CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204768Orig1s000

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 #:	204-768
Drug Name:	Tivorbex (indomethacin submicron particle) Capsules
Indication(s):	Treatment of mild to moderate acute pain in adults
Applicant:	Iroko Pharmaceuticals, LLC
Date(s):	Letter date: April 30, 2013 PDUFA date: February 28, 2014
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Yan Zhou, Ph.D.
Concurring Reviewer:	Janice Derr, Ph.D.
Medical Division:	Division of Anesthesia , Analgesia, and Addiction Products
Clinical Team:	Medical Officer: Anjelina Pokrovnichka, M.D. Medical Team Leader: Ellen Fields, M.D. Deputy Division Director: Sharon Hertz, M.D.
Project Manager:	Kimberly Compton
Keywords:	NDA review, clinical studies

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

Iroko Pharmaceuticals, LLC has submitted a New Drug Application (NDA) for Tivorbex, a new indomethacin drug product, seeking an indication for the treatment of mild to moderate acute pain in adults. Based on my review, I believe that the results from the two Phase 3 studies provided evidence that Tivorbex 20 mg three times daily (TID), 40 mg twice daily (BID) and 40 mg TID have an analgesic effect in the desired indication in comparison to placebo.

The submission contained two Phase 1 studies, one Phase 2 study and two Phase 3 studies. My review focuses only on two Phase 3 studies (Study IND3-08-04b and Study IND3-10-06) which were randomized, double-blind, multicenter, parallel group, multiple-dose studies evaluating the efficacy and safety of three dosing regimens of Tivorbex in subjects with acute postoperative pain following bunionectomy surgery. In both studies, subjects were randomized equally to receive Tivorbex Capsules 20 mg TID, 40 mg BID, 40 mg TID and placebo. In Study IND3-08-04b, celecoxib was also included as an additional treatment arm. One tablet of hydrocodone/acetaminophen 10 mg/325 mg or 1 tablet of oxycodone/acetaminophen 7.5 mg/ 325 mg was used as rescue medications.

In both Phase 3 studies, the primary efficacy endpoint was the time-weighted sum of pain intensity difference from baseline over 48 hours after the first dose. The primary efficacy analysis utilized an analysis of covariance (ANCOVA) model with baseline pain score as a covariate and treatment as a factor. To control multiplicity, a sequential testing procedure was applied for the comparisons of the three doses of Tivorbex with placebo.

The applicant used a hybrid BOCF/LOCF method to impute pain scores after early discontinuation. In 2010, the National Academy of Science (NAS) released a report on missing data. The report does not recommend single imputation approach to impute missing values. Although the proposed BOCF/LOCF method is a single imputation method, I am not concerned about it as very few subjects discontinued early in each reviewed study.

In the two Phase 3 studies, there were a high percentage of subjects in each treatment group who took rescue medications at least once. In Study IND3-08-04b, most arms had 89% or more subjects took rescue medications for pain management during the study. In Study IND3-10-06, most arms had 80% or more subjects took rescue medications for pain management during the study. When the percentage of subjects who take rescue medications is high, the approach to handling the pain scores after the rescue use may substantially influence the comparisons among treatment groups. In the applicant's primary analyses where all the pain scores after the first use of rescue medications were disregarded and replaced with the baseline pain scores, all Tivorbex treatment groups except Tivorbex 20 mg TID in Study IND3-10-06 were statistically significantly different from the placebo group. To evaluate the impact of the applicant's approach to handling pain scores after rescue use, I conducted additional sensitivity analyses in which the pre-rescue pain scores were carried forward to the next pain assessment (or pain assessments within a specified time window), if the pre-rescue pain scores were available. The applicant also conducted sensitivity analyses in which the pain scores within 4 hours after each dose of the rescue use were replaced with the baseline pain scores. All sensitivity analyses results were in favor of the active treatments including the lowest dose 20 mg TID. Since most of

subjects used the rescue medications more than 1 time, the primary analysis is not reasonable as all pain scores after the first rescue use were replaced by the baseline pain scores. Instead, the sensitivity analyses both I and the applicant conducted are more reasonable. Therefore, based on my review, I concluded that the two Phase 3 studies demonstrated the superiority of Tivorbex 20 mg TID, 40 mg BID and 40 mg TID over placebo in pain intensity reduction.

2. INTRODUCTION

2.1 Overview

Indomethacin is an approved drug in the United States since 1965 as a treatment for multiple indications including moderate to severe pain in conditions such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder and acute gouty arthritis. Iroko Pharmaceuticals, LLC is currently developing Tivorbex, a new formulation of indomethacin for the treatment of mild to moderate acute pain in adults. The applicant believes that the new formulation improves the dissolution (b) (4)
The applicant purports that Tivorbex provides similar effective analgesia at a 20% lower dose of currently approved indomethacin products and thus potentially leads to an improved safety profile.

The clinical development program of Tivorbex capsule was discussed between the agency and the applicant under IND 101,940.

In the special protocol assessment (SPA) – No Agreement Letter dated June 02, 2009, the agency stated the following:

- Study IND3-08-04b was not designed to assess the analgesic potency of study drug compared to celecoxib, therefore it was impossible to obtain a comparative claim regarding onset of analgesia for the study drug compared to celecoxib;
- The primary efficacy endpoint SPID48 should be calculated as a time-weighted average;
- The intent-to-treat (ITT) population should include all subjects who receive at least one dose of study drug;
- A strategy to handle multiplicity should be included if it was intended to claim efficacy of other doses of indomethacin;
- The applicant should also thoroughly collect and document as much information as possible to alleviate concerns regarding treatment-related dropouts;
- Covariates included in the primary analysis model should be specified;
- Subgroup analyses should be presented by age, gender and race.

In the SPA – No Agreement Letter dated September 14, 2009, the agency stated that the imputation method should be clarified as it was unclear whether LOCF or BOCF was used to impute the pain scores after the use of rescue medications.

In the End-of-Phase 2 meeting dated July 02, 2010, the agency reiterated that Study IND3-08-04b was not possible to obtain a comparative claim regarding onset of analgesia for the study drug compared to celecoxib. All comparative claims must be based on replicated data.

In the advice/information request letter dated August 14, 2012, the agency made comments and recommendations on the imputation methods for the missing data and pain scores after the rescue use. The following is quoted from the advice/information request letter:

> You propose to impute missing efficacy assessments using a baseline observation carried forward (BOCF) approach for subjects who take rescue or withdraw from the study for reasons including lack of efficacy or an adverse event and a last observation carried forward (LOCF) approach for subjects who withdraw due to other reasons.
>
> We acknowledge that your current statistical analysis plan has been written in accordance with the Division's previous comments. However, in 2010, the National Academy of Sciences (NAS) released a report, which was commissioned by FDA, concerning missing data. The report can be found online at http://www.nap.edu/catalog.php?record_id=12955. Following the release of the report, we have advised all sponsors to consider the NAS report when recommending strategies to handle missing data. Of note, the NAS does not favor single imputation methods for imputing missing values due to discontinuation from the study. In addition, the report recommends explicit specification of the causal estimand. The choice of a causal estimand may have important implications for trial design, conduct, and statistical inference. You should take the NAS report into consideration and either justify the appropriateness of your current strategy or propose an approach consistent with the NAS recommendations. We continue to favor methods which do not attribute a good score to a patient discontinuing due to an adverse event.
>
> It appears that you will disregard the efficacy assessments after a subject takes the first dose of rescue medication. We recommend you instruct subjects to record the pain score prior to rescue each time and impute that score for the next efficacy assessment.

The submission contained two Phase 1 studies, one Phase 2 study and two Phase 3 studies. My review focuses only on two Phase 3 studies (Study IND3-08-04b and Study IND3-10-06) which were randomized, double-blind, multicenter, parallel group, multiple-dose studies evaluating the efficacy and safety of three dosing regimens of Tivorbex in subjects with acute postoperative pain following bunionectomy surgery.

Table 1: List of studies included in this review

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design
IND3-08-04b (02/2012 – 06/2012)	US: 4 sites	Randomization: Tivorbex 20 mg TID n=91 Tivorbex 40 mg BID n=91 Tivorbex 40 mg TID n=93 Celecoxib n=93 Placebo n=94	Celecoxib placebo	randomized, double-blind, parallel group, multiple-dose, active and placebo-controlled, multicenter study in subjects with acute postoperative pain after bunionectomy
IND3-10-06 (05/2012 – 08/2012)	US: 4 sites	Randomization: Tivorbex 20 mg TID n=92 Tivorbex 40 mg BID	placebo	randomized, double-blind, parallel group, multiple-dose, placebo-controlled, multicenter

		n=93 Tivorbex 40 mg TID n=94 Placebo n=94		study in subjects with acute postoperative pain after bunionectomy

Source: Reviewer's analysis

2.2 Data Sources

In both Phase 3 studies, there were high percentages of subjects using rescue medications. Some subjects used the rescue mediations more than 1 time within 48 hours after dosing. However, the initially submitted datasets did not include Date/Time for each rescue use and other information that is necessary for my assessment of the influence of the rescue use on the treatment effects. An information request (IR) was sent on August 02, 2013. The following is quoted from the IR letter:

> In Study IND3-08-04b and IND3-10-06, there are high proportions of subjects using rescue medications. Some subjects used the rescue medications more than 1 time. For example, in Study IND3-08-04b, subject 003-091 in the (b) (4) 40mg TID group had a total of 5 rescue uses within 48 hours (Vicodin, Vicodin, Oxycocet, Oxycocet and Vicodin). However, only Date/Time of the first rescue use was included in the submitted efficacy assessment dataset ADEA. To facilitate ease of review of the impact of the use of rescue medications on the efficacy (b) (4) the dataset ADEA in both Phase 3 studies should include the following information:
>
> - Date/Time for each rescue use
> - For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 4-hour window from the previous rescue use
> - For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 6-hour window from the previous rescue use
> - For each pain assessment, there should be one variable to indicate whether the pain assessment takes place immediately after the first rescue use. Pain intensity and pain relief recorded immediately before the first rescue use should also be included.
>
> To facilitate our ongoing review of this submission, we request the datasets, along with associated documentation, no later than August 15, 2013.

The applicant responded and submitted the revised datasets on August 07, 2013. However, the revised datasets still did not include pain intensity and pain relief recorded immediately before the first rescue use. To request the information, another IR letter was sent out on August 08, 2013. The applicant provided a complete response on August 15, 2013. All data was supplied electronically as SAS transport files and can be found at the following location in the CDER electronic document room:
\\Cdsesub1\evsprod\NDA204768\0005\m5\datasets

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic data submitted by the applicant was of sufficient quality to allow a thorough review. I was able to locate the primary outcome as well as the secondary variables of interest.

3.2 Evaluation of Efficacy

3.2.1 Study IND3-08-04b

Study Design and Endpoints

Study IND3-08-04b was a Phase 3, randomized, double-blind, multicenter, parallel group, active and placebo-controlled, multiple-dose study evaluating the efficacy and safety of three dosing regimens of Tivorbex in subjects with acute postoperative pain following bunionectomy surgery. Subjects who experienced a pain intensity rating of at least 40 mm on a 100-mm Visual Analog Scale (VAS) within 9 hours of discontinuation of the regional anesthesia were eligible to be enrolled into the trial. Eligible subjects were randomized equally to one of the five treatments: Tivorbex 20 mg TID, Tivorbex 40 mg BID, Tivorbex 40 mg TID, placebo or celecoxib capsules 200 mg BID (administered as a 400 mg dose for the first dose). The randomization was stratified by study site.

One tablet of hydrocodone/acetaminophen 10 mg/325 mg was allowed orally every 4 to 6 hours as needed for pain before the anesthetic infusion was discontinued, and as rescue medication after the anesthetic infusion was discontinued and treatment with the study drug had been initiated. If subjects were unable to tolerate hydrocodone/acetaminophen 10 mg/325 mg or if there was insufficient pain relief, then 1 tablet of oxycodone/acetaminophen 7.5 mg/ 325 mg was administered orally every 6 hours as needed for pain. The total daily dose of rescue medication could not exceed 6 tablets.

After randomization, subjects were encouraged to wait for at least 1 hour after the first dose of study drug before receiving first rescue medication to allow time for the study drug to exert its pharmacologic effect. After randomization, subjects whose pain was not adequately managed by a combination of study drug and rescue medications or who developed unacceptable side effects during the study were discontinued from further study participation. Their pain was managed conventionally at the investigator's discretion.

Pain intensity and pain relief assessments were recorded in the inpatient subject diary at scheduled times during the 48-hour period after Time 0 (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hours) and immediately before the first use of rescue analgesia if it was before the 8-hour time point. Pain intensity was assessed based on a 100-mm Visual Analog Scale (VAS). Pain relief was assessed using a 5-point categorical scale. Time to perceptible and meaningful pain relief was evaluated using the 2-stopwatch method. Time to onset of analgesia was measured as time to perceptible pain relief conformed by meaningful pain relief. Pain intensity and pain relief assessments were also recorded before premature study termination. Subjects completed a subject's global evaluation of study drug at the end of the treatment period (Day 3) before discharge from the study site or immediately before the first dose of rescue medications (whichever occurred first).

The primary efficacy variable was the time-weighted sum of pain intensity difference from baseline over 48 hours after the first dose (VASSPID48). Secondary efficacy endpoints included the VASSPID24, time to onset of analgesia, time to first use of rescue medications and total amount of rescue use during the 48 hours. None of them was identified as key secondary endpoints.

Statistical Methodologies

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with baseline pain intensity as a covariate and treatment as a factor. The primary analysis population included all subjects who were randomized and received at least one dose of study medication. To control multiplicity, a sequential testing procedure was carried out for the comparisons of the three doses of Tivorbex with placebo in the following order:

1. Tivorbex 40 mg TID compared to placebo
2. Tivorbex 40 mg BID compared to placebo
3. Tivorbex 20 mg TID compared to placebo

There were no comparisons between Tivorbex and celecoxib in the primary analysis.

Missing pain assessments for subjects who discontinued early due to lack of efficacy, an adverse event (AE), or intolerance to study drug were imputed using a baseline observation carried forward (BOCF) approach. Missing pain assessments due to other reasons were imputed using a last observation carried forward (LOCF) approach. Intermittent missing pain assessments were imputed using linear interpolation. For subjects who took any dose of rescue medications, all scheduled pain assessments after the first dose of rescue medications were disregarded and imputed using a BOCF approach.

The applicant conducted a sensitivity analysis for the primary efficacy analysis by adding gender as a factor into the ANCOVA model. In response to the FDA Advice/Information Request Letter dated August 14, 2012, which was received after the study data had been unblinded and analyzed, additional post-hoc sensitivity analyses were conducted by the applicant. The BOCF imputation was limited to 4 hours following each dose of the rescue use. The Mixed Model Repeated Measures (MMRM) method that used all available data rather than imputing missing pain scores, were conducted. In addition, original protocol defined ANCOVA analysis was also repeated.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics for all treated subjects are presented in the appendix. The majority of the subjects were white (72%), and approximately 83% of all subjects were female. The mean age was 41 years. The demographic and baseline characteristics were generally balanced across the five treatment groups. Overall mean baseline pain intensity was 73 mm on a 100-mm VAS.

The disposition of subjects is shown in Table 2. A total of 462 subjects were randomized and all randomized subjects received the study medications. Each of the Tivorbex 40 mg TID and 40 mg

BID groups had three subjects discontinued early. Tivorbex 20 mg TID had two subjects discontinued early. No subjects in the celecoxib group discontinued early and four subjects in the placebo group discontinued early.

Table 2: Subject disposition in Study IND3-08-04b – Number (%) of Subjects

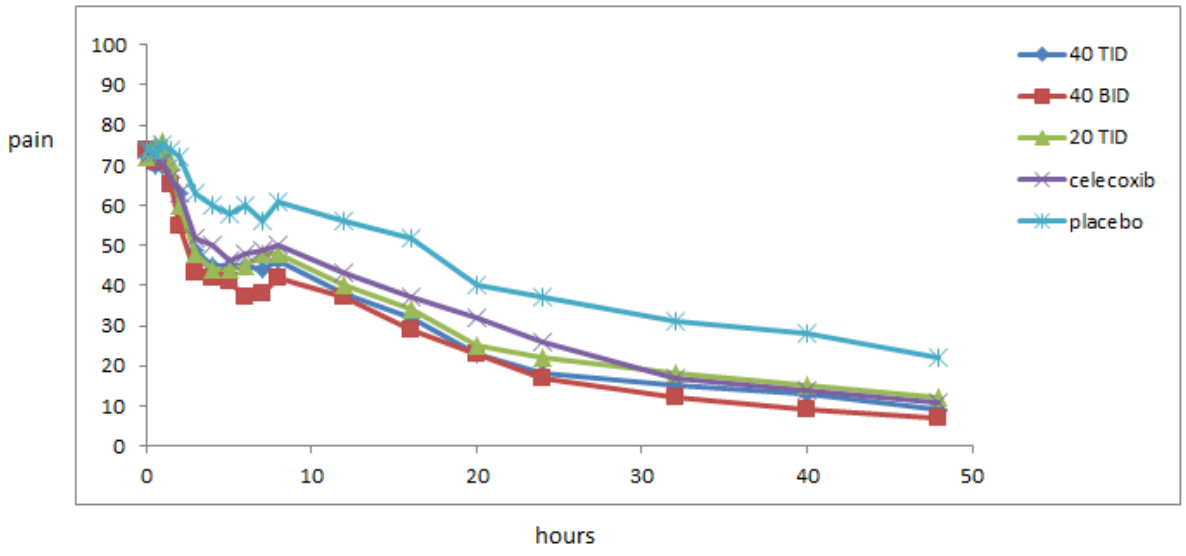
	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID		
Randomized	93	91	91	93	94
Completed	90 (97%)	88 (97%)	89 (98%)	93 (100%)	90 (97%)
Discontinued	3 (3%)	3 (3%)	2 (2%)		4 (3%)
Reason for discontinuation					
Lack of efficacy	1 (1%)	2 (2%)	2 (2%)		2 (2%)
Adverse event	2 (2%)	1 (1%)			2 (2%)

Source: Reviewer's Analysis

Results and Conclusions

The average of the actual observed pain scores over time for each treatment group is displayed in Figure 1. The overall trend of actual pain reduction over time is apparent for each treatment group. Among the treatments, subjects in the placebo group experienced the least pain reduction. The separation of the pain curve of the placebo from the three active treatments occurred after approximately 3 hours after dosing.

Figure 1: Average Pain over Time for Study IND3-08-04b (observed pain scores)



The primary analysis set included all 462 randomized subjects. I replicated the applicant's results for the primary efficacy analysis. Table 3 shows the results from the primary efficacy analysis. All three Tivorbex dosing regimens were superior to placebo in terms of the primary efficacy endpoint except Tivorbex 40 mg BID is borderline significantly superior to placebo. The

applicant conducted a sensitivity analysis by adding gender as an extra factor into the model. The results of this sensitivity analysis were similar to those of the primary analysis.

Table 3: Primary Efficacy Analysis for Study IND3-08-04b (BOCF after the first rescue use)

	Applicant's Analyses					Reviewer's Analyses				
	Tivorbex			Celecoxib	Placebo	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID			40 mg TID	40 mg BID	20 mg TID		
N	93	91	91	93	94	93	91	91	93	94
LS Mean (SE)	510 (92)	328 (93)	381 (93)	279 (92)	68 (91)	510 (92)	328 (93)	380 (93)	279 (92)	67 (91)
Difference in LS mean (SE)	442 (130)	260 (130)	313 (130)	212 (130)		443 (130)	261 (130)	313 (130)	212 (130)	
95% CI for diff. in LS mean	(187, 697)	(4, 516)	(57, 569)	(-43, 466)		(188, 697)	(5, 517)	(57, 569)	(-43, 466)	
p-value for treatment effect	<0.001	0.046	0.017	0.103		0.0007	0.046	0.017	0.103	

Source: Clinical Study Report Table 11-2 and Reviewer's Analysis.
LS: least square; SE: standard error; CI: confidence interval

The applicant used a hybrid BOCF/LOCF approach to impute pain scores after early discontinuation. Although it is a single imputation method which is not recommended by the NAS report, I am not concerned about it in this study as very few subjects (3%) discontinued early. The applicant replaced all the pain scores after the first use of the rescue medications with the baseline observations. In the acute pain setting, it is often likely that subjects will take rescue medications. As shown in Table 4, there were a high percentage of subjects taking rescue medications. For all treatment groups, approximately 89% of the subjects took rescue medications during the 48 hours. Placebo group had the highest percentage of subjects who took rescue medications. The majority of the subjects took their first rescue medication within 8 hours after the first dose. The median number of the rescue use within 48 hours was 2 for each of Tivorbex groups; while for the placebo group, the median number of the rescue use within 48 hours was 5.

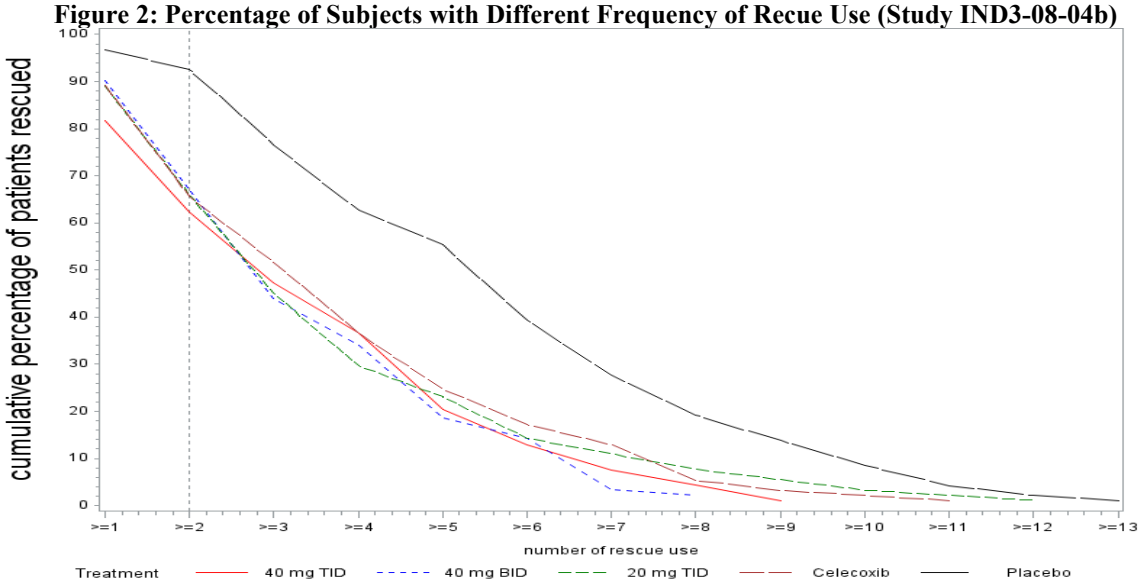
To further explore the usage of rescue medications, I depicted the percentages of subjects who took rescue medications for pain control over different frequencies of rescue use for each treatment group. As shown in Figure 2, there were consistently higher percentages of subjects in the placebo group than in the active treatment groups for each category of frequency. For example, approximately 93% of the subjects in the placebo group took rescue medications at least 2 times. In contrast, about 62% of the subjects in the Tivorbex 40 mg TID, 67% in the Tivorbex 40 mg BID, 66% in the Tivorbex 20 mg TID, 66% in the celecoxib groups took rescue medications at least 2 times.

Table 4: Rescue Use for Study IND3-08-04b

	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID		
Randomized	93	91	91	93	94
Subjects who took rescue within 48 hours	76 (82%)	82 (90%)	81 (89%)	83 (89%)	91 (97%)
Subjects who took rescue within first 8 hours	73 (78%)	78 (86%)	77 (85%)	81 (87%)	91 (97%)
Number of rescue use within first 24 hours					
mean (SD)	2.3 (1.7)	2.2 (1.4)	2.3 (1.7)	2.4 (1.6)	3.6 (1.7)
median	2	2	2	2	4
min, max	(0, 6)	(0, 5)	(0, 7)	(0, 6)	(0, 7)
Number of rescue use within 48 hours					
mean (SD)	2.7 (2.3)	2.7 (2.0)	3.0 (2.6)	3.1 (2.5)	5.0 (2.9)
median	2	2	2	3	5
min, max	(0, 9)	(0, 8)	(0, 12)	(0, 11)	(0, 13)

Source: Reviewer's Analyses

Figure 2: Percentage of Subjects with Different Frequency of Recue Use (Study IND3-08-04b)



When the percentage of subjects who take rescue medications is high, the approach to handling the pain scores after the rescue use may substantially influence the comparisons among treatment groups. As the study had a high percentage of subjects taking rescue medications, my review mainly focuses on assessing different imputation methods for pain scores after the rescue use. In response to the FDA Advice/Information Request Letter dated August 14, 2012, the applicant conducted post-hoc sensitivity analyses in which the BOCF imputation was limited to 4 hours following the rescue use. However, when they were preparing the response to the IR dated

August 02, 2013, the applicant discovered an error in the programming used for some of the sensitivity analyses. The limited 4-hour BOCF imputation was only applied for the pain scores following the first dose of rescue medications, rather than pain scores following each dose of rescue medications. The applicant revised their analyses and submitted an amendment on August 28, 2013. The amended analyses had no impact on the clinical conclusions included in the original submission. Table 5 presents the results from the post-hoc sensitivity analyses in which the BOCF imputation was limited to a 4-hour window after each rescue use and the primary efficacy endpoint was analyzed using the ANCOVA model that was used in the primary analysis. My results are slightly different from the applicant's results as the applicant's analyses only included the subjects who completed the study. The analyses results were in favor of the active treatments. The differences between the three active treatments and placebo were all statistically significant, which indicates that the active treatments in combination with the rescue medications produced superior analgesic effects to placebo in combination with the rescue medications. I also conducted a sensitivity analysis in which the BOCF imputation was limited to a 6-hour window after each rescue use. The analysis yielded similar results (Table 6).

Table 5: Sensitivity Analysis for Study IND3-08-04b (BOCF limited within 4 hours after each rescue use)

	Applicant's Revised Analyses					Reviewer's Analyses				
	Tivorbex			Celecoxib	Placebo	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID			40 mg TID	40 mg BID	20 mg TID		
N	90	88	88	93	90	93	91	91	93	94
LS Mean (SE)	2057 (87)	2127 (88)	1929 (88)	1838 (85)	1197 (87)	1988 (89)	2052 (90)	1905 (90)	1837 (89)	1149 (89)
Difference in LS mean (SE)	859 (123)	930 (123)	731 (123)	641 (122)		839 (126)	903 (126)	756 (126)	687 (126)	
95% CI for diff. in LS mean	(618, 1100)	(688, 1172)	(489, 974)	(402, 880)		(592, 1086)	(654, 1151)	(507, 1004)	(440, 934)	
p-value for treatment effect	<0.001	<0.001	<0.001	< 0.001		<0.001	<0.001	<0.001	< 0.001	

Source: Clinical Information Amendment Table 3.1.1-1 and Reviewer's Analyses

Table 6: Sensitivity Analysis for Study IND3-08-04b (BOCF limited within 6 hours after each rescue use)

	Reviewer's Analyses				
	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID		
N	93	91	91	93	94
LS Mean (SE)	1886 (94)	1886 (95)	1772 (95)	1677 (94)	925 (93)
Difference in LS mean (SE)	962 (132)	962 (133)	847 (133)	752 (132)	
95% CI for diff. in LS mean	(701, 1222)	(700, 1224)	(585, 1109)	(492, 1013)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001	< 0.001	

Source: Reviewer's Analyses

The study protocol stated that pain intensity would be assessed immediately before the first dose of rescue analgesia if administered before the 8-hour time point. To evaluate the impact of the applicant's approach to handling pain scores after rescue use, I also conducted a sensitivity analysis in which the pre-rescue pain scores were carried forward to the next assessment if the pre-rescue pain scores were available and observed pain scores after the rescue use were instead used if the pre-rescue pain scores were unavailable. The analysis results are presented in Table 7. The analysis results were also in favor of the active treatments.

Table 7: Sensitivity Analysis for Study IND3-08-04b (pre-rescue carried forward to the next assessment if it was available)

	Reviewer's Analyses				
	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID		
N	93	91	91	93	94
LS Mean (SE)	2286 (83)	2399 (84)	2205 (84)	2182 (83)	1558 (83)
Difference in LS mean (SE)	728 (117)	841 (118)	647 (118)	624 (117)	
95% CI for diff. in LS mean	(497, 959)	(609, 1073)	(414, 879)	(393, 855)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001	< 0.001	

Source: Reviewer's Analyses

In addition, I also conducted several sensitivity analyses in which the pain scores within a time window after the rescue use were replaced with the pre-rescue pain scores if the pre-rescue scores were available. My sensitivity analyses using different lengths of time window (such as 4 or 6 hours) yielded similar results.

The applicant also conducted a sensitivity analysis in which a MMRM model was utilized. Since the missing data is not a major issue in this study and it is difficult to justify the underlying assumptions for the MMRM model, I did not check the MMRM model that was used by the applicant as one sensitivity analysis.

Analyses results of the secondary efficacy endpoints were supportive to the primary analyses.

3.2.2 Study IND3-10-06

Study Design and Endpoints

Study IND3-10-06 was a Phase 3, randomized, double-blind, multicenter, parallel group, placebo-controlled, multiple-dose study evaluating the efficacy and safety of three dosing regimens of Tivorbex in subjects with acute postoperative pain following bunionectomy surgery. The study design and endpoint were the same as Study IND3-08-04b except that celecoxib was not included in the study.

Statistical Methodologies

The statistical methodology was the same as in Study IND3-08-06b, except that the sensitivity analysis that utilized the MMRM model was pre-specified in the protocol.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics for all treated subjects are presented in the appendix. The majority of the subjects were white (76%), and approximately 85% of all subjects were female. The mean age was 40 years. The demographic and baseline characteristics were generally balanced across the four treatment groups. Overall mean baseline pain intensity was 72 mm on a 100-mm VAS.

The disposition of subjects is shown in Table 8. A total of 373 subjects were randomized and all randomized subjects received the study medications. Each of the Tivorbex groups had two subjects discontinued early, and three subjects in the placebo group discontinued early.

Table 8: Subject disposition in Study IND3-10-06 – Number (%) of Subjects

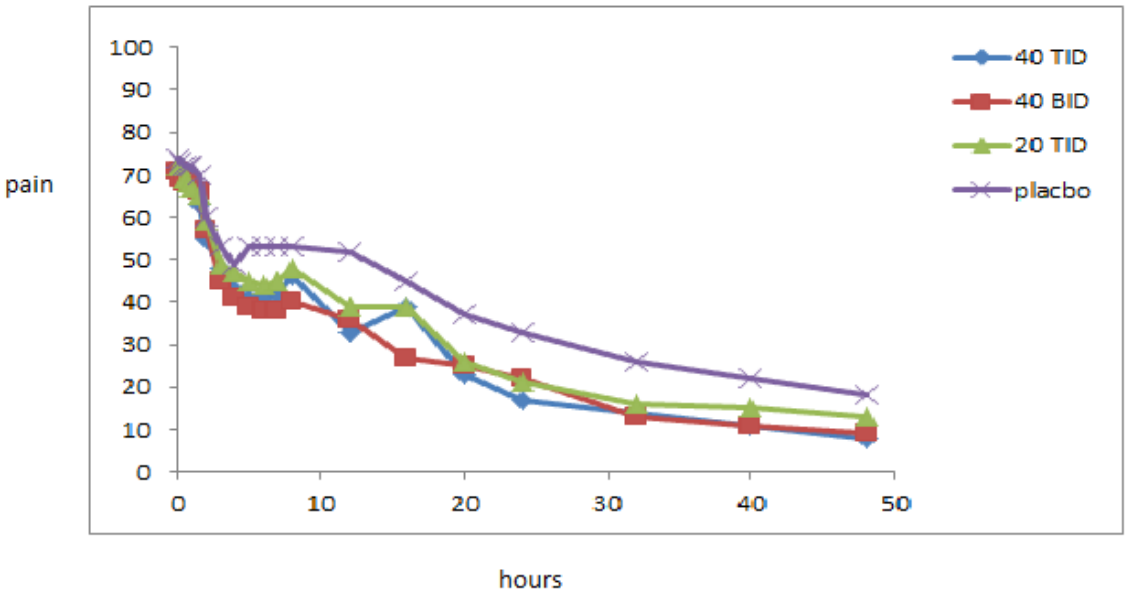
	Tivorbex			Placebo
	40 mg TID	**40 mg BID**	**20 mg TID**	
Randomized	94	93	92	94
Completed	92 (98%)	91 (98%)	90 (98%)	91 (97%)
Discontinued	2 (2%)	2 (2%)	2 (2%)	3 (3%)
Reason for discontinuation				
Lack of efficacy	1 (1%)		1 (1%)	3 (3%)
Adverse event		1 (1%)	1(1%)	
Lost to follow up	1 (1%)			
Investigator decision		1 (1%)		

Source: Reviewer's Analysis

Results and Conclusions

The average of the actual observed pain scores over time for each treatment group is displayed in Figure 3. Similar to Study IND3-08-04b, the overall trend of actual pain reduction over time is apparent for each treatment group. Among the treatments, subjects in the placebo group experienced the least pain reduction. The separation of the pain curve of the placebo from the three active treatments occurred after approximately 5 hours after dosing.

Figure 3: Average Pain over Time for Study IND3-10-06 (observed pain scores)



The primary analysis set included all 373 randomized subjects. I replicated the applicant's results for the primary efficacy analysis. Table 9 shows the results from the primary efficacy analysis. Only Tivorbex 40 mg TID and 40 mg BID were superior to placebo in terms of the primary efficacy endpoint.

Table 9: Primary Efficacy Analysis for Study IND3-10-06 (BOCF after the first rescue use)

	Applicant's Analyses				Reviewer's Analyses			
	Tivorbex			Placebo	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID		40 mg TID	40 mg BID	20 mg TID	
N	94	93	92	94	94	93	92	94
LS Mean (SE)	599 (106)	623 (106)	343 (107)	281 (106)	598 (106)	623 (106)	343 (107)	281 (106)
Difference in LS mean (SE)	318 (150)	342 (150)	62 (150)		318 (150)	342 (150)	62 (150)	
95% CI for diff. in LS mean	(23, 612)	(47, 637)	(-234, 357)		(23, 612)	(47, 637)	(-233, 357)	
p-value for treatment effect	0.034	0.023	0.680		0.035	0.023	0.680	

Source: Clinical Study Report Table 11-3 and Reviewer's Analysis.
LS: least square; SE: standard error; CI: confidence interval

Similar to Study IND3-08-04b, missing data was not a major issue in this study as very few subjects (2%) discontinued early. The applicant replaced all the pain scores after the first use of rescue medications with the baseline observations. As shown in the Table 10, there were also a high percentage of subjects taking rescue medications. For all treatment groups, approximately 83% of the subjects took rescue medications during the 48 hours. Placebo group had the highest percentage of subjects who took rescue medications. The majority of the subjects took their first rescue medication within 8 hours after the first dose. The median number of the rescue use

within 48 hours was 1 for Tivorbex 40 mg TID and 40 mg BID groups; while for the placebo group, the median number of the rescue use within 48 hours was 4.

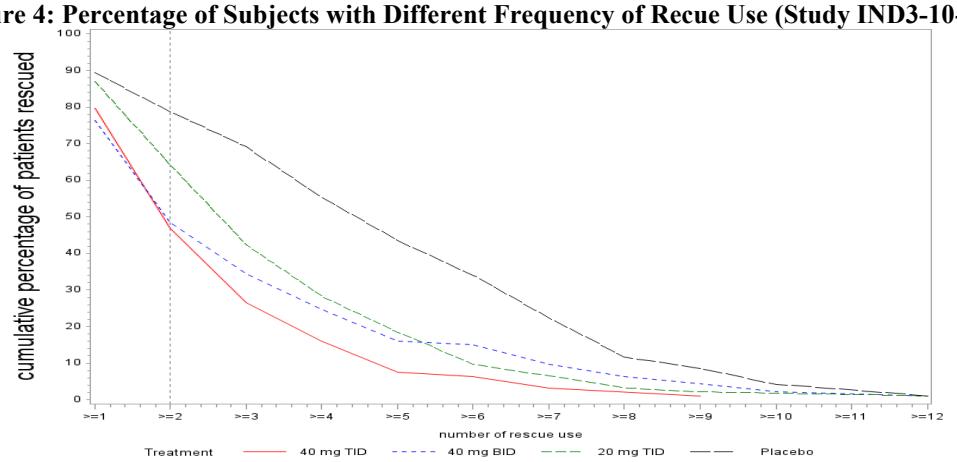
Table 10: Rescue Use for Study IND3-10-06

	Tivorbex			Placebo
	40 mg TID	**40 mg BID**	**20 mg TID**	
Randomized	94	93	92	94
Subjects who took rescue within 48 hours	75 (80%)	71 (76%)	80 (87%)	84 (89%)
Subjects who took rescue within first 8 hours	69 (73%)	67 (72%)	75 (82%)	81 (86%)
Number of rescue use within first 24 hours				
mean (SD)	1.6 (1.4)	1.9 (1.7)	2.1 (1.4)	3.0 (1.8)
median	1	1	2	3
min, max	(0, 6)	(0, 8)	(0, 6)	(0, 7)
Number of rescue use within 48 hours				
mean (SD)	1.9 (1.8)	2.4 (2.6)	2.7 (2.2)	4.2 (2.9)
median	1	1	2	4
min, max	(0, 9)	(0, 12)	(0, 12)	(0, 12)

Source: Reviewer's Analyses

To further explore the usage of rescue medication, I depicted the percentages of subjects who took rescue medications for pain control over different frequencies of rescue use for each treatment group. As shown in Figure 4, there were consistently higher percentages of subjects in the placebo group than in the active treatment groups for each category of frequency. For example, approximately 80% of the subjects in the placebo group took rescue medications at least 2 times. In contrast, about 46% of the subjects in the Tivorbex 40 mg TID, 48% in the Tivorbex 40 mg BID and 64% in the Tivorbex 20 mg TID groups took rescue medications at least 2 times.

Figure 4: Percentage of Subjects with Different Frequency of Recue Use (Study IND3-10-06)



Source: Reviewer's Analyses

As in the study IND3-08-04b, my review mainly focuses on assessing different imputation methods for pain scores after the rescue use. The applicant conducted post-hoc sensitivity analyses in which the BOCF imputation was limited to 4 hours following the rescue use. Similar to the Study IND3-08-04b, the limited 4-hour BOCF imputation was only applied for the pain scores following the first dose of rescue medications, rather than pain scores following each dose of rescue medications. The applicant revised their analyses in an amendment dated August 28, 2013. The amended analyses had no impact on the clinical conclusions included in the original submission. Table 11 presents the results from the post-hoc sensitivity analyses in which the BOCF imputation was limited to a 4-hour window after each rescue use and the primary efficacy endpoint was analyzed using the ANCOVA model that was same as in the primary analysis. The analyses results were in favor of the active treatments. The differences between the three active treatments and placebo were all statistically significant, which indicates that the active treatments in combination with the rescue medications produced superior analgesic effects to placebo in combination with the rescue medication. I also conduct a sensitivity analysis in which the BOCF imputation was limited to a 6-hour window after each rescue use. The analysis yielded similar results (Table 12).

Table 11: Sensitivity Analysis for Study IND3-10-06 (BOCF limited within 4 hours after each rescue use)

	Applicant's Revised analyses				Reviewer's Analyses			
	Tivorbex			Placebo	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID		40 mg TID	40 mg BID	20 mg TID	
N	93	91	90	91	94	93	92	94
LS Mean (SE)	2152 (88)	2107 (88)	1881 (89)	1393 (89)	2093 (93)	2068 (93)	1841 (94)	1352 (93)
Difference in LS mean (SE)	759 (125)	714 (125)	488 (125)		742 (131)	717 (132)	489 (132)	
95% CI for diff. in LS mean	(514, 1004)	(468, 961)	(241, 735)		(483, 1000)	(458, 975)	(230, 748)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	

Source: Clinical Information Amendment Table 3.2.1-1 and Reviewer's Analyses

Table 12: Sensitivity Analysis for Study IND3-10-06 (BOCF limited within 6 hours after each rescue use)

	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID	
N	94	93	92	94
LS Mean (SE)	2003 (95)	1933 (95)	1682 (96)	1162 (95)
Difference in LS mean (SE)	841 (134)	771 (135)	520 (135)	
95% CI for diff. in LS mean	(577, 1105)	(506, 1035)	(254, 785)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001	

Source: Reviewer's Analyses

Similar to Study IND3-08-04b, the study protocol also stated that pain intensity would be assessed immediately before the first dose of rescue analgesia if administered before the 8-hour time point. To evaluate the impact of the applicant's approach to handling pain scores after rescue use, I also conducted a sensitivity analysis in which the pre-rescue pain scores were carried forward to the next assessment if the pre-rescue pain scores were available and observed pain scores after the rescue use were instead used if the pre-rescue pain scores were unavailable. The analysis results are presented in Table 13. The analysis results were also in favor of the active treatments.

Table 13: Sensitivity Analysis for Study IND3-10-06 (pre-rescue carried forward to the next assessment if it was available)

	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID	
N	94	93	92	94
LS Mean (SE)	2284 (90)	2323 (91)	2135 (91)	1769 (90)
Difference in LS mean (SE)	515 (128)	554 (128)	366 (128)	
95% CI for diff. in LS mean	(264, 766)	(302, 806)	(114, 618)	
p-value for treatment effect	< 0.001	< 0.001	0.005	

Source: Reviewer's Analyses

Similar to Study IND-08-04b, I also conducted several sensitivity analyses in which the pain scores within a time window after the rescue use were replaced with the pre-rescue pain scores if the pre-rescue scores were available. My sensitivity analyses using different lengths of time window (such as 4 or 6 hours) yielded similar results. With the same reason that was stated for Study IND-08-04b, I didn't check the MMRM model that was used by the applicant as one sensitivity analysis.

Analyses results of the secondary efficacy endpoints were supportive to the primary analyses.

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Anjelina Pokrovnichka. The reader is referred to Dr. Pokrovnichka's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant conducted the subgroup analyses of the primary endpoint by age, race and gender using the per-protocol population (PP). I conducted subgroup analyses by age (≤ 45 or > 45 years old) for all the randomized subjects. My subgroup analyses did not reveal any issues that were concerning. Subgroup analysis for gender was not conducted because the majority of the study population was female (83% in Study IND3-08-04b and 85% in study IND3-10-06). Race was

also not included in the assessment of subgroups because the majority of the study population was white (72% in Study IND3-08-04b and 76% in Study IND3-10-06).

4.1 Gender, Race, Age, and Geographic Region

Table 14 presents subgroup summaries for age. I utilized the same ANCOVA model as in the analysis of the primary efficacy variable with additional terms for gender and its interaction with treatment. There was no statistically significant interaction between treatment and gender.

Table 14: Reviewer's subgroup analyses (pre-rescue carried forward to the next assessment if it was available)

		Tivorbex				
	statistics	**40 mg TID**	**40 mg BID**	**20 mg TID**	**celecoxib**	**placebo**
Study IND3-08-04b		N=93	N=91	N=91	N=93	N=94
Age						
<= 45	**n (%)**	55 (59%)	54 (59%)	51 (56%)	56 (60%)	57 (61%)
	Mean (SD)	2281 (898)	2585 (823)	1988 (1088)	2197 (963)	1603 (834)
> 45	**n (%)**	38 (41%)	37 (41%)	40 (44%)	37 (40%)	37 (39%)
	Mean (SD)	2259 (1069)	2175 (1077)	2405 (1051)	2190 (948)	1531 (1219)
Study IND3-10-06		N=94	N=93	N=92		N=94
Age						
<= 45	**n (%)**	61 (65%)	63 (68%)	55 (60%)		58 (62%)
	Mean (SD)	2218 (918)	2238 (1080)	2277 (745)		1748 (1123)
> 45	**n (%)**	33 (35%)	30 (32%)	37 (40%)		36 (38%)
	Mean (SD)	2213 (954)	2415 (1117)	1943 (970)		1944 (1125)

Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The applicant used a hybrid BOCF/LOCF method to impute pain scores after early discontinuation. The National Academy of Science (NAS) released a report on missing data in 2010. The report does not recommend single imputation approaches to imputing missing values as it is difficult to justify the underlying assumptions. Although the proposed BOCF/LOCF method is a single imputation method, I am not concerned about it in this NDA as very few subjects discontinued early in each of the reviewed Phase 3 studies.

In both Phase 3 studies, there were high percentages of subjects taking the rescue medications and most of subjects used rescue medications more than 1 time. When the percentage of subjects who take rescue medications is high, the approach to handling the pain scores after the rescue use may substantially influence the comparisons among treatment groups. In the primary efficacy analysis where all pain scores after the first use of the rescue medications were replaced with the baseline values, all active treatments except Tivorbex 20 mg TID in Study IND3-10-06

were statistically significant different from placebo. To evaluate the impact of the applicant's approach to handling pain scores after rescue use, I conducted sensitivity analyses in which pre-rescue pain scores were carried forward to the next pain assessment or pain assessments within a specified time window. The applicant also conducted sensitivity analyses in which only pain assessments within 4 hours of each rescue use were replaced with the baseline pain scores. All of the applicant's and my sensitivity analyses yielded statistically significant results. Since most of subjects used the rescue medications more than 1 time, the primary analysis is not reasonable as all pain scores after the first rescue use were replaced by the baseline pain scores. Instead, the sensitivity analyses both I and the applicant conducted were more reasonable.

5.2 Collective Evidence

In the primary efficacy analysis, all active treatments except Tivorbex 20 mg TID in Study IND3-10-06 were statistically significant different from placebo. However, in the sensitivity analyses both I and the applicant conducted (which were more reasonable), there was statistically significant difference between each dose of Tivorbex and placebo in terms of the sum of pain intensity difference over 48 hours. There was statistical evidence in favor of the efficacy of each dose of Tivorbex. In addition, all the treatment groups had high percentages of subjects who took rescue medications for pain control. The placebo group used more rescue medications than the active treatment group.

5.3 Conclusions and Recommendations

Based on my review of both Phase 3 studies, I conclude that Tivorbex 40 mg TID, 40 mg BID and 20 mg BID were more efficacious than placebo in acute pain reduction. However, I believe that the review team needs to consider the totality of evidence including findings from clinical pharmacology to decide whether the benefit-risk profile justify the approval of Tivorbex. As there were high percentages of subjects taking rescue medications for pain management during the study, I recommend including the information about the rescue use and the percentage of subjects who used rescue medications in the clinical study section in the labeling if the division decides to approve Tivorbex.

5.4 Labeling Recommendations

The applicant submitted the following wording for the clinical study section in the labeling for review:

14 Clinical Studies

(b) (4)

(b) (4)

I have the following general recommendations to the applicant:

- Remove (b) (4)
- Describe two Phase 3 studies separately;
- Add information for the enrolled population;
- Remove (b) (4)
- Replace Figure 14-1 with the curves of average pain intensity versus time over the first 48 hours for three Tivorbex groups as well as placebo group. The average pain intensity should be calculated using the observed pain scores without the imputation after the rescue use;
- Add the information of rescue medications and percentages of subjects who took rescue medications;
- Describe the efficacy results.

Appendix

Summary of Demographics and Baseline Characteristics

Study IND3-08-04b (Source: Clinical Study Report Table 11-1)

Category	Indomethacin Nanoformulation Capsule 40 mg TID (N = 93)	Indomethacin Nanoformulation Capsule 40 mg BID (N = 91)	Indomethacin Nanoformulation Capsule 20 mg TID (N = 91)	Celecoxib Capsule 200 mg[a] BID (N = 93)	Placebo (N = 94)	Total (N = 462)
Age (years)						
N	93	91	91	93	94	462
Mean (SD)	41.5 (11.4)	41.4 (12.4)	41.5 (13.4)	41.0 (12.3)	40.4 (13.3)	41.2 (12.5)
Median	41.0	40.0	42.0	41.0	40.5	41.0
(Min, max)	(19, 63)	(21, 68)	(18, 65)	(19, 65)	(19, 64)	(18, 68)
Gender (n [%])						
Male	14 (15.1)	19 (20.9)	12 (13.2)	16 (17.2)	17 (18.1)	78 (16.9)
Female	79 (84.9)	72 (79.1)	79 (86.8)	77 (82.8)	77 (81.9)	384 (83.1)
Ethnicity (n [%])						
Hispanic or Latino	19 (20.4)	18 (19.8)	18 (19.8)	17 (18.3)	18 (19.1)	90 (19.5)
Not Hispanic or Latino	74 (79.6)	73 (80.2)	73 (80.2)	76 (81.7)	76 (80.9)	372 (80.5)
Race (n [%])						
American Indian or Alaskan native	1 (1.1)	0	2 (2.2)	2 (2.2)	2 (2.1)	7 (1.5)
Asian	1 (1.1)	2 (2.2)	4 (4.4)	3 (3.2)	2 (2.1)	12 (2.6)
Black	28 (30.1)	19 (20.9)	19 (20.9)	16 (17.2)	23 (24.5)	105 (22.7)
Native Hawaiian or other Pacific Islander	1 (1.1)	1 (1.1)	2 (2.2)	0	1 (1.1)	5 (1.1)
White	63 (67.7)	67 (73.6)	66 (72.5)	72 (77.4)	65 (69.1)	333 (72.1)
Other	0	3 (3.3)	0	0	1 (1.1)	4 (0.9)
Baseline Pain Intensity (mm)						
N	93	91	91	93	94	462
Mean (SD)	72.8 (17.4)	73.7 (17.0)	72.2 (16.8)	73.5 (17.0)	73.7 (16.2)	73.2 (16.8)
Median	74.0	74.0	73.0	74.0	76.5	74.0
(Min, max)	(41, 100)	(41, 100)	(41, 100)	(43, 100)	(40, 100)	(40, 100)
Surgery duration (minutes)						
N	93	91	91	93	94	462
Mean (SD)	32.3 (7.9)	31.8 (7.8)	32.5 (8.4)	32.3 (7.6)	33.1 (7.2)	32.4 (7.8)
Median	32.0	33.0	31.0	32.0	33.0	32.0
(Min, max)	(16, 51)	(14, 56)	(12, 68)	(15, 51)	(16, 50)	(12, 68)
Weight (kg)						
N	93	91	91	93	94	462
Mean (SD)	75.8 (17.4)	72.4 (15.4)	74.8 (16.8)	73.7 (17.8)	74.2 (16.0)	74.2 (16.7)
Median	72.6	69.4	70.9	70.5	72.1	70.9
(Min, max)	(49.1, 152.7)	(48.2, 114.5)	(48.5, 116.3)	(47.3, 127.0)	(49.5, 112.7)	(47.3, 152.7)
Height (cm)						
N	93	91	91	93	94	462
Mean (SD)	166.1 (9.7)	165.9 (9.4)	164.7 (8.9)	166.4 (8.1)	167.9 (8.1)	166.2 (8.9)
Median	165.1	165.1	165.1	165.1	167.6	165.1
(Min, max)	(144.8, 198.1)	(142.2, 188.0)	(147.3, 188.0)	152.4, 188.0)	(149.9, 185.4)	(142.2, 198.1
BMI (kg/m^2)						
N	93	91	91	93	94	462
Mean (SD)	27.3 (4.9)	26.1 (5.0)	27.4 (5.3)	26.4 (5.3)	26.1 (4.9)	26.7 (5.1)
Median	27.0	25.0	27.0	25.0	25.0	26.0
(Min, max)	(18, 39)	(20, 38)	(19, 39)	(17, 40)	(19, 39)	(17, 40)

Study IND3-10-06 (Source: Clinical Study Report Table 11- 1, 11-2)

Variable	Indomethacin Nanoformulation Capsules 40 mg TID (n = 94)	40 mg BID (n = 93)	20 mg TID (n = 92)	Placebo (n = 94)	Total (N = 373)
Age, years					
n	94	93	92	94	373
Mean (SD)	40.2 (12.27)	38.9 (12.50)	41.3 (12.57)	40.7 (11.32)	40.3 (12.16)
Median	40.0	37.0	41.5	41.0	39.0
Minimum, maximum	(18, 65)	(18, 64)	(18, 65)	(19, 65)	(18, 65)
Sex, n (%)					
Male	14 (14.9%)	16 (17.2)	15 (16.3)	11 (11.7)	56 (15.0)
Female	80 (85.1)	77 (82.8)	77 (83.7)	83 (88.3)	317 (85.0)
Race, n (%)					
American Indian or Alaska native	2 (2.1)	2 (2.2)	0	1 (1.1)	5 (1.3)
Asian	2 (2.1)	2 (2.2)	2 (2.2)	2 (2.1)	8 (2.1)
Black or African American	15 (16.0)	25 (26.9)	21 (22.8)	19 (20.2)	80 (21.4)
Native Hawaiian or other Pacific Islander	0	1 (1.1)	2 (2.2)	0	3 (0.8)
White or Caucasian	77 (81.9)	66 (71.0)	69 (75.0)	70 (74.5)	282 (75.6)
Other	0	0	1 (1.1)	2 (2.1)	3 (0.8)
Ethnicity, n (%)					
Hispanic or Latino	15 (16.0)	26 (28.0)	12 (13.0)	20 (21.3)	73 (19.6)
Not Hispanic or Latino	79 (84.0)	67 (72.0)	80 (87.0)	74 (78.7)	300 (80.4)
Weight, kg					
n	94	93	92	94	373
Mean (SD)	73.81 (14.686)	72.77 (15.761)	74.99 (17.821)	71.22 (14.607)	73.19 (15.758)
Median	72.95	70.90	70.25	68.40	70.40
Minimum, maximum	(45.0, 115.6)	(48.6, 128.6)	(48.2, 135.6)	(47.2, 131.1)	(45.0, 135.6)
Height, cm					
n	94	93	92	94	373
Mean (SD)	166.28 (8.059)	165.65 (8.994)	166.52 (9.761)	165.61 (7.646)	166.01 (8.621)
Median	165.10	165.10	165.10	165.10	165.10
Minimum, maximum	(147.3, 190.5)	(147.3, 188.0)	(147.3, 190.5)	(149.9, 195.6)	(147.3, 195.6)
Body mass index, kg/m^2					
n	94	93	92	94	373
Mean (SD)	26.5 (4.49)	26.3 (4.34)	26.7 (4.73)	25.8 (4.57)	26.3 (4.53)
Median	27.0	26.0	26.0	25.0	26.0
Minimum, maximum	(19, 38)	(19, 36)	(18, 39)	(19, 39)	(18, 39)
Baseline pain intensity, mm					
n	94	93	92	94	373
Mean (SD)	71.0 (16.33)	71.2 (16.11)	72.3 (15.90)	73.9 (16.60)	72.1 (16.21)
Median	71.0	70.0	72.5	71.5	71.0
Minimum, maximum	(41, 100)	(40, 100)	(43, 100)	(42, 100)	(40, 100)
Surgery duration, minutes					
n	94	93	92	94	373
Mean (SD)	27.7 (7.45)	27.6 (7.95)	28.5 (8.63)	27.2 (6.59)	27.7 (7.67)
Median	27.0	28.0	28.0	26.5	27.0
Minimum, maximum	(13, 60)	(15, 59)	(15, 82)	(16, 48)	(13, 82)

Signature/Distribution List

Primary Statistical Reviewer:	Yan Zhou, Ph.D. Mathematical Statistician
Concurring Reviewer:	Janice Derr, Ph.D. Team Leader
Date:	January 9, 2013

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

/s/

YAN ZHOU
01/09/2014

JANICE A DERR
01/09/2014

Statistics Filing Checklist
Division of Biometrics II

Date: 06/20/13

NDA #: 204-768 Priority Classification: S

Trade Name [redacted] (b) (4) (indomethacin submicron particle) Capsules

Applicant: Iroko Pharmaceuticals, LLC

Date of Submission: 04/30/13

Indication: treatment of mild to moderate acute pain in adults

No. of Controlled Studies: 3

User Fee Goal Date: 02/28/14

Date of 45-Day Meeting: 06/20/13

Medical Officer: Anjelina Pokrovnichka

Project Manager: Kimberly Compton

Statistical Reviewer: Yan Zhou, Ph.D.

Statistical sections: Sections 2.5, 2.7 and 5.3.5

Comments:

1. It is fileable.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**NA**
Appropriate references included for novel statistical methodology (if present)	**NA**
Data from primary studies in electronic data room	**Yes**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**Yes**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Sites	Sample Size	Type of Control	Design	Duration of Treatment
IND3-08-04b (02/2012 – 06/2012)	4	Randomization: (b) (4) 40 mg TID N = 93 (b) (4) 40 mg BID N = 91 (b) (4) 20 mg TID N = 91 Celecoxib N = 93 Placebo N = 94	Celecoxib placebo	Phase 3, randomized, double-blind, parallel group, multiple-dose, active and placebo-controlled, multicenter study in patients with acute postoperative pain after bunionectomy	48 hours
IND3-10-06 (05/2012 – 08/2012)	4	Randomization: (b) (4) 40 mg TID N = 94 (b) (4) 40 mg BID N = 93 (b) (4) 20 mg TID N = 92 Placebo N = 94	placebo	Phase 3, randomized, double-blind, parallel group, multiple-dose, placebo-controlled, multicenter study in patients with acute postoperative pain after bunionectomy	48 hours
IND2-08-03 (09/2009 – 11/2009)	3	Randomization: (b) (4) 40 mg N = 51 (b) (4) 20 mg N = 50 Celecoxib N = 51 Placebo N = 51	Celecoxib placebo	Phase 2, randomized, double-blind, parallel group, single-dose, active and placebo-controlled, multicenter study in patients with acute dental pain after third molar extraction	8 hours

_____

Zhou, Yan
Mathematical Statistician

Concur: Janice Derr, Ph.D.
Team Leader

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

/s/

YAN ZHOU
06/21/2013

JANICE A DERR
06/21/2013