

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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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 204-592

Drug Name: Zorvolex (diclofenac acid)

Indication(s): Treatment of mild to moderate acute pain

Applicant: Iroko Pharmaceuticals, LLC

Date(s): Letter date: December 21, 2012, PDUFA date: October 20 , 2013

Review Priority: Standard

Biometrics Division: II

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1. EXECUTIVE SUMMARY

Iroko Pharmaceuticals, LLC submitted a New Drug Application for Zorvolex, a new formulation of diclofenac, seeking an indication for the treatment of mild to moderate acute pain. A Phase 3 efficacy study in patients with acute pain after bunionectomy was submitted to support the efficacy of Zorvolex. Based on my review, the study provided evidence that both Zorvolex 35 mg and 18 mg three times daily have an analgesic effect in the desired indication in comparison to placebo.

The clinical development program of Zorvolex was discussed at several meetings. In January 2010, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) issued an agreement letter for the Special Protocol Assessment (SPA) on the Phase 3 efficacy study DIC3-08-04. At the End-of-Phase 2 meeting, the applicant was informed that reliance on prior findings of efficacy for another diclofenac product and the Study DIC3-08-04 may be adequate to support an efficacy claim for the proposed indication.

Study DIC3-08-04 was a randomized, double-blind, multicenter, parallel, active and placebo-controlled study evaluating the efficacy and safety of two dosing regimens of Zorvolex in subjects with acute postoperative pain after bunionectomy. A total of 428 subjects were randomized equally to one of the four treatments for 48 hours: Zorvolex 35 mg three times daily (TID), Zorvolex 18 mg TID, celecoxib capsules 200 mg twice daily (BID), or placebo. One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted every 4 to 6 hours as the rescue medication. The primary efficacy variable was the time-weighted sum of pain intensity difference from baseline over 48 hours after the first dose. The primary efficacy variable was analyzed using an analysis of covariance 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 two doses of Zorvolex with placebo.

The study demonstrated the superiority of both Zorvolex 35 mg TID and 18 mg TID over placebo in pain intensity reduction. However, a high percentage of subjects in each treatment group took rescue medication at least once during the study. Approximately 82% of the subjects in the Zorvolex 35 mg group, 85% of the subjects in the Zorvolex 18 mg group, 85% of the subjects in celecoxib group and 97% of the subjects in the placebo group took rescue medication for pain management during the study. This might be due to the slow onset of analgesic action. For all the treatment groups including the active control, onset of analgesia occurred in less than 40% of the subjects. Approximately only 31% of the subjects in the Zorvolex 35 mg group, 25% of the subjects in the celecoxib group, 24% of the subjects in the Zorvolex 18 mg group, and 18% of the subjects in the placebo group experienced onset of analgesia within 1 hour after the first dose.

2. INTRODUCTION

2.1 Overview

Diclofenac is an approved drug in the United States as a treatment for multiple indications including mild to moderate pain. Iroko Pharmaceuticals, LLC (Iroko) is developing Zorvolex, a new formulation of diclofenac in the acid form, for the treatment of mild to moderate acute pain. Zorvolex is being filed as a 505(b)(2) application and relies on the previous findings of Cataflam safety and efficacy. The applicant believes that the new formulation improves the dissolution and absorption of diclofenac. The applicant purports that Zorvolex provides comparable pain relief to Cataflam 50 mg at a 20% lower dose of diclofenac and thus potentially leads to an improved safety profile.

The clinical development program of Zorvolex capsule was discussed at several meetings under IND 103,880. In December 2009, the applicant submitted a Special Protocol Assessment (SPA) for the Phase 3 study DIC3-08-04. In January 2010, the division issued an agreement letter on the Phase 3 efficacy study. In the agreement letter, the division stated that the secondary outcome variables for which no adjustment for multiplicity is planned are considered exploratory and therefore would not support a label claim. In addition, the applicant was advised that any comparative claims will require replicated demonstration of superiority over the same comparator. During the clinical development, the applicant referred to the new formulation as (b) (4). At the End-of-Phase 2 meeting in December 2010, the division informed the applicant that the drug product does not meet the agency's definition of a (b) (4). Furthermore, the division stated that reliance on prior findings of efficacy for another diclofenac product for acute pain and the proposed Phase 3 efficacy study DIC3-08-04 for the treatment of acute postoperative pain after bunionectomy may be adequate to support an efficacy claim for this indication.

2.2 Data Sources

The statistical review is based on data submitted for Study DIC3-08-04. The study data can be found at <\\Cdsub1\evsprod\NDA204592\0000\m5\datasets\dic3-08-04>.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted study tabulation datasets SDTM and analysis datasets AdaM in CDISC format. The submitted datasets and define documents are of acceptable quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study DIC3-08-04 was a Phase 3, randomized, double-blind, multicenter, parallel, active and placebo-controlled study evaluating the efficacy and safety of two dosing regimens of Zorvolex capsules in subjects with acute postoperative pain after bunionectomy. Subject who had a pain intensity rating ≥ 40 mm on a 100-mm Visual Analog Scale (VAS) within 9 hours of discontinuation of regional anesthesia were to be eligible. Eligible subjects were randomized equally to one of the four treatments: Zorvolex 35 mg TID, Zorvolex 18 mg TID, celecoxib capsules 200 mg BID, or placebo. Study drug was administered for 48 hours after the first dose.

Pain intensity and pain relief assessments were recorded in the inpatient subject diary at scheduled times during the 48-hour period after the first dose (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 before the 8-hour time point. Pain intensity was assessed based on 100-mm Visual Analog Scale (VAS). Pain relief was assessed based on 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 confirmed by meaningful pain relief. Pain intensity and pain relief assessments were also recorded before premature study termination. Subjects completed a patient's global evaluation of study drug at the end of the treatment period (Day 3) or immediately before the first dose of rescue medication (whichever occurs first).

One tablet of hydrocodone/acetaminophen 10 mg/325 mg was permitted as the rescue medication. If subjects were unable to tolerate hydrocodone/acetaminophen 10 mg/325 mg, then one tablet of oxycodone/acetaminophen 7.5 mg/325 mg was permitted orally every 6 hours as needed for pain management. The total daily dosage of rescue medication was not to exceed 6 tablets.

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 (measured as time to perceptible pain relief confirmed by meaningful pain relief), time to rescue, and total amount of rescue.

3.2.2 Statistical Methodologies

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with baseline pain score 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 two doses of diclofenac with placebo. Zorvolex 35 mg was compared to placebo first. Zorvolex 18 mg was compared to placebo only if Zorvolex 35 mg was significantly better than placebo. There were no comparisons between Zorvolex and celecoxib in the primary analysis.

Missing pain assessments for subjects who discontinued early due to lack of efficacy or adverse events were imputed using a baseline observation carried forward approach (BOCF). Missing pain assessments due to other reasons were imputed using a last observation carried forward approach (LOCF). For subjects who took any dose of rescue medication, subsequent pain

assessments after the first dose of rescue medication were disregarded and imputed using a BOCF approach. Intermittent missing pain assessments were imputed using linear interpolation.

The applicant conducted a sensitivity analysis for the primary efficacy analysis by adding gender as a factor into the ANCOVA model. Sensitivity analyses for the methods to handling missing values were not conducted.

Time to onset of analgesia was right censored at 8 hours for subjects who did not experience both perceptible pain relief and meaningful pain relief during the 48-hour interval or who required rescue medication prior to achieving perceptible or meaningful pain relief.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 428 subjects were randomized. All randomized subjects received the study medications. The subject disposition is shown in Table 1 with percentages based on the number of randomized subjects. Overall, a total of 421 (98%) subjects completed the study. No subjects in the Zorvolex 18 mg group discontinued the study early. Both the Zorvolex 35 mg and the celecoxib groups had one subject discontinued early due to investigator decision and subject request, respectively. Five subjects (5%) in the placebo group discontinued the study early, three of which due to lack of efficacy.

Table 1: Subject Disposition – Number (%) of Patients

	Zorvolex		Celecoxib BID	Placebo
	35 mg TID	18 mg TID		
Randomized	107	109	106	106
Completed	106 (99%)	109 (100%)	105 (99%)	101 (95%)
Discontinued	1 (1%)	0	1 (1%)	5 (5%)
Reason for discontinuation				
Subject request				1 (1%)
Investigator decision	1 (1%)			
Lack of efficacy			1 (1%)	3 (3%)
Lost to follow-up				1 (1%)

Source: Clinical study report (Table 14.1.1)

The demographic and baseline characteristics were generally comparable across treatment groups. A summary of selected demographic and baseline characteristics is provided in Table 2. The summary for race was reproduced using the applicant’s dataset, which differed slightly from the clinical study report. The majority of the subjects were female and white. Overall, the mean age was about 40 years. Approximately 85% of the subjects were white.

Table 2: Summary of Demographics and Baseline Characteristics

	Zorvolex			
	35 mg TID	18 mg TID	Celecoxib BID	Placebo
	N=107	N=109	N=106	N=106
Mean age (SD)	39 (12)	39 (12)	40 (12)	40 (13)
Mean weight (SD) (kg)	77 (19)	75 (17)	72 (16)	73 (14)
Mean height (SD) (cm)	167 (9)	167 (9)	165 (8)	167 (8)
Mean BMI (SD) (kg/m ²)	27 (6)	27 (5)	26 (5)	26 (5)
Baseline pain - mean (SD)	74 (16)	77 (16)	74 (17)	76 (16)
- (Min, Max)	(44, 100)	(41, 100)	(40, 100)	(40, 100)
Gender, n (%)				
Male	18 (17%)	15 (14%)	10 (9%)	14 (13%)
Female	89 (83%)	94 (86%)	96 (91%)	92 (87%)
Ethnicity, n (%)				
Hispanic or Latino	19 (18%)	24 (22%)	18 (17%)	17 (16%)
Not Hispanic or Latino	88 (82%)	85 (78%)	88 (83%)	89 (84%)
Race, n(%)				
Black or African American	17 (16%)	19 (17%)	22 (21%)	19 (18%)
White or Caucasian	84 (78%)	86 (79%)	73 (69%)	79 (74%)
Other	6 (6%)	4 (4%)	11 (10%)	8 (8%)

Source: Clinical study report (Table 14.1.2) and applicant's datasets; SD: standard deviation.

3.2.4 Results and Conclusions

I replicated the applicant's results for the primary efficacy analysis. Table 3 shows the results from the primary efficacy analysis. Both Zorvolex 35 mg and 18 mg were superior to placebo in terms of the primary efficacy endpoint. 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

Statistics	Zorvolex			
	35 mg TID	18 mg TID	Celecoxib BID	Placebo
n	107	109	106	106
LS Mean (SE)	524 (86)	393 (85)	390 (86)	77 (86)
95% CI	(355, 693)	(225, 561)	(220, 560)	(-93, 247)
Difference in LS mean(SE)	447 (122)	316 (121)	313 (122)	
95% CI for diff. in LS mean	(207, 687)	(77, 555)	(72, 554)	
p-value for treatment effect	<0.001	0.01	0.01	

Source: Clinical study report (Table 14.2.1.1); SE: standard error; CI: confidence interval; LS: least square.

The applicant used a hybrid LOCF/BOCF approach to impute pain scores after early discontinuation. Although it is a single imputation method, I am not concerned about it in this study as very few subjects (2%) discontinued early. The applicant replaced all the pain scores after the first use of the rescue medication with the baseline observations. When the percentage of subjects who take rescue medications is high, the approach to handling the pain scores after rescue may substantially influence the comparisons among treatments. In the acute pain setting, it is often likely that subjects will take rescue medications. Table 4 presents the percentage of subjects who took rescue medications for pain management during the study. For all treatment groups, more than 80% of the subjects took rescue. Placebo group had the highest percentage of subjects who took rescue. The majority of the subjects took their first rescue within 8 hours after the first dose, that is, before the second dose of the study medication. Figure 1 depicts the average pain intensity over time for each treatment group during the 48 hours after the first dose with pain scores after rescue imputed using a BOCF approach. Although the placebo group had the worst pain on average, there was not much pain reduction for all treatment groups. All the pain curves are rather flat after 10 hours. This is because the majority of the subjects took rescue during the first 8 hours and their pain scores after the first rescue were replaced by the corresponding baseline values.

Table 4: Rescue Medication – Number (%) of Subjects

	Zorvolex		Celecoxib BID	Placebo
	35 mg TID	18 mg TID		
Randomized	107	109	106	106
Subjects who took rescue	88 (82%)	93 (85%)	90 (85%)	103 (97%)
Subjects who took rescue within 8 hours after first dose	84 (78%)	88 (81%)	87 (82%)	101 (95%)

Source: applicant's datasets

Figure 1: Average Pain Over Time – BOCF After Rescue

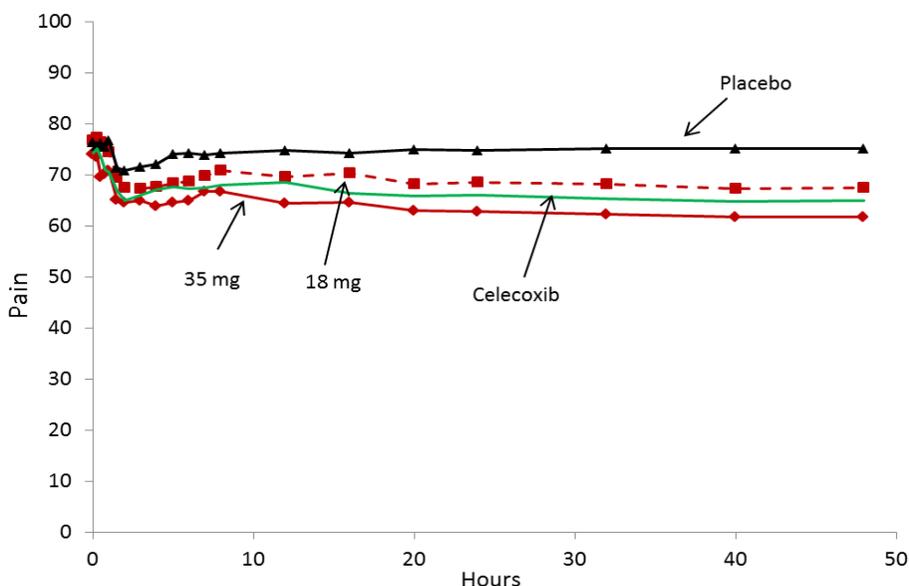


Figure 2 displays the average pain intensity over time for each treatment group without imputation for taking rescue, that is, the actual observed pain scores after rescue were used. The overall trend of actual pain reduction over time is apparent for each treatment group. Among the treatments, subjects 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. To compare the treatment effects under the influence of rescue medications in terms of the primary efficacy endpoint, I calculated the summed pain intensity difference over 48 hours using the observed pain scores after rescue and conducted an analysis using the same ANCOVA model as the one used in the primary analysis. The analysis results are presented in Table 5. 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.

Figure 2: Average Pain Over Time – No Imputation After Rescue

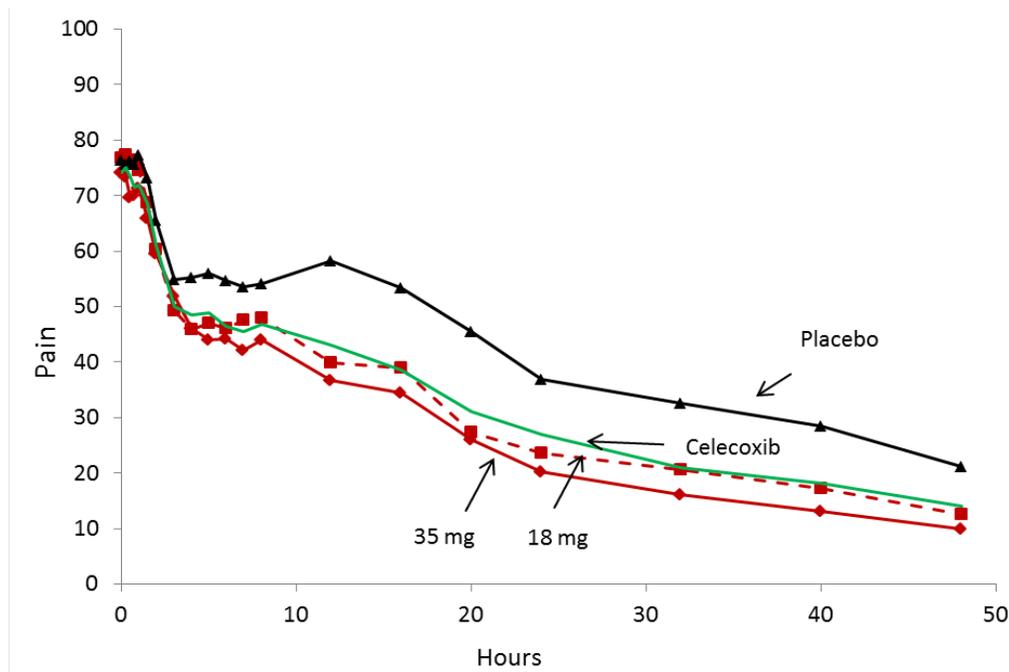


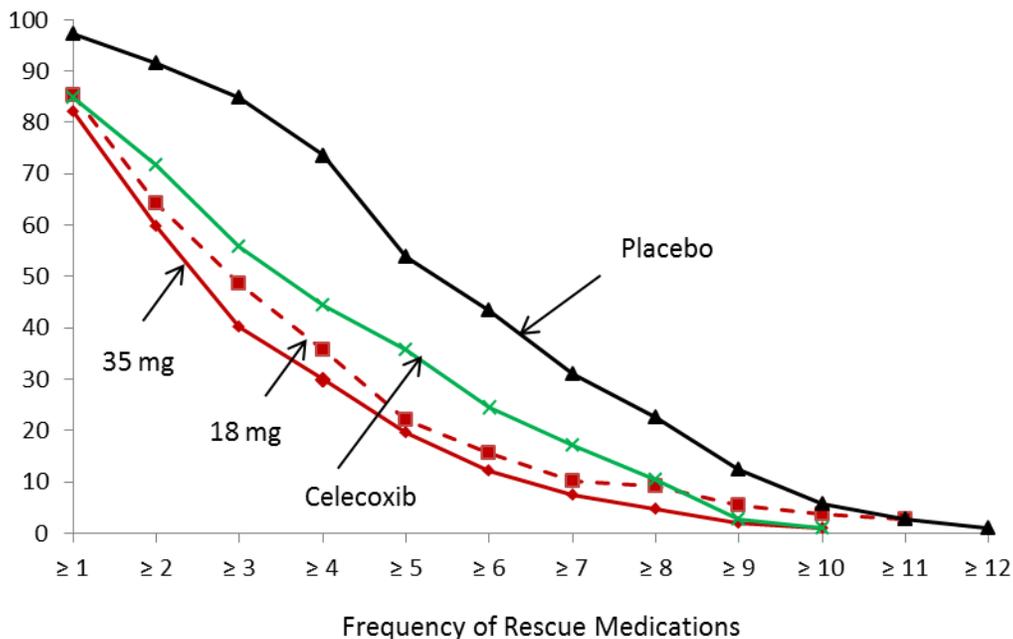
Table 5: Additional Efficacy Analysis for VASSPID48 – No Imputation After Rescue

Statistics	Zorvolex			Placebo
	35 mg TID	18 mg TID	Celecoxib BID	
n	107	109	106	106
LS Mean (SE)	2392 (82)	2293 (81)	2159 (82)	1661 (82)
95% CI	(2232,2553)	(2134,2452)	(1997,2320)	(1499,1823)
Difference in LS mean(SE)	731 (116)	632 (115)	498 (116)	
95% CI for diff. in LS mean	(503,960)	(405,859)	(269,726)	
p-value for treatment effect	<0.0001	<0.0001	<0.0001	

SE: standard error; CI: confidence interval; LS: least square.

To further compare the usage of rescue medication, I depicted the percentages of subjects who took rescue medications for pain control over different frequencies of rescue administration for each treatment group in Figure 3. There was consistently higher percentage of subjects in the placebo group than in the active treatment groups for each category of frequency. For example, approximately 85% of the subjects in the placebo group took rescue at least 3 times. In contrast, about 40% of the subjects in the Zorvolex 35 mg, 50% in the Zorvolex 18 mg, and 55% in the celecoxib groups took rescue medication at least 3 times.

Figure 3: Percentage of Subjects with Different Frequency of Rescue Use



For handling pain scores after taking rescue medications, DAAAP currently recommends replacing the pain scores that might be affected by the rescue medications with the pre-rescue pain score for efficacy analyses to minimize the impact of rescue medication. Thus, I conducted additional analyses in which the pain scores within a time window after taking a rescue medication were replaced with the pre-rescue pain score. Table 6 presents the results from an analysis in which the pain scores within 6 hours after rescue were replaced with the pre-rescue score. The analyses results were in favor of the active treatments. The pain curves showed the similar pattern as that observed in Figure 2. My analyses using different lengths of time window (such as 4 or 8 hours) yielded similar results.

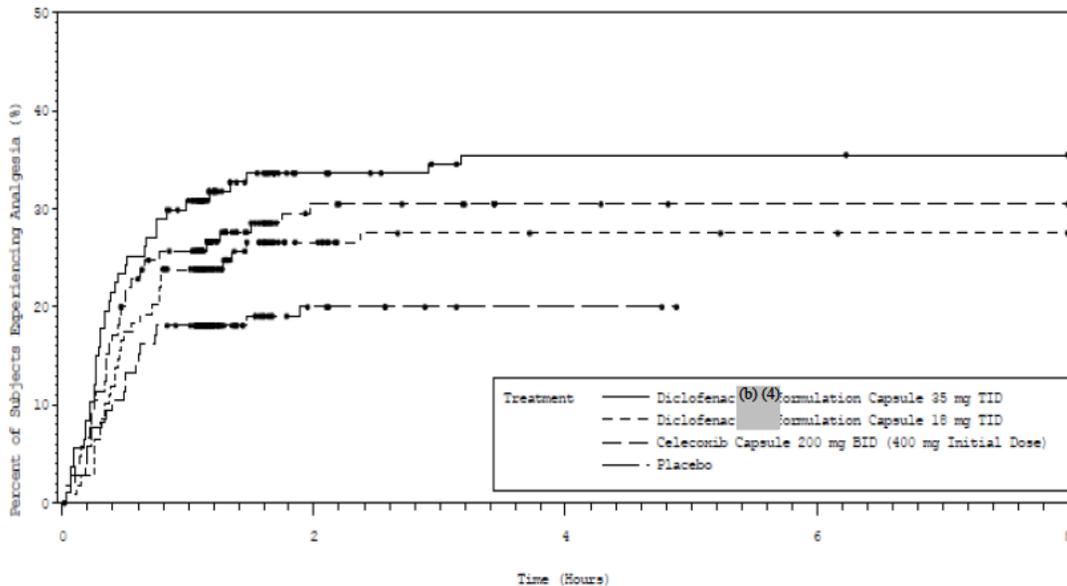
Table 6: Additional Efficacy Analysis for VASSPID48 – Pre-rescue Score Carried Forward for 6 hours

Statistics	Zorvolex		Celecoxib BID	Placebo
	35 mg TID	18 mg TID		
n	107	109	106	106
LS Mean (SE)	2221(82)	2097(81)	1976(83)	1407(83)
95% CI	(2060,2383)	(1937,2257)	(1813,2138)	(1245,1569)
Difference in LS mean(SE)	814(117)	690(116)	569(117)	
95% CI for diff. in LS mean	(585,1043)	(462,918)	(339,798)	
p-value for treatment effect	<0.0001	<0.0001	<0.0001	

SE: standard error; CI: confidence interval; LS: least square.

The cumulative distribution of time to onset of analgesia for each treatment group is shown in Figure 4. For all the treatment groups, onset of analgesia occurred in less than 40% of the subjects. Among the treatment groups, the Zorvolex 35 mg group had the highest percentage of subjects who experienced onset of analgesia whereas the placebo group had the lowest percentage. Approximately 31% of the subjects in the Zorvolex 35 mg group, 25% of the subjects in the celecoxib group, 24% of the subjects in the Zorvolex 18 mg group, and 18% of the subjects in the placebo group experienced onset of analgesia within 1 hour after the first dose.

Figure 4: Cumulative Distribution of Time to Onset of Analgesia



Source: Clinical Study Report (Figure 14.2.4)

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

3.3 Evaluation of Safety

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

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant performed the subgroup analyses of the primary endpoint by age, race and gender using the per-protocol population (PP). I conducted subgroup summaries by gender, age, and race for all the randomized subjects. For age, subjects were classified as ≤ 45 or >45 years old. For race, subjects were categorized as black, white or other races. The findings from the subgroups summaries were consistent with those observed in the overall population. All the active treatment groups were numerically better than the placebo group in the subpopulations.

4.1 Gender, Age and Race

Table 7 shows the subgroup summaries for gender, age and race.

Table 7: Subgroup Summaries of Primary Endpoint

Subgroups	Statistics	Zorvolex			
		35 mg TID (N=107)	18 mg TID (N=109)	Celecoxib BID (N=106)	Placebo (N=106)
Sex					
Female	n (%)	89 (83%)	94 (86%)	96 (91%)	92 (87%)
	Mean (SD)	479 (1109)	375 (922)	353 (888)	77 (350)
Male	n (%)	18 (17%)	15 (14%)	10 (9%)	14 (13%)
	Mean (SD)	751 (1326)	505 (1057)	746 (1228)	79 (286)
Age					
≤ 45	n (%)	71 (66%)	74 (68%)	71 (67%)	68 (64%)
	Mean (SD)	415 (970)	346 (921)	254 (746)	34 (152)
>45	n (%)	36 (34%)	35 (32%)	35 (33%)	38 (36%)
	Mean (SD)	739 (1423)	492 (977)	667 (1174)	154 (527)
Race					
Black or African American	n (%)	17 (16%)	19 (17%)	22 (21%)	19 (18%)
	Mean (SD)	1120 (1658)	533 (1075)	120 (517)	60 (246)
White or Caucasian	n (%)	84 (79%)	86 (79%)	73 (69%)	79 (75%)
	Mean (SD)	399 (961)	343 (876)	477 (1025)	87 (376)
Other	n (%)	6 (6%)	4 (4%)	11 (10%)	8 (8%)
	Mean (SD)	596 (1490)	808 (1583)	356 (799)	20 (70)

4.2 Other Special/Subgroup Populations

No other subgroup summaries were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The applicant used a hybrid LOCF/BOCF method to impute pain scores after early discontinuation. In 2010, the National Academy of Science (NAS) released a report on missing values. The report does not recommend single imputation approaches for imputing missing values due to dropouts for reasons including the difficulty to justify the underlying assumptions and the underestimation of the uncertainty of missing observation. Although the proposed LOCF/BOCF method is a single imputation method, I am not concerned about it in this study as very few subjects (2%) discontinued early.

To account for the influence of rescue medication, the applicant replaced all pain scores after the first use of the rescue medication with the baseline values. In this study, more than 80% of the subjects took rescue and the majority of them used rescue within several hours after the first dose. Thus, I was initially concerned about the applicant's method for handling the pain scores after rescue as the difference between treatments in terms of the primary endpoints might be purely driven by the differential percentages of subjects who took rescue. My concern was alleviated after my sensitivity analyses including the pain scores after rescue or replacing the pain scores affected by rescue with the pre-rescue pain score also yielded statistically significant results.

5.2 Collective Evidence

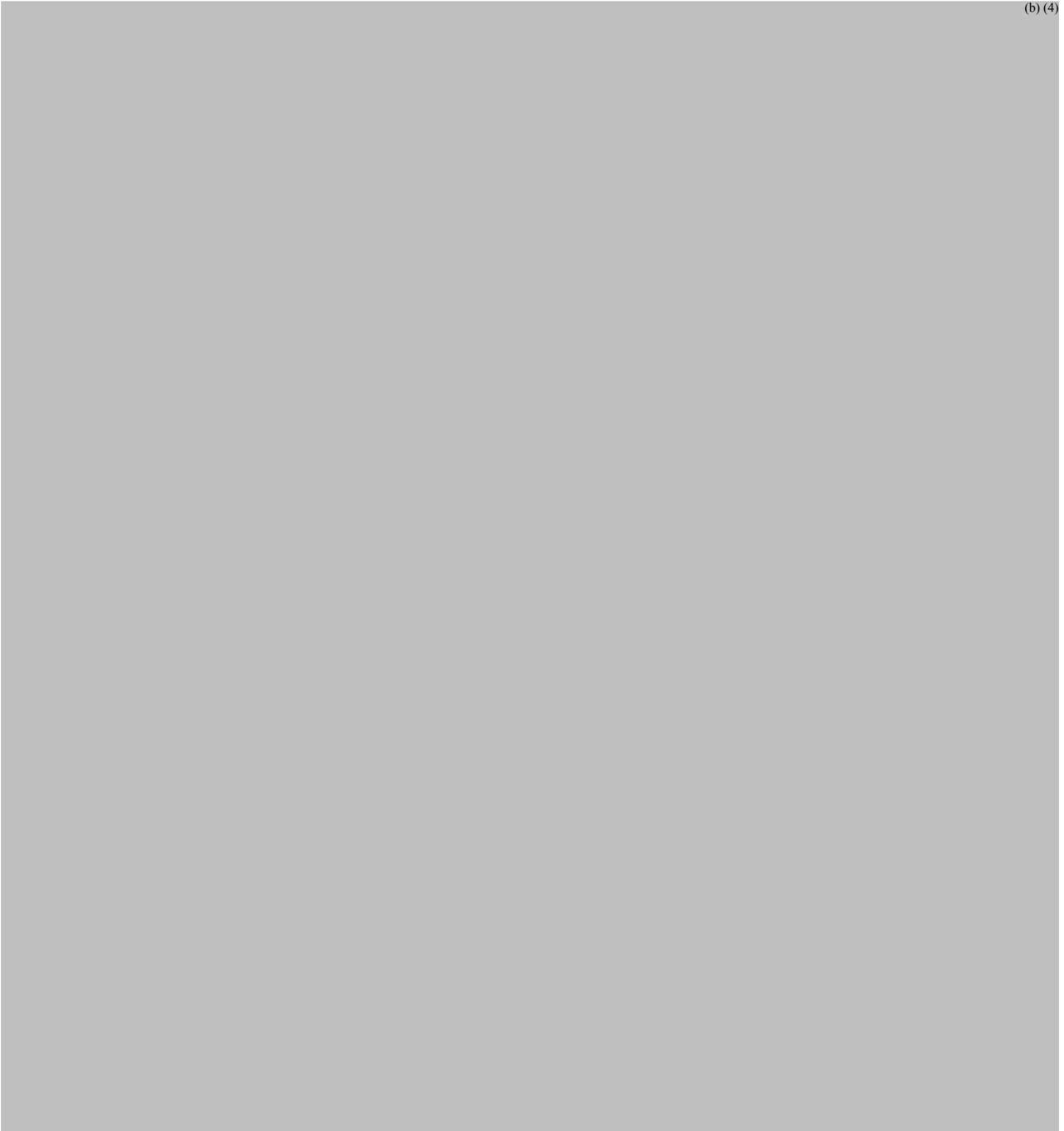
There was statistically significant difference between each dose of Zorvolex and placebo in terms of the sum of pain intensity difference over 48 hours. The results were not sensitive to the methods for handling missing values or the pain scores after rescue use. The secondary endpoints were also consistently in favor of Zorvolex in comparison to placebo. All the treatment groups had high percentages of subjects who took rescue for pain control. The Zorvolex groups had similar percentages of subjects who used rescue as the active control, celecoxib. The placebo group used more rescue than the active treatment group.

5.3 Conclusions and Recommendations

The study has demonstrated that both Zorvolex 35 mg and 18 mg were more efficacious than placebo in acute pain reduction. The review team will need to consider the totality of evidence including findings from clinical pharmacology to decide whether the benefit-risk profile justify the approval of the product. Since high percentage of subjects also took rescue medication for pain management during the study, I would recommend the applicant include the information about the rescue medication and the percentage of subjects who used rescue in the clinical study section of the label if the division decides to approve the product.

5.4 Labeling Recommendations

The applicant submitted the following wording for the clinical study section of the label for review:





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

/s/

FENG LI
09/11/2013

JANICE A DERR
09/11/2013

STATISTICS FILING CHECKLIST FOR NDA 204-592

NDA Number: 204-592 Applicant: Iroko Pharmaceuticals Stamp Date: Dec 20, 2012

Drug Name: diclofenac NDA/BLA Type: 505(b)(2)

On **initial** overview of the sNDA (resubmission): **Study DIC3-08-04**

	Content Parameter	Yes	No	NA	Comments
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		See comment 1
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

Comments:

1. The safety data was not examined for differences due to gender, race, or age. The clinical review team requested this information.

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 NDA 204-592

Study DIC3-08-04 was conducted to support the efficacy of diclofenac for treating post-operative pain after bunionectomy surgery. This was a randomized, double-blind, placebo- and active-controlled, 24-week study that was conducted at four sites in the United States. On Day 1 following surgery, the regional anesthetic nerve block was discontinued. Patients that had a pain intensity rating (100 mm VAS) of at least 40 mm on a 100 mm VAS were randomized to one of four treatments; placebo, diclofenac 18 mg, diclofenac 35 mg, or Celecoxib, in a 1:1:1:1 fashion. The primary efficacy endpoint was the summed pain intensity difference at 48 hours. The primary analysis, ANCOVA with treatment and the baseline pain score, was conducted using all randomized patients that received at least one dose of study drug. To account for multiple doses of diclofenac, the applicant used a sequential testing procedure. The 35 mg dose was compared to placebo first. If a significant difference was noted, p -value < 0.05 , the 18 mg dose was compared to placebo. The active control, Celecoxib, was not compared to placebo for the primary endpoint.

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/s/

DAVID M PETULLO
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