517	0	48 (9.3)
Week 16 to Week 20	490	0	41 (8.4)
Week 20 to Week 24	477	0	41 (8.6)
Week 24 to Week 32	444	0	51 (11.5)
Week 32 to Week 40	426	1 (0.2)	34 (8.0)
Week 40 to Week 48	407	0	39 (9.6)
Week 48 to Week 52	393	1 (0.3)	33 (8.4)
Week 12 to Week 48	409	0	49 (12.0)
Baseline to Week 52	394	1 (0.3)	53 (13.5)

Analyte Visit Comparison	Meloxicam SolutMatrix Capsules 10 mg (N=600)	
	n <sup>a</sup>	Normal to Low n (%)
<b>Diastolic Blood Pressure</b>		
Baseline to Week 1	598	6 (1.0)
Week 1 to Week 4	590	10 (1.7)
Week 4 to Week 8	565	13 (2.3)
Week 8 to Week 12	534	8 (1.5)
Week 12 to Week 16	517	10 (1.9)
Week 16 to Week 20	490	9 (1.8)
Week 20 to Week 24	477	5 (1.0)
Week 24 to Week 32	444	11 (2.5)
Week 32 to Week 40	426	5 (1.2)
Week 40 to Week 48	407	2 (0.5)
Week 48 to Week 52	393	9 (2.3)
Week 12 to Week 48	409	2 (0.5)
Baseline to Week 52	394	7 (1.8)
		Normal to High n (%)
		25 (4.2)
		19 (3.2)
		19 (3.4)
		15 (2.8)
		18 (3.5)
		23 (4.7)
		21 (4.4)
		18 (4.1)
		14 (3.3)
		10 (2.5)
		13 (3.3)
		11 (2.7)
		15 (3.8)

<sup>a</sup> Number of subjects with non-missing values at both visits in the Visit Comparison.  
 Note: Percentages are based on the number of subject with non-missing values at both visits in the Visit Comparison.  
 Baseline is the last measurement prior to the first dose of study drug.  
 For systolic blood pressure: Low is < 90 mmHg, Normal is ≥90 mmHg to ≤140 mmHg, High is > 140 mmHg.  
 For diastolic blood pressure: Low is < 60 mmHg, Normal is ≥60 mmHg to ≤90 mmHg, High is > 90 mmHg.  
 (Source: NDA 207233 Applicant's table pages 5-6 of Clinical Information Amendment 0007)

As demonstrated in the table above, when comparing systolic blood pressure at Baseline to systolic blood pressure at Week 52, 13.5% of the Vivlodex 10 mg group had a shift in systolic blood pressure from normal to high. The Baseline value is the last blood pressure measurement before beginning Vivlodex. Normal systolic blood pressure is defined as 90 to 140 mmHg. High systolic blood pressure is defined as >140 mmHg.

It is difficult to determine the significance of the cases of hypertension and elevated blood pressure present in trial MEL3-12-03 because there is no available statistic indicating how likely it is for an individual to develop high systolic blood pressure from normal systolic blood pressure over a 52 week period.

According to one publication, the “residual lifetime risk for hypertension for middle-aged and elderly individuals is 90%.” (Vasan et al., 2002) The mean age of subjects in trial MEL3-12-03 was 61.7 years.

Additionally, in trial MEL1-12-04, Vivlodex 10 mg had a 33% lower systemic exposure when compared to Mobic 15 mg tablets when taken under fasted conditions.

Iroko was contacted via email on August 4, 2015 with the following Information Request:

In trial MEL3-12-03, 4.2% of subjects had the treatment-emergent adverse event of hypertension, but in the clinical information amendment dated June 5, 2015, Table 2.2 Summary of Shifts in Blood Pressure Values from Normal Values to Low or High Values (Safety Population – MEL3-12-03), 13.5% of subjects appear to have had a shift in systolic blood pressure from normal to high from Baseline to Week 52. Explain why these changes in systolic BP were not reported as adverse events.

Iroko replied with the following response on August 7, 2015:

Study protocol MEL3-12-03 defined an Adverse Event (AE) as follows: “An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.”

Consequently, the judgement of the trial investigators was key in determining whether observed increases or decreases in vital signs or laboratory values qualified as clinically important changes. These investigator assessments considered several factors including the magnitude of the observed change, the clinical relevance of the change, and the subject’s medical history and status in order to determine whether the observed increase (or decrease) should be recorded as an AE.

The shift table provided in the clinical information amendment dated June 5, 2015 (Table 2.2) summarizes all occurrences of treatment-emergent shifts in diastolic and systolic blood pressure. Only those that were determined by the trial investigator(s) to be clinically important however would have been recorded as AEs, therefore it is to be expected that the number of adverse events for hypertension would be lower than the total number of numerical blood pressure shifts observed.

Iroko was again contacted via email on August 26, 2015 with the following Information Request:

Despite the lower AUC of Vivlodex 10 mg compared to Mobic 15 mg when taken under fasted conditions, there appears to be a higher incidence of hypertension with Vivlodex 10 mg in clinical trials. In MEL3-12-03, 4.2% of subjects had the treatment-emergent adverse event of hypertension. In the shift table that you sent on June 5, 2015, 13.5% of subjects in MEL3-12-03 had a shift in systolic blood pressure from normal to high from Baseline to Week 52. Yet, in clinical trials described in the Mobic Package Insert, hypertension occurred in less than 2% of patients receiving Mobic at any dose. Do you have additional thoughts on why this may be?

Iroko replied with the following response on August 31, 2015:

The adverse event rates reported in the Mobic Prescribing Information (PI) are from a 12-week controlled trial in patients with OA (Mobic PI, Table 1a), two 12-week controlled trials in patients with rheumatoid arthritis (RA) (Mobic PI, Table 1b), and controlled trials in OA patients of 4-6 weeks and 6 months in duration (Mobic PI, Table 2). Hypertension was reported in < 2% of patients who participated in these trials.

In contrast, MEL3-12-03 was an open-label trial in which 446 subjects received treatment with Vivlodex™ Capsules 10 mg daily for ≥ 6 months, and 391 were treated with Vivlodex™ Capsules 10 mg daily for ≥ 1 year in duration. The difference in duration between this trial and those in the Mobic PI, along with the absence of a placebo or active control group in MEL3-12-03, limit meaningful comparisons between rates of adverse events observed in the Vivlodex™ open-label trial to those reported in the Mobic PI.

More patients in the Phase 2/3 safety database described in the Mobic PI received meloxicam at a dose of 7.5 mg daily (11,134 patients) compared to those who received 15 mg daily (4,856 patients), the majority were from clinical trials ≤ 6 months in duration. Although it is reported that 661 patients received Mobic for up to 6 months and 312 patients for up to 1 year, the rates of hypertension in adults from long-term trials are not reported in the PI, nor in the published literature (Huskinsson 1996).

In MEL3-12-02, a 12-week, randomized, double-blind, placebo-controlled trial, Vivlodex™ Capsules were evaluated at daily doses of 5 mg and 10 mg in 402 subjects with clinically diagnosed OA. The design and duration of treatment with Vivlodex™ Capsules in this trial permits a more meaningful comparison of adverse events (AE) rates with those reported in the Mobic PI. In study MEL3-12-02, only 2 subjects (0.7%) receiving Vivlodex™ Capsules at either 5 mg or 10 mg once daily experienced AEs of hypertension, comparable to 1 subject (0.8%) in the placebo group. Both events were of moderate severity, and both occurred in subjects with documented hypertension in their prior medical history.

The shift tables provided to the Agency on June 5, 2015 summarized subjects from Vivlodex™ Capsules Phase 3 trials whose blood pressure values changed from normal (defined as ≥ 90 mm Hg and ≤ 140 mm Hg for systolic blood pressure [BP]) to high or low values at various visits. Blood pressure elevations that were determined by the trial investigator(s) to merit adverse event reporting were recorded as AEs, therefore the number of adverse events for hypertension and the total number of patients with numerical blood pressure shifts would be expected to differ.

In trial MEL3-12-03, shifts from normal values at baseline to high values at Week 52/ET occurred in 53 (13.5%) subjects. Of note, systolic BP shifts from high values at baseline to normal values at Week 52/ET also occurred in 35 (8.9%) subjects in this study, as presented in Post-hoc Table

14.3.11.5. Nearly half (272 [45.3%]) of the subjects in trial MEL3-12-03 reported hypertension as part of their baseline medical history. The prevalence of pre-existing hypertension, and the 52-week duration of treatment, could have contributed to the changes over time in both directions that were observed in systolic blood pressure values during the trial. A complete listing of blood pressure values for all subjects at all assessments is located in the NDA in Section 5.3.5.2 MEL3-12-03 Appendix 16.2.8, Listing 16.2.8.1.

It is possible for vital sign changes of small numerical magnitude to be classified as shifts in one direction or the other if the values crossed the threshold from one pre-defined range to another. To provide additional insight into the blood pressure shifts observed at Week 12/ET and Week 52/ET in trials MEL3-12-02 and MEL3-12-03, respectively, analyses were performed to determine the proportion of subjects whose BP values at these visits exceeded thresholds indicative of Stage 2 clinical hypertension, representing Grade 3 elevations as defined in the Common Terminology Criteria of Adverse Events (CTCAE) v4.03, June 14, 2010.

In study MEL3-12-02, 2 (1.6%) subjects treated with Vivlodex™ Capsules 10 mg and 1 (0.7%) subject treated with Vivlodex™ Capsules 5 mg had systolic blood pressure values at Week 12/ET that were  $\geq 160$  mm Hg. These rates are comparable to those observed in the placebo group (2 [1.5%]). There were no subjects treated with Vivlodex™ Capsules at either dose who experienced diastolic BP values  $\geq 100$  mm Hg. Complete results of this analysis are presented in Post-hoc Table 14.3.11.4, in Appendix 1.

The proportion of subjects in trial MEL3-12-03 with Grade 3 blood pressure values at the end of study treatment was similarly low. In this trial, 16 (2.8%) subjects had systolic BP values  $\geq 160$  mm Hg at Week 52/ET. In a subgroup analysis of subjects with normal systolic blood pressure values at baseline, 9 (1.8%) had systolic BP values  $\geq 160$  mm Hg at Week 52/ET. CTCAE Grade 3 elevations in diastolic blood pressure were observed at Week 52/ET in 3 (0.5%) subjects overall, and in 2 (0.4%) whose values were normal at baseline. Complete results of the analysis for study MEL3-12-03 are presented in post-hoc Table 14.3.11.6, in Appendix 2.

In summary, only 2 (0.7%) Vivlodex treated patients in the 12-week placebo controlled trial (MEL3-12-02) experienced AEs of hypertension. This is similar to the rate (<2%) reported in the controlled trials of similar duration in the Mobic prescribing information. In the 52-week open label trial of Vivlodex™ Capsules (MEL3-12-03), blood pressure shifts from normal to high (13.5%) and from high to normal (8.9%) were observed at the end of treatment. The difference in duration of treatment ( $\leq 6$  months vs. 1 year) is the most likely explanation for the rates of hypertension and observed blood pressure measures

#### 7.4.4 Electrocardiograms (ECGs)

In MEL1-12-04, ECG was only taken at screening.

In MEL3-12-02, ECGs were performed at Screening (Visit 1) and Visit 5 (Week 12) or Early Termination Visit. No subjects had a clinically significant change in ECG between these two time points.

In MEL3-12-03, ECGs were performed at Visit 1 (Screening) and Week 4. Sixty-four subjects (11.3%) had ECG changes during this time period from normal to abnormal. However, none of these changes was determined to be clinically significant by the investigator. 52.5% of subjects had an abnormal ECG at Screening that was deemed to

be clinically insignificant. At Week 4, one of these subjects had developed T-wave inversion (Subject 120-041). For more detail on Subject 120-041, see section 9.6 of this review.

#### 7.4.5 Special Safety Studies/Clinical Trials

No specific safety concerns were evaluated in special studies in the trials conducted to support this NDA.

#### 7.4.6 Immunogenicity

No issues related to the immunogenicity of Vivlodex were addressed in this NDA submission.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Because MEL3-12-02 evaluates Vivlodex 5 mg (N=138) and Vivlodex 10 mg (N=131) compared to placebo for 12 weeks, examination of MEL3-12-02 is the most reliable measurement of the dose-dependency of adverse events with Vivlodex. A table of TEAEs occurring in  $\geq 1\%$  of subjects in MEL3-12-02 is present in section 7.4.1 of this review. As demonstrated in this table, headache, abdominal discomfort, hypertension, and toothache occurred more frequently in the Vivlodex 10 mg treatment group than in the placebo or Vivlodex 5 mg treatment groups.

#### 7.5.2 Time Dependency for Adverse Event

The Applicant did not perform an analysis of time to adverse events in the safety population.

Excluding subjects in the placebo treatment group, the mean number of days a subject in MEL3-12-02 was in the trial before an adverse event occurred was 37.16 days. The median number of days before an adverse event occurred was 36 days.

In trial MEL3-12-03, the mean number of days a subject was in the trial before an adverse event occurred was 133.7 days. The median number of days before an adverse event occurred was 109 days.

#### 7.5.3 Drug-Demographic Interactions

The Integrated Safety Population included all subjects in Phase 3 trials and was evaluated by MAED analysis for age, sex, race, BMI and percentage of subjects in

those categories who had adverse events in each System Organ Class. A dose adjustment does not appear necessary in older patients based on this analysis. The class labeling for NSAIDs indicates that elderly patients have an increased risk for gastrointestinal events. This is consistent with the MAED analysis that was performed. Sex, BMI, and race do not appear to be linked to safety concerns with Vivlodex.

The Summary of Clinical Safety for this NDA noted that female patients had slightly higher incidences of urinary tract infection and osteoarthritis compared to male patients.

#### 7.5.4 Drug-Disease Interactions

The Integrated Safety Population was evaluated by MAED analysis for specific past medical history conditions (hypertension, cardiovascular procedure, ischemic cardiovascular condition, gastrointestinal, headache, hepatic, renal) and percentage of subjects in those categories who had adverse events in each System Organ Class. This analysis revealed that those with a cardiovascular procedure or ischemic cardiovascular disease in their medical history were more likely to have a TEAE in the cardiac disorders system organ class. Those with a gastrointestinal disease in their medical history were more likely to have a TEAE in the gastrointestinal disorders system organ class. This association is logical and not of clinical concern.

The Summary of Clinical Safety from the Applicant notes that:

- Treatment-emergent adverse events were higher in subjects in certain medical history subgroups of interest.
- Overall, new safety concerns were not linked to Vivlodex.

#### 7.5.5 Drug-Drug Interactions

The US Mobic Labeling cautions against concomitant use of the following:

- ACE inhibitors
- Angiotensin II antagonists
- Aspirin
- Beta-blockers
- Furosemide
- Cyclosporine
- Diuretics
- Lithium
- Methotrexate
- Warfarin
- Anticoagulants
- Thiazides
- Loop diuretics

The Integrated Safety Population was evaluated by MAED analysis for concomitant medications (including ACE inhibitors, angiotensin II antagonists, beta-blockers, platelet aggregation inhibitors, diuretics, CYP2C9 inhibitors, CYP2C9 substrates, and acetylsalicylic acid) and percentage of subjects in those categories who had adverse events in each system organ class. Concomitant medications were defined as medications (other than rescue medications in MEL3-12-02 or trial drug) that a subject took while receiving trial drug. It appears that drugs taken after the last dose of trial drug are also included as concomitant medications. This analysis revealed no new safety concerns with Vivlodex.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No new carcinogenicity studies were performed for Vivlodex. The US Mobic labeling states that long-term carcinogenicity studies in rats and mice given meloxicam did not have an increased incidence in tumor development.

### 7.6.2 Human Reproduction and Pregnancy Data

Meloxicam has not been studied in pregnant women in adequate and well-controlled clinical trials. In the clinical trials in this NDA, women who were pregnant or lactating were excluded. Meloxicam crosses the placenta and should not be used in women past 30 weeks gestational age because of the risk of closure of the ductus arteriosus in the fetus. Meloxicam is Pregnancy Category C in pregnant women up to 30 weeks gestational age, at which point meloxicam becomes Pregnancy Category D.

Meloxicam has been shown to be excreted in the milk of lactating rats, but it is unknown as to whether meloxicam is excreted in human milk.

According to the US Mobic labeling, in a study in which pregnant rats were given oral meloxicam 4 mg/kg/day during fetal organogenesis, meloxicam was not teratogenic. However, a study of pregnant rabbits given oral meloxicam 60 mg/kg/day during embryogenesis resulted in increased incidence of heart septum defects. Studies in rats given meloxicam 1 mg/kg/day and rabbits given meloxicam 5 mg/kg/day demonstrated embryolethality when given throughout organogenesis. (US Mobic labeling 2012)

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Iroko Pharmaceuticals submitted a Pediatric Study Plan and requested a full waiver for conducting pediatric studies for the proposed indication of (b) (6) of osteoarthritis pain. In a letter dated July 2, 2014, DAAAP agreed with Iroko's intent not to conduct pediatric studies. Mobic is approved for patients 2 years of age and older.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the US Mobic labeling, there is limited experience with overdose of meloxicam. Generally, acute NSAID overdose has the following symptoms: lethargy, nausea and vomiting, and epigastric pain. Gastrointestinal bleeding may occur. Hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest may occur. NSAID overdose can cause gastrointestinal bleeding. Treatment is supportive and activated charcoal can

be helpful if given within 1 to 2 hours of overdose. Meloxicam clearance can be accelerated by cholestyramine. (US Mobic labeling 2012)  
Meloxicam is not known to have drug abuse potential, nor has it been associated with symptoms of withdrawal or rebound.

## 7.7 Additional Submissions / Safety Issues

No additional safety issues of concern have been identified that were not discussed in other sections of this review.

## 8 Postmarket Experience

No postmarketing safety data exists for Vivlodex because it has not been registered in any country. Meloxicam has been marketed in the United States for 14 years.

## 9 Appendices

### 9.1 Literature Review/References

The Applicant performed PubMed searches and submitted 19 references with this NDA for the purpose of obtaining pharmacokinetic, efficacy, and safety information pertaining to Vivlodex. These references mostly involved meloxicam, but also pertained to other NSAIDs and the class of NSAIDs.

48 additional references considered by the Applicant to be relevant to this NDA were also cited in the literature search portion of this submission.

The Medical Officer reviewing the clinical literature for the Applicant concludes that no safety or efficacy information that would modify the profile of meloxicam for use in osteoarthritis has been recognized.

### 9.2 Labeling Recommendations

After review of the proposed labeling, the following changes are recommended from a clinical perspective. Reviewer's comments follow the Applicant's proposed wording as it appears in the referenced section.

Section: Clinical Trials Experience

In this section, it is stated that 869 patients with osteoarthritis pain were enrolled in Phase 3 trials and were administered Vivlodex. From additional materials submitted, it is unclear if 867, 868, or 869 subjects should be considered to have received one dose of

Vivlodex in Phase 3 clinical trials. The Applicant should clarify that this number is correct.

Section: DOSING AND ADMINISTRATION

The Applicant should specify in the labeling that Vivlodex 5 mg and Vivlodex 10 mg performed similarly on the primary efficacy endpoint. Therefore, patients should start with Vivlodex 5 mg, and if it fails, consider increasing the dose to Vivlodex 10 mg.

**9.3 Advisory Committee Meeting**

No advisory committee meeting was conducted for this application.

**9.4 Serious Adverse Events in MEL3-12-03**

The following table described SAEs in MEL3-12-03.

**Table 52 SAEs in MEL3-12-03**

Subject	Age (years)/sex	Verbatim Term	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
101-002	71 F	Chest pain (non-cardiac)	Not related	Not related
101-004	59 M	Coronary artery stenosis with stent placement	Not related	Potentially related
103-002	61 M	Bacterial meningitis	Not related	Not related
103-003	54 M	Acute sigmoid diverticulitis	Possible	Potentially related
107-005	76 M	Hypertension Urgency	Not related	Potentially related
109-006	74 M	Worsening Coronary Artery Disease	Not related	Potentially related
111-006	73 F	Gastro esophageal Reflux Disease	Possible	Potentially related
112-020	62 F	Acute Perforated Appendicitis	Not related	Not related
112-027	77 M	3 X 4 mm left thalamus hemorrhagic infarct	Not related	Not related
114-006	52 M	Fourth cranial nerve palsy	Not related	Not related
118-014	63 F	Motor Vehicle Accident; L3 compression fracture	Not related	Not related
118-027	72 F	Left carotid stenosis	Not related	Not related
119-004	58 F	COPD exacerbation	Not related	Not related
120-006	71 F	Left and right breast cancer	Not related	Not related
120-020	64 F	Diverticular hemorrhage; anemia	Probably	Potentially related
123-010	74 F	Worsening of chostochondritis	Not related	Not related
123-011	56 M	Congestive Heart Failure	Not related	Potentially related
123-016	62 F	Transvaginal Mesh Removal	Not related	Not related
124-015	56 F	Invasive Ductal Adenocarcinoma Right	Not related	Not related

Subject	Age (years)/sex	Verbatim Term	Relatedness to trial drug per investigator	Relatedness to trial drug per reviewer
		Breast		
124-023	40 F	Angina Pectoris	Not related	Potentially related
124-041	55 M	Diverticulitis	Not related	Not related
124-051	68 F	Chest Pain- etiology undetermined	Not related	Not related
125-009	62 M	Bilateral pulmonary embolism and acute systolic heart failure	Not related	Not related
125-013	70 F	Postpolypectomy syndrome	Not related	Not related
131-006	58 M	Cardiac Chest Pain	Not related	Potentially related
131-009	71 M	Left Lower Lobe Pneumonia; Acute Hypoxic Hypercarbic Respiratory Failure; Acute Renal Failure	Not related; Not related; Unlikely to be related	Not related
132-001	73 F	Left Renal Pelvic High Grade Transitional Cell Carcinoma	Not related	Not related
133-006	67 F	Sepsis with MSSA; Acute Kidney Injury; ARDS	Possibly related; Not related; Not related	Not related
134-010	76 F	Squamous Cell Lung Carcinoma	Not related	Not related
134-014	55 F	Probable Drug Induced Hepatitis	Possibly related	Potentially related
136-007	57 F	Acute Bronchitis	Not related	Not related
137-010	71 M	Bilateral Acute Pulmonary Emboli	Not related	Potentially related
138-010	49 F	Duodenal Ulcer Haemorrhage; Gastric Ulcer Haemorrhage	Probably related	Potentially related
142-022	60 M	Left Anterior Chest Pain Non-cardiac	Not related	Not related

The following are summary narratives of SAEs that are potentially related to trial drug:

Subject 101-004

This subject is a 59-year-old male. His first dose of Vivlodex 10 mg was on May 13, 2013. He had a past medical history of coronary artery disease. On an unknown date, the subject presented to his primary care physician with a report of several years of chest pain. An ECG was performed, followed by a stress test on (b) (6) the results of which were consistent with myocardial ischemia. On (b) (6), he had a cardiac catheterization with stent placement. His last dose of trial drug was February 17, 2014. An additional cardiac catheterization with stent placement was performed on (b) (6). Cardiovascular thrombotic events are in the US Mobic labeling WARNINGS AND PRECAUTIONS section.

Subject 103-003

This subject is a 54-year-old male. His first dose of Vivlodex 10 mg daily was on April 23, 2013. His last dose of trial drug was August 22, 2013. On (b) (6) the subject experienced diverticulitis for which he was admitted to the hospital.

Subject 107-005

This subject is a 77-year-old male with a history of, among other things, hypertension, diabetes, coronary artery disease, myocardial infarction, transient ischemia attack, congestive cardiac failure, and pulmonary hypertension. His first dose of Vivlodex 10 mg was on April 18, 2013. On (b) (6), the subject experienced hypertensive crisis and dyspnea with exertion. His last dose of trial drug was on August 13, 2013. Hypertension is in the US Mobic labeling WARNINGS AND PRECAUTIONS section.

Subject 109-006

This subject is a 74-year-old male with a history of, among other things, coronary artery disease, hypertension, and peripheral vascular disease. His first dose of Vivlodex 10 mg was on June 3, 2013. On (b) (6), he experienced worsening coronary artery disease for which he was hospitalized and required percutaneous coronary intervention. His last dose of trial drug was July 2, 2013. Cardiovascular thrombotic events are in the US Mobic labeling WARNINGS AND PRECAUTIONS section.

Subject 111-006

This subject is a 73-year-old female. Her first dose of Vivlodex 10 mg was May 8, 2013. Her last dose of trial drug was September 23, 2013. On September 6, 2013, she had gastro esophageal reflux (GERD) of moderate severity. She described symptoms consistent with experiencing GERD 3 weeks prior to this date. Her last dose of trial drug was September 23, 2013. Gastro esophageal reflux is in the ADVERSE REACTIONS section of the US Mobic labeling.

Subject 120-020

This subject is a 64-year-old female. Her first day of Vivlodex 10 mg was May 1, 2013. Her last dose of trial drug was May 15, 2013. On (b) (6), she experienced intestinal diverticular hemorrhage and anemia. Her hemorrhage resolved on (b) (6). Ulceration and perforation of the intestine are included in the US Mobic labeling WARNINGS AND PRECAUTIONS section.

Subject 123-011

This subject is a 56-year-old male with a past medical history of, among other things, hypertension, diabetes, and pacemaker. His first day of Vivlodex 10 mg was May 15, 2013. His last dose of trial drug was October 15, 2013. On (b) (6), he experienced congestive heart failure. Cardiac failure is in the ADVERSE REACTIONS section of the US Mobic labeling.

Subject 124-023

This subject is a 40-year-old female with a history of hypertension and smoking. Her first dose of Vivlodex 10 mg was on April 5, 2013. On (b) (6), she experienced angina pectoris. Her last dose of trial drug was on July 23, 2013. Angina pectoris is in the ADVERSE REACTIONS section of the US Mobic labeling.

Subject 131-006

This subject is a 58-year-old male with a history of hypertension and smoking. His first dose of Vivlodex 10 mg was on April 25, 2013. On (b) (6), he experienced angina pectoris. His last dose of Vivlodex was on September 6, 2013. Angina pectoris is in the ADVERSE REACTIONS section of the US Mobic labeling.

Subject 134-014

This subject is a 55-year-old female. She began Vivlodex 10 mg daily on April 23, 2013. On approximately (b) (6), she experienced right breast implant rupture. Her breast implants were removed on (b) (6). In the perioperative period, she received the following medications in addition to Vivlodex 10 mg daily:

- (b) (6): lorazepam, pregabalin, oxycodone/acetaminophen
- (b) (6): cefadroxil
- (b) (6) tramadol and Vicodin

On (b) (6), she began to experience pruritus, pale stool, and dark urine.

On (b) (6), she began taking hydroxyzine 100 mg three times daily for the pruritus. On (b) (6), she had symptoms consistent with jaundice. The last dose of Vivlodex was on December 1, 2013. The following is a table of her hepatic labs:

**Table 53 Lab values for Subject 134-014**

Date	Alk Phos (U/L)	ALT (U/L)	AST (U/L)	Bilirubin (µmol/L)
(b) (6)	72	31	21	10.3
(b) (6)	75	28	21	8.6
(b) (6)	74	23	21	12
(b) (6)	75	22	17	13.7
(b) (6)	69	26	23	12
(b) (6)	69	26		12
(b) (6)	190	80		171
(b) (6)	180	57	30	183
(b) (6)	160	57		183
(b) (6)	180	80	30	
(b) (6)	175	65		174
(b) (6)	184	79	43	162
(b) (6)	95	81	30	21
Reference range high	98	33	34	20.5

On (b) (6), after being on Vivlodex 10mg daily for 224 days, she had severe drug-induced liver injury.

On (b) (6), MRI revealed hepatomegaly. (b) (6), a liver biopsy was performed, revealing changes consistent with drug-induced hepatitis. Drug-induced liver injury (DILI) was considered by the investigator to be likely related to Vivlodex. Her drug-induced liver injury may be related to Vivlodex, but the timing of the liver injury—immediately after a surgical procedure in which she received other medications—indicates that the DILI may be related to another medication or may be related to the combination of Vivlodex and another medication.

Subject 137-010

This subject is a 71-year-old male who experienced bilateral acute pulmonary emboli and thrombi in right femoral, popliteal, and peroneal veins. May 2, 2013 was his first day of Vivlodex. His past medical history included morbid obesity. On (b) (6), he had the SAE of pulmonary embolism. On (b) (6), venous duplex Doppler showed thrombus in right superficial femoral vein, popliteal, and peroneal veins. The investigator considered the pulmonary embolism to be not related to Vivlodex. Thrombotic events may be caused by Vivlodex, and therefore pulmonary embolism may be caused by Vivlodex.

Subject 138-010

This subject is a 49-year-old female. Her first day of Vivlodex 10 mg was April 17, 2013. On (b) (6), she had duodenal ulcer hemorrhage and gastric ulcer hemorrhage. Her last dose of trial drug was November 15, 2014. Her hemorrhage resolved on (b) (6). Bleeding and ulceration of the intestine are included in the US Mobic labeling WARNINGS AND PRECAUTIONS section.

**9.5 Treatment-Emergent Adverse Events leading to study discontinuation in MEL3-12-02**

The following table describes TEAEs leading to trial discontinuation in MEL3-12-02.

**Table 54 TEAEs leading to trial discontinuation in MEL3-12-02**

Subject	Age (years)	Verbatim Term	Relatedness to trial drug per investigator	Treatment group	Relatedness to trial drug per reviewer
106-003	62 F	Worsening OA of right knee	Not related	Vivlodex 5 mg	Not related
106-019	49 F	Edema Bilateral Legs	Probably	Placebo	Not related
109-005	59 F	Dislocated Elbow	Not related	Placebo	Not related
120-001	59 F	Petechial Rash Bilateral Legs	Probably	Placebo	Not related
123-004	72 F	Dizziness/ Abdominal Cramps	Possible/ Unlikely	Placebo	Not related
124-033	66 F	Worsening of hypertension	Probably	Vivlodex 10	Potentially

Subject	Age (years)	Verbatim Term	Relatedness to trial drug per investigator	Treatment group	Relatedness to trial drug per reviewer
				mg	related
125-021	68 F	Stomach Pain	Not related	Vivlodex 5 mg	Potentially related
126-004	56 M	Toothache	Not related	Placebo	Not related
131-002	72 M	Elevated LFTs	Possible	Vivlodex 10 mg	Potentially related
132-012	84 M	Low potassium/ worsening of hypertension	Unlikely/ unlikely	Vivlodex 10 mg	Not related
132-014	78 F	Shortness of breath	Possible	Vivlodex 10 mg	Potentially related
134-005	62 F	Intermittent Chest Pain - NFI	Possibly related	Placebo	Not related

Below is a summary of TEAEs leading to study discontinuation in MEL3-12-02 that may be potentially related to Vivlodex:

Hypertension

Subjects 124-033 and 132-012 experienced hypertension that was potentially related to Vivlodex. Hypertension is in the WARNINGS AND PRECAUTIONS section of the US Mobic labeling.

Stomach pain

Subject 125-021 experienced stomach pain that was potentially related to Vivlodex. Abdominal pain is in the ADVERSE REACTIONS section of the US Mobic labeling.

Elevated liver function tests

Subject 131-002 experienced elevated LFTs that were potentially related to Vivlodex. Elevation of liver tests is in the WARNINGS AND PRECAUTIONS section of the US Mobic labeling.

Shortness of breath

Subject 132-014 experienced shortness of breath that was potentially related to Vivlodex. Dyspnea is in the ADVERSE REACTIONS section of the US Mobic labeling.

**9.6 Treatment-Emergent Adverse Events leading to trial discontinuation in MEL3-12-03 (excluding SAEs mentioned in section 9.4 of this review)**

The following table described TEAEs leading to trial discontinuation in MEL3-12-03.

**Table 55 TEAEs leading to trial discontinuation in MEL3-12-03 (excluding SAEs mentioned in section 9.4 of this review)**

Subject	Age (years)/ sex	Verbatim Term	Relatedness to study drug per investigator	Relatedness to study drug per reviewer
101-007	57 F	Gastric Ulcer	Probably related	Potentially related

Subject	Age (years)/ sex	Verbatim Term	Relatedness to study drug per investigator	Relatedness to study drug per reviewer
102-006	55 F	Superficial Gastric Ulcers	Probably related	Potentially related
103-004	55 F	Worsening Persistent Diarrhea	Possibly related	Potentially related
104-021	54 F	Nausea	Probably related	Potentially related
104-025	84 M	Hyperbilirubinemia	Possibly related	Potentially related
106-002	63 M	Worsening Liver Functions	Not related	Potentially related
106-014	67 M	Worsening Left Knee Pain	Not related	Not related
106-047	54 F	Fluid retention	Possibly related	Potentially related
106-050	64 F	GI upset	Probably related	Potentially related
106-056	75 F	GI upset	Possibly related	Potentially related
106-070	44 M	Elevated Liver Enzymes	Possibly related	Potentially related
107-005	76 M	Dyspnea with exertion / tricuspid valve incompetence	Not related	Not related
109-001	62 M	Worsening of left knee osteoarthritis	Unlikely related	Not related
111-007	80 F	Chest Wall Irritation	Unlikely related	Not related
111-010	70 F	Worsening of Hypertension	Possibly related	Potentially related
112-023	81 M	Dysphasia	Possibly related	Potentially related
114-002	57 M	Elevated Liver Enzymes	Possibly related	Potentially related
114-008	54 F	Right Kidney Mass	Not related	Not related
115-009	61 F	Elevated Liver Function Tests	Possibly related	Potentially related
117-008	53 F	Diarrhea/ nervousness	Possibly related	Potentially related
118-018	64 M	Elevated Serum Creatinine	Probably related	Potentially related
120-009	66 F	Rash	Probably related	Potentially related
120-017	59 F	Anemia	Probably related	Potentially related
120-019	55 F	Worsening Right Knee Pain Due to Injury; numbness right foot; right thigh pain	Not related	Not related
120-039	69 F	Acid Reflux	Not related	Potentially related
120-040	56 F	Drowsiness	Possibly related	Potentially related
120-041	56 F	EKG T wave inversion ischemia/possible CAD	Possibly related	Potentially related
122-025	58 F	Worsening of superficial phlebitis right lower leg	Not related	Not related
123-001	56 M	Elevated LFT values	Possibly related	Potentially related
123-013	61 F	Elevated Liver Function Test	Possibly related	Potentially related
124-003	82 F	Gastric Ulcer	Probably related	Potentially related
124-031	52 M	Worsening of heartburn	Possibly related	Potentially related
125-014	56 F	Nausea	Probably related	Potentially related
126-001	70 F	Epigastric pain	Probably related	Potentially related
126-003	50 F	Elevated blood pressure	Possibly related	Potentially related
126-004	61 F	Hypertension	Possibly related	Potentially related
126-005	56 M	Abdominal cramping; diarrhea; blood in stool	Unlikely related	Potentially related
126-006	68 F	Increased hypertension/ lower extremity edema	Probably related	Potentially related
127-003	69 F	Worsening of lower leg edema	Probably related	Potentially related
131-005	59 F	Worsening GERD	Possibly related	Potentially related
133-002	75 F	Left achilles tendonitis	Not related	Not related

Subject	Age (years)/ sex	Verbatim Term	Relatedness to study drug per investigator	Relatedness to study drug per reviewer
133-003	56 F	Rash left lower leg worsening	Possibly related	Potentially related
133-008	85 F	Non-compliance with study drug (medication over-dosing error)	Unlikely related	Not related
133-015	73 F	Abdominal pain	Possibly related	Potentially related
133-018	60 F	Worsening of left hip pain	Not related	Not related
134-001	61 M	Urinary retention	Unlikely related	Not related
134-017	70 F	Schiatzki ring; erosive gastritis	Not related; possibly related	Potentially related
137-016	56 F	Dry mouth; headache	Possibly related	Potentially related
137-019	76 F	Worsening OA hip pain	Not related	Not related
137-036	65 M	Elevated potassium	Unlikely related	Not related
137-041	77 M	Stomach pain	Possibly related	Potentially related
138-008	62 F	Intermittent upset stomach	Probably related	Potentially related
138-018	77 F	Elevation in creatinine levels/ elevation in BUN	Probably related	Potentially related
138-028	57 F	GERD	Possibly related	Potentially related
142-005	49 M	Worsening osteoarthritis right and left knee	Not related	Not related
142-007	68 F	Increased osteoarthritis pain right knee	Not related	Not related
142-025	55 F	Worsening left knee osteoarthritis	Unlikely related	Not related

Note: the above table does not include SAEs that led to study discontinuation. Those are included in the SAEs for MEL3-12-03 in section 9.4 of this review

Below is a summary of TEAEs leading to study discontinuation in MEL3-12-03 that may be potentially related to Vivlodex:

Gastrointestinal adverse events

Subjects 101-007, 102-006, and 124-003 experienced a gastric ulcer or gastric ulcers. Subjects 103-004 and 117-008 experienced diarrhea. Subjects 104-021 and 125-014 experienced nausea. Subjects 106-050, 106-056, 126-001, 133-015, 137-041, and 138-008 experienced some form of abdominal pain or discomfort. Subjects 120-039, 124-031, 131-005, and 138-028 experienced gastro esophageal reflux or worsening of gastro esophageal reflux. Subject 126-005 had abdominal cramping, diarrhea, and blood in the stool. Subject 134-017 experienced gastritis. Subject 137-016 had dry mouth.

All of the gastrointestinal adverse events noted in the paragraph above are present in some form in the US Mobic labeling.

Hepatic adverse events

Subject 104-025 experienced elevated bilirubin. Subjects 106-002, 106-070, 114-002, 115-009, 123-001, and 123-013 experienced worsening or elevated liver function tests.

All of the hepatic adverse events noted in the paragraph above are present in some form in the US Mobic labeling. Elevation of liver tests is in the WARNINGS AND PRECAUTIONS section. Bilirubinemia is present in the US Mobic labeling in a list of adverse drug reactions that have occurred in clinical trials with Mobic.

#### Renal adverse reactions

Subjects 118-018 and 138-018 experienced elevated creatinine. Subject 138-018 also experienced elevation in BUN. Increased creatinine and BUN are present in the US Mobic labeling in a list of adverse drug reactions that have occurred in clinical trials with Mobic.

#### Fluid retention and edema

Subjects 106-047 and 127-003 experienced fluid retention or edema. Subject 126-006 experienced lower extremity edema. In the WARNINGS AND PRECAUTIONS of the US Mobic labeling, it is mentioned that fluid retention and edema are seen in some patients on NSAIDS.

#### Headache

Subject 137-016 experienced headache. Headache is present in the US Mobic labeling as an adverse event that has occurred in clinical trials with Mobic.

#### Nervousness

Subject 117-008 experienced nervousness. This adverse event is present in the US Mobic labeling as an adverse drug reaction that occurred in a clinical trial with Mobic.

#### Rash

Subjects 120-009 and 133-003 experienced rash. Rash is present in the US Mobic labeling as an adverse event that has occurred in clinical trials with Mobic.

#### Anemia

Subject 120-017 experienced anemia. Anemia is in the WARNINGS AND PRECAUTIONS section of the US Mobic labeling.

#### Hypertension

Subjects 111-010, 126-003, 126-004, and 126-006 experienced elevated blood pressure, hypertension, or worsening hypertension. Hypertension is present in the WARNINGS AND PRECAUTIONS section of the US Mobic labeling.

#### Other adverse events

The following adverse events are not presently mentioned in the US Mobic labeling:

- Subject 112-023 experienced dysphasia.
- Subject 120-040 experienced drowsiness. "Fatigue" is present in the ADVERSE REACTIONS section of the US Mobic labeling.

- Subject 120-041 experienced myocardial ischemia and possible coronary artery disease.

## 9.7 Additional Narratives for Adverse Events of Clinical Concern

For MEL3-12-02:

### **Cardio-embolic AE of clinical concern:**

Subject 123-007 is a 58-year-old female who experienced heart palpitations and chest pain. She was in the Vivlodex 5 mg treatment group.

### **Hepatic AE of clinical concern:**

Subject 108-007 is a 75-year-old female in the Vivlodex 10 mg treatment group who experienced elevated liver enzymes. This was considered to be a severe adverse event and is described more thoroughly in section 7.3.4.2 of this review.

Subject 112-014 is a 62-year-old female in the Vivlodex 5 mg treatment group who experienced mild elevated liver function tests. ALT and AST eventually returned to normal after discontinuing study drug, but alkaline phosphatase remained slightly elevated. This subject completed the trial and did not discontinue study drug early. The increase in liver function tests is potentially related to trial drug. Below is a table displaying her hepatic labs:

**Table 56 Hepatic labs for Subject 112-014**

Date	Visit	Alkaline Phosphatase (U/L)	ALT (U/L)	AST (U/L)
4/12/2013	Screening/Baseline	75	29	30
5/30/2013	Week 6	86	93	59
7/08/2013	Week 12	97	102	58
7/17/2013		104	106 (> 3 x ULN)	74
8/28/2013		104	27	27

Note: ref range high in females are the following: alk phos 98; ALT 33; AST 34

Subject 131-002 is a 72-year-old male in the Vivlodex 10 mg treatment group who experienced elevated liver function tests of moderate severity. His AST reached a peak of > 9 x ULN and his ALT reached a peak at > 7 x ULN. His final dose of trial drug was May 2, 2013, after which point, his liver function tests began to decline and eventually returned to normal. Below is a table displaying his hepatic labs:

**Table 57 Hepatic labs for Subject 131-002**

Date	Visit	Alkaline Phosphatase (U/L)	ALT (U/L)	AST (U/L)
3/11/2013	Screening/Baseline	44	17	21
4/29/2013	Week 6	66	330 (> 7 x ULN)	381 (>9 x ULN)
5/03/2013		52	75	29
5/29/2013	Week 12	46	20	24

Note: ref range high in males are the following: alk phos 129; ALT 44; AST 39

**Renal AE of clinical concern:**

Subject 108-013 is a 46-year-old male in the Vivlodex 10 mg treatment group who experienced increased BUN of mild severity. His BUN was elevated at Screening, but increased slightly as measured at Week 12. The final dose of trial drug was at Week 12 on July 18, 2013. Following discontinuation of trial drug, his BUN returned to normal. His BUN measurements are displayed in the table below:

**Table 58 Renal labs for Subject 108-013**

Date	Visit	BUN (mmol/L)
4/10/2013	Screening	8.9
6/04/2013	Week 6	8.2
7/18/2013	Week 12	10
7/25/2013		7.5

Note: ref range high for BUN is 8.2 mmol/L

**For MEL3-12-03:**

**Cardio-embolic AE of clinical concern:**

Subject 101-004 is a 59-year-old male who experienced coronary artery disease, stenosis, and stent placement. This case is described in more detail in section 9.4 of this review.

Subject 109-006 is a 74-year-old male who experienced worsening of coronary artery disease. This case is described in more detail in section 9.4 of this review.

Subject 112-023 is an 81-year-old male who experienced aphasia. His first day of trial drug was May 21, 2013. After 108 days of Vivlodex 10 mg, on (b) (6) he had aphasia of moderate severity. This resolved on (b) (6)

Subject 118-015 is a 71-year-old male who experienced coronary artery disease. His first dose of Vivlodex was April 17, 2013. On (b) (6) he experienced coronary artery disease and he had an angioplasty on (b) (6), at which point the AE was considered to be resolved. His last dose of Vivlodex was April 14, 2014.

Subject 118-027 is a 72-year-old female who experienced transient ischemic attack and carotid artery stenosis. Her first day of trial drug was May 21, 2013. On (b) (6) she experienced a transient ischemic attack with left upper extremity numbness and dizziness. Imaging of the neck revealed 80% left internal carotid artery stenosis.

Subject 120-041 is a 56 year-old female who experienced coronary artery disease, myocardial ischemia, and T-wave inversion. She had a medical history of hypertension, dyspnea, sleep apnea syndrome, and obesity. She began trial drug on May 29, 2013.

On (b) (6) the subject had a 12-lead ECG with significant T wave abnormalities not present on the Screening ECG.

Subject 123-011 is a 56-year-old male who experienced severe congestive heart failure. This case is described in more detail in section 9.4 of this review.

Subject 124-023 is a 40-year-old female who experienced angina pectoris. This case is described in more detail in section 9.4 of this review.

Subject 124-051 is a 68-year-old female who experienced coronary artery disease with mild blockage, supraventricular premature complexes, and chest pain. She had a medical history of coronary artery occlusion since 2005 and hypertension since 2010. She first took Vivlodex on May 29, 2013. On (b) (6) she experienced worsening hypertension. On (b) (6), she had chest pain and presented to medical care. An ECG showed tachycardia and supraventricular premature complexes. Three sets of cardiac enzymes were normal. Left heart catheterization and angiogram on (b) (6) revealed mild coronary artery disease. Stenosis in the posterolateral branch had progressed to 30% to 40% from 10% blockage on an angiogram in 2009.

Subject 125-009 is a 62-year-old male who experienced acute systolic heart failure and bilateral pulmonary embolism. This patient represents a subject death. For additional detail, see section 7.3.1 of this review.

Subject 131-006 is a 58-year-old male who experienced angina. This case is described in more detail in section 9.4 of this review.

Subject 137-010 is a 71-year-old male who experienced bilateral acute pulmonary emboli and thrombi in right femoral, popliteal, and peroneal veins. This case is described in more detail in section 9.4 of this review.

**GI bleeding of clinical concern:**

Subject 108-001 is a 57-year-old female who experienced rectal hemorrhage. Her first day of Vivlodex was April 16, 2013. On September 6, 2013, she had the adverse event of diarrhea. On September 13, 2013, she has the adverse event of rectal hemorrhage of mild severity. This resolved on September 15, 2013. Her last day of Vivlodex was April 15, 2014.

Subject 120-020 is a 64-year-old female who experienced diverticular hemorrhage. This case is described in more detail in section 9.4 of this review.

Subject 138-010 is a 49-year-old female who experienced duodenal ulcer and gastric ulcer hemorrhage. This case is described in more detail in section 9.4 of this review.

Subject 142-019 is a 63-year-old male who experienced rectal hemorrhage. His first day of Vivlodex was May 14, 2013. On July 3, 2013, he experienced the adverse event of constipation. On July 8, 2013, he experienced the adverse event of rectal hemorrhage of mild severity. This was considered to have resolved on July 9, 2013. His last dose of Vivlodex was April 16, 2014.

**Renal AE of clinical concern:**

Subject 107-006 is a 56-year-old female who experienced renal failure. Her first day of Vivlodex was April 10, 2013 and her last day of Vivlodex was April 8, 2014. At the time that she experienced this adverse event, she was on dyazide for hypertension. The following is a table of her renal labs:

**Table 59 Renal labs for Subject 107-006**

Date	BUN (mmol/L)	Creatinine (µmol/L)
4April 2013	5	68
8May2013	3.9	82
5June2013	4.3	85
2July2013	3.6	74
25September2013	2.5	64
19November2013	7.9	126
14January2014	5.4	88
11March2014	4.6	74
8April2014	6.8	90

note: ref range high for BUN is 8.2 mmol/L. ref range high for creatinine in females is 97 µmol/L.

Subject 109-004 is a 61-year-old male who experienced elevated creatinine. His first dose of Vivlodex was on May 1, 2013 and his last dose of Vivlodex was on April 29, 2014. His renal labs are listed in the table below.

**Table 60 Renal labs for Subject 109-004**

Date	BUN (mmol/L)	Creatinine (µmol/L)
16April2013	8.9	98
28May2013	7.5	86
26June2013	6.8	98
24July2013	10.4	118
16October2013	11.1	125
24October2013	7.5	83
10December2013	8.6	85
4February2014	8.9	86
1April2014	8.6	91
29April2014	9.3	80

Note: ref range high for BUN is 8.2 mmol/L. ref range high for creatinine in males is 115 µmol/L

Subject 118-018 is a 64-year-old male who experienced elevated serum creatinine. He had medical history of hypertension and type 2 diabetes. His first day of Vivlodex was April 23, 2013. Vivlodex was discontinued because of the increasing creatinine. His last day of Vivlodex was July 17, 2013. The adverse event of increased creatinine was not considered resolved. The following is a table of his creatinine measurements:

**Table 61 Renal labs for Subject 108-018**

Date	Creatinine (µmol/L)
16April 2013	121
20May2013	124
23May2013	111
17June2013	137
15July2013	149
22July2013	167
29July2013	200

Note: ref range high for creatinine in males is 115 µmol/L

Subject 127-004 is a 66-year-old male who experienced increased creatinine. He had a medical history of hypertension. His first day of Vivlodex was May 21, 2013. His last day of Vivlodex was May 21, 2014. The following is a table of his renal labs:

**Table 62 Renal labs for Subject 127-004**

Date	Creatinine (µmol/L)	BUN (mmol/L)
14May2013	126	10.4
18June2013	144	7.9
15July2013	128	9.3
15August2013	148	11.1
5November2013	134	6.4
25February2014	133	6.8
24April2014	134	7.5
21May2014	130	8.2

Note: ref range high for BUN is 8.2 mmol/L. ref range high for creatinine in males is 115 µmol/L

Subject 131-009 is a 71-year-old male who experienced acute renal failure. He had a medical history of hypertension and diabetes. His first day of Vivlodex was May 21, 2013. His last day of Vivlodex was on September 29, 2013. On (b) (6) the subject was hospitalized for pneumonia and suffered from COPD of moderate severity. Worsening hypertension occurred on (b) (6). Acute respiratory failure occurred on (b) (6). He was intubated and placed on a ventilator. On (b) (6) he experienced hypotension and was treated with intravenous norepinephrine. The serious adverse event of acute renal failure occurred on (b) (6), which improved after treatment with intravenous fluids. However, acute renal failure was noted to be continuing at last report.

Subject 133-006 is a 67-year-old female who experienced acute kidney injury. She had a medical history of hypertension. Her first day of Vivlodex was April 3, 2013. On (b) (6), she experienced staphylococcal sepsis and acute kidney injury. Her last dose of Vivlodex was February 8, 2014.

Subject 138-018 is a 77-year-old female who experienced elevations in BUN and creatinine. She had a medical history of hypertension. Her first day of Vivlodex was April 18, 2013. Her last day of Vivlodex was July 18, 2013. The increased BUN and

creatinine resolved after discontinuation of Vivlodex. The following table displays her renal labs:

**Table 63 Renal labs for Subject 138-018**

Date	Creatinine (µmol/L)	BUN (mmol/L)
10April2013	103	11.8
15May2013	107	10.7
12June2013	96	6.8
12July2013	116	12.1
16July2014	140	15.4
22July2014	80	7.5

Note: ref range high for BUN is 8.2 mmol/L. ref range high for creatinine in females is 97 µmol/L

Subject 138-033 is a 78 year-old female who experienced elevated BUN and creatinine. She had a medical history of hypertension. Her first day of Vivlodex was May 29, 2013. Her last day of Vivlodex was May 27, 2014. The following table displays her renal labs:

**Table 64 Renal labs for Subject 138-033**

Date	Creatinine (µmol/L)	BUN (mmol/L)
20May2013	103	7.9
26June2013	111	10
22July2013	104	6.4
19August2013	129	9.3
26August2013	133	10.7
3September2013	112	8.2
14October2013	111	9.3
11November2013	120	9.3
8January2014	118	7.9
4March2014	115	8.9
29April2014	118	7.5
17May2014	116	8.2

Note: ref range high for BUN is 8.2 mmol/L. ref range high for creatinine in females is 97 µmol/L

## 9.8 Clinical Investigator Financial Disclosure

Application Number: NDA 207233

Submission Date(s): December 23, 2014

Applicant: Iroko Pharmaceuticals, LLC

Product: Vivlodex Capsules

Reviewer: Amelia Lockett

Date of Review: July 30, 2015

Clinical Review  
 Lockett  
 NDA 207233  
 Vivlodex ( (b) (4) meloxicam)

Covered Clinical Study (Name and/or Number): MEL1-11-01, MEL1-12-04, MEL3-12-02, MEL3-12-03

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>90 principal investigators and 404 sub-investigators</u> . Note: Some of these investigators are counted multiple times because they were involved in more than one trial or in more than one role in a trial.		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> <i>Investigators did not submit form 3455. They instead submitted another, similar form verifying financial arrangements with the following questions described below. No financial interests were disclosed on this form by any investigator.</i>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/> <u>N/A</u>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/> <u>N/A</u>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

*The Applicant submitted Form FDA 3454 "CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS" with an attached list of clinical investigators for clinical trials MEL1-11-01, MEL1-12-04, MEL3-12-02, and MEL3-12-03. On this form, Vice President of Regulatory Affairs at Iroko indicates none of the listed clinical investigators had disclosable financial interests or arrangements.*

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

*Investigators did not submit form 3455. They instead submitted another, similar form, verifying financial arrangements with the following questions:*

Indicate by marking **YES** or **NO** if any of the financial interests or arrangements of concern to FDA (and described below) apply to you, your spouse, or dependent children:

Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study. This should include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. If yes, please describe:

Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments made to the investigator or the institution to support activities that have a monetary value great than \$25,000 (i.e., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria)

If yes, please describe:

A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreement. If yes, please describe:

A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or an equity interest in a publicly traded company exceeding \$50,000.

If yes, please describe:

OR

I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.

After reviewing the financial disclosure forms, the following notable problems were identified with the financial disclosure forms:

1. One sub-Investigator at site 109 in trial MEL3-12-02 did not confirm or deny financial interests or arrangements, but (b) (6) signed the financial disclosure form. Site 109 randomized two subjects in trial MEL-3-12-02.

2. For MEL3-12-03 Site 113 with Principal Investigator (PI): David W. Chen, MD, two staff members did not sign a financial disclosure after being added to form 1572. According to the PI David Chen, they had left the site and were unavailable to complete the form. Site 113 randomized no subjects in trial MEL3-12-03.

The above problems do not affect the approvability of Vivlodex.

#### Reference List

Huskisson, E.C., Ghozlan, R., Kurthen, R., Degner, F.L., and Bluhmki, E. (1996). A long-term study to evaluate the safety and efficacy of meloxicam therapy in patients with rheumatoid arthritis. *Br J Rheumatol. 35 Suppl 1*, 29-34.

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Reginster, J.Y., Distel, M., and Bluhmki, E. (1996). A double-blind, three-week study to compare the efficacy and safety of meloxicam 7.5 mg and meloxicam 15 mg in patients with rheumatoid arthritis. *Br J Rheumatol. 35 Suppl 1*, 17-21.

Ruperto, N., Nikishina, I., Pachanov, E.D., Shachbazian, Y., Prieur, A.M., Mouy, R., Joos, R., Zulian, F., Schwarz, R., Artamonova, V., Emminger, W., Bandeira, M., Buoncompagni, A., Foeldvari, I., Falcini, F., Baildam, E., Kone-Paut, I., Alessio, M., Gerloni, V., Lenhardt, A., Martini, A., Hanft, G., Sigmund, R., and Simianer, S. (2005). A randomized, double-blind clinical trial of two doses of meloxicam compared with naproxen in children with juvenile idiopathic arthritis: short- and long-term efficacy and safety results. *Arthritis. Rheum. 52*, 563-572.

Vasan, R.S., Beiser, A., Seshadri, S., Larson, M.G., Kannel, W.B., D'Agostino, R.B., and Levy, D. (2002). Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA 287*, 1003-1010.

Yocum, D., Fleischmann, R., Dalgin, P., Caldwell, J., Hall, D., and Roszko, P. (2000). Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern. Med 160*, 2947-2954.

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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.**  
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/s/  
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MARY A LUCKETT  
09/17/2015

ELLEN W FIELDS  
09/17/2015



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application?  Pivotal Study #1 MEL3-12-02            Indication: Osteoarthritis pain  Pivotal Study #2 Indication:				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Primary endpoint agreed to in meeting minutes 12/03/12: the mean changes from baseline for WOMAC pain subscale score. This was the primary endpoint for the pivotal study.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Previously submitted PSP—we agree with request for full waiver
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial	X			

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No review issues have been identified.

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Reviewing Medical Officer Date

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Clinical Team Leader Date

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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.**  
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/s/  
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MARY A LUCKETT  
02/04/2015

ELLEN W FIELDS  
02/04/2015  
concur