CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207233Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207233
Supplement #:	000
Drug Name:	Vivlodex (meloxicam)
Indication(s):	(b) (4) of pain of osteoarthritis
Applicant:	Iroko Properties, Inc.
Date(s):	Submitted: December 23, 2014 PDUFA date: October 23, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewers:	Katherine B. Meaker, MS
Concurring Reviewers:	Freda Cooner, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Amelia Luckett, M.D. Ellen Fields, M.D.
Project Manager:	Allison Meyer

Keywords: Clinical Study

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1 EXECUTIVE SUMMARY

The active ingredient in Vivlodex Capsules is meloxicam, a nonsteroidal anti-inflammatory drug (NSAID) approved in tablet form. The indications for meloxicam include (b) (4) of pain due to osteoarthritis (OA). Vivlodex Capsule is a new formulation intended to provide similar pain relief at lower dose levels than the currently marketed products containing meloxicam.

This application includes a single phase 3 clinical study, MEL3-12-02, conducted at 40 sites in the US. It was a randomized, double-blind, parallel arm, fixed-dose, placebo-controlled study which included two dose levels of Vivlodex (5 mg or 10 mg). Treatment was taken once daily. Patients were at least 40 years old, with a BMI ≤ 40 kg/m^2, with OA of the knee or hip. Eligible patients were current, chronic users of NSAIDS and/or acetaminophen for (b) (4) of OA Pain, and had a score of at least 40 on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score at screening (on a 0-100 mm VAS scale). After the screening visit, patients discontinued use of NSAIDS or pain medications prior to the baseline visit. A flare in OA pain, defined as an increase of at least 15 mm in the WOMAC pain scale from screening to baseline, was required for enrollment.

The single primary efficacy endpoint was the change in WOMAC pain from baseline to Week 12. Other assessments of OA pain, such as WOMAC function subscale, total WOMAC score, and Patient Global Impression of Change (PGIC) were collected in the study as secondary endpoints, not intended to support an efficacy labeling claim. The protocol specified that no adjustment for multiple endpoints would be made.

The planned analysis model was a mixed model for repeated measurements (MMRM) model which included observed data at baseline, Week 2, Week 6, and Week 12 on blinded study treatment. This methodology does not impute data for missing values. The concern with the approach, discussed at the End of Phase 2 (EOP2) and pre-NDA meetings with the applicant, is that the model assumes missing at random (MAR). The applicant planned few sensitivity analyses intended to address this concern regarding discontinuation reasons which could be attributed to treatment received, i.e., not at random.

The results of the efficacy analyses showed that both doses of Vivlodex capsules (5 mg or 10 mg) were statistically significantly different from placebo in the reduction of pain due to OA after a flare during screening. Additional analyses, using alternate models or methods for handling missing data, provided supportive evidence. Both Vivlodex dose groups showed consistently better reduction in pain on the WOMAC pain subscale comparing to placebo.

Secondary endpoints of clinical interest to Dr. Luckett were WOMAC function subscale and the Patient Global Impression of Change (PGIC). On both outcomes, the results for the Vivlodex groups were favorable compared to the placebo group. The applicant did not plan in the protocol to adjust for multiplicity, so the results of these secondary endpoints are not appropriate for inclusion in the labeling for any efficacy claims.

My conclusion is that the results of Study MEL3-12-02 show sufficient evidence of efficacy to support an indication of (b) (4) of pain due to OA of the knee or hip for Vivlodex 5 mg and 10 mg dose strengths.

2 INTRODUCTION

2.1 Overview

Vivlodex capsules contain meloxicam, an NSAID previously approved for (b) (4) of OA pain under the trade name Mobic.

The clinical development plan was discussed at the End of Phase 2 meeting on November 13, 2012. The applicant subsequently conducted a single phase 3 study (MEL3-12-02) in patients with OA of the knee or hip. Study MEL3-12-02 is a multicenter, double-blind, double-dummy, parallel arm, placebo-controlled study. All sites were in the United States. Patients with more than one joint with OA designated the most painful one as the target joint.

Initial eligibility, including severity of pain and OA symptoms, was determined at the screening visit. Patients who were taking OA pain management treatment (NSAIDs or other therapies) were instructed to discontinue use to monitor for a flare in OA pain. A flare was defined as an increase of at least 15 mm in the WOMAC pain subscale after stopping prior therapy. At the Baseline Visit (4 to 14 days later), final eligibility was assessed and qualified patients were randomized to receive one of the three blinded treatments for 12 weeks. The WOMAC pain, function, stiffness, and other measurements of OA symptoms, were only collected at the clinic visits: Randomization (Baseline), Week 2, Week 6, and Week 12.

2.2 Data Sources

The clinical study report and all efficacy datasets were submitted to the electronic document room: \\CDSESUB1\EVSPROD\NDA207233\0000. All the necessary documentation to complete my review was provided.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data for the efficacy study were submitted in the required format and with sufficient documentation for my review. The derived endpoints provided by the applicant were pre-specified in the protocol. The plan for imputation of missing data was discussed with the Agency in the End of Phase 2 and pre-NDA meetings, held on November 13, 2012, and July 22, 2014, respectively. The analyses provided in the clinical study report followed the statistical analysis plans.

3.2 Evaluation of Efficacy: Study MEL3-12-02

3.2.1 Study Design and Endpoints

Objectives: The objective of Study MEL3-12-02 was to evaluate the efficacy, safety of Vivlodex capsules compared to placebo for the (b) (4) of pain due to OA.

Design: Study MEL3-12-02 is a multicenter, double-blind, double-dummy, parallel arm, placebo-controlled study. The patient population is adults aged 40 or older with chronic OA of the knee or hip. Patients were taking nonsteroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen for (b) (4) of OA pain prior to screening; and had a WOMAC pain subscale VAS score that was ≥ 40 mm (on a scale of 0-100 mm) at Baseline. Between the Screening and Baseline visits, potential subjects discontinued use of OA pain medications or therapies. At the Baseline visit (4-14 days later) a flare in OA pain, defined as an increase of at least 15 mm in WOMAC pain from Screening, was required for enrollment and randomization to the study.

There were three treatment arms (Meloxicam 5 mg; Meloxicam 10 mg; placebo) with a planned enrollment of 402 patients to be randomized at a 1:1:1 ratio (134 per treatment arm). It was conducted at 40 sites in the United States.

Sample size: The applicant planned for hierarchical testing of each of the meloxicam treatment arms versus placebo. There was no intent to compare the two meloxicam dose groups to each other. First the Meloxicam 10 mg treatment arm would be tested against placebo, and if significant at the 0.05 α level, then the Meloxicam 5 mg treatment arm would be tested against placebo. The sample size was determined to detect a minimal difference of 10.75 mm between each treatment group and placebo group with at least 90% power (assumed standard deviation of 27 mm).

Endpoints: The primary efficacy endpoint was defined as the change from baseline to Week 12 in the WOMAC pain subscale. The baseline pain score was recorded after the flare in OA pain had been determined, just prior to randomization. The WOMAC pain score is a 0-100 mm VAS scale with a low value representing less pain, the desirable outcome.

There are two additional subscales in the WOMAC questionnaire: function and stiffness. These endpoints, along with total WOMAC score, were assessed as secondary endpoints. These were recorded at all clinic visits (Screening, Baseline, Week 2, Week 6, and Week 12).

The Patient Global Impression of Change questionnaire (PGIC) was collected only at the Week 12 visit. This is a categorical scale asking the patient to recall "How would you rate your change in overall status since beginning treatment with trial drug?" There are 7 response options from very much improved to very much worse.

The efficacy analysis dataset is the intent-to-treat (ITT) population that included all randomized patients.

3.2.2 Statistical Methodologies

Analysis of the primary efficacy endpoint - Change from Baseline to Week 12 in WOMAC pain subscale
The WOMAC pain subscale includes five questions about OA pain in different physical scenarios. Each is recorded on a 0-100 mm visual analog scale. The average of the 5 values is calculated as the WOMAC pain score, also on a 0-100 mm scale. The change from Baseline to Week 12 was calculated for each subject. A reduction in the WOMAC outcome represents an improvement in OA pain.

The applicant's primary analysis used a restricted maximum likelihood (REML) based mixed model for repeated measurements (MMRM) analysis. The model included treatment arm, site, and gender as factors, and baseline pain as the covariate. Data at Week 2, Week 6, and Week 12 were included. This model only utilizes observed data, with no imputation for missing data. It relies on the assumption that missing data are missing at random (MAR) rather assuming that the likelihood of missing data is related, to some degree, to the treatment received.

Typically for treatment of OA studies, the WOMAC pain outcome is analyzed using an ANCOVA model with factor terms for treatment, site, randomization stratification factor (if any), and baseline pain score as the covariate. Missing data are imputed prior to the ANCOVA model analysis based on reasons for discontinuation. I applied this ANCOVA approach to further investigate the applicant's results and to assess the potential impact of the rates and reasons for discontinuations across the treatment groups.

The applicant planned a hierarchical closed testing approach to control the overall Type I significance level with multiple dose comparisons. The Meloxicam 10 mg arm was compared to

placebo at α of 0.05. If significant (superiority vs. placebo) then the Meloxicam 5 mg treatment arm was tested vs. placebo at α of 0.05 for superiority.

Secondary efficacy endpoints
In the protocol the applicant defined secondary endpoints and pre-specified associated analyses. There was no adjustment for testing of multiple endpoints in order to control the overall Type I error rate for the study. The results of the secondary endpoints will not be appropriate for inclusion in the labeling for any efficacy claims. The need for appropriate Type I error rate control if the results were intended for labeling claims was discussed with the applicant at the EOP2 and pre-NDA meetings.

Analysis of secondary efficacy endpoint – WOMAC Function subscale:
The WOMAC function subscale consists of 17 items regarding impact of OA on daily activities. Each item is scored on a 0-100 mm VAS scale from 0 = No difficulty to 100 = Extreme difficulty. The 17 scores are averaged for the function subscale outcome. The change from Baseline to Week 12 in the WOMAC function subscale was calculated and analyzed using the same methods as the primary endpoint. Between group comparisons were not pre-specified in the protocol.

Analysis of secondary efficacy endpoint – Patient Global Impression of Change:
This assessment instrument is only recorded at the end of the study. Patients are asked to recall their overall change in pain status. There are seven response categories, three degrees of improvement, no change, and three degrees of worsening. I present the summary statistics for the seven categories by treatment arm, as well as a single "Percent of Subjects who Improved" responder outcome. There were no between-group comparisons conducted.

Analysis of secondary efficacy endpoint - Cumulative Responder Analysis:
During the screening phase, patients discontinued prior analgesic therapy for 4-14 days. A flare in OA pain during this time between the Screening and Baseline visits without therapy was required for eligibility in the study design. For the Cumulative Responder Analysis, a subject's response to treatment was defined as the percentage reduction in OA pain score from Baseline to Week 12. If the OA pain at Week 12 was worse (greater) than that at Baseline, then that patient was classified as a non-responder. All subjects who discontinued the study prior to Week 12 of the double-blind treatment phase were considered non-responders and were assigned a 0% reduction OA pain score. Results are presented on a cumulative distribution graph by treatment group.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients were randomized on a 1:1:1 basis to the three treatment arms. The disposition of patients is shown in Table 1. There was no notable imbalance in the numbers of patients who dropped out or in the reasons for discontinuation across the groups. At the End-of-Phase 2 (EOP2) and pre-NDA meetings, FDA statistical reviewers cautioned the Applicant about the proposed handling of missing data approach due to discontinuations. The Applicant did not change the planned primary efficacy analysis model (MMRM), but instead added sensitivity analyses to assess the impact of the drop-outs. The balance across the treatment groups may minimize the potential of missing data biasing the results. This is discussed further in Section 3.2.4.

Table 1: Patient Disposition: Study MEL3-12-02

	Meloxicam 5mg	**Meloxicam 10mg**	**Placebo**
Randomized	139	130	134
Received Study Treatment (ITT)	139 (100%)	130 (100%)	133 (99%)
Discontinued	17 (12%)	18 (14%)	18 (14%)
Reason for Discontinuation:			
Adverse Event	2 (1%)	4 (3%)	6 (5%)
Lack of Efficacy	7 (5%)	3 (2%)	5 (4%)
Lost to Follow-up	1 (1%)	2 (1%)	2 (2%)
Protocol Violations	3 (2%)	2 (1%)	3 (2%)
Withdrew Consent	4 (3%)	3 (2%)	2 (2%)
Other	0 (0%)	4 (3%)	0 (0%)
Completed Study	122 (88%)	112 (86%)	116 (87%)

Source: Clinical Study Report Table 10

The demographic characteristics were mostly balanced across the three groups, as shown in Table 2. The only notable imbalance among the groups is for the target joint for the OA pain assessment (hip or knee). This was not included as a stratification variable in the randomization. In the placebo group, 16% had OA in the hip, versus 11% in the other two groups. I did a subgroup analysis on this variable, which showed no difference in treatment effect by OA target joint.

Table 2: Demographic Characteristics: Study MEL3-12-02

	Meloxicam 5mg N=138 [a]	**Meloxicam 10mg N=131** [a]	**Placebo N=133**
Age (years)			
Mean (SD)	61 (9)	60 (9)	61 (9)
Median	60	60	60
Min, Max	42, 83	40, 84	42, 87
Gender n (%)			
Male	49 (35%)	47 (36%)	41 (31%)
Female	89 (65%)	84 (64%)	92 (69%)
Race n (%)			
Caucasian	108 (78%)	98 (75%)	110 (83%)
African American	27 (20%)	29 (22%)	23 (17%)
Asian	0 (0%)	1 (1%)	0 (0%)
Other	4 (3%)	3 (2%)	0 (0%)
BMI (kg/m^2)			
Mean (SD)	31 (5)	31 (5)	31 (5)
Median	31	30	31
Min, Max	18, 41	19, 40	19, 44
Target OA Joint n (%)			
Hip	15 (11%)	14 (11%)	21 (16%)
Knee	123 (89%)	117 (89%)	112 (84%)

[a] One subject was randomized to Meloxicam 10 mg but received Meloxicam 5 mg blinded treatment.
Source: Clinical Study Report Tables 11-1 and 11-2

The summary statistics for baseline OA pain characteristics are shown in Table 4. The patients in the three groups were similar in terms of severity of symptoms of OA as measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index subscales and total score.

Table 4: Baseline Characteristics: Study MEL3-12-02

	Meloxicam 5mg N=138 [a]	**Meloxicam 10mg N=131** [a]	**Placebo N=133**
WOMAC Pain Subscale			
Mean (SD)	73 (15)	72 (14)	73 (15)
Median	73	72	75
Min, Max	44, 99	40, 100	42, 100
WOMAC Function Subscale			
Mean (SD)	67 (18)	68 (17)	69 (18)
Median	69	69	68
Min, Max	25, 98	7, 97	(22, 99)
WOMAC Stiffness Subscale			
Mean (SD)	70 (18)	69 (20)	73 (17)
Median	73	72	75
Min, Max	9, 99	19, 100	21, 100
Total WOMAC Score			
Mean (SD)	68 (16)	69 (15)	70 (16)
Median	69	69	70
Min, Max	32, 97	16, 97	27, 99

[a] One subject was randomized to Meloxicam 10 mg but received Meloxicam 5 mg blinded treatment.
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
Each subscale and total normalized to 0 – 100 mm VAS.
Higher scores on WOMAC indicate worse pain, stiffness, and functional limitations.
Source: Clinical Study Report Table 11-2

3.2.4 Results and Conclusions

Analysis of the primary efficacy endpoint - Change from Baseline to Week 12 in WOMAC pain subscale

The applicant's analyses for the primary efficacy endpoint, the change from baseline to Week 12 in WOMAC pain subscale are presented in Table 5. The MMRM model approach uses data from all timepoints (rather than just Baseline and Week 12) to model the treatment effect over the length of treatment. No imputation for missing data is conducted. The results indicate that both Meloxicam dose groups are statistically superior to placebo group for reduction in OA pain (p-values < 0.01)

Table 5: Applicant's Primary Efficacy Analysis of Study MEL3-12-02: Change from Baseline to Week 12 in WOMAC pain subscale

Table 11-5 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	Meloxicam SoluMatrix Capsules 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)[a]	-25.68 (2.636)	-36.52 (2.485)	-34.41 (2.678)
95% CI[a]	(-30.86, -20.50)	(-41.40, -31.63)	(-39.68, -29.15)
Comparison vs placebo[a]			
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.

[a] LS mean, LS mean differences (treatment - placebo), 95% confidence intervals, and *P* values were obtained

Source: Clinical Study Report Table 11-5.

The applicant performed a variety of sensitivity analyses, including a Per Protocol analysis (using MMRM), a "Penalized" approach in which bad pain scores were imputed for subjects who discontinued and the resulting dataset was analyzed using MMRM; and a pattern-mixture model which grouped subjects into 2 patterns (completers and non-completers). All the sensitivity analyses showed that both Meloxicam treatment arms were statistically significantly better than placebo for (b) (4) of OA pain. These provide support evidence that the missing data had minimal impact on the applicant's primary analysis results or conclusions.

For my reanalysis, I applied an ANCOVA model and used the applicant's "Penalized" imputation data set since it applied a conservative approach to ensure positive outcomes were not imputed for patients who discontinued. The results of my reanalysis are shown in Table 6, and are consistent with the applicant's results and conclusions from their primary analysis.

Table 6: Study MEL3-12-02; Primary Efficacy Analysis [WOMAC Pain Subscale]

Primary Endpoint: Change from Baseline to Week 12 in WOMAC Pain Subscale	**Meloxicam 5 mg N=139**	**Meloxicam 10 mg N=130**	**Placebo N=133**
LS Mean [a] Std Error	-36.8 2.6	-33.6 2.9	-25.3 2.7
Difference: (Meloxicam – placebo) p-value (vs. placebo)	 -11.5 (3.1) < 0.001	 -8.3 (3.1) 0.02	

[a] Estimated Change from Baseline to Week 12 in WOMAC Pain subscale based on the ANCOVA model with treatment, site, and baseline pain.

Source: SAS dataset adeff.xpt

In the protocol, the applicant did not pre-specify formal statistical testing of any endpoints except the primary efficacy endpoint. Secondary endpoints were defined and analyses planned, but without control of the overall Type I error rate for multiplicity. Dr. Luckett asked me to confirm the following secondary endpoints of clinical interest to her as supportive evidence of efficacy. Discussion of secondary endpoints serves as supportive evidence but is not adequate for inclusion in the labeling.

Secondary efficacy endpoint - Change from Baseline to Week 12 in WOMAC Function Subscale: Table 7 shows my results for the change from baseline to Week 12 in WOMAC function subscale. I analyzed this endpoint using an ANCOVA model with terms for treatment, site, and baseline function score. The results are similar to those on the primary endpoint (WOMAC pain), indicating patients in each of the Meloxicam treatment groups had improved OA function compared to the placebo group.

Table 7: Study MEL3-12-02; Secondary Efficacy Analysis [WOMAC Function Subscale]

Primary Endpoint: Change from Baseline to Week 12 in WOMAC Function Subscale	**Meloxicam 5 mg N=139**	**Meloxicam 10 mg N=130**	**Placebo N=133**
LS Mean [a] Std Error	-28.8 2.7	-28.1 2.9	-17.3 2.8
Difference: (Meloxicam – placebo)	-11.5 (3.2)	-8.3 (3.2)	

[a] Estimated Change from Baseline to Week 12 in WOMAC Function subscale based on the ANCOVA model with treatment, site, and baseline pain.

Source: SAS dataset adeff.xpt

Secondary efficacy endpoint – Patient Global Impression of Change (PGIC)

At Week 12 (or early termination) patients were asked to rate their change in overall status since beginning treatment in the study. Response categories are:

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

Table 8 shows the results for all seven categories, as well as the three "improved" categories combined. The proportion of patients reporting any improvement is higher in either Meloxicam treatment group than in the placebo group.

Table 8: Study MEL3-12-02; Secondary Efficacy Analysis [Patient Global Impr. Of Change]

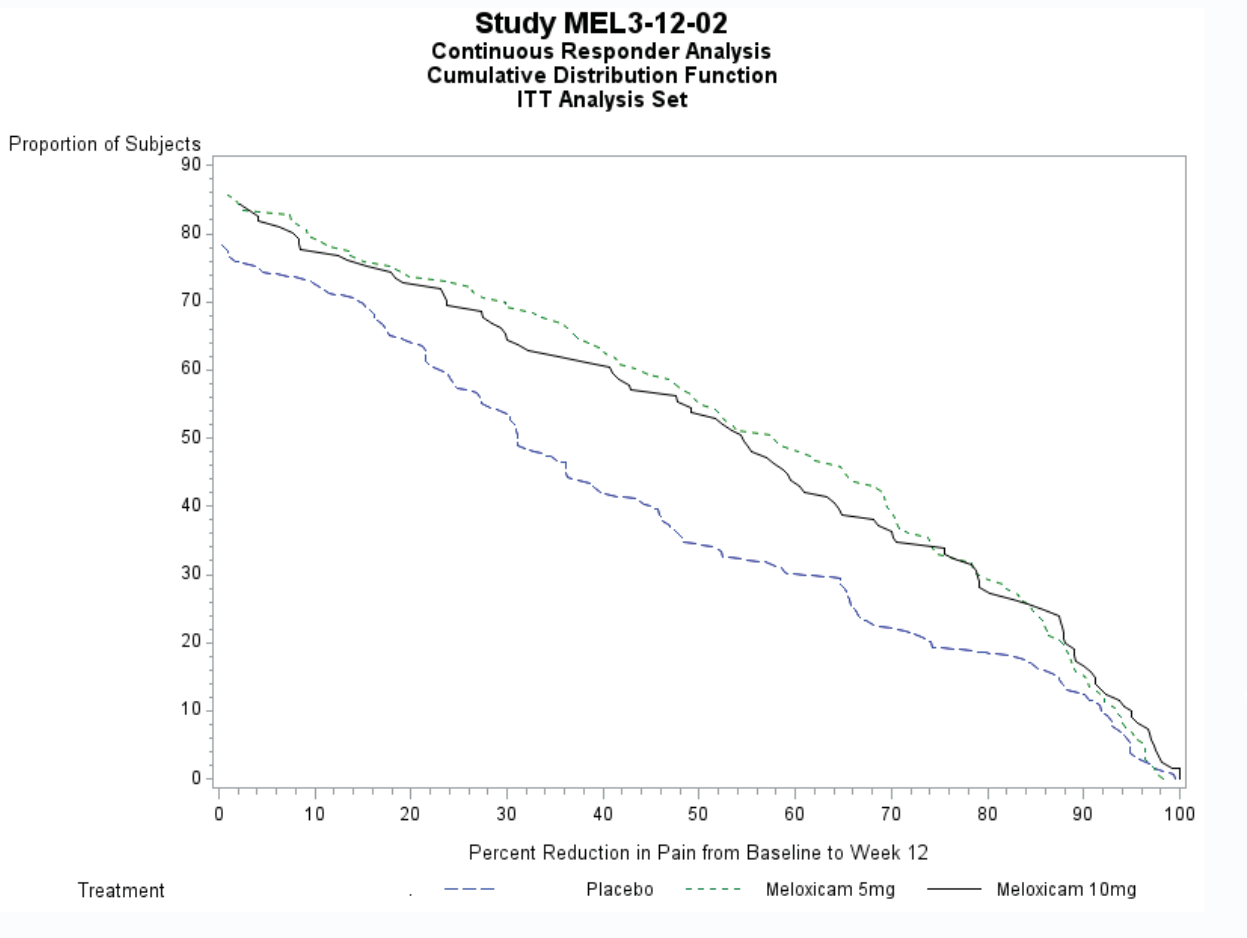
Patient Impression: Change in overall status from start of treatment to Week 12 (or Early Termination) n (%)	**Meloxicam 5mg N=139**	**Meloxicam 10mg N=130**	**Placebo N=133**
Very Much Improved	28 (20%)	28 (21%)	19 (15%)
Much Improved	40 (29%)	38 (29%)	33 (25%)
Minimally Improved	41 (30%)	39 (30%)	32 (24%)
No Change	20 (15%)	12 (9%)	23 (17%)
Minimally Worse	2 (1%)	5 (4%)	14 (11%)
Much Worse	4 (3%)	2 (2%)	8 (6%)
Very Much Worse	1 (1%)	1 (1%)	1 (1%)
Missing	2 (1%)	6 (5%)	3 (2%)
Combined Any Improvement	109/138 (79%)	105/131 (80%)	84/133 (63%)

Source: SAS dataset adeff.xpt

Secondary efficacy endpoint – Continuous Responder Analysis:

The Baseline pain score was recorded after patients were not taking analgesic therapy for their OA pain. The percent improvement from Baseline to Week 12 was calculated, and then graphed as a cumulative distribution function showing proportion of subjects who achieved each level of percentage improvement (Figure 1). All patients who discontinued from the study during the double-blind treatment phase were classified as non-responders, as were patients with negative or zero improvement. These provide consistent support of the efficacy for both dose groups of Meloxicam versus placebo.

Figure 1:



The results of the efficacy outcomes analyses from Study MEL3-12-02 provide consistent evidence in support of the efficacy of Meloxicam 5 mg and 10 mg doses for the (b) (4) of pain from OA.

3.3 Evaluation of Safety

The evaluation of safety has been completed by Dr. Luckett. She did not request any additional safety analyses for my review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 9 shows mean treatment effects by treatment arm for the gender, age and race subgroups. The results show no notable differences across the subgroups. All study sites were in the US so a regional subgroup analysis was not necessary. The study was not designed or powered to make any comparative statements on subgroups.

Table 9: Subgroup Analyses: Age, Gender, and Race – Reviewer's Results

Primary Endpoint: Change from Baseline to Week 12 in WOMAC Pain Subscale						
	Meloxicam 5 mg		**Meloxicam 10 mg**		**Placebo**	
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Age group						
< 65 years	93	-40 (25)	82	-37 (26)	86	-28 (27)
≥ 65 years	40	-38 (24)	39	-35 (23)	43	-29 (23)
Gender						
Female	87	-40 (24)	76	-39 (25)	89	-27 (26)
Male	46	-38 (25)	45	-33 (26)	40	-31 (25)
Race						
Caucasian	103	-40 (24)	90	-38 (23)	108	-29 (25)
Non-Caucasian	30	-36 (27)	31	-33 (32)	21	-28 (29)

Source: SAS dataset adeff.xpt

4.2 Other Special/Subgroup Populations

I analyzed the results by target location of OA: hip or knee. As mentioned earlier, this baseline characteristic was not included as a stratification variable, and as a result the placebo group had a higher proportion of patients with OA in the hip (16%) than the two Meloxicam treatment groups (11%). As shown in Table 10, there were no notable differences across the hip/knee OA subgroups for treatment effects.

Table 10: Target OA Joint Subgroup Descriptive Statistics

Primary Endpoint: Change from Baseline to Week 12 in WOMAC Pain Subscale						
	Meloxicam 5 mg		**Meloxicam 10 mg**		**Placebo**	
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Target OA Joint						
Hip	15	-40 (28)	12	--54 (25)	20	-31 (30)
Knee	118	-39 (24)	109	-35 (25)	109	-28 (25)

Source: SAS dataset adeff.xpt

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The rate of and reasons for dropouts in Study MEL3-12-02 were fairly balanced across the treatment groups. The results from all analysis approaches were generally consistent, indicating the impact of dropouts and assumptions about missing data were not affecting the qualitative conclusions regarding the treatment effect.

5.2 Collective Evidence

At the End-of-Phase 2 meeting, held on November 13, 2012, it was agreed that a single successful well-controlled multicenter OA flare study would be sufficient to support efficacy for Meloxicam 5 mg or 10 mg doses. Study MEL3-12-02 provides sufficient and consistent evidence in favor of the Meloxicam arms.

5.3 Conclusions and Recommendations

The results of Study MEL3-12-02 indicate that Meloxicam 5 mg and 10 mg doses are statistically significantly better than placebo for the change from baseline in OA pain. Supportive evidence was provided by secondary endpoints (WOMAC function subscale; Patient Global Impression of Change; proportion of patients who reported various levels of reduction in pain from baseline to Week 12) which were consistently favoring both Meloxicam dose groups.

My conclusion is that the results of Study MEL3-12-02 provide sufficient evidence of efficacy for (b) (4) of pain due to osteoarthritis in the knee or hip for Meloxicam 5 mg and 10 mg doses.

5.4 Labeling Recommendations

In the proposed label, Study MEL3-12-02 is described accurately and concisely in the Clinical Studies section. Only the results for the single primary endpoint, Change in WOMAC Pain subscale are reported. This is appropriate.

The applicant included a continuous responder graph in the proposed label. The first version did not have subjects who discontinued classified as non-responders. We requested that change, and the applicant submitted a corrected graph in the revised label.

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

/s/

KATHERINE B MEAKER
10/21/2015

FREDA COONER
10/21/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207233 **Applicant: Iroko Properties, Inc.** **Stamp Date: 12/23/14**

Drug Name: Vivlodex (meloxicam) **NDA/BLA Type: Std**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___yes__

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	Date
Supervisor/Team Leader	Date

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/s/

KATHERINE B MEAKER
01/20/2015

FREDA COONER
01/21/2015