

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204592Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 204592
Priority or Standard Standard

Submit Date(s) December 20, 2012
Received Date(s) December 20, 2012
PDUFA Goal Date October 20, 2013
Division / Office DAAAP/ODE II

Reviewer Name(s) Steven Galati M.D.
Review Completion Date September 17, 2013

Established Name Diclofenac
(Proposed) Trade Name Zorvolex
Therapeutic Class NSAID
Applicant Iroko Pharmaceuticals

Formulation(s) Capsule
Dosing Regimen 18-35mg taken TID
Indication(s) Treatment of acute mild to moderate pain
Intended Population(s) Patients with mild to moderate acute pain

Table o Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	7
1.4	Recommendations for Postmarket Requirements and Commitments	7
2	INTRODUCTION AND REGULATORY BACKGROUND	7
2.1	Product Information	7
2.2	Tables of Currently Available Treatments for Proposed Indications	7
2.3	Availability of Proposed Active Ingredient in the United States	8
2.4	Important Safety Issues With Consideration to Related Drugs.....	8
2.5	Summary of Presubmission Regulatory Activity Related to Submission	9
2.6	Other Relevant Background Information	11
3	ETHICS AND GOOD CLINICAL PRACTICES.....	11
3.1	Submission Quality and Integrity	11
3.2	Compliance with Good Clinical Practices	11
3.3	Financial Disclosures.....	13
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	13
4.4	Clinical Pharmacology.....	13
5	SOURCES OF CLINICAL DATA.....	14
5.1	Tables of Studies/Clinical Trials	14
5.2	Review Strategy	15
5.3	Discussion of Individual Studies/Clinical Trials.....	15
6	REVIEW OF EFFICACY	48
	Efficacy Summary.....	48
6.1	Indication.....	49
6.1.1	Methods	49
6.1.2	Demographics.....	49
6.1.3	Subject Disposition	49
6.1.4	Analysis of Primary Endpoint(s)	49
6.1.5	Analysis of Secondary Endpoints(s).....	53
6.1.7	Subpopulations	54
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ...	55
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	55
6.1.10	Additional Efficacy Issues/Analyses.....	55

7	REVIEW OF SAFETY	55
	Safety Summary	55
7.1	Methods	56
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	56
7.1.2	Categorization of Adverse Events	56
7.2	Adequacy of Safety Assessments	57
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	57
7.2.2	Explorations for Dose Response	57
7.2.4	Routine Clinical Testing	57
7.3	Major Safety Results	57
7.3.1	Deaths	57
7.3.2	Nonfatal Serious Adverse Events	58
7.3.3	Dropouts and/or Discontinuations	58
7.3.4	Significant Adverse Events	58
7.4	Supportive Safety Results	59
7.4.1	Common Adverse Events	59
7.4.3	Vital Signs	60
7.4.5	Special Safety Studies/Clinical Trials	61
7.5	Other Safety Explorations	61
7.5.1	Dose Dependency for Adverse Events	61
7.5.2	Time Dependency for Adverse Events	61
7.5.3	Drug-Demographic Interactions	61
7.6	Additional Safety Evaluations	63
7.6.3	Pediatrics and Assessment of Effects on Growth	63
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	65
7.7	Additional Submissions / Safety Issues	66
8	POSTMARKET EXPERIENCE	67
9	APPENDICES	68
9.1	Literature Review/References	68
9.2	Labeling Recommendations	68
9.3	Advisory Committee Meeting	70
	APPENDIX	71

Table of Tables

Table 1: Brand Name Diclofenac Products and Indications	8
Table 2: Key Presubmission Regulatory Activity	9
Table 3: OSI Inspected Clinical Sites	12
Table 4: Results of the OSI Review by Site.....	13
Table 5: Clinical Trials Submitted in Support of this Application.....	14
Table 6: Dosing of Treatment Groups DIC3-08-04.....	17
Table 7: Schedule of Events	22
Table 8: Demographic Characteristics – Safety Population	28
Table 9: Summary of Baseline Characteristics – Safety Population.....	29
Table 10: Summary of Major Protocol Violations	30
Table 11: Applicants Statistical Analysis (ANCOVA) of ITT Population.....	32
Table 12: Model 2: Gender as Covariate.....	34
Table 13: Analysis of the Visual Analogue Scale Summed Pain Intensity Difference Over 0 to 4 Hours, 0 to 8 Hours, and 0 to 24 Hours—Intent-to-Treat Population	36
Table 14: Analysis of Total Pain Relief Over 0 to 4 Hours, 0 to 8 Hours, 0 to 24 Hours, and Over 0 to 48 Hours — Intent-to Treat Population	37
Table 15: Time to Onset of Analgesia (Measured as Time to Perceptible Pain Relief Confirmed by Meaningful Pain Relief) — Intent-to-Treat Population.....	39
Table 16: Summary of Peak Pain Relief — Intent-to-Treat Population	41
Table 17: Time to Meaningful Pain Relief – ITT Population	42
Table 18: Time to First Use of Rescue Medication — Intent-to-Treat Population.....	43
Table 19: Patient’s Global Evaluation of Trial Drug — ITT Population	44
Table 20: Study Schedule	46
Table 21 – Rescue in DIC3-08-04	50
Table 22 – Sensitivity Analysis of SPID48 Using Observed Pain Scores Regardless of Rescue	50
Table 23: Additional Efficacy Analysis for VASSPID48 – Pre-rescue Score Carried Forward for Six hours	53
Table 24: Subgroup Analysis on the Primary Endpoint.....	54
Table 25: Summary of Severe Treatment-Emergent Adverse Events by Preferred Term	58
Table 26: Summary of Most Frequent Treatment-Emergent Adverse Events (5% or More of Subjects in Any Treatment Group) by Preferred Term — Safety Population ...	60
Table 27: Subgroup Analysis by Age – Safety Population	62
Table 28: Summary of Most Frequent Treatment Emergent Adverse Events (5% or More of Subjects in Any Diclofenac Treatment Group) by Preferred Term — Study DIC3-08-04 - Safety Population with Overall Population and Subgroups by Gender	62
Table 29: Proposed Timeline for Pediatric Studies	65
Table 30: Additional Requested Clinical Submissions to NDA 204592	66

Table of Figures

Figure 1: Subject Disposition for Controlled Trial DIC3-08-04.....	27
Figure 2: VASSPID-48 Results in the ITT population with Baseline Pain as Only Covariate.....	33
Figure 3: Time to Onset of Analgesia – ITT Population.....	40
Figure 4: Average Pain Over Time – BOCF After Rescue	51
Figure 5: Average Pain Over Time Using Observed Pain Scores (No Imputation)	52
Figure 6: Percentage of Subjects with Different Frequency of Rescue Medications	53

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval with revisions to the proposed label.

1.2 Risk Benefit Assessment

The Applicant submitted the results of a pivotal Phase 3 trial using the to-be-marketed formulation, in conjunction with the Agency's previous findings of safety and efficacy for the reference drug Cataflam (NDA 020142), for the treatment of acute mild to moderate pain. I have determined that this trial was designed and conducted in a reasonably adequate and well-controlled fashion that is sufficient to rely upon for a determination of efficacy and safety. The data reviewed, in the pivotal controlled clinical trial, in patients with acute pain after bunionectomy, support the effectiveness of diclofenac acid capsules for the treatment of acute pain in this population as evidenced by the statistical significance of the primary endpoint compared to placebo and the clinically meaningful benefit of this finding. The safety data did not demonstrate any new safety signal beyond what is already known for diclofenac. The safety profile for the intended patient population is acceptable.

Benefits:

- Evidence of effectiveness was established in a single, pivotal, placebo-controlled trial using the primary endpoint, VAS summed pain intensity difference (VASSPID) over 0 to 48 hours and was further confirmed in a sensitivity analysis on this endpoint using observed pain scores (see Section 6 for more details).
- The primary efficacy analysis is further supported by results in favor of diclofenac on various secondary endpoints.
- Diclofenac is a well-established analgesic and this dosage form offers an additional treatment option for patients with mild to moderate acute pain.

Risks:

- No new safety signal was identified in review of this application.
- The most commonly reported adverse events were postprocedural edema and nausea. Review of the safety data does not suggest a relationship between these events and diclofenac. Edema was likely related to the bunionectomy, and it occurred at approximately the same frequency across all groups. Nausea was most common in the placebo group, likely due to the increase in opioid rescue in that group.

Overall, the risk-benefit profile of diclofenac acid capsules in this population is favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have identified no further safety issues in the review of this application that warrant additional postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The following pediatric studies are required:

- Study 1: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 6 to < 17 years of age with acute pain.
- Study 2: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain.
- Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain.

2 Introduction and Regulatory Background

2.1 Product Information

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Diclofenac is a potent inhibitor of both COX-1 and COX-2. The efficacy of diclofenac is associated with the inhibition of COX-2 while the adverse effects of diclofenac are probably related to inhibition of COX-1, which causes a decrease in prostaglandin synthesis. The Applicant developed a new formulation (as an acid form called Zorvolex) of diclofenac capsules in 18mg and 35mg doses to be taken three times per day. This new formulation was studied in a single, pivotal trial in patients with acute pain after bunionectomy.

Zorvolex (diclofenac acid capsules) are immediate release capsules with the proposed indication for the treatment of mild to moderate pain in adults. The Applicant's rationale for developing Zorvolex is that they purport their technology significantly reduces particle size promoting the dissolution and absorption of diclofenac. The Applicant believes the improved dissolution properties of Zorvolex are associated with rapid absorption resulting in comparable pain relief to Cataflam 50 mg tablets at a 20% lower dose of diclofenac than Cataflam 50 mg tablets. They also purport that the lower dose may have the potential for an improved safety profile compared with Cataflam 50 mg tablets.

2.2 Tables of Currently Available Treatments for Proposed Indications

Alternative treatment options include other prescription strength NSAIDs and acetaminophen.

2.3 Availability of Proposed Active Ingredient in the United States

Multiple approved drug products containing the active ingredient diclofenac are available and marketed in the United States as a treatment for multiple indications (Table 1).

Table 1: Brand Name Diclofenac Products and Indications

Drug Product Name	NDA	Approval Date	Dose Form	Indication
Zipsor	22202	06/16/2009	Capsule	Relief of mild to moderate pain
Pennsaid	20947	11/04/2009	Lotion	Treatment of signs and symptoms of osteoarthritis
Diclofenac Patch	21234	01/31/2007	Patch	Treatment of pain in minor sports injuries
Voltaren Gel	22122	10/17/2007	Gel	Treatment of osteoarthritis of joints amenable to superficial treatment such as the hands and knees
Voltaren	19201	07/28/1988	Tablet	Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis Acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis
Cataflam	20142	11/24/1993	Tablet	Treatment of primary dysmenorrhea Relief of mild to moderate pain; signs and symptoms of osteoarthritis and rheumatoid arthritis
Voltaren XR	20254	03/8/1996	Tablet	Treatment of rheumatoid arthritis and osteoarthritis

2.4 Important Safety Issues With Consideration to Related Drugs

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patient's with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. NSAIDs are contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAID's cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Multiple products containing the active ingredient diclofenac have previously been approved in the United States for a number of indications, as listed above (Table 1). The application for Zorvolex (diclofenac acid) Capsules was submitted and filed as a 505(b)(2) NDA relying upon the Agency's previous findings of safety and efficacy for Cataflam (020142). During the clinical development, the Applicant referred to their drug as Zorvolex "(b)(4)." However during the End of Phase 2 meeting held on November 9, 2010, the Division informed the Applicant that "(b)(4)" must be "(b)(4)". Therefore, the drug product does not meet the Agency definition of a "(b)(4)". Upon submission of the NDA, the Applicant referred to Zorvolex as "(b)(4)" instead of "(b)(4)".

The drug development program was conducted under IND 103880. Key regulatory activity related to this NDA is noted in Table 2 that follows.

Table 2: Key Presubmission Regulatory Activity

Date	Meeting/ Submission Type	Comments
5/11/2009	Advice Letter	<ul style="list-style-type: none"> Agreement on initial approach to pivotal, acute pain study
1/29/2010	Special Protocol Assessment: Agreement for Protocol DIC3-08-04	<ul style="list-style-type: none"> The overall design of Protocol DIC3-08-04, a randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled trial of diclofenac "(b)(4)" capsules for the treatment of acute post-operative pain after bunionectomy, is acceptable to support an efficacy claim for the treatment of mild to moderate acute pain Agreement on design, primary endpoint (VAS SPID48), and imputation methods Comparative claims would require replicated demonstration of superiority
11/9/2010	Type B End of Phase 2 Meeting	<ul style="list-style-type: none"> 505(b)(2) pathway appropriate Pediatric requirements: efficacy, safety, and PK using

Date	Meeting/ Submission Type	Comments
		<p>an age-appropriate formulation in patients 1 to < 2 years with acute pain; safety and PK using an age-appropriate formulation in patients ^(b)₍₄₎ to < 17 years with acute pain; may be possible to waive the pediatric study requirements for ages birth to 1 year because there is evidence strongly suggesting that the drug product would be ineffective or unsafe in this age group</p> <ul style="list-style-type: none"> • Reliance on prior findings of efficacy for another diclofenac product for acute pain and the proposed Phase 3 study (DIC3-08-04) for the treatment of acute post-operative pain after bunionectomy may be adequate to support an efficacy claim for this indication • Should Iroko choose to conduct the efficacy study without food intake restrictions, this would not be sufficient to demonstrate the lack of a clinical food effect • Safety data on at least 350 patients
3/16/2012	Proprietary Name (Zorvolex)	<ul style="list-style-type: none"> • Conditional acceptance of proposed proprietary name
6/7/2012	Pre-NDA Meeting	<ul style="list-style-type: none"> • Reference drug is Cataflam • Waivers will be determined by the Pediatric Research Committee, however, it appears reasonable to consider a waiver of studies for pediatric patients up to one year of age

Date	Meeting/ Submission Type	Comments
		<ul style="list-style-type: none">• Applicant should consider studying food effect on analgesic efficacy to avoid labeling instructions about taking your product on an empty stomach

2.6 Other Relevant Background Information

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidances for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The datasets were not in Study Data Tabulation Model (SDTM) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable. A number of information requests were sent to the Applicant for additional information, and the responses were timely and adequate (see Section 7.7, Table 29).

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

The Office of Scientific Investigations (OSI) conducted routine inspection of two clinical investigator sites in support of this NDA (see Table 3). The sites were selected based on the number of enrolled subjects.

Table 3: OSI Inspected Clinical Sites

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site 001 Premier Research Group Limited 3200 Red River, Suite 300 Austin, TX 78705 Contact: PI: Michael Gold, DPM, PA Phone: 512-320-1600 Fax: 512-320-0313	Study DIC3-08-04	143	Treatment of mild to moderate acute pain in adults. Endpoint VASSPID-48
Site 002 Premier Research Group Limited 5089 South 900 East, Suite 200 Salt Lake City, UT 84117 Contact: PI: Thomas Schiffgen, DPM Phone: 801-266-8900 Fax: 801-266-0791	Study DIC3-08-04	117	Treatment of mild to moderate acute pain in adults. Endpoint VASSPID-48

Source: Adapted from Clinical Study Report (CSR), Appendix 16.1.4.1

Site 001 received a classification of Voluntary Action Indicated (VAI). The OSI reviewer, Dr. Cynthia Kleppinger, determined the violations had no significant impact on the safety or efficacy data. In general, the inspectional findings support validity of data as reported by the Applicant under this NDA. Below is a summary from Dr. Kleppinger's Clinical Inspection Summary (Table 4).

Table 4: Results of the OSI Review by Site

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Final Classification
Michael Golf, DPM, PA Premier Research Group Limited Site # 001	Study DIC3-08-04 143 enrolled	May 14-20, 2013	VAI
Thomas Schiffgen, DPM Premier Research Group Limited	Study DIC3-08-04 117 enrolled	June 10-12, 2013	NAI- preliminary

Key:

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

Source: Dr. Cynthia Kleppinger's OSI Clinical Inspection Summary, page 2

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", attached with a list of 44 of the 45 investigators listed in the study reports, certifying that they had no financial interests or arrangements to disclose (see Appendix for Clinical Investigator Financial Disclosure).

One sub-investigator at site 001 was referenced as being out of the office and would be sent a copy of the financial interests form to sign at a later date. Given only one sub-investigator failed to fill out the financial interests form and none of the remaining investigators had financial interests or arrangements to disclose, the possibility of bias in the results based on financial interests is unlikely.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No clinically relevant data was submitted to or reviewed by the chemistry manufacturing and controls, clinical microbiology, preclinical and pharmacology/toxicology review disciplines.

4.4 Clinical Pharmacology

The study DIC1-12-07, conducted with commercial scale, serves as the pivotal clinical pharmacology study for this application (n=35). This study evaluated the relative bioavailability (BA) of 35mg of diclofenac acid capsules compared to Cataflam 50mg tablets, as well as dose-proportionality and food effect. The design compared a 20% lower dose of diclofenac acid compared to the reference drug Cataflam. Under fasted

conditions, the study showed a 26% lower (geometric mean) peak concentrations (Cmax) and 23% lower (geometric mean) AUC (AUC_{0-t} and AUC_{0-∞}) when comparing diclofenac acid to Cataflam. There was no difference in time to reach peak concentrations (Tmax) between diclofenac acid capsules and Cataflam tablets (~1 hour for both). Under fed conditions, diclofenac acid capsules compared to Cataflam showed a 48% lower Cmax and 26% and 23% lower (geometric mean) AUC_{0-t} and AUC_{0-∞} values, respectively. The Tmax for diclofenac acid was delayed by ~1 hour compared to Cataflam (Cataflam-2.33 hr vs. diclofenac acid -3.32 hr) under fed conditions. There were no differences in elimination half-life (T1/2) between diclofenac acid and Cataflam under fasted or fed conditions.

The smaller particle size of diclofenac acid capsules has provided no additional advantage in either rate (Cmax and Tmax) or the extent of absorption (AUC) compared to Cataflam when taken under fasted conditions. In contrast, when taken under fed conditions, diclofenac acid capsules has delayed rate of absorption compared to the Cataflam (decreased Cmax and delayed Tmax).

The 18 and 35 mg diclofenac capsules show dose proportional pharmacokinetics for Cmax and AUC under fasted conditions. When taken under fed conditions, diclofenac capsules shows 60%, 14% and 11% lower Cmax, AUC_{0-t}, and AUC_{0-∞}, respectively compared to fasted conditions. Taking diclofenac with food delayed the Tmax by 2.32 hours (1.0 hour fasted vs 3.32 hours fed). Please see the full clinical pharmacology review by Dr. Suresh Narahariseti for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials conducted in support of this supplemental NDA for Diclofenac (b) (4) capsules are listed in below (Table 5).

Table 5: Clinical Trials Submitted in Support of this Application

Clinical Trial	Population	Number of Subjects	Relevance
<i>Clinical Trials Contributing to Efficacy Review (Controlled Trials)</i>			
DIC3-08-04	Bunionectomy	Zorvolex = 216 Placebo = 101 Celecoxib = 105	Contains efficacy data in pain population
<i>Clinical Trials Contributing to Safety Review</i>			
DIC3-08-04	Bunionectomy	Zorvolex = 216 Placebo = 101 Celecoxib = 105	Contains safety data in the pain population
DIC1-12-07	Healthy volunteers	N =38	Contains safety and PK data in the pain population

Source: Derived from Applicant's submission, NDA 204592

5.2 Review Strategy

DIC3-08-04 (controlled trial) is the pivotal trial reviewed for efficacy and safety. The primary analyses of both safety and efficacy will rely only on DIC3-08-04, along with the Agency's previous findings of safety and effectiveness for diclofenac [505(b)(2)]. The Applicant submitted other studies that will provide support for the pivotal trial. DIC2-08-03 is a Phase 2, proof-of-concept (POC) study using the POC formulation and not the commercial formulation. DIC2-08-03 was reviewed to support efficacy and safety of the pivotal trial, but not as a primary source of data. The design and results from the individual controlled trials submitted in support of efficacy in the indicated population are reviewed in Section 5.3, Discussion of Individual Studies/Clinical Trials. The primary efficacy analyses of trial DIC3-08-04 were confirmed by Dr. Feng Li, statistical reviewer.

In addition to the studies in Table 1, the Applicant submitted additional safety information (b) (4) and an additional pharmacokinetic (PK) study using the POC formulation in DIC1-08-01. The (b) (4) trials are ongoing and the Applicant submitted interim analyses without the raw datasets, so they will not be included in the formal safety analysis. However, these trials were briefly reviewed to detect potential safety signals (see relevant sections in Section 7 of this review).

5.3 Discussion of Individual Studies/Clinical Trials

Trial DIC3-08-04

"A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active- and Placebo-Controlled Study of Diclofenac (b) (4) formulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy"

Conducted from 10/26/2011 to 2/21/2012

Four sites, all located in the United States

Protocol

Objective/Rationale

The primary objective is to evaluate the analgesic efficacy of diclofenac capsules compared with placebo in subjects with acute postoperative pain after bunionectomy

The secondary objectives are the following:

- To evaluate the safety of diclofenac (b) (4) capsules compared with placebo in subjects with acute postoperative pain after bunionectomy.
- To evaluate the time to onset of analgesia for diclofenac capsules compared with the standard formulation of celecoxib.

Overall Design

This was to be a Phase 3, multicenter, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study to evaluate the safety and efficacy of 2 dosing regimens of diclofenac (35 mg 3 times daily [TID] or 18 mg TID) in subjects with acute postoperative pain after bunionectomy. On Day 1 of the study, when subjects requested pain medication, a Visual Analog Scale (VAS) assessment was to be performed. Subjects with a pain intensity rating ≥ 40 mm on a 100-mm VAS within 9 hours of discontinuation of regional anesthesia were to be eligible. Pain intensity (VAS) and pain relief (5-point categorical scale) assessments were to be performed during the 48 hour period after Time 0. The Applicant did not include procedures for whether patients were to be dosed study medications with or without food restriction in the protocol. The Division sent an information request to clarify this issue, and the Applicant responded on 2/12/2013. The Applicant explained the dosing on an empty stomach was achieved as a result of the post-surgical design and the majority of subjects received their initial dose of study medication on an empty stomach. Subsequent doses of study medication were based on elapsed time relative to the initial dose, rather than on pre-set times of day (i.e., although the initial dose was given to most subjects on an empty stomach, there were no specified food restrictions for subsequent dosing). Safety was to be assessed by the incidence of treatment-emergent AEs (TEAEs) and changes in vital sign measurements. TEAEs were to be recorded during the inpatient portion of the study as well as 1 week after discharge. The TEAEs after discharge were to be reported to the investigator at a 1 week follow-up visit.

Treatment

Once the pain intensity entry criteria were to be met, subjects were to be randomly assigned to 1 of 4 treatment groups: diclofenac capsules 35 mg TID or 18 mg TID; placebo; or celecoxib capsules 200 mg BID (Table 6). Study drug was to be administered in a QID regimen for 48 hours after the first dose, with a maximum of 4 doses (active and/or dummy) in a 24-hour period. One tablet of hydrocodone/acetaminophen 10 mg/325 mg was to be allowed every 4 to 6 hours as needed for rescue.

Table 6: Dosing of Treatment Groups DIC3-08-04

Treatment group	DAY 1				DAY 2			
	Dose 1 (0 h)	Dose 2 (8 h)	Dose 3 (12 h)	Dose 4 (16 h)	Dose 5 (24 h)	Dose 6 (32 h)	Dose 7 (36 h)	Dose 8 (40 h)
35 mg TID	35 mg + P	35 mg	P	35 mg	35 mg	35 mg	P	35 mg
18 mg TID	18 mg + P	18 mg	P	18 mg	18 mg	18 mg	P	18 mg
Placebo	P + P	P	P	P	P	P	P	P
Celecoxib	200 mg + 200 mg	P	200 mg	P	200 mg	P	200 mg	P

Abbreviation: P, placebo.

Note: First dose on Day 1 only includes 2 capsules for each treatment regimen.

Source: Applicant's Protocol p. 39

Population and Procedures

Inclusion/Exclusion Criteria

Planned enrollment was to be 424 subjects (106 per treatment group) post bunionectomy. Subjects were to be randomized 1:1:1:1 to active treatment arms, active comparator or placebo arm.

Inclusion Criteria

- Male or female ≥ 18 and ≤ 65 years of age
- Classified by the anesthesiologist as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System
- Undergone primary, unilateral, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures
- Pain intensity rating of ≥ 40 mm on a 100-mm VAS during the 9-hour period after discontinuation of the anesthetic block
- Body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m²
- If female and of childbearing potential, is non-lactating and non-pregnant (has negative pregnancy test results at Screening [serum] and on the day of surgery prior to surgery [urine])¹

¹ If childbearing potential, must practice birth control through one of the following methods: Hormonal therapy for minimum of 1 full cycle before study, total abstinence since last menses before trial, IUD, or double-barrier method

- Able to provide written informed consent
- Willing and able to comply with study requirements (including diet, alcohol, and smoking restrictions), complete the pain evaluations, remain at the study site for ≥ 72 hours, and return for follow-up 7 ± 2 days after surgery

Exclusion Criteria

- History of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any NSAIDs²
- Any surgical complications or other issues that could compromise the safety of the subject or could confound the results of the study
- History or evidence of alcoholism or drug abuse or misuse within 2 years of Screening
- Clinically significant unstable medical conditions³
- Condition, other than one associated with the current bunionectomy that could generate levels of pain sufficient to confound the results of the study⁴
- Significant psychiatric disorder that would affect ability to comply with the study
- Tested positive either on the urine drug screen or on the alcohol breathalyzer
- Clinically significant GI event (e.g., peptic ulcer, GI bleed, gastric ulcers) within 6 months before Screening
- Condition of the GI or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance
- Is considered by the investigator, for any reason to be an unsuitable candidate to receive the study drug
- Receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening⁵
- Receiving anticoagulants
- Systemic corticosteroids (either oral or parenteral) within 3 months before Screening
- Received or will require any analgesic medication within 5 half-lives (or, if half-life is unknown, within 48 hours) before surgery
- History of chronic use (defined as daily use for > 2 weeks) of NSAIDs, opiates, or glucocorticoids within 6 months before study drug administration⁶
- Treated with agents that could affect the analgesic response within 2 weeks before dosing

² Includes NSAID induced bronchospasm, allergy, or these reactions to any other drugs to be used in the study

³ Cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the investigator, could compromise the subject. Hepatic disease: ≥ 3 times the upper limit of normal [ULN] for any liver function test. Renal: creatinine ≥ 1.5 times the ULN

⁴ E.g., severe osteoarthritis of the target joint

⁵ Excluding squamous or basal cell carcinoma of the skin

⁶ Aspirin at a daily dose of ≤ 325 mg was to be allowed for cardiovascular prophylaxis if stable for 30 days

- Clinically significant laboratory or 12-lead electrocardiogram (ECG) finding at Screening
- Difficulties swallowing capsules
- Previously participated in another clinical study of diclofenac capsules or received any investigational drug or device or investigational therapy within 30 days before Screening

Procedures

The study was to consist of a Screening Phase, Inpatient Treatment Phase after surgery (Days 0-3) and a Follow-up visit (5 to 9 days after surgery). The local anesthetic technique to be used for this surgery comprised a combination of a popliteal sciatic nerve block (PSB), to establish and maintain surgical field anesthesia, and a continuous sciatic infusion to provide an effective method of controlling pain in the immediate postoperative period. 40 mL of ropivacaine 0.5% was to be used to establish the PSB. Mepivacaine 0.5% was to be used to provide continuous postoperative pain management until discontinued around 3 am on Day 1. The subjects were to receive the study medication after eligibility confirmed and met pain requirements on the VAS score. The medication was to be administered QID for 48 hours after the first dose, with a maximum of 4 doses (active and/or dummy) in a 24-hour period. Details of the study procedures are described below (Table 7).

Screening (Days – 28 to -1 before surgery)

- Informed consent signed
- Inclusion/exclusion criteria reviewed
- Demographic information
- Medical history
- Physical examination, height and weight
- Vital signs⁷
- ECG and clinical laboratory tests (chemistry, hematology and urinalysis)
- Pregnancy test (serum)
- Urine drug screen (UDS)
- X-ray and podiatric examination
- Concomitant medications reviewed and recorded

Surgery (Day 0)

- Confirm inclusion/exclusion criteria and medical history
- Vital signs repeated
- Pregnancy test (urine)

⁷ Blood pressure, heart rate, respiratory rate, temperature to be measured at Screening and before surgery on Day 0. Vitals were to be measured immediately before, and 1 hour after the first dose of study drug each day, and before study end.

- UDS
- Alcohol breathalyzer test
- Concomitant medications reviewed and recorded
- Adverse events recorded

The treatment period consists of Days 1-3 after surgery. Time 0 on Day 1 was to be when the first medication was to be administered.

Treatment Period (Days 1-3)

Before dosing:

- VAS pain intensity assessment was to be administered during the 9-hour period after discontinuation of the anesthetic block to screen for eligibility
- Vital signs
- Discontinue anesthetic block at approximately 3 AM
- Concomitant medications reviewed and recorded
- Adverse events recorded

Baseline/First dose (Time 0)

- Vital signs
- Assign randomization number
- Pain assessments⁸
- Administer study drug in QID regimen after first dose (active and or dummy)
- Start stopwatches for perceptible and meaningful pain relief
- Concomitant medications reviewed and recorded
- Adverse events recorded

Subsequent doses (Days 1-3)

- Vital signs
- Pain assessments
- Administer study drug
- Patient's global evaluation of study drug⁹
- Concomitant medications reviewed and recorded
- Adverse events recorded
- Dispense postoperative pain medication and outpatient subject diary (Day 3)
- Discharge from study site

⁸ Pain intensity (VAS) assessments were to be recorded by the subject in the inpatient subject diary at Baseline before the first dose of study drug (Day 1/Time 0). Pain intensity (VAS) and pain relief (5-point categorical scale) assessments will be recorded at the following time points:

- First dose: 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after Time 0, and immediately before the first use of rescue analgesia if before the 8-hour time point.
- Subsequent doses: 12, 16, 20, 24, 32, 40, and 48 hours after Time 0, and before premature study termination

⁹ To be completed at end of the treatment period (Day 3) before discharge from the study site or immediately before the first dose of rescue medication (whichever occurs first)

Follow-up (5 to 9 days after surgery) or early termination

- Physical examination (abbreviated)
- Vital signs
- Concomitant medications reviewed and recorded
- Adverse events recorded
- Collect and review diary

Table 7: Schedule of Events

	Screening (-28 days to -1 day before surgery)	Surgery Day 0	Day 1 (before dosing)	Treatment Period Day 1 through Day 3		Follow-up Day 7 ± 2 days (5 to 9 days after surgery) or ET
				Baseline/First dose (Time 0)	Subsequent doses	
Written informed consent	X					
Inclusion/exclusion criteria	X	X (update)				
Demographics	X					
Medical history	X	X (update)				
Physical examination ^a	X					X
Vital signs ^b	X	X	X	X	X	X
Height, weight, and BMI	X					
12-lead electrocardiogram	X					
Clinical laboratory tests (hematology, chemistry, urinalysis)	X					
Pregnancy test for female subjects ^c	X	X				
Urine drug screen ^d	X	X				
Alcohol breathalyzer test		X				
X-ray and podiatric examination ^e	X					
First metatarsal bunionectomy procedure		X				
Discontinue anesthetic block at approximately 3 AM ^f			X			
Assign randomization number				X		
Pain assessments ^g				X	X	
Administer study drug ^h				X	X	
Start stopwatches for perceptible and meaningful pain relief ⁱ				X		
Patient's global evaluation of study drug ^j					X	
Concomitant medications	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Dispense postoperative pain medication and outpatient subject diary ^k					X	
Discharge subject from the study site ^l					X	
Collect and review diary for completion						X

Clinical Review
Steven Galati M.D.
NDA 204592
Zorvolex/Diclofenac acid capsules

Abbreviations: BMI, body mass index; ET, early termination; VAS, Visual Analogue Scale.

- a A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated physical examination, including an examination of the subject's surgical site, will be performed at the Follow-up Visit.
- b Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured at Screening and before surgery on Day 0. From Day 1 through discharge from the study site, vital signs will be measured immediately before and 1 hour after the first dose of study drug each day. Vital signs will also be measured before study termination.
- c Serum pregnancy test at Screening and urine pregnancy test before surgery on Day 0. Test results must be negative for the subject to continue in the study.
- d Collected at Screening and before surgery on Day 0. Test results must be negative for the subject to continue in the study except in cases where a valid physician's prescription can be verified.
- e Radiographs taken within 6 months before Screening will be acceptable.
- f Immediately after the block is discontinued, the subjects will be instructed to request pain medication when they experience pain.
- g Pain intensity (VAS) assessments will be recorded by the subject in the inpatient subject diary at Baseline before the first dose of study drug (Day 1/Time 0). Pain intensity (VAS) and pain relief (5-point categorical scale) assessments will be recorded at the following time points:
 - First dose: 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after Time 0, and immediately before the first use of rescue analgesia if before the 8-hour time point.
 - Subsequent doses: 12, 16, 20, 24, 32, 40, and 48 hours after Time 0.
 - Before premature study termination.
- h The first dose of study drug will be administered within 9 hours after the anesthetic block has been discontinued when pain intensity is ≥ 40 mm on a 100-mm VAS. Study drug will be administered from Day 1 through Day 3.
- i Start stopwatches as soon as the first dose of study drug is administered.
- j Subjects will complete a patient'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 medication (whichever occurs first).
- k Before discharge from the study site on Day 3.
- l On Day 3.

Source: Applicant's Protocol, from Appendix 1, p.50

Subject Withdrawal

Subjects were to be free to withdraw from participation in this study at any time, for any reason, and without prejudice. Subjects were to be discontinued from the study at any time, in the best interest of the subject, at the discretion of the investigator.

- If a subject was to be withdrawn before completing the study, the reason for withdrawal was to be entered on the appropriate case report form (CRF)

Subjects could also be withdrawn from the study for the following reasons:

- Adverse events
 - Any AE was to be followed to a satisfactory resolution until it became stable or was to be explained by another known cause(s)
- Lack of therapeutic effect
- Noncompliance with procedures

Evaluations/Endpoints

Subjects were to complete the pain intensity assessment first and the pain relief assessment second. Subjects were to assess their current pain intensity using a 100-mm VAS. The VAS is a horizontal line 100 mm in length with “No Pain” as the left anchor (0 mm) and “Worst Possible Pain” as the right anchor (100 mm). Pain intensity was to be assessed before Time 0; at 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 after Time 0; and immediately before the first dose of rescue analgesia if before the 8-hour time point.

The pre-specified primary efficacy variable was to be VAS summed pain intensity difference (VAS SPID) (calculated as time-weighted averages) over 0 to 48 hours (VAS SPID-48) after Time 0. No secondary efficacy variables were identified as key.

Secondary efficacy variables identified in the protocol included:

- Pain Relief
- Stopwatch Assessment (time to onset of meaningful pain relief)
- Patient’s Global Evaluation of Study Drug
- VAS pain intensity difference (VAS PID) at each scheduled time point after Time 0
- VAS pain intensity score at each scheduled time point
- VAS SPID over 0 to 4 hours (VAS SPID-4), over 0 to 8 hours (VAS SPID-8), and over 0 to 24 hours (VAS SPID-24) after Time 0
- Total Pain Relief (TOTPAR) over 0 to 4 hours (TOTPAR-4), over 0 to 8 hours (TOTPAR-8), over 0 to 24 hours (TOTPAR-24), and over 0 to 48 hours (TOTPAR-48) after Time 0
 - TOTPAR is a pain relief score on a 5-point categorical scale with the following descriptors: none, a little, some, a lot, and complete

- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia)
- Total use of opioid rescue analgesia over 0 to 24 hours and over 0 to 48 hours

Safety Assessments

- Incidence of TEAEs
- Vital sign measurements
- Physical examination (excluding the genitourinary exam) will be performed at Screening. An abbreviated confirmatory physical assessment will be performed at the Follow-up Visit (or Early Termination Visit).
- Laboratory tests:
 - Hematology: hemoglobin, hematocrit, platelet count, white blood cell count (including differential)
 - Chemistry: glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, albumin
 - Urinalysis: pH, specific gravity, blood, glucose, protein, ketones
 - Alcohol breathalyzer test will be performed before surgery on Day 0
 - Urine drug screen samples will be collected at Screening and before surgery on Day 0
 - Serum pregnancy test will be collected at Screening and a urine pregnancy test sample will be collected before surgery on Day 0
- ECG at Screening
- Prior and concomitant medications

Statistical Plan

The primary efficacy variable was to be the VASSPID-48 (calculated as a time-weighted average) after Time 0. The intent-to-treat (ITT) population was to consist of all subjects who received at least 1 dose of study drug. The ITT population was to be the primary population for the efficacy analysis. Membership in the analyses populations was to be determined before unblinding. For the primary endpoint, missing observations was to be imputed using baseline-observation-carried-forward (BOCF) for subjects who withdrew from the study due to lack of efficacy or an AE/intolerance to study drug. The BOCF imputation will be applied in place of all scheduled assessments after the time of early termination due to lack of efficacy or an AE/intolerance to study drug using the baseline observation taken before Time 0. For subjects who took any dose of rescue medication, subsequent measures after the first dose of rescue medication were to be disregarded. Instead, all scheduled assessments after the first dose of rescue medication were imputed using the BOCF (using baseline observation taken before time 0). For subjects who withdrew from the study due to reasons other than lack of efficacy

or an AE/intolerance to study drug, missing observations for pain intensity and pain relief was to be imputed using last-observation-carried-forward (LOCF). Diligent monitoring and data review was to be implemented before database lock to ensure that the reasons for withdrawal were correctly identified. The LOCF imputation was to be applied in place of all scheduled assessments after the time of early termination due to reasons other than lack of efficacy or an AE/intolerance to study drug.

The primary analysis was to be conducted using sequential testing for the 2 diclofenac capsule treatments in the following order: 35 mg TID and 18 mg TID. It was to be performed using an analysis of covariance (ANCOVA) model, which were to include treatment effect as the factor and baseline pain intensity as the covariate. The analysis was to be based on a 2-sided test at the significance level of 0.05.

Results

Subject Overview

A total of 428 potential subjects were screened, and 428 subjects were randomized into the trial. All randomized and treated subjects were evaluated for TEAEs. Three populations were analyzed in this trial:

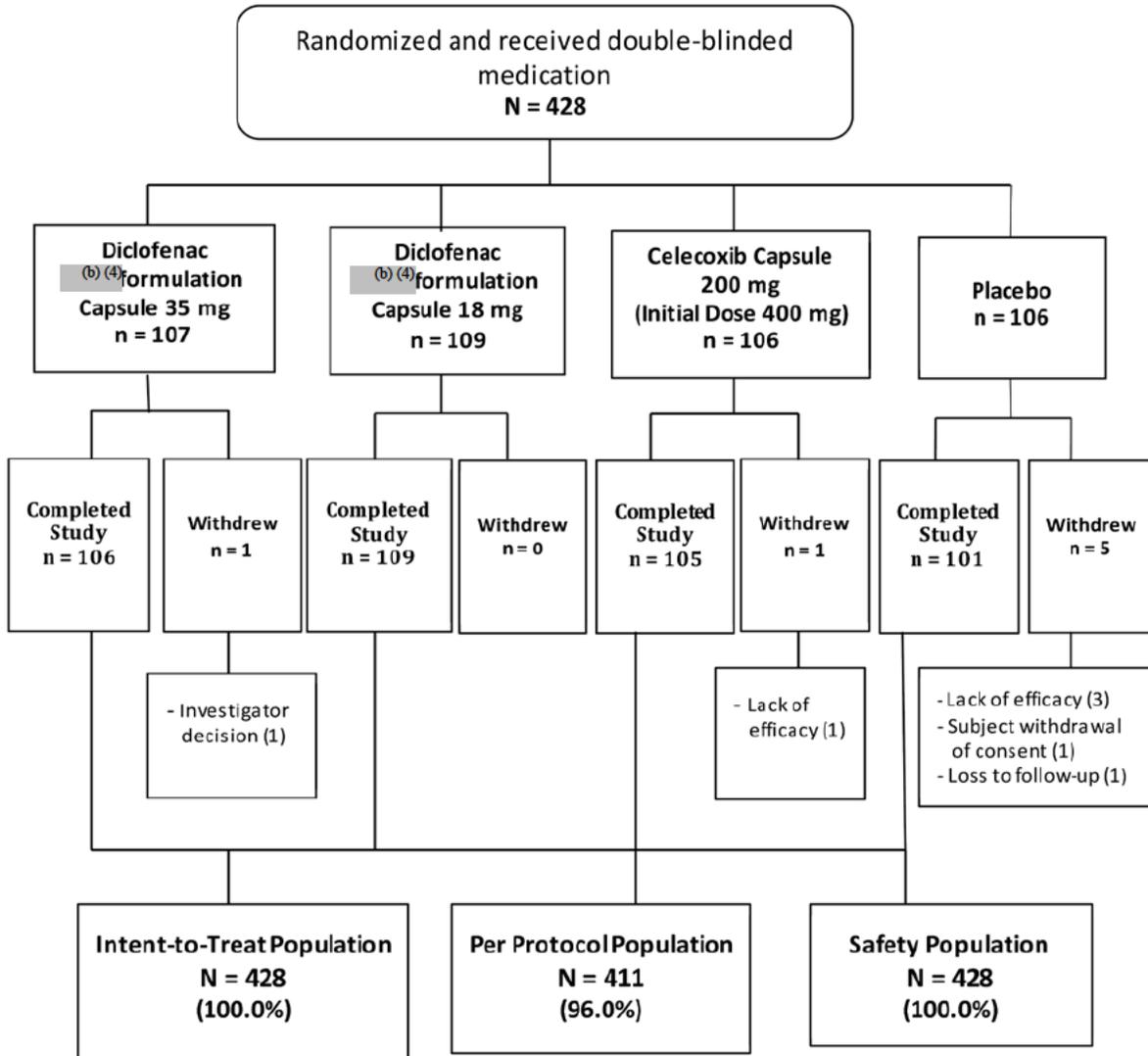
- ITT population (N = 428)
- PP population (N = 411)
- Safety population (N = 428)

All randomized subjects met the criteria for inclusion into the ITT and Safety population. A total of 411 subjects met the criteria for inclusion in the PP population (i.e., all ITT subjects who remained in the trial for at least 48 hours of treatment and had not incurred a major protocol violation).

Subject Disposition

The largest number of discontinuations occurred in the placebo treatment group (accounting for 5 of the 7 subjects who withdrew from the trial). A total of 421 subjects completed the trial. Refer to the figure below (Figure 1) for subject disposition in the controlled trial. One subject withdrew from the trial in the diclofenac group (35mg). The Applicant reported this was due to an investigator decision when learned of exclusionary medical history (stomach ulcer) following subject enrollment, and withdrew the subject from further treatment. The diclofenac groups had no discontinuations due to an AE.

Figure 1: Subject Disposition for Controlled Trial DIC3-08-04



Source: Applicant's Submitted Clinical Study Report p. 49

Demographics

The demographics were generally comparable across treatment groups in the study. The Safety population was diverse, consisting of American Indian, Asian, Black or African American, native Hawaiian, and White males and females with ages ranging from 18 to 65 years (Table 8). The trial population was predominantly female (371 subjects [86.7%]) and White (329 subjects [76.9%]). The mean age was 39.7 years.

Table 8: Demographic Characteristics – Safety Population

Variable	Diclofenac (b) (4) Formulation Capsule		Celecoxib Capsule 200 mg ^a (n = 106)	Placebo (n = 106)	Total (N = 428)
	35 mg (n = 107)	18 mg (n = 109)			
Age, years					
n	107	109	106	106	428
Mean (SD)	39.3 (11.8)	39.4 (11.7)	40.3 (11.9)	39.9 (12.6)	39.7 (12.0)
Median	39.0	37.0	39.0	41.0	39.0
Minimum, maximum	18, 65	19, 62	19, 64	19, 64	18, 65
Sex, n (%)					
Male	18 (16.8%)	15 (13.8%)	10 (9.4%)	14 (13.2%)	57 (13.3%)
Female	89 (83.2%)	94 (86.2%)	96 (90.6%)	92 (86.8%)	371 (86.7%)
Race, n (%)					
American Indian or Alaska native	3 (2.8%)	1 (0.9%)	5 (4.7%)	1 (0.9%)	10 (2.3%)
Asian	1 (0.9%)	0	4 (3.8%)	5 (4.7%)	10 (2.3%)
Black or African American	19 (17.8%)	20 (18.3%)	23 (21.7%)	20 (18.9%)	82 (19.2%)
Native Hawaiian or other Pacific Islander	1 (0.9%)	3 (2.8%)	2 (1.9%)	2 (1.9%)	8 (1.9%)
White or Caucasian	86 (80.4%)	87 (79.8%)	75 (70.8%)	81 (76.4%)	329 (76.9%)
Ethnicity, n (%)					
Hispanic or Latino	19 (17.8%)	24 (22.0%)	18 (17.0%)	17 (16.0%)	78 (18.2%)
Not Hispanic or Latino	88 (82.2%)	85 (78.0%)	88 (83.0%)	89 (84.0%)	350 (81.8%)
Weight, kg					
n	107	109	106	106	428
Mean (SD)	76.898 (18.7)	74.656 (16.8)	72.377 (15.6)	72.694 (14.0)	74.166 (16.4)
Median	72.700	72.700	69.750	71.057	71.800
Minimum, maximum	48.60, 130.18	48.20, 127.30	46.40, 112.49	46.40, 122.92	46.40, 130.18
Height, cm					
n	107	109	106	106	428
Mean (SD)	166.617 (9.1)	166.913 (8.9)	165.105 (7.5)	166.667 (7.7)	166.330 (8.3)
Median	165.100	165.100	163.449	165.735	165.100
Minimum, maximum	148.59, 187.96	149.86, 190.50	144.78, 198.12	147.32, 182.88	144.78, 198.12
Body mass index, kg/m ²					
n	107	109	106	106	428
Mean (SD)	27.5 (5.7)	26.6 (5.0)	26.4 (5.2)	26.0 (4.5)	26.6 (5.1)
Median	26.0	27.0	26.0	25.0	26.0
Minimum, maximum	9, 40	18, 39	18, 39	17, 40	17.40

Source of data: Section 14.1, Table 14.1.2

Abbreviations: SD = standard deviation.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

Source: Applicants Clinical Study Report p. 52

The predominance of female subjects is reflective of and consistent with the epidemiology of the underlying disease process, bunions. The demographic characteristics were generally balanced across the 4 treatment groups, with the exception of a slightly smaller number of males in the celecoxib treatment group

compared with the diclofenac 35-mg treatment group (10 subjects [9.4%] and 18 subjects [16.8%], respectively). This difference is likely not to bias the clinical relevance of the findings.

Screening/Baseline Disease Characteristics

Baseline pain intensity on the VAS pain scale had a mean (SD) value of 75.4 mm (16.27) and was evenly balanced across the treatment groups. Baseline characteristics of the Safety population are summarized overall, and by treatment group in Table 9 below. The length of surgical procedure was consistent across treatment groups [mean (SD) of 29.2 minutes (8.67)].

Table 9: Summary of Baseline Characteristics – Safety Population

Variable	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule	Placebo	Total
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	(n = 106)	(N = 428)
Baseline pain intensity, mm					
n	107	109	106	106	428
Mean (SD)	74.1 (16.1)	76.7 (15.9)	74.2 (16.8)	76.3 (16.3)	75.4 (16.3)
Median	75.0	76.0	74.0	77.0	76.0
Minimum, maximum	(44, 100)	41, 100)	(40, 100)	(40, 100)	(40, 100)
Surgery duration, minutes					
n	107	109	106	106	428
Mean (SD)	28.2 (6.7)	28.9 (6.9)	29.7 (11.1)	29.9 (9.4)	29.2 (8.7)
Median	28.0	29.0	29.0	28.0	28.0
Minimum, maximum	(16, 48)	15, 52)	(16, 115)	(16, 72)	(15, 115)

Source of data: Section 14.1, Table 14.1.2

Abbreviations: SD = standard deviation.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

Source: Applicant's Clinical Study Report p.53

Prior and Concomitant Drug Treatments

Prior medications included all medications that started and ended prior to trial drug administration and excluded all preoperative and intraoperative medications. Almost all the subjects used some prior medications. The most frequently used prior medications across treatment groups were mepivacaine (391 subjects [91.4%]), Vicodin (261 subjects [61.0%]), Oxycocet (132 subjects [30.8%]), and ibuprofen (118 subjects [27.6%]). 415 (97%) of the subjects used a concomitant medication during the study, a definition which included any medication use that ended on or after trial drug administration until the Follow-up visit (5 to 9 days after surgery), excluding rescue. The most frequent concomitant medication was Vicodin (237 subjects [55.4%]), followed by ibuprofen (210 subjects [49.1%]), cefazolin (124 subjects [29.0%]), cephalexin (66 subjects [15.4%]), multivitamins (42 subjects [9.8%]), metoclopramide (40 subjects [9.3%]), and Oxycocet (32 subjects [7.5%]).

The use of prior medications appeared to be comparable across treatment groups. Relevant concomitant medications appeared to be comparable across treatment groups. Natural Opium Alkaloids were slightly higher in the placebo group than other treatment groups, as expected, given they were not receiving the benefit of an NSAID during the treatment period. This difference is minor and would not be expected to bias the results.

Protocol Violations

There were 12 subjects for whom major protocol deviations were reported and were generally balanced across the 4 treatment groups. Overall, the largest number of deviations were for “assessments not completed” (in 9 subjects).

Table 10: Summary of Major Protocol Violations

	Diclofenac 35mg (N=107)	Diclofenac 18mg (N=109)	Celecoxib 200mg (400mg initial dose) N-106	Placebo (N=106)	Total (N=428)
Subjects with any major protocol deviations	3 (2.8%)	3 (2.8%)	4 (3.8%)	2 (1.9%)	12 (2.8%)
Assessment Not Done	2 (1.9%)	3 (2.8%)	3 (2.8%)	1 (0.9%)	9 (2.1%)
Exclusion Criteria	1 (0.9%)	0	0	0	1 (0.2%)
IP Dosing Error	0	0	1 (0.9%)	0	1 (0.2%)
Other	0	0	0	1 (0.9%)	1 (0.2%)

Source: Adapted from Applicant’s Clinical Study Report, Table 14.1.4 p. 124

The treatment groups were comparable with regard to protocol violations (Table 10). A single patient in the diclofenac group withdrew due to meeting an exclusion criterion after randomization.

Dosing Information

The planned duration of double-blind treatment was to be 48 hours after surgery.

Efficacy Results

Overview

The Applicant’s analysis demonstrated the superiority of diclofenac with respect to placebo for the primary endpoint (VASSPID-48) with statistical significance. Results for the ITT population are presented for the primary and secondary efficacy variables. In

the case of the primary efficacy variable, the PP population was performed as a sensitivity analysis. No secondary endpoints were identified as key endpoints.

Primary endpoint results:

- Treatment with diclofenac compared to placebo was statistically significant for all groups when compared to placebo measuring VAS summed pain intensity difference (VASSPID) over 0 to 48 hours.
- 35-mg diclofenac ($P < 0.001$)
- 18-mg diclofenac ($P < 0.010$)
- Celecoxib treatment ($P < 0.011$)

Secondary endpoints (none identified as key):

- VAS pain intensity difference (VASPID) at each scheduled time point after Time 0
- VAS pain intensity score at each scheduled time point
- VASSPID over 0 to 4 hours (VASSPID-4), over 0 to 8 hours (VASSPID-8), and over 0 to 24 hours (VASSPID-24) after Time 0
- Total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR-4), over 0 to 8 hours (TOTPAR-8), over 0 to 24 hours (TOTPAR-24) after Time 0, and over 0 to 48 hours (TOTPAR-48) after Time 0
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief)
- Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0
- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia)
- Total use of opioid rescue analgesia over 0 to 24 hours and over 0 to 48 hours
- Patient's global evaluation of trial drug

Primary Efficacy Results

The primary efficacy analysis was based on the primary endpoint, VASSPID-48, in the ITT population. Baseline pain on to the VAS pain scale was a mean (SD) value of 75.4 (16.27) mm and was evenly balanced across treatment groups. The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) model, which included treatment effect as the factor and baseline pain intensity as the covariate (Model 1). Table 11 below shows the primary analysis (Model 1). The results are also presented in Figure 2.

Table 11: Applicants Statistical Analysis (ANCOVA) of ITT Population

Statistic	(b) (4), Diclofenac formulation Capsule		Celecoxib Capsule 200 mg^a	Placebo
	35 mg (n = 107)	18 mg (n = 109)	(n = 106)	(n = 106)
Overall				
n	107	109	106	106
Mean (SD)	524.315 (1146.1)	392.954 (937.0)	390.468 (925.1)	76.887 (340.6)
Median (minimum, maximum)	2.750 (-154.50, 4391.75)	0.500 (-56.00, 3727.00)	3.125 (-42.75, 4281.75)	-0.875 (-40.50, 2480.25)
Model 1 (primary) ^b				
LS mean (SE)	524.048 (86.2) (354.549, 693.547)	392.247 (85.5) (225284, 561.211)	390.221 (86.6) (219.944, 560.499)	77.102 (86.6) (-93.151, 247.355)
95% CI				
Comparison vs placebo ^c				
LS mean difference (SE)	446.946 (122.2935)	316.145 (121.5971)	313.119 (122.5676)	
95% CI for LS mean difference	(206.567, 687.324)	(77.136, 555.155)	(72.202, 554.037)	
P value for difference	<0.001	0.010	0.011	

Source of data: [Section 14.2, Table 14.2.1.1](#)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LS = least squares; SD = standard deviation; SE = standard error.

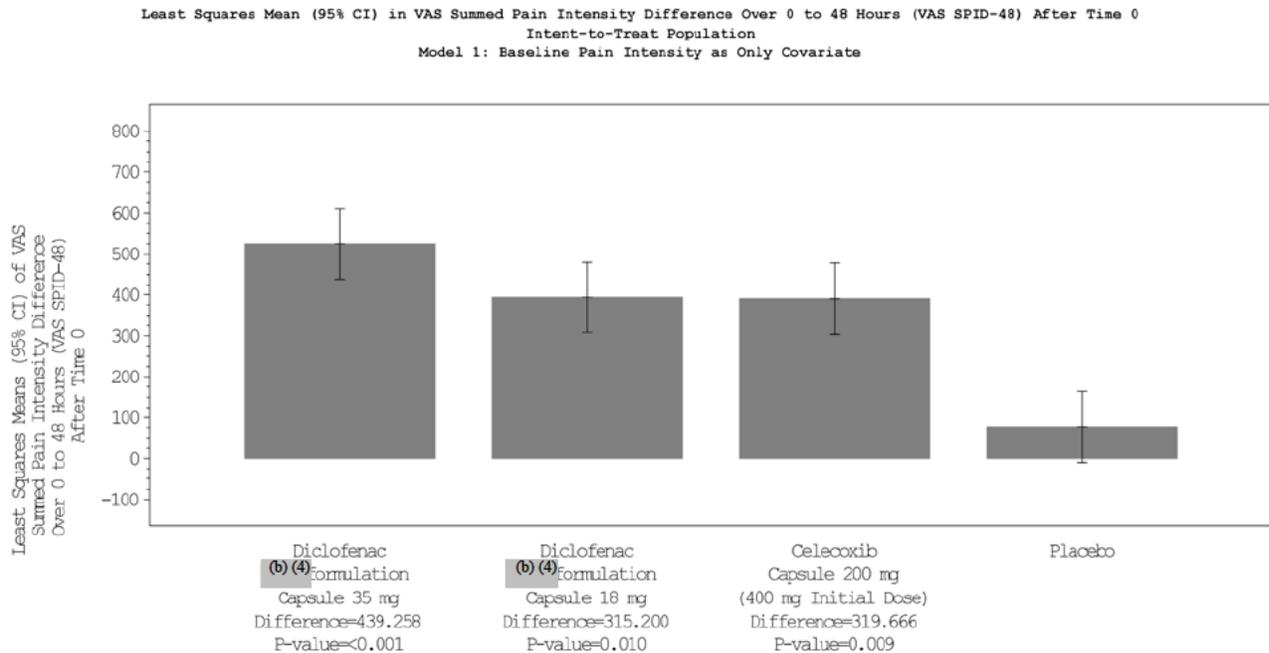
^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Model 1 included baseline pain intensity as only covariate.

^c The LS mean differences (treatment – placebo), 95% CIs, and P values were obtained from analysis of covariance models with appropriate baseline variables as covariates and with treatment as a factor, as indicated.

Source: Applicant's Clinical Study Report, Table 11-3, p. 56

Figure 2: VASSPID-48 Results in the ITT population with Baseline Pain as Only Covariate



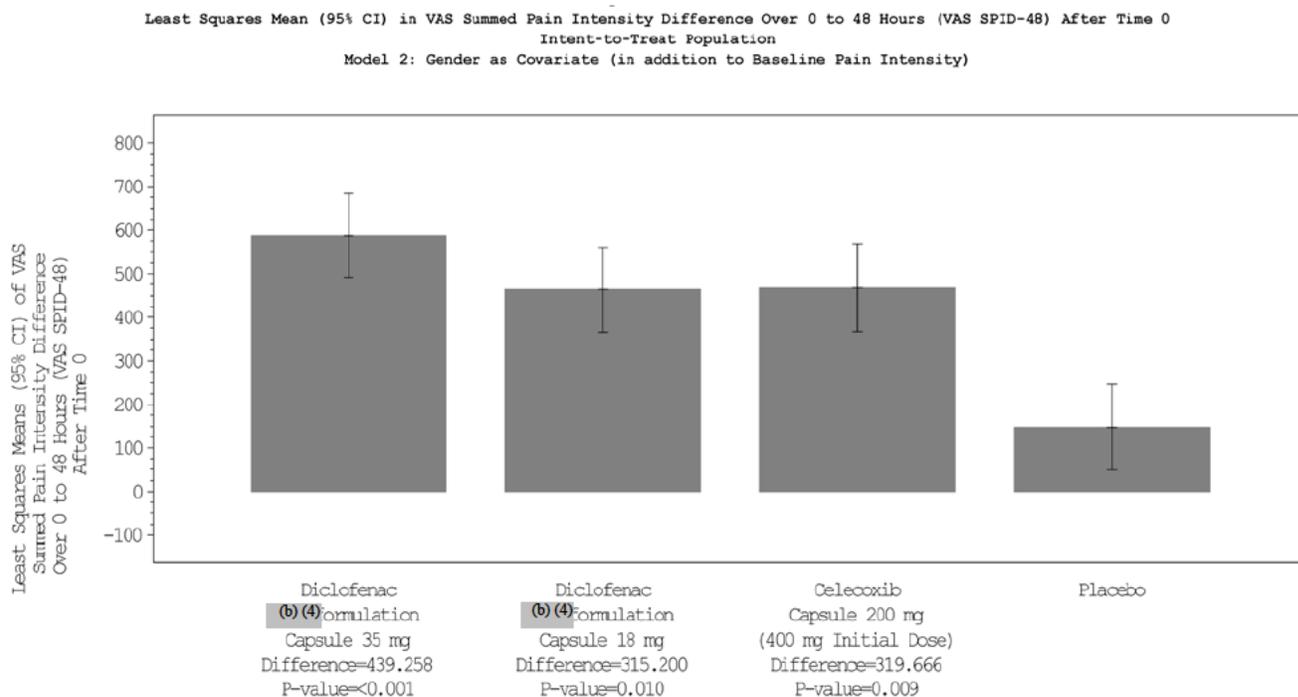
Note: LS Means (SE) for each treatment group were displayed in the bar chart. 'Difference' refers to LS mean difference between each treatment group and the placebo. P-value were from ANCOVA analysis. Source data: Table 14.2.1.1.

Source: Applicant's Clinical Study Report, Figure 14.2.1.1, p. 129

For Model 1 (Table 11), the LS mean (standard error [SE]) was used in the primary analysis. In comparison with the placebo group, the largest difference in Squares mean (SE) was seen for the 35-mg diclofenac treatment group (446.946 [122.2935]) indicating a statistically significant difference ($P < 0.001$). Differences in the 18-mg diclofenac group 316.145 (121.5971) ($P < 0.010$) and the celecoxib treatment group 313.119 (122.5676) ($P < 0.011$) compared with the placebo group were of a lesser magnitude than the 35mg diclofenac.

The Applicant performed a sensitivity analysis using gender as a covariate (Model 2) in addition to baseline pain intensity. The results of this analysis were consistent with those of the main model (Table 12).

Table 12: Model 2: Gender as Covariate



Note: LS Means (SE) for each treatment group were displayed in the bar chart.
 'Difference' refers to LS mean difference between each treatment group and the placebo. P-value were from ANCOVA analysis.
 Source data: [Table 14.2.1.1](#).

Source: Applicant Clinical Study Report, p.130

The Applicant's primary efficacy results using the PP population were generally comparable to those using the ITT population. Analysis of VASSPID-48 was also performed in different subpopulations (age, race, and gender) using the PP population. The PP population included 411 subjects instead of the 428 ITT population. Although the number is lower in the PP, this is still adequate for the subgroup analysis given that the sample size is similar. Dr. Feng Li performed additional analyses of the primary endpoint by gender, age and race for all the randomized subjects. The subgroups summaries were consistent with those observed in the overall population.

Both diclofenac groups (18mg and 35mg) for ages < 45 years were comparable to the overall findings in the ITT group. However, in the group ages > 45 years, the diclofenac 18mg treatment group was not statistically significant with regard to the primary endpoint (P=0.201). This may be due to the smaller number of subjects in this subpopulation, however there was a trend towards superiority over placebo. With regard to race, most subjects were white and findings in other races were somewhat limited given the small sample sizes. The sample sizes were also limited in the male subpopulation (n=18 and 15 for diclofenac 35mg and 18mg treatment groups,

respectively). Statistical significance was not reached in the male group, and once again may be due to lack of power. The female subpopulation showed statistical significance in both the 35mg and 18 diclofenac treatment groups ($p=0.001$ and 0.017 , respectively). Overall, these analyses were not powered to detect differences in these subpopulations. However, even when there was not statistical significance, the results trended towards favoring diclofenac when compared to placebo using the primary endpoint.

Secondary Efficacy Results

The following are a summary of the Applicant's results.

- Summed Pain Intensity Difference Over 0 to 4 Hours, Over 0 to 8 Hours, and Over 0 to 24 Hours (Table 13)
 - Significant analgesia was evident in the 35mg diclofenac treatment group when compared to placebo during the 0-8 hour period as measured by the VASSPID-8 ($p=0.009$)
 - By 24 hours (VASSPID-24) all treatment groups were superior to placebo

Table 13: Analysis of the Visual Analogue Scale Summed Pain Intensity Difference Over 0 to 4 Hours, 0 to 8 Hours, and 0 to 24 Hours—Intent-to-Treat Population

Statistic	Diclofenac (b) (4) Formulation Capsule		Celecoxib Capsule	Placebo
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	(n = 106)
VAS SPID-4				
n	107	109	106	106
Mean (SD)	31.568 (68.6)	27.450 (64.9)	25.109 (62.9)	14.406 (53.5)
Median (minimum, maximum)	1.500	0.250	2.750	-1.125
Comparison vs placebo ^b	(-74.50, 255.00)	(-56.00, 313.00)	(-42.75, 293.75)	(-40.50, 275.50)
P value for difference	0.043	0.109	0.183	
VAS SPID-8				
n	107	109	106	106
Mean (SD)	64.689 (138.5)	56.404 (132.6)	51.675 (122.4)	23.151 (84.9)
Median (minimum, maximum)	1.750	0.500	3.125	-1.125
Comparison vs placebo ^b	(-154.50, 551.75)	(-56.00, 670.00)	(-42.75, 649.75)	(-40.50, 577.50)
P value for difference	0.009	0.029	0.050	
VAS SPID-24				
n	107	109	106	106
Mean (SD)	230.708 (499.9)	177.101 (418.3)	170.845 (393.0)	48.811 (186.5)
Median (minimum, maximum)	2.750	0.500	3.125	-0.875
Comparison vs placebo ^a	(-154.50, 2087.75)	(-56.00, 1783.00)	(-42.75, 2097.75)	(-40.30, 1128.50)
P value for difference	<0.001	0.004	0.004	

Source of data: [Section 14.2 Table 14.2.2.1](#)

Abbreviations: SD = standard deviation; VAS SPID-4 = Visual Analogue Scale Summed Pain Intensity Difference over 0 to 4 hours; VAS SPID-8 = Visual Analogue Scale Summed Pain Intensity Difference over 0 to 8 hours; VAS SPID-24 = Visual Analogue Scale Summed Pain Intensity Difference over 0 to 24 hours.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Nominal P values from 2-sample t-tests comparing the placebo group with other treatment groups.

Source: Applicant's Clinical Study Report, Table 11-4, p. 59

- Total Pain Relief Over 0- to-4 Hours, Over 0- to-8 Hours, Over 0- to- 24 Hours, and Over 0- to- 48 Hours (Table 14)
 - Assesses pain using a categorical scale
 - At the 0- to 4-hour time period, only the mean TOTPAR scores for the Diclofenac 35-mg group demonstrated pain relief compared with that of the placebo group
 - For the TOTPAR-8, TOTPAR-24, and TOTPAR-48 scores, values were highest in the diclofenac 35-mg group; values for the diclofenac 18-mg and celecoxib 200-mg groups were similar.

Table 14: Analysis of Total Pain Relief Over 0 to 4 Hours, 0 to 8 Hours, 0 to 24 Hours, and Over 0 to 48 Hours — Intent-to-Treat Population

Statistic	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule	Placebo
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	(n = 106)
TOTPAR-4				
n	107	109	106	106
Mean (SD)	2.530 (3.6)	2.112 (3.5)	2.226 (3.5)	1.387 (2.7)
Median (minimum, maximum)	0.750 (0.00, 13.75)	0.250 (0.00, 14.00)	0.625 (0.00, 14.00)	0.000 (0.00, 12.00)
Comparison vs placebo ^a				
<i>P</i> value for difference	0.009	0.091	0.053	
TOTPAR-8				
n	107	109	106	106
Mean (SD)	4.652 (7.5)	3.690 (6.8)	3.840 (6.8)	1.943 (4.4)
Median (minimum, maximum)	0.750 (0.00, 26.75)	0.250 (0.00, 25.00)	0.750 (0.00, 26.00)	0.000 (0.00, 22.75)
Comparison vs placebo ^a				
<i>P</i> value for difference	0.002	0.026	0.017	
TOTPAR-24				
n	107	109	106	106
Mean (SD)	13.325 (25.9326)	10.186 (21.3384)	10.670 (22.2595)	3.566 (10.8804)
Median (minimum, maximum)	0.750 (0.00, 90.00)	0.250 (0.00, 74.75)	0.750 (0.00, 84.25)	0.000 (0.00, 68.50)
Comparison vs placebo ^b				
<i>P</i> value for difference	<0.001	0.005	0.004	
TOTPAR-48				
n	107	109	106	106
Mean (SD)	28.054 (58.1)	21.635 (48.1)	22.972 (51.1)	4.925 (19.4)
Median (minimum, maximum)	0.750 (0.00, 186.00)	0.250 (0.00, 166.00)	0.750 (0.00, 180.25)	0.000 (0.00, 180.25)
Comparison vs placebo ^b				
<i>P</i> value for difference	<0.001	<0.001	<0.001	

Source of data: Section 14.2, Table 14.2.2.2

Abbreviations: SD = standard deviation; TOTPAR-4 = total pain relief over 0 to 4 hours; TOTPAR-8 = total pain relief over 0 to 8 hours; TOTPAR-24 = total pain relief over 0 to 24 hours; TOTPAR-48 = total pain relief over 0 to 48 hours.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Nominal *P* values are from 2-sample *t* tests comparing the placebo group with other treatment groups.

Source: Applicant's Clinical Study Report, Table 11-5, p. 62

- Visual Analogue Scale Pain Intensity Difference
 - The mean VASPID values measured against the baseline value for each active treatment group and the placebo group were evaluated and compared at each scheduled time point after Time 0
 - Subjects in diclofenac and celecoxib treatment groups demonstrated evidence of analgesia during the initial 0-5 hour period (35mg diclofenac

showed significance at 4 hours) following the start of treatment followed by substantial continued improvement in analgesia up to 48 hours

- Visual Analogue Scale Pain Intensity Score
 - The 35mg diclofenac group showed statistical significance from placebo before the other treatment groups (consistently after the 3 hour time point)
 - The 18mg diclofenac group did not reach statistical significance from placebo until the 20 hour time point ($p=0.035$), whereas celecoxib reached statistical significance at the 5 hour time point ($p=0.039$)
- Time to Onset of Analgesia (Table 15)
 - The Cox proportional hazards regression model analysis was used to evaluate time to onset of analgesia
 - The mean times to onset were 2.2 and 1.8 hours for the 35mg and 18mg groups, respectively
 - The hazard ratio (95% CI) for the time to onset of analgesia for Diclofenac 35 mg versus placebo was 1.8 (1.06, 3.12) ($P = 0.030$) and demonstrated a difference for only this treatment group
 - Figure 3 illustrates the difference between treatment groups and placebo.
 - The greatest difference is between Diclofenac 35mg and placebo, and most notable between the 0-2 hour time points

Table 15: Time to Onset of Analgesia (Measured as Time to Perceptible Pain Relief Confirmed by Meaningful Pain Relief) — Intent-to-Treat Population

Statistic	Diclofenac (b) (4) Formulation Capsule		Celecoxib Capsule 200 mg ^a	Placebo (n = 106)
	35 mg (n = 107)	18 mg (n = 109)	(n = 106)	
Subjects analyzed, n (%)	38 (35.5%)	30 (27.5%)	32 (30.2%)	21 (19.8%)
Subjects censored, n (%)	69 (64.5%)	79 (72.5%)	73 (68.9%)	84 (79.2%)
Mean (SE) (hour) ^b	2.2 (0.14)	1.8 (0.09)	1.5 (0.07)	1.6 (0.06)
Log-rank <i>P</i> value ^c	0.126			
Restricted model 1				
Log-rank <i>P</i> value ^d	0.483	0.486		
Cox proportional hazards model ^e				
Hazard ratio (95% CI)	1.2 (0.74, 1.92)	0.9 (0.54, 1.46)		
Treatment <i>P</i> value	0.462	0.635		
Gender <i>P</i> value	0.691	0.762		
Baseline pain intensity <i>P</i> value	0.130	0.004		
Restricted model 2				
Log-rank <i>P</i> value ^f	0.025	0.312	0.103	
Cox proportional hazards model ^g				
Hazard ratio (95% CI)	1.8 (1.06, 3.12)	1.3 (0.76, 2.32)	1.5 (0.85, 2.57)	
Treatment <i>P</i> value	0.030	0.319	0.166	
Gender <i>P</i> value	0.684	0.793	0.641	
Baseline pain intensity <i>P</i> value	0.593	0.057	0.014	

Source of data: Section 14.2, Table 14.2.4

Abbreviations: CI = confidence interval; NA = not estimable with Kaplan-Meier method; Q = quartile; SE = standard error.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Values are Kaplan-Meier estimates for the time to response.

^c Values were obtained by using the Kaplan-Meier log-rank test to compare the time to response among 4 treatment groups.

^d The log-rank test was used to compare a high dose or a low dose of trial drug and reference medication (ie,

(b) (4) formulation 35 mg versus celecoxib 200 mg; Diclofenac (b) (4) formulation 35 mg versus celecoxib 200 mg).

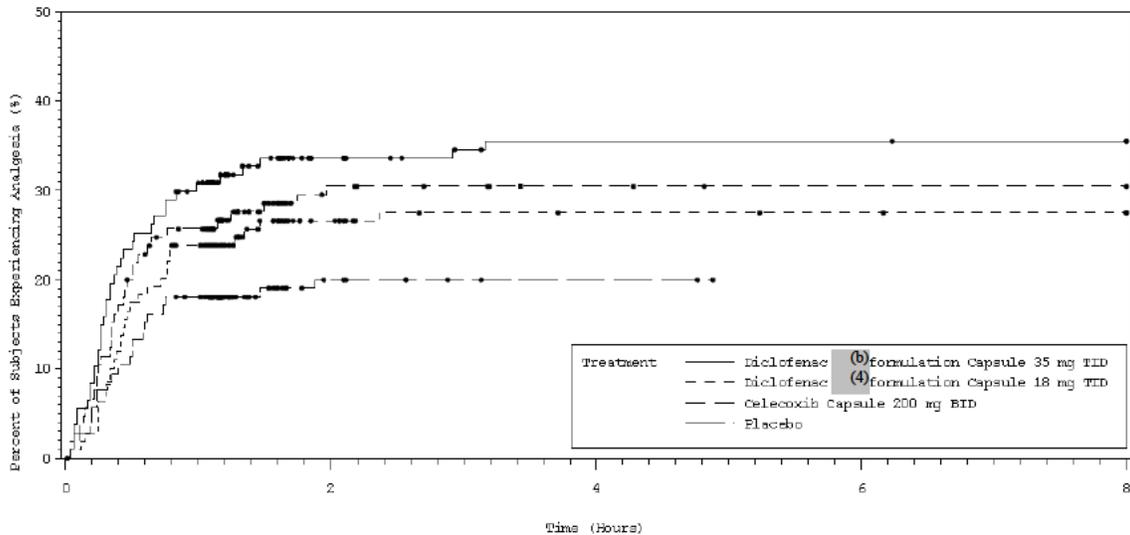
^e Cox proportional hazard regression models included treatment and gender as factor and baseline pain intensity as covariate and compared high dose or low dose of trial drug and reference medication (ie, Diclofenac (b) (4) formulation 35 mg versus celecoxib; Diclofenac (b) (4) formulation 18 mg versus celecoxib). For example, to obtain any of the *P* values under the “Diclofenac (b) (4) formulation Capsule 35 mg” column, only subjects receiving Diclofenac (b) (4) formulation Capsule 35 mg and celecoxib were included (ie, the model tested the hypothesis “the hazard rates in Diclofenac (b) (4) formulation Capsule-35 mg and celecoxib groups are equal”).

^f The log-rank test was used to compare each treatment group with the placebo group (ie, only those subjects receiving each applicable treatment or placebo were included in the analysis).

^g Cox proportional hazard regression models included treatment and gender as factor and baseline pain intensity as covariate and compared each trial drug treatment separately with placebo treatment. For example, to obtain any of the *P* values under the “Diclofenac (b) (4) formulation Capsule 35 mg” column, only subjects receiving Diclofenac (b) (4) formulation Capsule 35 mg and placebo were included (ie, the model tested the hypothesis “The hazard rates in the placebo and Diclofenac (b) (4) formulation Capsule 35 mg groups are equal”).

Source: Applicant’s Clinical Study Report, p. 68

Figure 3: Time to Onset of Analgesia – ITT Population



Source: Applicant's Clinical Study Report, p. 69

- Pain Relief Scores at Each Scheduled Time Point
 - Pain relief was assessed using a 5-point categorical Likert scale (“none,” “a little,” “some,” “a lot,” and “complete”) at each scheduled time point
 - At 1.5 hours after trial entry, only the results of the diclofenac 35-mg group were different compared with those of the placebo group ($P = 0.013$) and this continued at each subsequent scheduled time assessment
 - Results are supportive of the analysis of time to onset of analgesia
- Peak Pain Relief
 - All active treatment groups were better than those for the placebo group (Table 16)

Table 16: Summary of Peak Pain Relief — Intent-to-Treat Population

Statistic	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule	Placebo (n = 106)
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	
None (0)	45 (42.1%)	47 (43.1%)	42 (39.6%)	55 (51.9%)
Little (1)	20 (18.7%)	30 (27.5%)	26 (24.5%)	29 (27.4%)
Some (2)	14 (13.1%)	5 (4.6%)	15 (14.2%)	8 (7.5%)
A Lot (3)	10 (9.3%)	11 (10.1%)	13 (12.3%)	13 (12.3%)
Complete (4)	18 (16.8%)	16 (14.7%)	10 (9.4%)	1 (0.9%)
<i>P</i> value ^b	0.002	0.016	0.009	

Source of data: [Section 14.2, Table 14.2.6.1](#)

Abbreviations: ITT = intent-to-treat; SD = standard deviation.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b The *P* values were obtained from a Cochran-Mantel-Haenszel test comparing active treatment group and placebo group.

Note: The imputed pain relief scores were used in this summary table, the category of pain relief was based on the actual imputed pain relief values.

Source: Applicant's Clinical Study Report, Table 11-8, p. 70

- Time to Peak Pain Relief
 - For the placebo treatment group, only 3 subjects (2.8%) were analyzed and 101 subjects (95.3%) were censored
 - In the first restricted model, the hazard ratio (95% CI) was 1.3 (0.69, 2.48) for the diclofenac 35-mg group and 0.6 (0.32, 1.28) for the diclofenac 18-mg group
- Time to First Perceptible Pain Relief
 - In the Kaplan-Meier log rank test, there were no differences between the treatment groups (log-rank *P* value = 0.401)
- Time to Meaningful Pain Relief (Table 17)
 - Restricted Model 1 compared diclofenac to celecoxib
 - Restricted Model 2 compared active treatment groups with placebo
 - No differences in times to response among the 4 treatment groups (*P* = 0.692)
 - Model 1: No differences comparing both the diclofenac 35-mg and the diclofenac 18-mg treatment groups with the celecoxib group (*P* = 0.848 and *P* = 0.572, respectively)
 - Model 2: Difference compared with placebo were as follows: diclofenac 35-mg group, *P*=0.309; diclofenac 18-mg group, *P* = 0.715; and for the celecoxib group, *P* = 0.417)

Table 17: Time to Meaningful Pain Relief – ITT Population

Statistic	Diclofenac (b) (4) Formulation Capsule		Celecoxib Capsule	Placebo
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	(n = 106)
Subjects analyzed, n (%)	38 (35.5%)	30 (27.5%)	32 (30.2%)	21 (19.8%)
Subjects censored, n (%)	69 (64.5%)	79 (72.5%)	73 (68.9%)	85 (80.2%)
Mean (SE) (hour) ^b	3.1 (0.27)	2.7 (0.15)	2.8 (0.18)	2.4 (0.11)
Log-rank <i>P</i> value ^c	0.692			
Restricted model 1				
Log-rank <i>P</i> value ^d	0.848	0.572		
Cox proportional hazards model ^e				
Hazard ratio (95% CI)	1.1 (0.69, 1.77)	0.9 (0.56, 1.52)		
Treatment <i>P</i> value	0.686	0.742		
Gender <i>P</i> value	0.131	0.742		
Baseline pain intensity <i>P</i> value	0.396	0.036		
Restricted model 2				
Log-rank <i>P</i> value ^f	0.309	0.715	0.417	
Cox proportional hazards model ^g				
Hazard ratio (95% CI)	1.4 (0.78, 2.36)	1.1 (0.61, 1.90)	1.2 (0.65, 2.05)	
Treatment <i>P</i> value	0.288	0.804	0.617	
Gender <i>P</i> value	0.345	0.876	0.473	
Baseline pain intensity <i>P</i> value	0.625	0.085	0.036	

Source of data: Section 14.2, Table 14.2.8

Abbreviations: CI = confidence interval; ITT = intent-to-treat; NA = not estimable with Kaplan-Meier method; Q = quartile; SE = standard error.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Values are Kaplan-Meier estimates for the time to response.

^c Kaplan-Meier log-rank test was used to compare the time to response among 4 treatment groups.

^d The log-rank test was used to compare high dose or low dose of trial drug and reference medication (ie, (b) (4) formulation 35 mg versus celecoxib; Diclofenac (b) (4) formulation 35 mg versus celecoxib).

^e Cox proportional hazard regression models included treatment and gender as factors and baseline pain intensity as a covariate and compared a high dose or a dose of the trial drug and reference medication (ie, Diclofenac (b) (4) formulation 35 mg versus celecoxib; Diclofenac (b) (4) formulation 18 mg versus celecoxib). For example, to obtain any of the *P* values under the “Diclofenac (b) (4) formulation Capsule 35 mg” column, only subjects receiving Diclofenac (b) (4) formulation Capsule 35 mg and celecoxib were included (ie, the model tested the hypothesis “the hazard rates in the Diclofenac (b) (4) formulation Capsule 35-mg and celecoxib groups are equal”).

^f The log-rank test was used to compare each treatment group with the placebo group (ie, only those subjects receiving each applicable treatment or placebo were included in the analysis).

^g Cox proportional hazard regression models included treatment and gender as factors and baseline pain intensity as a covariate and compared each trial drug treatment separately with placebo treatment. For example, to obtain any of the *P* values under the “Diclofenac (b) (4) formulation Capsule 35 mg” column, only subjects receiving Diclofenac (b) (4) formulation Capsule 35 mg and placebo were included (ie, the model tested the hypothesis “The hazard rates in the placebo and Diclofenac (b) (4) formulation Capsule 35-mg groups are equal”).

Source: Applicant’s Clinical Study Report, p. 76

- Use of Rescue Medication
 - Total overall use of rescue medication during the 0- to 24-hour and the 0- to 48-hour time periods was similar for the 3 active treatment groups and, as expected, was higher for the placebo group
 - The time to first use of rescue medication (Table 18) was not different when comparing diclofenac and celecoxib groups (Restricted Model 1)
 - Table 18 also shows the time to first use of rescue was different for all treatment groups when compared to placebo (Restricted Model 2)
 - The first use of rescue medication occurred at a differing rate than for the placebo group (hazard ratio [95% CI] for the diclofenac 35-mg, diclofenac 18-mg, and celecoxib treatment groups, which were 0.6 [0.44, 0.79], 0.7 [0.49, 0.87], and 0.7 [0.52, 0.92], respectively)

Table 18: Time to First Use of Rescue Medication — Intent-to-Treat Population

Statistic	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule	Placebo (n = 106)
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	
Subjects analyzed, n (%)	88 (82.2%)	93 (85.3%)	93 (85.3%)	103 (97.2%)
Subjects censored, n (%)	19 (17.8%)	16 (14.7%)	16 (15.1%)	3 (2.8%)
Mean (SE) (hour) ^b	5.9 (0.78)	9.1 (1.56)	4.9 (0.68)	2.7 (0.45)
Log-rank <i>P</i> value ^c	<0.001			
Restricted model 1				
Log-rank <i>P</i> value ^d	0.423	0.873		
Cox proportional hazards model ^e				
Hazard ratio (95% CI)	0.9 (0.67, 1.21)	0.9 (0.70, 1.25)		
Treatment <i>P</i> value	0.488	0.664		
Gender <i>P</i> value	0.040	0.474		
Baseline pain intensity <i>P</i> value	0.059	<0.001		
Restricted model 2				
Log-rank <i>P</i> value ^f	<0.001	0.001	0.004	
Cox proportional hazards model ^g				
Hazard ratio (95% CI)	0.6 (0.44, 0.79)	0.7 (0.49, 0.87)	0.7 (0.52, 0.92)	
Treatment <i>P</i> value	<0.001	0.003	0.013	
Gender <i>P</i> value	0.286	0.671	0.456	
Baseline pain intensity <i>P</i> value	0.829	0.003	0.013	

Source of data: Section 14.2, Table 14.2.10

Source: Applicant's Clinical Study Report, p. 78

- Subject's Global Evaluation of Trial Drug
 - Patients in all 3 treatment groups had differing responses compared with the placebo group (Table 19)

Table 19: Patient's Global Evaluation of Trial Drug — ITT Population

Statistic	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule 200 mg ^a	Placebo	Total
	35 mg (n = 107)	18 mg (n = 109)	(n = 106)	(n = 106)	(N = XX)
Poor	59 (55.1%)	72 (66.1%)	66 (62.3%)	81 (76.4%)	278 (65.0%)
Fair	16 (15.0%)	13 (11.9%)	16 (15.1%)	11 (10.4%)	56 (13.1%)
Good	11 (10.3%)	7 (6.4%)	6 (5.7%)	9 (8.5%)	33 (7.7%)
Very good	11 (10.3%)	8 (7.3%)	9 (8.5%)	5 (4.7%)	33 (7.7%)
Excellent	10 (9.3%)	9 (8.3%)	9 (8.5%)	0	28 (6.5%)
Missing	0	0	0	0	0
<i>P</i> value ^b	<0.001	0.012	0.004		

Source of data: Section 14.2, Table 14.2.12

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b The *P* values were obtained from the Cochran-Mantel-Haenszel test comparing the active treatment group and the placebo group.

Source: Applicant's Clinical Study Report, p. 80

There is a trend towards increased efficacy for the diclofenac 35mg group compared to the 18mg group. However, primary and secondary endpoints support the efficacy of the 18mg dose when compared to placebo. The secondary analyses generally favored a treatment effect for diclofenac. However, no adjustments were made by the Applicant to control for multiplicity on these endpoints.

Safety Findings

A brief summary of the safety findings for this clinical trial is provided herein. A complete discussion of safety can be found in Section 7.

Deaths

No subjects died during the trial.

Serious Adverse Events (SAEs)

One subject experienced a serious AE during the trial. The subject was in the Celecoxib group.

Discontinuations Due to Adverse Events

No subject discontinued due to an AE during the trial.

Common Adverse Events

77 (72%) and 84 (77.1%) subjects experienced at least 1 TEAE in the 35mg and 18mg diclofenac groups, respectively. 86 (81.1%) and 83 (78.3%) subjects experienced at

least 1 TEAE in the Celecoxib and placebo groups, respectively. The most frequent AEs were nausea (23.4%, 31.2%), headache (10.3%, 15.6%) and dizziness (4.7%, 15/6%) in 35mg and 18mg diclofenac groups, respectively.

Trial DIC2-08-03

“A Phase 2, Randomized, Double-Blind, Single-Dose, Parallel-Group, Active- and Placebo-Controlled Study of Diclofenac (b) (4) formulation (b) (4) Capsules for the Treatment of Pain After Surgical Removal of Impacted Third Molars”

Conducted from 10/7/09 to 12/15/09

This study was conducted at three sites within the United States.

Overview

This study is a Proof-of-Concept (POC), Phase 2 study, used as only supportive evidence of efficacy and safety. This study did not use the commercial formulation and is not included in the primary analysis of safety or efficacy, and will only be briefly reviewed in this report. The primary objective was to evaluate the analgesic efficacy and safety of diclofenac capsules compared with placebo. This is a brief review of the primary analysis of efficacy and safety data from this study.

Protocol

Key Inclusion Criteria:

- ≥ 18 and ≤ 50 years of age
- Extraction of 2 or more third molars. At least 1 of the third molars must have been a fully or partially bone-impacted mandibular molar
- Moderate to severe pain intensity (a score of ≥ 50 mm on a 100-mm Visual Analogue Scale [VAS]) within 6 hours after surgery
- Good health

Key Exclusion Criteria:

- Allergy to NSAIDs
- Substance abuse
- Any medication within 5 half-lives of dosing the study drug
- Significant medical condition
- History of chronic use of NSAIDs, opioids, steroids

Subjects were to be randomized in a 1:1:1:1 ratio to receive 1 oral dose of diclofenac (b) (4) capsules (18 mg or 35 mg), celecoxib capsules (400 mg), or placebo.

During the 12 hours following Time 0, subjects completed efficacy and safety assessments. Subjects remained at the study site overnight and were discharged the morning of Day 2. Upon discharge from the study site, subjects were to be given a diary to record concomitant medications taken and AEs experienced after discharge. On Day

8 (± 2 days), subjects were to return to the study site for an abbreviated confirmatory physical assessment and concomitant medication and AE assessments. Study procedures are outlined in Table 20 below.

Treatments

Subjects were to receive 1 oral dose of 1 of the following treatments:

- One 18-mg diclofenac Capsule and 1 placebo capsule
- One 35-mg diclofenac Capsule and 1 placebo capsule
- Two 200-mg celecoxib capsules
- Two placebo capsules

Table 20: Study Schedule

	Screening (Days -28 to -1)	Day of Surgery (Day 1) ^a						Day 2	Follow-up (Day 8 ± 2 days) or ET
		Preop	Postop						
			Predose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h		
Written informed consent	X								
Assign a screening number	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Medical history	X	X ^b							
Physical examination ^c	X							X	
Vital signs ^d	X	X	X				X	X	
Height, weight, and BMI	X								
Clinical laboratory tests (hematology, chemistry, urinalysis)	X								
Pregnancy test for female subjects of childbearing potential ^e	X	X							
Urine drug screen	X	X							
Alcohol breathalyzer test		X							
Oral radiography ^f	X								
Review study restrictions with subject	X								
Pain intensity (VAS) ^g			X		X	X	X		
Randomization			X						
Dosing with study drug				X					
Stopwatch assessment ^h				X					
Pain relief (5-point categorical scale) ^g					X	X	X		
Global evaluation of study drug ⁱ							X		
Concomitant medications		X ^b	X	X	X	X	X	X	
Adverse events ^l		X	X	X	X	X	X	X	
Dispense rescue medication/pain medications							X		
Collect unused rescue medication/pain medications								X	
Dispense/collect subject diary							X	X	
Discharge from study site							X		

Clinical Review
Steven Galati M.D.
NDA 204592
Zorvolex/Diclofenac acid capsules

Abbreviations: BMI, body mass index; ET, early termination; h, hour(s); min, minute(s); Preop, preoperative; Postop, postoperative; VAS, visual analogue scale.

a. Times listed were relative to dosing with study drug.

b. Medical history and concomitant medication use since Screening were to be updated on Day 1 before surgery.

c. A complete physical examination (excluding the genitourinary examination) was performed at Screening. An abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck, was performed at the Follow-up Visit (or Early Termination Visit).

d. Vital signs were recorded after the subject had been in a sitting position for 5 minutes at the following times: at Screening, before surgery, before Time 0, 12 hours after Time 0, and/or immediately before the first dose of rescue medication, and at the Follow-up Visit (or Early Termination Visit).

e. Serum pregnancy test at Screening and urine pregnancy test before surgery on Day 1 (female subjects of childbearing potential only). Test results had to be negative for the subject to continue in the study.

f. Oral radiographs taken within 1 year before Screening were acceptable and did not need to be repeated.

g. Pain assessments were conducted at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after Time 0 and immediately before the first dose of rescue medication. Pain intensity was also assessed predose. At each assessment time point, the pain intensity assessment was completed first and the pain relief assessment was completed second. Subjects were not permitted to compare their responses with their previous responses.

h. Two stopwatches were started immediately after the subject had swallowed the second capsule of study drug with 8 ounces of water (Time 0). Subjects recorded the time to perceptible and meaningful pain relief, respectively, by stopping the stopwatches.

i. Subjects completed a global evaluation of study drug 12 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurred first).

j. Adverse events were monitored and recorded from the time of signing of the informed consent form until the Follow-up Visit (or Early Termination Visit).

Source: Applicant's Clinical Study Report, DIC2-08-03, p. 24

Efficacy

The primary efficacy endpoint was the sum of total pain relief (TOTPAR) over 0 to 12 hours (TOTPAR-12) after Time 0. The TOTPAR was calculated using the pain relief score (5-point categorical scale). The primary analysis (Model 1) was completed using an ANCOVA model that included TOTPAR-12 as the response variable, treatment effect as the factor, and baseline pain intensity as the covariate.

- The LS mean (95% CI) was 16.893 (13.215, 20.571) for the diclofenac 35 mg group and 5.486 (1.802, 9.170) for the placebo group
- The LS mean difference (95% CI) inTOTPAR-12 between active treatment and placebo was 11.407 (6.195, 16.619) for the diclofenac 35 mg group, and the difference was statistically significant ($P < 0.001$) in favor of the active treatment
- The LS mean difference (95% CI) in TOTPAR-12 for the 18mg diclofenac and celecoxib groups compared to placebo was 17.770 (14.020, 21.520) and 14.685 (11.008, 18.363), respectively. Both groups showed a difference that was statistically significant ($P < 0.001$) in favor of the active treatment
- Additional analyses using gender, baseline pain and surgical trauma rating as covariates showed results consistent with the primary analysis (Model 1)

Safety

- 202 subjects were enrolled in this study and randomized into the four treatment groups
- All subjects received one dose
- There were no deaths or other treatment-emergent SAEs (1 subject experienced an SAE during Screening)
- One subject discontinued due to a TEAE of incision site hemorrhage in the celecoxib group
- TEAEs occurred most frequently in subjects treated with celecoxib 400 mg (62.7%, 32/51) followed in decreasing order of incidence by subjects treated with diclofenac 35 mg (60.8%, 31/51), diclofenac 18 mg (55.1%, 27/49), and placebo (52.9%, 27/51)

Conclusion

- Diclofenac groups 18mg and 35mg, showed a significant difference in TOTPAR-12 endpoint analysis when compared to placebo
- There were no concerning safety signals
- The results of this trial serve as supportive evidence of safety and efficacy for diclofenac 35 mg and 18 mg capsules
- The data from this trial will not serve as the basis for any labeling claims given the drug used in this study was not the to-be-marketed formulation

6 Review of Efficacy

Efficacy Summary

Based on the review of a pivotal Phase 3 trial (DIC3-08-04), and a POC Phase 2 study (DIC2-08-03), evaluating 18 and 35mg of diclofenac capsules, there is evidence of efficacy for both dosages for the treatment of acute pain as evaluated in an acute postoperative pain population. The Applicant seeks an indication of acute mild-to-moderate pain. For inclusion into the trial, patients must have had a minimum VAS pain score of 40mm. For both trials, the analyses of the primary endpoints were statistically significant in favor of the 18mg and 35mg diclofenac capsules. However, DIC2-08-03 used a proof-of-concept formulation and can only provide supportive evidence. Therefore, the data from DIC2-08-03 cannot be used to support any labeling claims.

The prespecified primary endpoint for the clinical trial DIC3-08-04 was the VASSPID-48. The Applicant utilized the 505(b)(2) pathway, and will rely on the Agency's previous efficacy and safety findings for the diclofenac product, Cataflam. Therefore, the Division agreed with the Applicant's plan to perform a single well-controlled pivotal Phase 3 trial to support their application using the VASSPID-48 as the primary endpoint for efficacy. The bunionectomy pain model was used in the pivotal Phase 3 trial and is a validated pain model.

Since this application is supported by one pivotal Phase 3 clinical trial (DIC3-08-4), much of the information with regard to efficacy is described in detail in Section 5.3. Section 6 will discuss the statistical reviewer's confirmatory and additional analyses and provide a high-level summary of the key findings.

As described in Sections 1 and 2, the Applicant's hypothesized that their formulation of diclofenac would show increased dissolution and absorption rates leading to comparable efficacy at a lower dose and a possible improved safety profile compared to the reference drug. However, none of the efficacy studies included the reference drug, Cataflam, therefore, no comparative conclusion can be made with regard to efficacy or safety between the Applicant's drug and the reference drug. Celebrex was used in the pivotal trial for assay sensitivity, but the study was not designed to evaluate comparative efficacy between diclofenac and Celebrex.

6.1 Indication

The proposed indication is for the management of mild to moderate acute pain. Although, subjects with a pain intensity rating ≥ 40 mm on a 100-mm VAS within 9 hours of discontinuation of regional anesthesia were eligible for enrollment in the pivotal efficacy trial, a vast majority of patients used rescue medication (see discussion below). Therefore, the previously agreed upon indication, for the management of mild to moderate acute pain, is appropriate.

6.1.1 Methods

See Section 5.3.

6.1.2 Demographics

See Section 5.3.

6.1.3 Subject Disposition

See Section 5.3.

6.1.4 Analysis of Primary Endpoint(s)

The Applicant's primary endpoint for trial DIC3-08-04 was the VAS summed pain intensity difference (VASSPID) (calculated as time-weighted averages) over 0 to 48 hours (VASSPID-48) after Time 0. The VASSPID-48 was the agreed upon primary endpoint discussed in numerous meetings with the Applicant and the Division during the clinical development process. The VASSPID is an acceptable endpoint for an acute pain trial as it provides a measure of pain intensity over the entire duration of dosing. The Applicant used baseline pain as the covariate and the imputation method was BOCF after a subject used rescue medication or withdrew because of lack of efficacy or an AE/intolerance to the trial drug. For subjects who withdrew from the trial due to reasons other than lack of efficacy or an AE/intolerance to trial drug, missing values were imputed by using LOCF. When the percentage of subjects who take rescue medications is high, this approach to handling pain intensity scores after rescue may substantially influence the comparisons among treatment groups. This method may penalize a treatment group with a higher percentage of subjects who used rescue and more than 80% of the subjects took rescue with the placebo group having the most rescue medication use (Table 21). One treatment group might appear more efficacious than another if fewer subjects in that group requested rescue (i.e., diclofenac compared with placebo).

Table 21 – Rescue in DIC3-08-04

	Diclofenac		Celecoxib	Placebo
	35 mg	18 mg		
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

The Applicant's analyses of efficacy showed superiority of diclofenac when compared to placebo. The Applicant also conducted a sensitivity analysis by adding gender as a factor into the model. The results of this sensitivity analysis were consistent with those of the primary analysis. See Section 5.3 for the Applicant's analyses of the results from trial DIC3-08-04. Our statistician, Dr. Feng Li, confirmed the Applicant's results and additionally performed a sensitivity analysis which used observed pain scores with no imputation method. Dr. Li's analysis was used to evaluate any potential problems with the Applicant's imputation strategy for rescue medication use. The results of this analysis were consistent with the Applicant's original primary efficacy analysis showing that all treatment groups were superior to placebo (Table 22). This analysis, coupled with the Applicant's findings, provides confidence of the drug's efficacy when compared to placebo.

Table 22 – Sensitivity Analysis of SPID48 Using Observed Pain Scores Regardless of Rescue

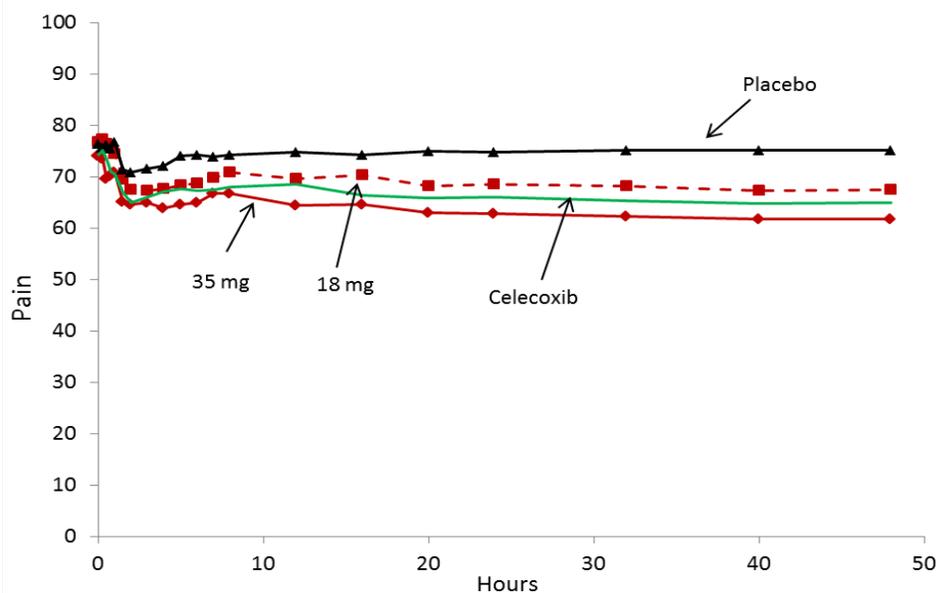
Statistics	Diclofenac 35mg	Diclofenac 18mg	Celecoxib	Placebo
N	107	109	106	106
LS Mean (SE)	2392(82)	2293(81)	2159(82)	1661(82)
95% CI	(2232, 2553)	(2134,2452)	(1997,2320)	(1499,1823)
Difference in LS Mean (SE)	731(116)	632(115)	498(116)	
95% CI for diff. in LS Mean	(503,960)	(405,859)	(269,726)	
p-value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

Source: Dr. Feng Li's Statistical Review

Figure 4 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. All the pain curves are rather flat after 10 hours, and it appears as though pain intensity did not substantially decrease over the course of the study for subjects in any of the treatment groups. This is because that 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.

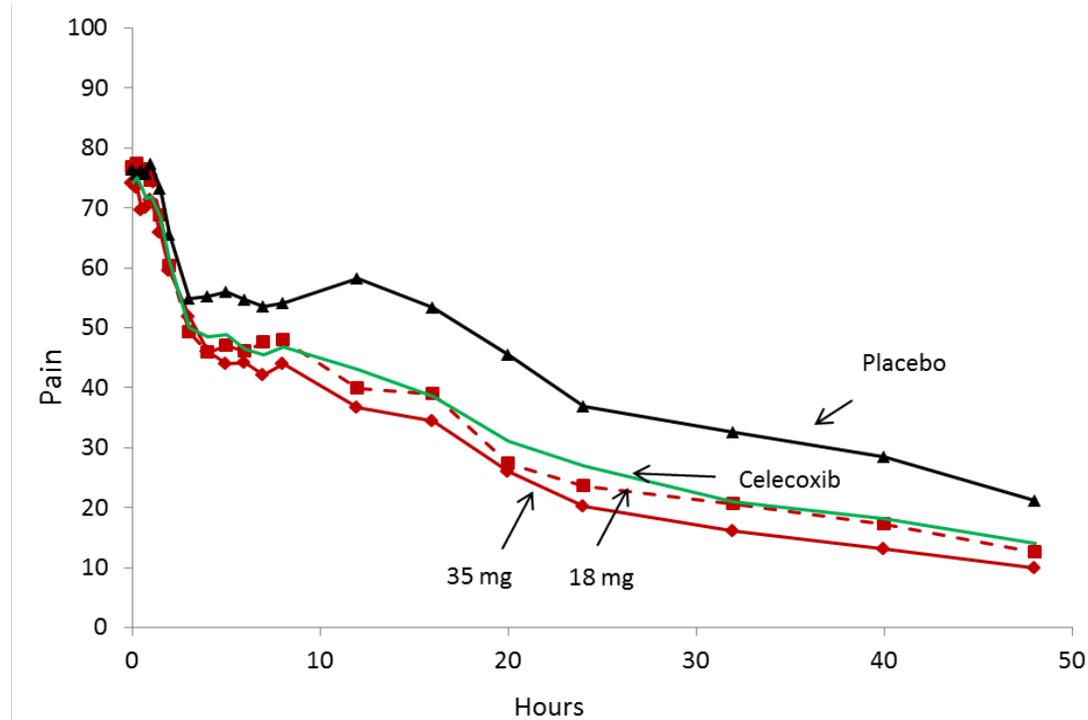
Figure 4: Average Pain Over Time – BOCF After Rescue



Source: Dr. Feng Li's Statistical Review

In Figure 5 below, it now becomes evident that pain intensity decreased over time in all groups when observed pain intensity scores are used rather than utilizing a BOCF imputation strategy for subjects who used rescue medication. The curve shows a greater decrease in pain with the diclofenac groups when compared to placebo. The separation of the placebo pain curve from the three active treatments occurred after approximately 3 hours after dosing. This supports the finding of efficacy of the diclofenac groups when compared to placebo.

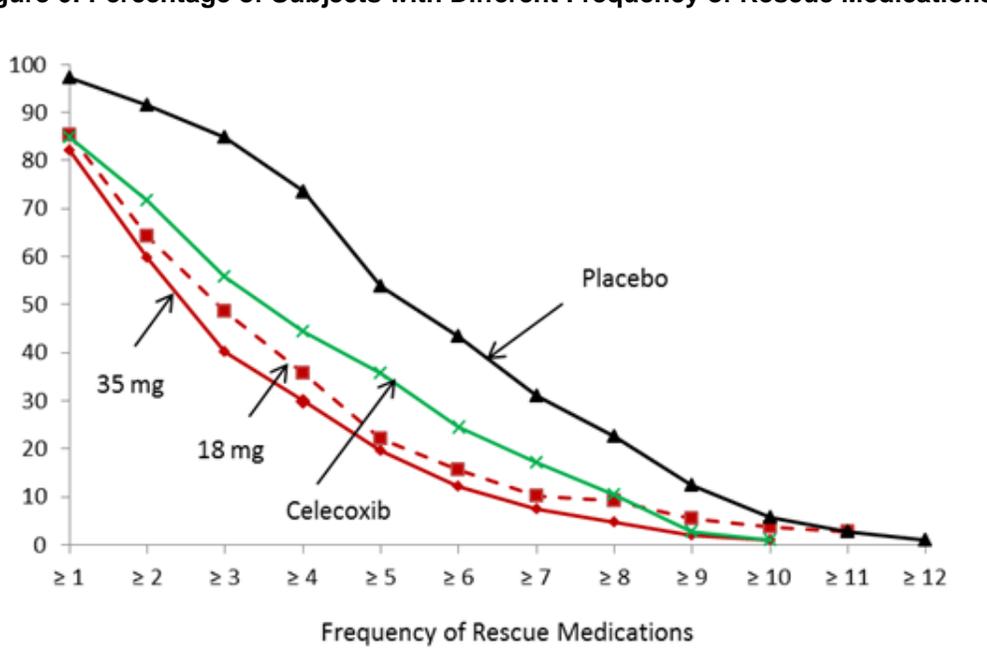
Figure 5: Average Pain Over Time Using Observed Pain Scores (No Imputation)



Source: Dr. Feng Li's Statistical Review

Dr. Li also performed an analysis of the frequency of rescue among groups. The frequency of rescue was consistently higher in subjects in the placebo group than in the active treatment groups (Figure 6). 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 diclofenac 35 mg, 50% in the diclofenac 18 mg, and 55% in the celecoxib groups took rescue medication at least 3 times.

Figure 6: Percentage of Subjects with Different Frequency of Rescue Medications



Source: Dr. Feng Li's Statistical Review

Dr. Li performed an additional analysis in which the pain scores, within a time window after taking a rescue medication, were replaced with the pre-rescue pain score (Table 23) Table 23 shows the results from an analysis in which the pain scores within 6 hours after rescue were placed with the pre-rescue score. The analyses results were in favor of the active treatments. Dr. Li also performed additional analyses using different time windows after rescue (e.g., 4 hours), and the results were similar.

Table 23: Additional Efficacy Analysis for VASSPID48 – Pre-rescue Score Carried Forward for Six hours

Statistics	Diclofenac			Celecoxib	Placebo
	35 mg	18 mg			
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	

Source: Dr. Feng Li's Statistical Review

6.1.5 Analysis of Secondary Endpoints(s)

No secondary endpoints were identified as key by the Applicant. However, the Applicant performed exploratory secondary analyses to support the findings of efficacy

for diclofenac 18mg and 35 mg in the pivotal trial. The Applicant's analyses are presented in Section 5.3.

Time to Onset of Analgesia

See section 5.3 for the Applicant's results on time to onset of analgesia. Of note, the diclofenac 35 mg group had the highest percent of subjects who experienced onset of analgesia whereas the placebo group had the lowest percent.

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

6.1.7 Subpopulations

Dr. Li analyzed the primary endpoint by subpopulations including 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 subgroup analysis were consistent with those observed in the overall population. All the active treatment groups were numerically better than the placebo group in the subpopulations. Table 24 shows the subgroup analysis for gender, age and race.

Table 24: Subgroup Analysis on the Primary Endpoint

Subgroups	Statistics	Diclofenac			
		35 mg (N=107)	18 mg (N=109)	Celecoxib (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)

Source: Dr. Feng Li's Statistical Review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Diclofenac was evaluated at doses of 18 and 35 mg, given three times per day, in one adequate and well-controlled trial. Both the 18mg and 35mg groups showed statistical significance in the primary analysis when compared to placebo. Dr. Feng Li's sensitivity analysis, described in Section 6.1.4, confirmed both groups superiority over placebo. In general, there were supportive findings in both treatment groups through the secondary analyses as well. There is a trend towards improved efficacy and time to onset among the diclofenac 35mg subjects compared to the 18mg group. However, no clear dose response can be determined from the design and analyses performed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The indication is for acute pain supported by a 48-hour clinical trial. This section is not relevant to this indication.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant did not design the study to show a direct comparison in efficacy between either diclofenac group and celecoxib. Therefore, comparative claims cannot be made between these treatment groups.

7 Review of Safety

Safety Summary

The pivotal trial, DIC3-08-04, will be discussed in this section unless otherwise stated. The safety profile of diclofenac capsules, for the indication of acute pain, was assessed in 216 subjects who received at least 1 dose of diclofenac (35mg and 18mg groups). Diclofenac was given three times per day (both 35mg and 18mg groups) in the single, pivotal trial where 215 subjects received diclofenac for 48 hours after bunionectomy. No new significant safety concerns were identified for diclofenac in general or that were unique to diclofenac capsules.

The Applicant submitted a 505(b)(2) application referencing the approved drug, Cataflam (NDA020142). The information available within this application appears adequate to assess the safety of diclofenac capsules in the acute pain population in conjunction with the established safety profile for diclofenac. The Applicant's rationale for their formulation of diclofenac is based on their hypothesis that the increased dissolution and absorption due to particle size may allow less drug product to be used and therefore an improved safety profile over Cataflam. There is no head-to-head trial

with the reference drug, Cataflam. Therefore, no comparative conclusion can be made with regard to safety between the Applicant's drug and the reference drug.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Trial DIC3-08-04 is the study used for the safety analysis and is described in detail in Section 5.3. The POC study, DIC2-08-03, was also discussed in Section 5.3 and only provides supportive information as it was conducted using the POC formulation.

Additional studies DIC1-12-07 (PK study using POC formulation) (b) (4) are briefly discussed, but only used as supportive evidence of safety.

Trial DIC3-08-04 was a controlled-trial conducted in the United States which consisted of 428 subjects randomized into four groups. Diclofenac groups (35mg and 18mg three times per day) consisted of 216 subjects. The trial was 48 hours of treatment. The entire 428 subjects were included in the safety group.

Deleted Sections

- Sub-section 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence was deleted. This section was not relevant to this application because no data was pooled.
- No data was submitted to inform a discussion of Sub-sections 7.2.3 Special Animal and/or In Vitro Testing and 7.2.5 Metabolic, Clearance, and Interaction Workup, and these sections were deleted
- Sub-sections 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class was not relevant and was deleted
- Sub-sections 7.4.2 Laboratory Findings, and 7.4.4 Electrocardiograms (ECGs) were 7.4.6 Immunogenicity, 7.5.4 Drug-Disease Interactions, 7.5.5 Drug-Drug Interactions were not studied in this application and were deleted
- No data was submitted to sub-sections 7.6.1 Human Carcinogenicity, 7.6.2 Human Reproduction and Pregnancy Data and were deleted
- Subsection 7.3.5 was deleted because there are no submission specific primary safety concerns to discuss

7.1.2 Categorization of Adverse Events

All treatment emergent adverse events (TEAEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.0 or higher. At each level of summarization (system organ class, preferred term, or severity), subjects were counted only once. If a subject experienced more than 1 TEAE within a preferred term, only the TEAE with the greatest severity was included. All adverse events (AEs) that occurred

on or after trial drug administration, or any preexisting AEs that after trial drug severity increased in severity or frequency, were considered TEAEs.

7.2 Adequacy of Safety Assessments

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

Exposure

The exposure was generally comparable across placebo and treatment groups. Although the requisite number of patients have not been exposed as requested by the Division at the End-of-Phase 2 meeting, the number of subjects exposed to diclofenac acid capsules (n=216) is adequate given the established safety profile of diclofenac. The doses (three times per day of 35mg and 18mg) and duration (48 hours) are adequate to assess safety for the intended population of acute pain.

Demographics

The population is largely comprised of White females, however, the treatment and placebo groups appear to be comparable with respect to baseline demographics, baseline pain scores and other subject characteristics. Demographic information is reviewed in more detail in Section 5.3.

7.2.2 Explorations for Dose Response

The Applicant did not submit an analysis exploring a dose response for safety, however, see Section 7.5.1 for a brief discussion of this topic..

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for the pivotal trial in Section 5.3, which appears adequate for this population.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this trial.

7.3.2 Nonfatal Serious Adverse Events

There was only 1 SAE, and this subject was in the celecoxib group. The subject had a deep vein thrombosis after completion of the trial.

7.3.3 Dropouts and/or Discontinuations

No subject discontinued due to an AE. One subject (001-104) in the diclofenac group discontinued due to an investigator decision. Review of the case report form showed that the subject reported a history of a gastric ulcer, which is an exclusion criterion, and was discontinued from the study.

7.3.4 Significant Adverse Events

There were three severe TEAEs in the diclofenac groups (Table 25). As shown in the table below, the placebo group experienced more severe AEs than any treatment groups. No subject experienced a TEAE that resulted in their withdrawal from the trial.

Table 25: Summary of Severe Treatment-Emergent Adverse Events by Preferred Term – Safety Population

Severe TEAE - Preferred Term	Diclofenac (b) (4) Formulation Capsule		Celecoxib Capsule 200 mg ^a (n = 106)	Placebo (n = 106)	Total (N = 428)
	35 mg (n = 107)	18 mg (n = 109)			
Any severe TEAE ^b	2 (1.9%)	1 (0.9%)	3 (2.8%)	8 (7.5%)	14 (3.3%)
Constipation	0	0	0	1 (0.9%)	1 (0.2%)
Nausea	1 (0.9%)	0	3 (2.8%)	5 (4.7%)	9 (2.1%)
Vomiting	0	1 (0.9%)	2 (1.9%)	1 (0.9%)	4 (0.9%)
Fatigue	0	0	0	1 (0.9%)	1 (0.2%)
Procedural pain	1 (0.9%)	0	0	0	1 (0.2%)
Dizziness	0	0	0	1 (0.9%)	1 (0.2%)

Abbreviations: TEAE = treatment-emergent adverse event.

Source of data: [Section 14.3.1, Table 14.3.1.3](#)

Source: Applicant's Clinical Study Report, p.87

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant defined the safety population as all subjects who received at least one dose of study drug. A TEAE was defined as any AE that occurred on or after trial drug administration or any preexisting disease or condition that after trial drug administration increased in frequency or severity or changed in quality. Overall, TEAEs were mostly considered to be of mild intensity (221 subjects [51.6%]). There were 95 subjects (22.2%) in whom TEAEs of moderate intensity were reported and 14 subjects (3.3%) in whom severe TEAEs were reported (3 in diclofenac groups as described in Section 7.3.4). 330 subjects (77.1%) reported at least 1 TEAE during the 7-day trial period. Slightly higher numbers of subjects in the celecoxib treatment group experienced TEAEs (86 subjects [81.1%]) compared with the diclofenac 18-mg treatment group (84 subjects [77.1%]), the placebo treatment group (83 subjects [78.3%]), and the diclofenac 35-mg treatment group (77 subjects [72.0%]).

A summary of TEAEs in 5% or more subjects in any treatment group are reviewed below (Table 26). TEAEs are comparable across treatment groups or more prevalent in placebo groups. Constipation was more common in the 18mg diclofenac group [12(11%)] when compared to placebo [4(3.8%)]. The 35mg diclofenac group [6(5.6%)] did not show much disparity when compared to placebo with regard to constipation, suggesting this observation may not be a relevant TEAE. Nausea and dizziness were more common in placebo groups, and likely due to rescue opioid medications. Overall, the AE profile in this acute setting appears comparable to placebo. I performed an analysis on the Applicant's dataset and found no substantial differences that would affect my perception of the adverse event profile.

Table 26: Summary of Most Frequent Treatment-Emergent Adverse Events (5% or More of Subjects in Any Treatment Group) by Preferred Term — Safety Population

Preferred term	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule	Placebo (n = 106)	Total (N = 428)
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)		
ANY TEAE	77 (72.0%)	84 (77.1%)	86 (81.1%)	63 (78.3%)	330 (77.1%)
Postprocedural edema	35 (32.7%)	36 (33.0%)	35 (33.0%)	34 (32.1%)	140 (32.7%)
Nausea	25 (23.4%)	34 (31.2%)	29 (27.4%)	39 (36.8%)	127 (29.7%)
Headache	11 (10.3%)	17 (15.6%)	11 (10.4%)	16 (15.1%)	55 (12.9%)
Dizziness	5 (4.7%)	17 (15.6%)	11 (10.4%)	17 (16.0%)	50 (11.7%)
Vomiting	7 (6.5%)	13 (11.9%)	15 (14.2%)	13 (12.3%)	48 (11.2%)
Post-procedural hematoma	4 (3.7%)	12 (11.0%)	8 (7.5%)	11 (10.4%)	35 (8.2%)
Constipation	6 (5.6%)	12 (11.0%)	9 (8.5%)	4 (3.8%)	31 (7.2%)
Pruritus	6 (5.6%)	4 (3.7%)	4 (3.8%)	4 (3.8%)	18 (4.2%)
Paraesthesia	2 (1.9%)	2 (1.8%)	8 (7.5%)	3 (2.8%)	15 (3.5%)

Source of data: [Section 14.3.1, Table 14.3.1.5](#)

Abbreviations: TEAE = treatment-emergent adverse event.

NOTE: All data are presented as n (%). For each preferred term, subjects were only counted once.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Any subject who had AEs leading to discontinuation was counted.

Source: Applicants Clinical Study Report, p. 86

The Applicant's submitted label also included TEAs of flatulence and muscle spasms, occurring at 3% and 1% respectively. These events occurred at similar frequencies to placebo, flatulence (2%) and muscle spasms (2%), and likely do not represent a new safety signal for diclofenac.

7.4.3 Vital Signs

Systolic blood pressure (SBP) showed a small decrease during the study within all the treatment groups when compared to placebo, most notably in the 35mg diclofenac group. Subjects in all groups had similar baseline SBP measurements. Change from Baseline to 1 Hour after first dose of Day 2 showed a mean decrease of 11.3 mmHg in the 35mg diclofenac group compared to a decreased of 3.1 mmHg in placebo. It is unclear why this decrease occurred, possibly due to an improvement in pain given these changes were also seen in the 18mg diclofenac and celecoxib groups. Otherwise, there were no notable differences in vital sign parameters between the diclofenac group and the placebo group.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were included in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no evidence of a dose relationship for TEAEs and diclofenac 35 mg or diclofenac 18 mg. The patient population was in general good health and the duration of exposure was limited to 48 hours. Therefore, we did not expect a large number of TEAEs in general. Overall, the TEAEs for diclofenac were comparable to the celecoxib and placebo arms in the number of and type of events. However, no comparative safety claims to celecoxib can be made, as the study was not designed to assess this.

7.5.2 Time Dependency for Adverse Events

There was no formal analysis performed on time dependency for AEs. This trial only includes a 48-hour post-operative exposure period, therefore, a thorough analysis is not practical.

7.5.3 Drug-Demographic Interactions

Age

Of the 428 subjects randomized into study DIC3-08-04, 284 (66.4%) were ≤ 45 years and 144 (33.6%) were > 45 years. Mean (SD) age was 39.7 (12.0) years. Of the 216 subjects who received diclofenac Capsules, 145 (67.1%) were < 45 years and 71 (32.9%) were > 45 years. Consistent with the overall population, the most frequently reported TEAEs in the age subgroups for diclofenac capsules were post-procedural edema and headache. Similar to the overall population in the study, TEAEs mostly occurred at comparable rates within the age range subgroups.

One notable finding in the age subgroup analysis was that patients treated with diclofenac in the < 45 years subgroup had a higher frequency of nausea compared to the ≥ 45 years subgroup (Table 27). Although this trend was not observed in the placebo group, interpretation of this finding is limited given the small number of subjects in the > 45 years subgroup.

Table 27: Subgroup Analysis by Age – Safety Population

Preferred term	Diclofenac ^{(b) (4)} formulation Capsule		Celecoxib Capsule 200 mg ^a n/N (%)	Placebo n/N (%)	Total n/N (%)
	35 mg n/N (%)	18 mg n/N (%)			
Nausea	25/107 (23.4)	34/109 (31.2)	29/106 (27.4)	39/106 (36.8)	127/428 (29.7)
≤45 years	20/71 (28.2)	27/74 (36.5)	20/71 (28.2)	25/68 (36.8)	92/284 (32.4)
>45 years	5/36 (13.9)	7/35 (20.0)	9/35 (25.7)	14/38 (36.8)	35/144 (24.3)

Source: Applicant’s Efficacy-Information-Amendment, p. 10

Gender

As expected for a population of subjects undergoing bunionectomy surgery, the majority (371 [86.7%]) were female, compared to 57 (13.3%) males. In a subgroup analysis that summarized TEAEs by gender, results were similar to those observed in the overall study population. Nausea was reported less frequently by males compared to females in the 35mg diclofenac group (5.6% vs. 27%) but not in the 18mg diclofenac group (33.3% vs. 30.9%). Within the diclofenac groups, headache, constipation, and vomiting were also reported less frequently in males compared to females (Table 28).

Table 28: Summary of Most Frequent Treatment Emergent Adverse Events (5% or More of Subjects in Any Diclofenac Treatment Group) by Preferred Term — Study DIC3-08-04 - Safety Population with Overall Population and Subgroups by Gender

Preferred term	Diclofenac ^{(b) (4)} formulation Capsule		Celecoxib Capsule 200 mg ^a n/N (%)	Placebo n/N (%)	Total n/N (%)
	35 mg n/N (%)	18 mg n/N (%)			
ANY TEAE	77/107 (72.0)	84/109 (77.1)	86/106 (81.1)	63/106 (78.3)	330/428 (77.1)
Male	11/18 (61.1)	12/15 (80.0)	6/10 (60.0)	10/14 (71.4)	39/57 (68.4)
Female	66/89 (74.2)	72/94 (76.6)	80/96 (83.3)	73/92 (79.3)	291/371 (78.4)
Postprocedural edema	35/107 (32.7)	36/109 (33.0)	35/106 (33.0)	34/106 (32.1)	140/428 (32.7)
Male	4/18 (22.2)	5/15 (33.3)	3/10 (30.0)	5/14 (35.7)	17/57 (29.8)
Female	31/89 (34.8)	31/94 (33.0)	32/96 (33.3)	29/92 (31.5)	123/371 (33.2)
Nausea	25/107 (23.4)	34/109 (31.2)	29/106 (27.4)	39/106 (36.8)	127/428 (29.7)
Male	1/18 (5.6)	5/15 (33.3)	1/10 (10.0)	3/14 (21.4)	10/57 (17.5)
Female	24/89 (27.0)	29/94 (30.9)	28/96 (29.2)	36/92 (39.1)	117/371 (31.5)
Headache	11/107 (10.3)	17/109 (15.6)	11/106 (10.4)	16/106 (15.1)	55/428 (12.9)
Male	1/18 (5.6)	1/15 (6.7)	1/10 (10.0)	3/14 (21.4)	6/57 (10.5)
Female	10/89 (11.2)	16/94 (17.0)	10/96 (10.4)	13/92 (14.1)	49/371 (13.2)
Dizziness	5/107 (4.7)	17/109 (15.6)	11/106 (10.4)	17/106 (16.0)	50/428 (11.7)
Male	0/18 (0)	2/15 (13.3)	0/10 (0)	1/14 (7.1)	3/57 (5.3)
Female	5/89 (5.6)	15/94 (16.0)	11/96 (11.5)	16/92 (17.4)	47/371 (12.7)
Vomiting	7/107 (6.5)	13/109 (11.9)	15/106 (14.2)	13/106 (12.3)	48/428 (11.2)
Male	0/18 (0)	1/15 (6.7)	0/10 (0)	1/14 (7.1)	2/57 (3.5)
Female	7/89 (7.9)	12/94 (12.8)	15/96 (15.6)	12/92 (13.0)	46/371 (12.4)
Postprocedural hematoma	4/107 (3.7)	12/109 (11.0)	8/106 (7.5)	11/106 (10.4)	35/428 (8.2)
Male	1/18 (5.6)	0/15 (0)	1/10 (10.0)	3/14 (21.4)	5/57 (8.8)
Female	3/89 (3.4)	12/94 (12.8)	7/96 (7.3)	8/92 (8.7)	30/371 (8.1)
Constipation	6/107 (5.6)	12/109 (11.0)	9/106 (8.5)	4/106 (3.8)	31/428 (7.2)
Male	0/18 (0)	0/15 (0)	1/10 (10.0)	0/14 (0)	1/57 (1.8)
Female	6/89 (6.7)	12/94 (12.8)	8/96 (8.3)	4/92 (4.3)	30/371 (8.1)

Source: Applicant’s Efficacy-Information-Amendment, p. 7

Interpretation of a meaningful difference between genders is limited by the small number of males in this study.

Race

The majority of the 428 subjects in the study were White or Caucasian (322 [75.2%]) or Black or African American (77 [18.0%]). The numbers of subjects in the remaining individual race/ethnicity subgroups were as follows: 9 (2.1%) Asian, 7 (1.6%) American Indian or Alaska Native, 6 (1.4%) Native Hawaiian or other Pacific Islander, and 7 (1.6%) Other. Given the small numbers of subjects in certain subgroups, the analysis is limited to the White and Black subgroups.

Postprocedural edema, the most commonly reported TEAE for subjects in the diclofenac treatment groups, occurred at a higher frequency for black subjects (23 [63.9%]) than for white subjects (45 [26.5%]). Nausea (7 [41.2%]) and vomiting (3 [17.6%]) occurred at higher frequencies for black subjects in the diclofenac 35 mg treatment group than for white subjects receiving the same treatment (18 [21.4%]) for nausea, 4 [4.8%] for vomiting). The small number of black subjects in this treatment group limits the interpretation of this analysis.

The TEAEs reported by intensity for subjects in the diclofenac treatment groups were generally similar for both black and white subjects, with the majority of reported events considered to be of mild intensity for both groups.

7.6 Additional Safety Evaluations

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies have been carried out in pediatric patients. The Division outlined the requirements for the Applicant's pediatric plan during the end-of-Phase 2 meeting (minutes recorded on November 9, 2010). In summary, the Division stated that efficacy studies for pediatric patients over the age of 2 years for this product are not required as efficacy can be extrapolated from adults in this age range. However, the Applicant was informed they must study the efficacy, safety, and pharmacokinetics of their product, with an age-appropriate formulation, for patients ages 1-2 years with mild to moderate acute pain. For age groups 2-17 years of age, the Applicant was informed they must study the pharmacokinetics and safety with an age-appropriate formulation. The Division also explained that with regard to requirements for ages birth to 1 year, a waiver may be possible due to immaturity of the enzymes required to metabolize diclofenac. This may suggest the drug product would be ineffective and unsafe in that pediatric age range.

The Applicant submitted a pediatric plan with their NDA that was not consistent with the above discussion with the Division. The Applicant cited the reason for not developing an age-appropriate formulation for use in patients ages 1-6 years (with mild to moderate acute pain) (b) (4)



On February 01, 2013, the Division sent an information request outlining the inconsistency of the Applicant's pediatric plan and the previous discussion at the End-of-Phase 2 meeting. The Applicant responded with similar comments to the reasons cited above for not developing an age appropriate formulation.

On August 22, 2013, the Division engaged in a teleconference with the Applicant regarding the pediatric plan. The Division and the Applicant agreed upon an updated pediatric plan that is consistent with the Division's requirements. The Applicant plans to conduct the following clinical studies:

Study 1: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 6 to < 18 years of age with acute pain.

Study 2: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain.

Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain.

The Applicant also plans on studying the older pediatric age groups first and make their best estimate of an appropriate dose for the other age groups based on pharmacokinetic modeling from this initial study.

The Applicant submitted a timeline for their proposed pediatric studies (Table 29)

Table 29: Proposed Timeline for Pediatric Studies

Studies	Final Protocol Submission Date	Study Start Date	Final Report Submission
6 years - < 18 years (Study 1)	November 1, 2014	May 3, 2015	May 3, 2017
2 years - < 6 years (Study 2)	June 6, 2015	January 6, 2016	January 6, 2018
1 year to < 2 years (Study 3)	January 6, 2018	July 30, 2018	July 30, 2020

Source: The Applicant's Amended Pediatric Study Plan, Table 10.1

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on September 4, 2013. The PeRC did not agree with the Division to grant a partial waiver in pediatric patients aged birth to less than one year because the product would be ineffective and/or unsafe in this age group. The PeRC acknowledged that this reason has been used for previous NSAID products (immaturity of CYP2C9) but there was concern expressed that granting a waiver for this reason would set a potentially dangerous precedent. The PeRC noted that it may not be worth the "risk" to study this product for this population but that other products metabolized by CYP2C9 may be important to be studied in the 0 to 6 month population. This topic will be discussed further between the Division and PeRC. The PeRC recommended granting a partial waiver in pediatric patients aged birth to less than one year because the product does not represent a meaningful therapeutic benefit over existing therapies. The PeRC agreed with the Division on the proposed studies in pediatric patients aged 1 to less than 17 years and to grant a deferral in this age range because the product is ready for approval in adults.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no instances of overdose in the diclofenac (b) (4) capsules clinical studies. The Applicant's summary of clinical safety identified no examples in the literature describing overdoses with various formulations of diclofenac. The Applicant also stated that diclofenac does not have abuse potential and that there is no evidence identified in the literature for the abuse of prescription preparations containing diclofenac. No evidence of withdrawal symptoms, indicated by exacerbation of AEs after withdrawal of diclofenac, were reported in any of the clinical studies conducted by the Applicant or in any of the clinical studies reviewed in the literature search.

7.7 Additional Submissions / Safety Issues

The Applicant submitted additional safety data from completed PK studies and/or studies using the POC formulation. Safety data from these studies are of limited applicability since two of the studies (DIC1-08-01 and DIC2-08-03) used a different formulation than the pivotal study (DIC3-08-04) and the PK study using the commercial formulation (DIC1-12-07) was only a single dose study. However, based on my review of the safety data from these studies, no new significant safety concerns for diclofenac are identified.

(b) (4)



8 Postmarket Experience

Zorvolex (diclofenac acid) capsules have not been registered in any country and there are no postmarketing data.

9 Appendices

9.1 Literature Review/References

The Applicant submitted 98 clinical and nonclinical references performed through the PUBMED database. Many references discussed NSAIDs in relation to safety, not specific to diclofenac.

Pharmacokinetics, genetics, Tension-type headache treatment review, orthopedic injuries/ sprain, postoperative Dental Pain, OA, Pediatric Analgesic Clinical Trial Designs workshop, in vitro studies, NSAID review articles with regard to safety, postunionectomy pain, Cochrane reviews of diclofenac, migraines, and safety reviews of gastrointestinal and cardiovascular complications were all included.

9.2 Labeling Recommendations

Based on review of the proposed labeling provided in the submission, the following are clinical recommendations. My comments are italicized and, they follow the Applicant's proposed wording as it appears in the referenced section of the proposed label (bolded).

Section 2.1 Dosage Information

"...the dosage is 18 mg or 35 mg three times daily (b) (4)

(b) (4) ."

Although the Applicant reported that most subjects were given their initial dose of study medication before 7 AM, and thus likely on an empty stomach, the pivotal study DIC3-08-04 did not specify the timing of study medication administration with regard to food intake. Given that efficacy for this product was demonstrated in this trial and that many patients are likely to have been dosed on a fed stomach after the initial dosing, (b) (4)

Also, safety is not a concern with regard to taking the medication in a fasting or fed state. In addition, I propose adding in language that efficacy may be decreased in patients who take this medication on a fed stomach, based on the fed/fasted PK findings for Zorvolex.

Section 4 Contraindications

(b) (4)

(b) (4)



Section 5 Warnings and Precautions

The proposed language is consistent with NSAID class labeling.

Section 6.1 Clinical Trials Experience

(b) (4)



Section 8 Use in Special Populations

A consult was sent to the Pediatric and Maternal Health Staff to comment on the relevant portions of this section.

Section 14 Clinical Studies

(b) (4)



9.3 Advisory Committee Meeting

No advisory Committee meeting was held for this product.

APPENDIX 9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 204592

Submission Date(s): December 20, 2012

Applicant: Iroko

Product: Diclofenac acid capsules (Zorvolex)

Reviewer: Steven Galati

Date of Review: 9.12.2013

Covered Clinical Study (Name and/or Number): Dic3-08-04

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>45</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>none identified</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None identified</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

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

The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, attached with a list of 44 of the 45 investigators listed in the study reports, certifying that they had no financial interests or arrangements to disclose. One sub-investigator at site 001 was referenced as being out of the office and would be sent a copy of the financial interests form to sign at a later date.

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

Given only one sub-investigator failed to fill out the financial interests form and none of the remaining investigators had financial interests or arrangements to disclose, the possibility of bias in the results based on financial interests is unlikely.

¹ See [web address].

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

/s/

STEVEN A GALATI
09/17/2013

JOSHUA M LLOYD
09/17/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204592

Applicant: Iroko

Stamp Date: 12/20/2012

**Drug Name : Zorvolex
(diclofenac acid)**

**NDA/BLA Type: Standard
Review**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			ECTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Refers back to SCS
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Refers back to SCE
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) referencing Cataflam (N20142)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study DIC3-08-04: A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active- and Placebo-Controlled Study of Diclofenac ^{(b) (4)} formulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy Indication: Acute mild-to-moderate pain	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		X		Data has been collected, but the Applicant has not provided a safety analysis of subgroups (i.e., age/sex/race). A re-analysis will be requested.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	505(b)(2)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?		X		However, the exposure appears acceptable
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					

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

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			However, the submitted plan is not consistent with advice given at EOP2 meeting. An amended pediatric plan will be requested.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Additional CRFs will be requested for patients who discontinued for "other" reasons.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

The following issues were identified during the filing review, and clarification was requested through an information request. However, please remind the Applicant of the following issues in the 74-day letter:

1. The information you described under Section 2.7.4.11.1 in the Summary of Clinical safety for age, sex, and race is inadequate. Your summary of safety should include an analysis of safety data by gender, age, and racial subgroups [21 CFR 314.50(5)(vi)(a)] based on data from your clinical studies. Provide this analysis.
2. For study DIC1-12-07, provide the details surrounding the reasons subjects discontinued for the reasons of other, consent withdrawn, and protocol violations. Alternatively, identify the location within your submission where this information can be found.
3. For study DIC3-08-04, provide case report forms for all subjects who withdrew from the study.
4. Per the End of Phase 2 meeting minutes (refer to the discussion under Question 7), the Phase 3 bunionectomy trial would be conducted with an "empty stomach" food restriction. Clarify whether subjects were administered study medication on an empty stomach or a fed state. If this was not implemented, provide justification for not doing so.

Steven Galati M.D.

Reviewing Medical Officer

2/1/2013

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Joshua Lloyd, M.D.
Clinical Team Leader

2/1/2013
Date

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

/s/

STEVEN A GALATI
02/01/2013

JOSHUA M LLOYD
02/01/2013