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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204-768
Priority or Standard	Standard
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Division / Office	DAAAP
Reviewer Name(s)	Anjelina Pokrovnichka, M.D.
Review Completion Date	January 15, 2014
Established Name	Indomethacin submicron particle
(Proposed) Trade Name	Tivorbex
Therapeutic Class	NSAID
Applicant	Iroko Pharmaceuticals, LLC
Formulation(s)	Oral
Dosing Regimen	Capsules 20 mg and 40 mg
Indication(s)	Treatment of mild to moderate acute pain
Intended Population(s)	Patients with mild to moderate acute pain

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval with revisions to the proposed label.

1.2 Risk Benefit Assessment

To support the indication for use of Tivorbex Capsules for the treatment of mild to moderate acute pain, the Applicant submitted two Phase 3 trials in bunionectomy patients using the to-be-marketed formulation, in conjunction with the Agency's previous findings of safety and efficacy for the reference drug Indocin (NDA 016059). I have determined that both trials were 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 two Phase 3 clinical trials, in patients with acute pain after bunionectomy, support the effectiveness of Tivorbex Capsules for the treatment of acute pain in this population. The Division's efficacy analyses of the primary endpoint, including analyses to account for the high percentage of rescue medication use and the recommended approach of the National Academy of Science (NAS) for imputation of missing data, showed that treatment with Tivorbex Capsules was superior to placebo in both Phase 3 trials. The safety data did not demonstrate any new safety signal beyond what is already known for indomethacin. The safety profile for the intended patient population is acceptable.

Benefits:

- Evidence of effectiveness was established for Tivorbex Capsules 40 mg bid and 40 mg tid doses in two placebo-controlled Phase 3 trials using the pre-specified analysis for the primary endpoint, VAS summed pain intensity difference (VASSPID) over 0 to 48 hours. These results were confirmed by a series of sensitivity analyses to account for the use of rescue medication and to utilize different strategies for imputation of missing data. Evidence of effectiveness was established for the Tivorbex Capsules 20 mg tid dose in one of the Phase 3 trials using the pre-specified analysis of the primary endpoint, but all of the sensitivity analyses were positive for this dose in both Phase 3 trials.
- The primary efficacy analysis is further supported by results in favor of Tivorbex Capsules on various secondary endpoints.
- Indomethacin 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 nausea, post procedural edema, headache, dizziness, vomiting, post procedural hemorrhage, and constipation, with similar frequency across all active treatment groups.

Overall, the risk-benefit profile of Tivorbex 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 under PREA:
Study 1: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of indomethacin in pediatric patients 6 through 17 years of age

Study 2: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of indomethacin in pediatric patients 2 through 6 years of age

Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age appropriate formulation of indomethacin in pediatric patients 1 through 2 years of age

2 Introduction and Regulatory Background

2.1 Product Information

Tivorbex™ (indomethacin submicron particle) Capsules are a new indomethacin drug product developed by Iroko Pharmaceuticals, LLC (Iroko) for the treatment of mild to moderate acute pain in adults. Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, antiinflammatory, and analgesic properties, which are due to decreased prostaglandins in peripheral tissues mediated by inhibition of cyclooxygenase (COX) enzymes involved in the synthesis of prostaglandins. The proprietary SoluMatrix™ manufacturing technology has been used to reduce indomethacin drug substance particle sizes in Tivorbex Capsules and to enhance rates of dissolution (b) (4) Tivorbex Capsules contain either 20 mg or 40 mg of indomethacin as the sole analgesic ingredient, representing a

20% reduction in dosage compared with currently available oral indomethacin products (Indomethacin 25 mg and 50 mg capsules).

2.2 Tables of Currently Available Treatments for Proposed Indications

Several products from the NSAID class, acetaminophen, and acetaminophen/opioid combination analgesics are available on the market for the indication of treatment of mild to moderate acute pain.

2.3 Availability of Proposed Active Ingredient in the United States

Indomethacin was first approved by the United States (US) Food and Drug Administration (FDA) in 1965 as Indocin® 25 mg and 50 mg capsules (Merck and Co., Inc.). It has since been discontinued for reasons not related to safety or efficacy. The discontinued NDA was recently acquired by iCeutica Operations, LLC who remains its current holder.

Indomethacin is indicated for the management of moderate to severe pain in conditions such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis, tendinitis, or both), acute gouty attack, and for closure of hemodynamically significant patent ductus arteriosus in premature infants.

Multiple approved drug products containing the active ingredient indomethacin are available and marketed in the United States. The following table lists the approved NDAs for indomethacin:

Table 1: Indomethacin products

Drug name and Application #	Dosage form/Route	Strength	Company
Indomethacin 18-851	Capsule; oral	25 gm and 50mg	HERITAGE PHARMS INC
Indomethacin 18-858	Capsule; oral	25mg	MYLAN
Indomethacin 22-536	Injectable For closure of patent ductus arteriosus in premature infants	EQ 1mg base/vial	FRESENIUS KABI USA
Indomethacin 18332 (Indocin)	Suspension; oral	25mg/5ml	IROCO PHARMS

Indomethacin 18878 (Indocin)	Injectable	EQ 1mg base/vial	RECORDATI RARE

2.4 Important Safety Issues With Consideration to Related Drugs

Similar to other NSAIDs, indomethacin is associated with the risk of cardiovascular (CV) and gastrointestinal (GI) adverse effects such as CV thrombotic events, stomach and intestinal ulcers, and bleeding.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The IND 101,940 for Tivorbex for the treatment of acute mild to moderate pain was first submitted to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in January 2009.

Key milestones in the clinical development program are noted below.

Table 2: Regulatory History

SPA – No Agreement Letter (July 2009) Study IND 3-08-04 "A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active- and Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy."	One of the secondary objectives for Study IND 3-08-04 was time to onset of analgesia for study drug compared to celecoxib. The Division stated: • It is not possible to obtain a comparative claim regarding onset of analgesia because the study is not designed to assess the analgesic potency of study drug compared to celecoxib • Comparisons of onset of analgesia without data regarding analgesic potency are not meaningful. • All efficacy claims must be based on replicated data.
	Regarding the primary efficacy endpoint, the Division confirmed that VASSPID-48 calculated as a time-weighted average is acceptable. • For claims of efficacy for all 3 doses (b) (4) studied (40mg TID, 40 mg BID, and 20 mg BID) based on comparisons to placebo, strategy to handle multiplicity must be included
	The Division informed the applicant that: • ITT must include all subjects who received at least one dose of study drug • Pre-specify the covariates that will be included in the

	model for the primary analysis. • Subgroup analyses must be presented by age, gender, and race.
	Regarding imputation strategies to account for missing data, the Sponsor proposed • BOCF for subjects who take rescue or withdraw from the study for reasons including lack of efficacy or an adverse event and LOCF for subjects who withdraw due to other reasons The Division informed the applicant that: • Since adverse events may be masked in other categories describing the reason for discontinuation, you must thoroughly collect and document as much information as possible to alleviate concerns regarding treatment-related dropouts.
	The number of adequate and well-controlled Phase 3 efficacy studies required will depend on the similarities in the concentration-time curves of the reformulated drug compared to the RLD.
SPA – No Agreement Letter (September 2009) Study IND 3-08-04	Clarification for the imputation method requested. Because there was inconsistency between the protocol text and the SAP text.
EOP2 (June 2010)	NDA submission pathway: • 505(b)(2) NDA is the appropriate submission pathway
	• Phase 2 dental pain model trial may serve as a supportive study • All comparative claims must be based on replicated data
	Pediatric plan: • The Division did not agree with Iroko 's plan to request a waiver for pediatric subjects (b) (4) and deferral for pediatric subjects (b) (4) • Develop an age appropriate formulation to dose the younger age patients. If you think it would be unsafe to use this drug in patients under a particular age, submit supporting scientific justification • Conduct pediatric studies during the development cycle and do not wait until after approval of the NDA • Conduct pediatric studies in older pediatric populations first and then conduct studies in younger populations

	Safety database: • Safety data base of 500 subjects is acceptable, barring unexpected safety signal
	Nanoscale definition: • The Division confirmed that the definition of nanoscale is less than 100 nanometers • Tivorbex does not meet the less than 100 nanometers criteria
	(b) (4)
	Nonclinical safety studies • Not required to support the safety of indomethacin for an NDA, provided clinical exposure is within the approved limits of the reference drug
	PK information • Information regarding relative BA against the reference drug, dose proportionality between 20 mg and 40 mg strengths and food effect on the 40 mg strength) obtained from the single-dose study is sufficient to support filing an NDA
Advice Information Letter (August 2012)	• We acknowledge that your current statistical analysis plan has been written in accordance with the Division's previous comments. However, in 2010, the NAS released a report, which was commissioned by FDA, concerning missing data. You should take the NAS report into consideration and either justify the appropriateness of your current strategy or propose an approach consistent with the NAS recommendations. We recommend you instruct subjects to record the pain score prior to rescue each time and impute that score for the next efficacy assessment. • You propose to exclude all medications within five half-lives of the prohibited medication before dosing with study medication. Considering that some medications may have a long half-life, we recommend you exclude medications within five days before dosing with study drug if its half-life is unknown.

Pre-NDA (October 2012)	• 505 (b)(2) to rely on 1) For safety and efficacy data: Indocin® 25 mg and 50 mg capsules application (iCeutica Operations, LLC), NDA 016059 - discontinued for reasons not related to safety or efficacy 2) For biolinking purposes: Ph1 trials against Indomethacin 50 mg capsules (Mylan Pharaceuticals, Inc., ANDA 070-624) is acceptable
	• Positive results from the two pivotal Phase 3 studies and definitive PK characterization of the Ph3 formulation are adequate to support filing of the NDA for the treatment of acute mild to moderate pain
	• Presents efficacy results for each individual study and not pooled • Include ISE and ISS in Module 5, and a shorter overview in Section 2.7
	• Pooling the 2 pivotal Ph3 in the ISS is acceptable • Include CRF's for deaths, SAEs and discontinuations due to AEs • PREA requirements discussed at the EOP2 were reiterated
	• Including Medication Guide with the product label is acceptable
	• SAS-data format submission is acceptable

SAP-Statistical Analysis Plan
NAS- National Academy of Sciences
LOCF-Last Observation Carried Forward
BOCF- Baseline Observation Carried Forward
ISS-Integrated Summary of Safety
ISE-Integrated Summary of Efficacy

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application for NDA 204-768 was submitted in eCTD format. The navigation of the application was easy, links were active, table of contents and bookmarks for the original protocols were provided, datasets with definition tables were provided, narratives for subjects who experienced serious adverse events (SAE) or discontinued due to safety issues were provided. The integrated summary of safety and efficacy (ISS and ISE) were located in Module 2

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

Francis Clark, Site 002 IND3-08-04b
Screened: 160
Randomized: 126

Jason B. Dickerson, Site 002 IND3-10-06
Screened: 124
Randomized: 105

These particular sites were selected for inspection because of:
- Enrollment of large number of subjects
- Principal investigators and study sites participated in both pivotal Phase 3 trials

The OSI inspection of the two sites selected found no violations that could impact the safety or efficacy data.

3.2 Compliance with Good Clinical Practices

The submitted bunionectomy and dental pain efficacy and safety trials appeared to be conducted under acceptable ethical standards. There were minor protocol violations which were not considered to have an influence on the trial results (see Section 5.3 for details).

3.3 Financial Disclosures

Applicant provided financial information for the principal and sub-investigators who participated in all clinical studies: IND 1-08-01, IND1-12-07, IND2-08-03, IND3-08-04b, and IND3-10-06). There were no financial incentives considered to adversely affect the integrity of the data (see Appendix 1, Clinical Investigator Financial Disclosure Review).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The formulation development of Tivorbex Capsules included a POC Formulation and a Commercial Formulation that is intended for commercialization. The POC Formulation of Tivorbex Capsules utilized a (b) (4) process. The Commercial Formulation of Tivorbex Capsules utilizes a (b) (4) process.

The indomethacin PK parameters from trial IND1-08-01, which utilized POC Formulation, and trial IND1-12-07, which utilized the Commercial Formulation, were comparable for the Cmax, AUC0-inf, and the tmax. In addition, the relative bioavailability of indomethacin from Tivorbex Capsules 40 mg and Indomethacin 50 mg capsules was similar in both trials. These results suggest that the POC and the Commercial Formulations of Tivorbex Capsules perform similarly in vivo.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The application for Tivorbex Capsules 20 mg and 40 mg drug product is being filed as a 505(b)(2) NDA which relies in part on the previous findings of Indocin for safety and efficacy in conjunction with nonclinical literature. The published nonclinical pharmacologic, pharmacokinetic (PK) and toxicologic literature, surveyed by the Applicant from 1963-2012, for indomethacin and existing indomethacin products demonstrates that this drug compound is well characterized and has been extensively reviewed. No new nonclinical primary or secondary pharmacology studies of Tivorbex Capsules were conducted.

A single-dose comparative PK study of Tivorbex Capsules in dogs was performed (Study 1609-001) to evaluate and compare Tivorbex Capsules (Indomethacin Nanoformulation Capsules) to Indomethacin IR 25 mg. No signs of toxicity were identified in this study. Based on AUC values, the systemic indomethacin animal to human plasma ratios provide for a 2.4 to 6.3-fold higher plasma exposure in dogs than the demonstrated plasma concentrations in humans following a single Tivorbex Capsule 20 mg, 40 mg or 50 mg administration.

Analytical assessments of the indomethacin drug substance and of the Tivorbex Capsules drug product identified five known indomethacin-related degradants. These drug substance and drug product degradants were subjected to literature review (through 2012, inclusive) performed by the Applicant. However, the toxicologic information was limited and the compounds were considered to be incompletely characterized with respect to toxicity potential. The Applicant conducted an in silico computational genotoxicity assessment employing the MC4PC modules (Ashby alerts modules and GeneTox set), and the output of the Informatics and Computational Safety Analysis Staff method expert call for the five degradants. It was concluded that there is no evidence of genetic toxicity to humans based on the results of the in silico computational analysis. No additional nonclinical pharmacology, PK or toxicology studies were conducted.

4.4 Clinical Pharmacology

The Tivorbex Capsules clinical pharmacology program consisted of two relative bioavailability Phase 1 trials (IND1-08-01 and IND1-12-07) of crossover design in healthy subjects under fed and fasted conditions. The IND1-08-01 trial utilized the POC Formulation and the IND1-12-07 trial utilized the Commercial Formulation.

The two Phase 1 trials determined the relative bioavailability of indomethacin from Tivorbex Capsules 20 mg and 40 mg (Test Product) and Indomethacin 50 mg capsules (Reference Drug), the effect of food on the rate and extent of indomethacin absorption from Tivorbex Capsules 40 mg (and Indomethacin 50 mg capsules for IND1-08-01 only), and the dose proportionality between the different Tivorbex Capsules dosage strengths in 40 healthy subjects under fed and fasted conditions. The primary pharmacokinetic parameters analyzed in each of the trials included Cmax, tmax, and AUC0-inf.

The systemic indomethacin exposure (AUC0-inf) from Tivorbex Capsules 40 mg was lower compared with Indomethacin 50 mg capsules, and proportional to the 20% reduction of indomethacin in Tivorbex Capsules 40 mg (~20% reduction in AUC0-inf).

Indomethacin was detected in the plasma of some subjects as early as 10 minutes postdose. The mean times to achieve peak indomethacin plasma concentration (tmax) demonstrated that absorption of indomethacin was faster for Tivorbex Capsules 40 mg than Indomethacin 50 mg capsules. Similar Cmax was achieved for both drug products.

Food decreased the rate of indomethacin absorption but not the overall extent of indomethacin exposure for Tivorbex Capsules 40 mg and Indomethacin 50 mg capsules. For both indomethacin drug products, Cmax was lower, tmax occurred later, and the AUC0-inf was unchanged under fed conditions compared with fasted conditions.

The trials also demonstrated that the two doses of Tivorbex Capsules, 20 mg and one 40 mg, were dose proportional under fasting conditions. For both trials, Cmax and AUC0-inf were proportional to the indomethacin dosage in Tivorbex Capsules.

4.4.1 Mechanism of Action

The primary mechanism of analgesic action of indomethacin involves inhibition of prostaglandin synthesis mediated by inhibition of COX enzymes. Prostaglandins reduce the threshold for stimulation of peripheral nerve sensory receptors and increase the responsiveness of nociceptors. Reversal of this process is thought to represent the basis for the peripheral analgesic activity of NSAIDs

4.4.2 Pharmacodynamics

The pharmacodynamics of indomethacin apply to the Tivorbex Capsules.

4.4.3 Pharmacokinetics

The pharmacokinetics of indomethacin such as distribution, metabolism, and excretion, apply to the Tivorbex Capsules. Following single oral doses of Tivorbex capsules 20 mg or 40 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about approximately 1 and 2 mcg/mL, respectively, at about 1.67 hours. Indomethacin is virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours following dosing. Administration of Tivorbex Capsules 20 mg and 40 mg was associated with dose proportional pharmacokinetics. Tivorbex capsules results in 46% lower C_{max}, 9% lower $AUC_{inf,,}$ and 1.33 hr delayed T_{max} (1.67 hr during fasted versus 3.00 hr during fed) under the fed condition compared to the fasted condition. The effect of food on indomethacin pharmacokinetics is comparable between Tivorbex capsules and indomethacin IR capsules.

- Distribution and plasma protein binding

Indomethacin is highly bound (about 99%) to serum. Indomethacin distribution to tissues has been shown to be lower than that of plasma; however, indomethacin readily penetrates into and out of the synovial fluid where concentrations can reach plasma levels by about 5 hours postdosing. Indomethacin crosses the blood-brain barrier, although cerebrospinal fluid concentrations are low. It also crosses the placenta and appears in breast milk.

- Metabolism

Indomethacin exists in the plasma as the active parent drug and its inactive desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in unconjugated. The primary catabolic pathway is demethylation of indomethacin to O-desmethylindomethacin mediated by the hepatic microsomal system, followed by extramicrosomal deacylation

to O-desmethyl-N-deschloro-benzoylindomethacin. The O-demethylation of indomethacin to the major metabolite, O-desmethylindomethacin, is primarily mediated by enzyme CYP2C9.

- Excretion

Indomethacin and its metabolites are eliminated via renal, biliary, and fecal excretion. About 60% (26% as indomethacin and its glucuronide) of an oral dosage is recovered in urine as drug and metabolites, and 33% (1.5% as indomethacin) is recovered in feces. The mean half-life of indomethacin is estimated to be approximately 4.5 hours. Indomethacin undergoes appreciable enterohepatic circulation through excretion of its glucuronide into the bile followed by indomethacin recycling after hydrolysis. The rate of enterohepatic circulation is variable, but is estimated to range from 27% to 115%. Hepatic function may alter excretion of indomethacin.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The core clinical development program supporting the 505(b)(2) NDA submission for Tivorbex Capsules 20 mg and 40 mg for the treatment of mild to moderate acute pain consists of five clinical trials:.

Table 3: Table of clinical studies

Trial Number, Dates, Phase	Trial Design	Number of Sites	Treatments	N Enrolled/ Completed	Trial Population, Demographics	Use of Data
IND1-08-01 04-Mar-2009 to 03-Apr-2009 Phase 1	Randomized, Single-Dose, Five-Way Crossover, Relative Bioavailability Study	1	A: (b) (4) 40 mg – fasted B: 20 mg – fasted C: Indomethacin 50 mg – fasted D: (b) (4) 40 mg – fed E: Indomethacin 50 mg – fed All treatments were single dose.	40/40	Healthy subjects 20 M / 20 F Mean age: 37.6 yrs (18 to 79 yrs)	Pharmacokinetics and Safety (conducted with POC Formulation[a])
IND1-12-07 05-Sep-2012 to 20-Nov-2012 Phase 1	Randomized, Single-Dose, Four-Way Crossover, Relative Bioavailability Study	1	A: (b) (4) 20 mg – fasted B: 40 mg – fasted C: 40 mg – fed D: Indomethacin 50 mg – fasted All treatments were single dose.	40[c]/36	Healthy subjects 33 M / 7 F Mean age: 36.5 yrs (19 to 54 yrs)	Pharmacokinetics and Safety (conducted with Commercial Formulation[b])
IND2-08-03 02-Sep-2009 to 20-Nov-2009 Phase 2	Randomized, Double-Blind, Single-Dose, Parallel-Group, Active- and Placebo-Controlled Study	3	- (b) (4) 20 mg - 40 mg - Celecoxib 400 mg - Placebo	203/203	Patients with postoperative pain following third molar extraction 71 M / 132 F Mean age: 22.1 yrs (18 to 35 yrs)	Efficacy and Safety (conducted with POC Formulation)
IND3-08-04b 13-Feb-2012 to 12-Jun-2012 Phase 3	Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active- and Placebo-Controlled Study	4	- (b) (4) 40 mg TID - 40 mg BID - 20 mg TID - Celecoxib 400 mg initial dose then 200 mg BID - Placebo	462/450	Patients with postoperative pain following bunionectomy 78 M / 384 F Mean age: 41.2 yrs (18 to 68 yrs)	Efficacy and Safety (conducted with Commercial Formulation)
IND3-10-06 21-May-2012 to 29-Aug-2012 Phase 3	Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study	4	- (b) (4) 40 mg TID - 40 mg BID - 20 mg TID - Placebo	373 / 364	Patients with postoperative pain following bunionectomy 56 M / 317 F Mean age: 40.3 yrs (18 to 65 yrs)	Efficacy and Safety (conducted with Commercial Formulation)

Abbreviations: F=female; M=male; N=number; yrs=years; POC=Proof of Concept; TID=3 times daily; BID=twice daily
a POC Formulation: Initial formulation (b) (4)
b Commercial Formulation: formulation used in all Phase 3 trials and in the Phase 1 (IND1-12-07) trial that is the same formulation to be used for commercial production.
c 41 subjects were randomized but only 40 were enrolled as 1 subject was withdrawn prior to dosing

(Source: Applicant's Table 5.2 from Tabular listing of all clinical trials, pp. 1-2)

5.2 Review Strategy

The review of efficacy focused on two Phase 3 trials, IND3-08-04b and IND3-10-06. The third molar extraction Phase 2 trial, IND2-08-03, considered to provide only supportive data is not reviewed in detail.

The review of safety focused on data from the two Phase 3 bunionectomy trials that were pooled and contributed most of the safety data.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Protocol IND3-08-04b

Title: "A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active- and Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy"

Objectives
Primary: Analgesic efficacy of Indomethacin Nanoformulation Capsules compared with placebo in subjects with acute postoperative pain after bunionectomy

Secondary:
- Safety of Indomethacin Nanoformulation Capsules compared with placebo in subjects with acute postoperative pain after bunionectomy
- Time to onset of analgesia for Indomethacin Nanoformulation Capsules compared with celecoxib

Trial Design
This was to have been a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled trial in patients with bunionectomy surgery. The study was to have been conducted at four centers in the United States.

The duration of the study was to have been approximately 6 weeks, which includes up to a 4-week screening period, a 3-day treatment period (72 hours of confinement with 48 hours of treatment), and a Post-treatment Follow-up Visit approximately 1 week after surgery.

Trial Population
The eligibility criteria were to have been:
- Male or female ≥ 18 and ≤ 65 years of age
- Classified as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System
- Had undergone primary, unilateral, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures
- Experience a pain intensity (PI) rating of ≥ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour period after discontinuation of the anesthetic block

Subjects were to have been excluded for:

- History of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any nonsteroidal anti-inflammatory drugs (NSAIDs, including indomethacin and celecoxib)
- Alcoholism or drug abuse or misuse within 2 years of Screening or evidence of tolerance or physical dependence before dosing with study drug
- Clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease
- Ongoing condition, other than one associated with the current primary, unilateral, first metatarsal bunionectomy that could generate levels of pain sufficient to confound the results of the study
- Significant psychiatric disorder
- Clinically significant gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding
- Surgical or medical condition of the GI or renal system that, in the opinion of the investigator, might significantly alter the absorption, distribution, or excretion of any drug substance
- Receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening
- Currently receiving anticoagulants
- Received a course of systemic corticosteroids (either oral or parenteral) within 3 months before Screening
- Has received or will require any analgesic medication within 5 half-lives (or, if half-life is unknown, within 48 hours) before surgery
- Chronic use (defined as daily use for > 2 weeks) of NSAIDs, opiates, or glucocorticoids within 6 months. Aspirin at a daily dose of ≤ 325 mg is allowed for cardiovascular prophylaxis
- Significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥ 3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactate dehydrogenase, or creatinine ≥ 1.5 times the ULN)
- Clinically significant laboratory or 12-lead electrocardiogram (ECG) finding

Trial Medications

Eligible subjects were to have been randomly assigned in 1:1:1:1:1 ratio to one of the five treatment groups:

- Indomethacin Nanoformulation Capsules 40 mg TID,
- Indomethacin Nanoformulation Capsules 40 mg BID
- Indomethacin Nanoformulation Capsules 20 mg TID
- Placebo
- Celecoxib capsules
    - 200 mg BID (administered as a 400 mg dose for the first dose)

Table 4: Treatment groups (IND3-08-04b)

	DAY 1				DAY 2			
Treatment group	**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)**
40 mg TID	40 mg + P	40 mg	P	40 mg	40 mg	40 mg	P	40 mg
40 mg BID	40 mg + P	P	40 mg	P	40 mg	P	40 mg	P
20 mg TID	20 mg + P	20 mg	P	20 mg	20 mg	20 mg	P	20 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

(Source: Applicant's table from 16.1.1 Protocol Synopsis, p.11)

Trial Conduct

Subjects were to have been admitted to the study site on the morning of the scheduled surgery (Day 0), and remain there until postoperative Day 3. On Day 0, subjects were to undergo primary, unilateral, first metatarsal bunionectomy after establishment of regional anesthesia using a popliteal sciatic nerve block (PSB). The regional anesthesia was to be continued postoperatively via a continuous anesthetic infusion. Subjects could receive supplemental analgesia with an opioid/acetaminophen combination product (see Rescue Medications) during the continuous infusion period to help control breakthrough pain if the regional anesthetic infusion appeared to be ineffective. If the regional anesthetic infusion and supplemental analgesia did not effectively control the subject's postoperative pain, then the subject was to have been discontinued from the study.

On Day 1, the regional anesthetic infusion was to have been discontinued at approximately 3 AM. During the 9-hour period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥ 40 mm on a 100-mm VAS were eligible to be enrolled into the study.

Subjects were to have been randomly assigned to one of five treatment groups: Indomethacin Nanoformulation Capsules 40 mg TID, 40 mg BID, or 20 mg TID; placebo; or celecoxib capsules 200 mg BID (administered as a 400-mg dose for the first dose).

After randomization, subjects whose pain could not be adequately managed by a combination of study drug and rescue medication, or who developed unacceptable side effects during the study, were to have been discontinued from further study participation.

At discharge, patients were to have been instructed to record concomitant medications taken and AEs in their outpatient subject diary and to return the outpatient subject diary to study personnel at the Follow-up Visit (5 to 9 days after Surgery).

Rescue Medications

One tablet of hydrocodone/acetaminophen 10 mg/325 mg orally every 4 to 6 hours as needed for:

- pain before the anesthetic infusion is discontinued
- rescue medication after the anesthetic infusion is discontinued and treatment with the study drug has been initiated

If subjects were unable to tolerate hydrocodone/acetaminophen 10 mg/325 mg or if there was insufficient PR, then 1 tablet of oxycodone/acetaminophen 7.5 mg/325 mg could have been administered orally every 6 hours as needed for pain. The total daily dosage of rescue medication could not exceed 6 tablets.

After randomization, subjects were to have been encouraged to wait for at least 1 hour after the first dose of study drug before receiving first rescue medication to allow time for the study drug to exert its pharmacologic effect.

Trial Procedures

The following table presents the time of events and assessments planned to be taken:

Table 5: Trial procedures (IND3-08-04b)

	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

(Source: Applicant's table from 16.1.1 Protocol and protocol amendments, pp. 53-54)

Efficacy Assessments

- Pain Intensity (PI) (VAS) at Baseline
- PI (VAS) and pain relief (PR) using 5-point categorical scale) recorded in the inpatient subject diary 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
  - before the first use of rescue analgesia if before the 8-hour time point
  - premature study termination
- Time to perceptible and meaningful PR using the 2-stopwatch method
- 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)

Safety Assessments

- Physical exam
- Vital signs
- AEs
- Concomitant medications

Statistical Analysis

Primary efficacy variable:

- The primary efficacy variable was to have been VAS summed pain intensity difference (VAS SPID) (calculated as a time-weighted average) over 0 to 48 hours (VAS SPID-48) after Time 0

Secondary efficacy variables:
- VAS PID at each scheduled time point after Time 0
- VAS PI 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
- 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 PR confirmed by meaningful PR)
- PR score on a 5-point categorical scale at each scheduled time point after Time 0
- Peak PR
- Time to peak PR
- Time to first perceptible PR
- Time to meaningful PR
- 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 study drug

Safety Variables
- Incidence of treatment-emergent adverse events (TEAEs)
- Physical examination findings
- Changes in vital sign measurements

Statistical analysis methods
The analysis populations were to have been the following:
- Intent-to-treat (ITT) population, the primary population for the efficacy analysis: all subjects who received at least one dose of trial drug.
- Per-protocol (PP) population, utilized to evaluate the sensitivity of the primary efficacy analysis: all ITT subjects who remained in the trial for at least 48 hours of treatment and who did not incur a major protocol violation that would challenge the validity of their data.
- Safety population: all subjects treated with study drug

The primary analysis was to have been conducted using sequential testing for the three Indomethacin Nanoformulation Capsule treatments in the following order: 40 mg TID, 40 mg BID, and 20 mg TID. An analysis of covariance (ANCOVA) model was to have been

used, with treatment effect as the factor and baseline pain intensity as the covariate. The analysis was to have been based on a 2-sided test at the significance level of 0.05.

The primary efficacy endpoint was to have consisted of the comparisons of trial treatment with placebo in the following sequential order, to maintain the Type I error rate of $\alpha = 0.05$:
1. Indomethacin Nanoformulation Capsules 40 mg TID
2. Indomethacin Nanoformulation Capsules 40 mg BID
3. Indomethacin Nanoformulation Capsules 20 mg TID

Failure of any stage in the sequence implied automatic failure of all subsequent stages. Other comparisons between the treatment groups were to have been considered secondary, and no further adjustments for multiple comparisons were implemented

For continuous secondary endpoints such as pain intensity score (VAS) at each scheduled time point, pain intensity difference (VAS PID) at each scheduled time point, peak pain intensity, TOTPAR-4, TOTPAR-8, TOTPAR-24, TOTPAR-48, VAS SPID-4, VAS SPID-8, and VAS SPID-24, descriptive statistics (such as mean, standard error, median, minimum, and maximum) were to have been provided for each treatment group. For ordinal secondary endpoints such as PR score at each scheduled time point, peak PR, and patient's global evaluation of study drug, descriptive summaries were to have been provided to include the number and percentage of subjects within each category for each treatment group.

For each time-to-event endpoint, the Kaplan-Meier method was to have been used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) was to have been based on data collected using the 2-stopwatch method following the first dose of study drug. Time to onset of analgesia was to have been right-censored at 8 hours for subjects who did not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0 or who required rescue medication prior to achieving perceptible or meaningful pain relief.

For the proportion of subjects using rescue medication, a logistic regression model that adjusts for baseline pain intensity (if necessary, the CMH test) was to have been used to evaluate the treatment effect.

Subgroup analysis by age, gender, and race were to have been performed.

For pain intensity, missing observations were to have been 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 was to have been 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.
Pain relief missing observations were to have been imputed using 0 (no pain relief) for subjects who withdrew from the study due to lack of efficacy or an AE/intolerance to study drug.

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 were to have been imputed using last-observation-carried-forward (LOCF).

The LOCF imputation was to have been 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.

For subjects who took any dose of rescue medication, subsequent measures after the first dose of rescue medication were to have been disregarded. Instead, all scheduled assessments after the first dose of rescue medication were to have been imputed using BOCF using the baseline observation taken before Time 0.

Sample size calculation
A sample size of 460 subjects total, 92 subjects per treatment group, was calculated assuming a study power of approximately 85% to detect a minimal difference of 535 between an active treatment arm and placebo in VAS SPID-48 using a 2-sample t test with a 0.05 two-sided significance level and a minimal difference of 535 in VAS SPID-48 (using the 2-sample t-test) between Indomethacin Nanoformulation Capsules 40 mg TID and placebo (the primary efficacy test).

Trial Results
Protocol violations
There were 3 major protocol deviations that occurred during the trial. All were reported for subjects in the Indomethacin Nanoformulation Capsule 40 mg BID treatment group and included inclusion criterion, investigational product dosing error, and a rescue medication dosing error in 1 subject each (shown on the table below). Each protocol deviation occurred at a different study site. Because of the small number, it is unlikely that the violations greatly impacted the primary efficacy results.

Table 6: Protocol violations (IND3-08-04b)

Table 10-1 Summary of Major Protocol Deviations (Safety Population)

Category	Indomethacin Nanoformulation Capsule 40 mg TID (n = 93) n (%)	Indomethacin Nanoformulation Capsule 40 mg BID (n = 91) n (%)	Indomethacin Nanoformulation Capsule 20 mg TID (n = 91) n (%)	Celecoxib Capsule 200 mg[a] BID (n = 93) n (%)	Placebo (n = 94) n (%)	Total (N = 462) n (%)
Subjects with any major protocol deviation	0	3 (3.3)	0	0	0	3 (0.6)
Inclusion criteria	0	1 (1.1)	0	0	0	1 (0.2)
IP dosing error[b]	0	1 (1.1)	0	0	0	1 (0.2)
Rescue medication error	0	1 (1.1)	0	0	0	1 (0.2)

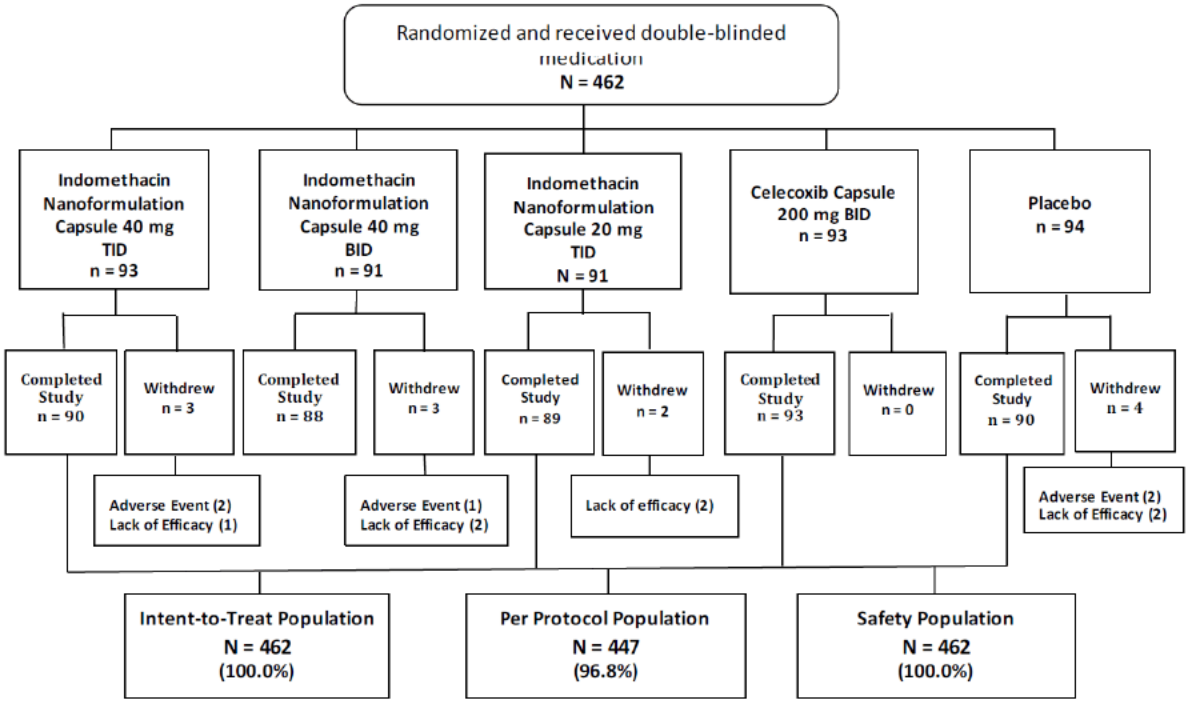
(Source: Applicant's table from Study Report Body, p. 55)

Enrollment/ Subject disposition

A total of 606 potential subjects were screened, and 462 subjects were randomized into the trial. There were 450 subjects who completed the trial. An overall total of 12 subjects were discontinued from the trial because of lack of efficacy (7 subjects [1.5%]) or the occurrence of an AE (5 subjects [1.1%]). Numbers of discontinuations were similar across treatment groups with the exception of the celecoxib treatment group in which there were no subjects who discontinued. The enrollment/disposition for the randomized subjects is presented on the figure below.

Figure 1: Subject disposition (IND3-08-04b)

Figure 10-1 Subject Disposition Flowchart (All Subjects)



(Source: Applicant's Figure 10-1 from Study Report, p. 54)

Extent of exposure

All 462 subjects received study drug according to their randomization assignment and were included in the safety analysis population.

Demographics

The trial population was predominantly female (384 subjects [83.1%]) and this is expected for bunionectomy surgery. The majority was Caucasian (333 subjects [72.1%]), not Hispanic or Latino (372 subjects [80.5%]), and had a mean age of 41.2 years. Across all five treatment groups, the youngest subject was 18 years and the oldest subject was 68 years. The demographic characteristics were balanced across the five treatment groups.

Overall mean (SD) baseline pain intensity was 73.2 (16.8), and was similar across the five treatment groups.

Table 7: **Patient demographic characteristics (IND3-08-04b)**

Table 11-1 Demographic and Baseline Characteristics (Safety Population)

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

Baseline medical characteristics and concomitant therapy

Medical history and concomitant diseases were similar between the treatment groups. With regards to the concomitant medication use, medications taken by at least 5% of subjects included the following: mepivacaine (446 subjects [96.5%]); Vicodin® (265 subjects [57.4%]); ibuprofen (123 subjects [26.6%]); Oxycocet® (125 subjects [27.1%]); multivitamins (69 subjects [14.9%]); paracetamol (29 subjects [6.3%]), and fish oil (28 subjects [6.1%]). The distribution of patients taking these medications was similar among treatment groups.

Applicant's Efficacy Analysis

Primary Analysis

The primary efficacy endpoint was the VAS SPID calculated as a time-weighted average over 0 to 48 hours (VAS SPID-48) after Time 0. The summed pain intensity difference (SPID) was calculated using the pain intensity difference (PID) at each follow-up time point weighted (multiplied) by the amount of time since the prior assessment. The 48-hour SPID value was the assessment utilized in the primary efficacy analysis. An ANCOVA model with baseline pain intensity as the only covariate (model 1) was use in the analysis of the primary endpoint. As a supporting sensitivity analysis, the covariate of gender was added to the ANCOVA model in addition to baseline pain intensity.

In response to an FDA Advice Letter dated 14 Aug 2012, the Applicant performed additional post hoc analyses to assess the impact of using single-method imputation techniques to address missing data in the analysis of the primary endpoint.

The first analysis used a restricted maximum likelihood (REML)-based MMRM analysis methodology. Least square mean (SE) values for VAS SPID were comparable for all active treatment groups. In addition, to further investigate the effect of BOCF imputation following the receipt of rescue medication on the results of the primary analysis, the original protocol-defined ANCOVA analysis was repeated, wherein BOCF imputation was limited to the 4 hours following receipt of rescue medication.

The Applicant found with respect to the primary efficacy variable that all Indomethacin Nanoformulation treatment groups (40 mg TID, 40 mg BID, and 20 mg TID) were associated with significant reduction in pain (VAS SPID-48 ITT; $P \leq 0.05$) compared with placebo. For celecoxib, the VAS SPID-48 scores did not achieve statistical significance compared with placebo. The MMRM analysis revealed significant differences compared with the placebo across the four active treatment groups ($P<0.001$). The additional post hoc ANCOVA, which excluded only efficacy assessments performed up to 4 hours following receipt of rescue medication, also demonstrated significant treatment benefits in favor of Indomethacin Nanoformulation compared with placebo for all three treatment regimens ($P<0.001$). A summary of the results is presented on the table below:

Table 8: Analysis of VAS SPID-48 ITT population (IND3-08-04b)

Parameter[a]	(b) (4) Capsules			Celecoxib 200 mg bid[b]	Placebo
	40 mg tid n=93	40 mg bid n=91	20 mg tid n=91	n=93	n=94
VASSPID-48 (ANCOVA)[c]	509.6 (91.9) *P*<0.001	328.0 (92.9) *P*=0.046	380.5 (92.9) *P*=0.017	279.4 (91.9) *P*=0.103	67.8 (91.4) --
VASSPID-48 (MMRM)[d, e]	2025.4 (69.1) *P*<0.001	2135.5 (69.9) *P*<0.001	1930.9 (69.9) *P*<0.001	1840.4 (68.8) *P*<0.001	1195.7 (68.9) --
VASSPID-48 (Posthoc ANCOVA)[c, d]	2056.5 (86.7) *P*<0.001	2127.4 (87.7) *P*<0.001	1928.6 (87.7) *P*<0.001	1838.2 (85.3) *P*<0.001	1197.3 (86.7) --

(Source: Applicant's table from 2.7.3 Overview of clinical efficacy, page 14, amendment submission from August 30, 2013)

A second sensitivity analysis was also performed using the MMRM model that penalized patients who dropped out of the study early.

Table 9: **VAS SPID-48, penalized MMRM (Study IND3-08-04b)**

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Post-Hoc Table 14.2.1.7-r
Analysis of VAS Summed Pain Intensity Difference (VASSPID[1]) over 0 to 48 Hours (VASSIPD-48) - Penalized VAS PID MMRM Analysis
ITT Population

Statistic	Indomethacin Nanoformulation Capsule 40 mg TID (N=93)	Indomethacin Nanoformulation Capsule 40 mg BID (N=91)	Indomethacin Nanoformulation Capsule 20 mg TID (N=91)
LS Means (SE)	2022.255 (68.6702)	2115.805 (69.5139)	1930.773 (69.4309)
95% CI	(1887.38, 2157.127)	(1979.27, 2252.333)	(1794.40, 2067.139)
Comparison vs. Placebo			
Difference in LS Mean (SE)	826.474 (96.9786)	920.024 (97.5635)	734.992 (97.5252)
95% CI for Difference in LS Mean	(636.005, 1016.943)	(728.407, 1111.641)	(543.449, 926.535)
P value for Difference	<0.001	<0.001	<0.001

Statistic	Celecoxib Capsule 200 mg (400 mg Initial Dose) (N=93)	Placebo (N=94)
LS Means (SE)	1840.384 (68.4224)	1195.782 (68.4682)
95% CI	(1705.99, 1974.773)	(1061.30, 1330.254)
Comparison vs. Placebo		
Difference in LS Mean (SE)	644.603 (96.7912)	
95% CI for Difference in LS Mean	(454.499, 834.707)	
P value for Difference	<0.001	

(Source: Applicant's post-hoc table 14.2.1.7-r from Study Report Body p. 371, August 30, 2013 amendment submission)

Secondary Efficacy Variables

- Pain Intensity Difference Over 0 to 4 Hours, Over 0 to 8 Hours, and Over 0 to 24 Hours

As secondary analyses, the SPIDs were assessed for various time periods following trial entry: 0 to 4 hours, VAS SPID-4; 0 to 8 hours, VAS SPID-8; and 0 to 24 hours, VAS SPID-24. Analgesia was evident in the Indomethacin Nanoformulation Capsule 40 mg TID and 40 mg BID treatment groups during the 0- to 4-hour period and for the three Indomethacin Nanoformulation Capsule and the celecoxib groups at 0 to 8 hours, followed by continued improvement in analgesia measured by VAS SPID up to 48 hours.

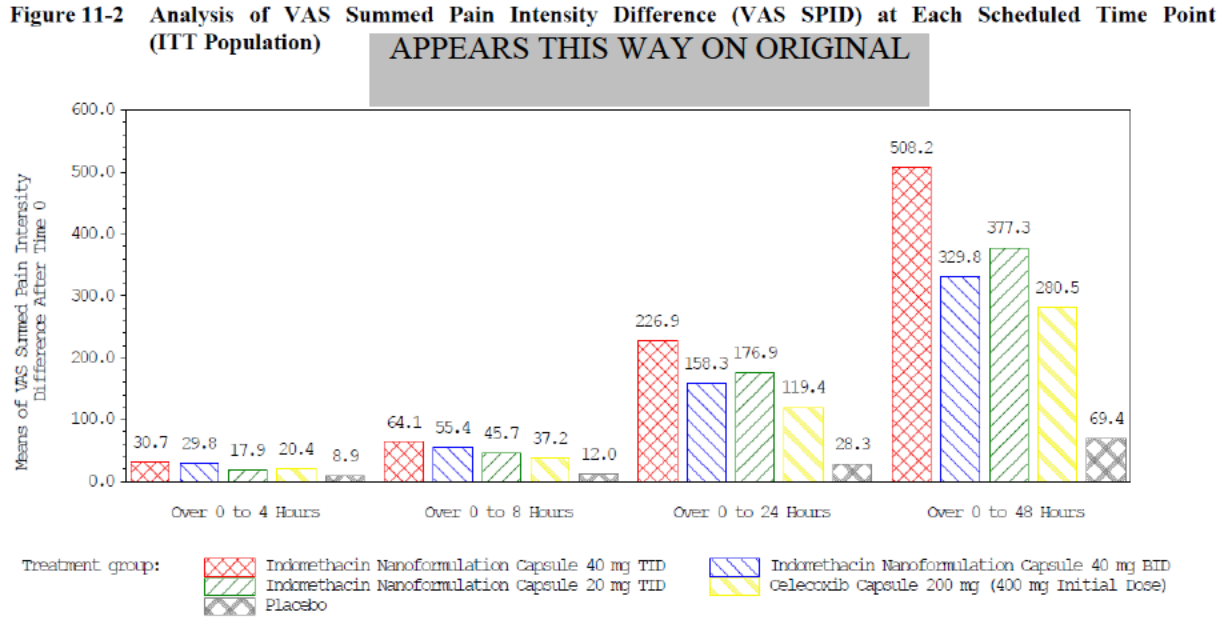
Table 10: VAS SPID at scheduled time points (IND3-08-04b)

Table 11-5 Analysis of Visual Analogue Scale Summed Pain Intensity Difference Over 0 to 4 Hours, Over 0 to 8 Hours, and Over 0 to 24 Hours (ITT Population)

	Indomethacin Nanoformulation Capsule			Celecoxib Capsule 200 mg[a]	
Statistic	40 mg TID (N = 93)	40 mg BID (N = 91)	20 mg TID (N = 91)	BID (N = 93)	Placebo (N = 94)
VAS SPID-4					
n	93	91	91	93	94
Mean (SD)	30.7 (74.9)	29.8 (70.8)	17.9 (57.1)	20.4 (54.6)	8.9 (38.3)
Median	0.0	2.0	-2.5	1.0	-1.1
Min, max	(-81.3, 293.0)	(-54.0, 329.2)	(-89.5, 228.5)	(-52.3, 250.8)	(-45.5, 218.4)
Comparison vs placebo[b]					
P value for difference	0.013	0.014	0.211	0.098	
VAS SPID-8					
N	93	91	91	93	94
Mean (SD)	64.1 (144.6)	55.4 (132.4)	45.7 (122.7)	37.2 (97.4)	12.0 (49.9)
Median	0.0	2.0	-2.5	1.0	-1.1
Min, max	(-188.7, 631.1)	(-54.0, 512.2)	(-89.5, 584.0)	(-50.7, 475.1)	(-45.5, 275.7)
Comparison vs placebo[b]					
P value for difference	0.001	0.004	0.017	0.028	
VAS SPID-24					
n	93	91	91	93	94
Mean (SD)	226.9 (500.9)	158.3 (405.2)	176.9 (469.6)	119.4 (329.6)	28.3 (132.1)
Median	0.0	2.0	-2.5	1.3	-1.1
Min, max	(-108.0, 2144.7)	(-54.0, 1704.4)	(-89.5, 1945.0)	(-50.7, 1527.4)	(-45.5, 1036.9)
Comparison vs placebo[b]					
P value for difference	<0.001	0.004	0.004	0.015	

(Source: Applicant's table from Study Report Body page 67, August 30, 2013 amendment submission)

Figure 2: VAS SPID at scheduled time points (IND3-08-04b)



(Source: Applicant's figure from Study Report Body page 68, August 30, 2013 amendment submission)

- Total Pain Relief Over 0 to 4 Hours. Over 0 to 8 Hours, Over 0 to 24 Hours, and Over 0 to 48 Hours

The patterns for total pain relief for the periods 0 to 4 hours, 0 to 8 hours and 0 to 24 hours were similar to the pattern observed for the analysis of VAS SPID scores noted above.

- Time to onset of analgesia

The mean time to onset of analgesia occurred earlier than placebo (1.6 hours) in the Tivorbex Capsules 40 mg tid group (1.3 hours) and the Tivorbex Capsules 20 mg treatment group (1.3 hours), but no statistical significance was reached. Substantial (ranging from 66.7% to 74.5%) numbers of subjects were censored. There was no evidence of a substantial difference in the time to onset of analgesia for the Indomethacin Nanoformulation Capsule groups and the celecoxib group.

Figure 3: **Time to onset of analgesia, ITT (IND3-08-04b)**

Figure 11-4 Time to Onset of Analgesia (Measured as Time to First Perceptible Pain Relief Confirmed by Meaningful Pain Relief) after Time 0 (ITT Population)

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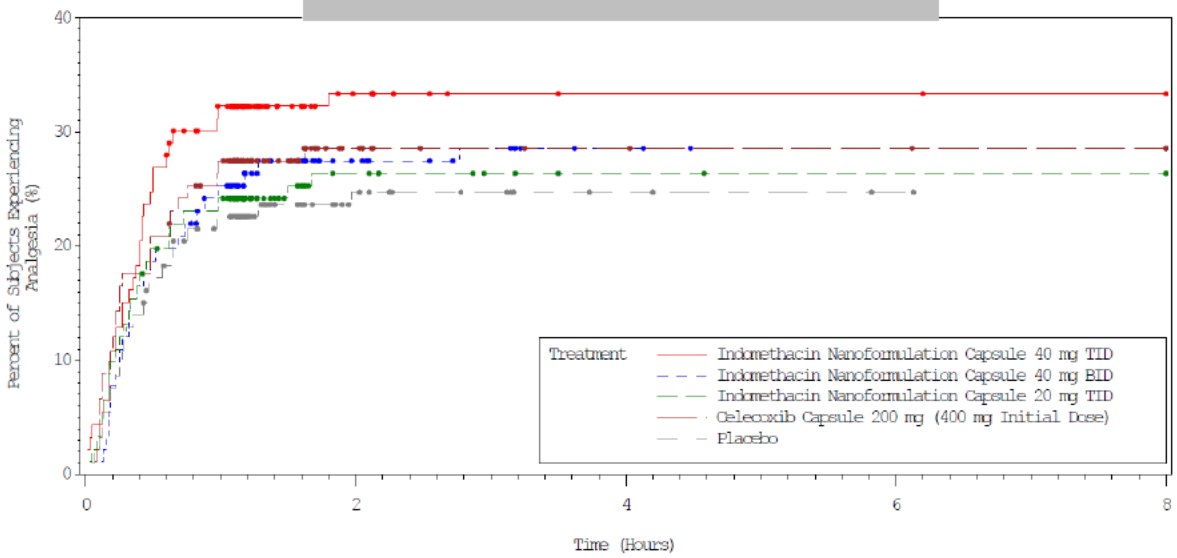


(Source: Applicant's figure from Study Report Body page 78, August 30, 2013 amendment submission)

- Peak Pain Relief (PR)

The Applicant found that mean time to peak PR was similar for all of the Tivorbex treatment groups (ranging 17.0 to 25.1 hours) and occurred earlier than that for the placebo group (approximately 33.5 hours). There were no differences between the Tivorbex treatment groups and the celecoxib group (P=0.307). There were no differences in the time to peak PR for the 4 active treatment groups and placebo.

- Use of Rescue Medication

The Applicant found that there was evidence of a dose response for rescue medication use for the three Tivorbex groups. The amount of rescue medication used was somewhat greater in the placebo group. The mean time to first use of rescue medication occurred later in the Tivorbex Capsules treatment groups compared with both celecoxib and placebo, 4 hours for the Tivorbex 40 mg TID group, 6 hours for the Tivorbex 40 mg BID group, 6 hours for the Tivorbex 20 mg TID group, 3 hours for the Celecoxib 200 mg BID group, and 2 hours for the placebo group.

It is of note that a substantial number of subjects in all treatment groups used rescue medication in this study.

Table 11: Use of rescue medication by treatment group (IND3-08-04b)

Table 14.2.9
Proportion of Subjects Using Rescue Medication
ITT Population

Statistics	Indomethacin Nanoformulation Capsule 40 mg TID (N=93)	Indomethacin Nanoformulation Capsule 40 mg BID (N=91)	Indomethacin Nanoformulation Capsule 20 mg TID (N=91)	Celecoxib Capsule 200 mg (400 mg Initial Dose) (N=93)	Placebo (N=94)
Rescue medication usage					
Yes	76 (81.7%)	82 (90.1%)	81 (89.0%)	83 (89.2%)	91 (96.8%)
No	17 (18.3%)	9 (9.9%)	10 (11.0%)	10 (10.8%)	3 (3.2%)
Missing	0	0	0	0	0
Odds Ratio (95% C.I.)[1]	0.148 (0.042, 0.525)	0.300 (0.079, 1.147)	0.269 (0.072, 1.014)	0.274 (0.073, 1.029)	
P value [1]	0.003	0.078	0.052	0.055	

(Source: Applicant's table 14.2.9 from Study Report, Section 14, August 30, 2013 amendment submission)

- Subjects' Global Evaluation of Study Drug

The Applicant found that subjects in both the Tivorbex Capsules 40 mg tid and 40 mg bid treatment groups demonstrated positive global evaluation of trial drug compared with placebo.

Table 12: Subject's Global Evaluation of Trial Drug – ITT Population (IND3-08-04b)

	IND3-08-04b					
	(b) (4) Capsules			Celecoxib Capsules	Placebo	Total
Global Evaluation Response	40 mg tid n=93	40 mg bid n=91	20 mg tid n=91	200 mg[a] bid n=93	n=94	N=462
Excellent	16 (17.2)	8 (8.8)	6 (6.6)	2 (2.2)	1 (1.1)	33 (7.2)
Very good	6 (6.5)	6 (6.6)	5 (5.5)	9 (9.8)	2 (2.1)	28 (6.1)
Good	3 (3.2)	7 (7.7)	8 (8.8)	7 (7.6)	5 (5.3)	30 (6.5)
Fair	13 (14.0)	15 (16.5)	6 (6.6)	17 (18.5)	16 (17.0)	67 (14.5)
Poor	55 (59.1)	55 (60.4)	66 (72.5)	57 (62.0)	70 (74.5)	303 (65.7)
P value[d]	<0.001	0.003	0.060	0.018	--	--

(Source: Applicant's table from Summary of clinical efficacy, 2.7.3, p. 74, August 30, 2013 amendment submission)

5.3.2. Protocol IND3-10-06

Title: "A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy"

The trial design for this study is identical to IND03-08-04b study except that there was no active celebrex comparator treatment group.

In addition, the MMRM model used for the primary efficacy variable (VASSPID-48) wherein BOCF imputation of post-rescue efficacy assessments was limited to only those assessments conducted within 4 hours of a subjects' dose of rescue medication, was prospectively included in the SAP prior to finalization.

Trial Results

Protocol violations

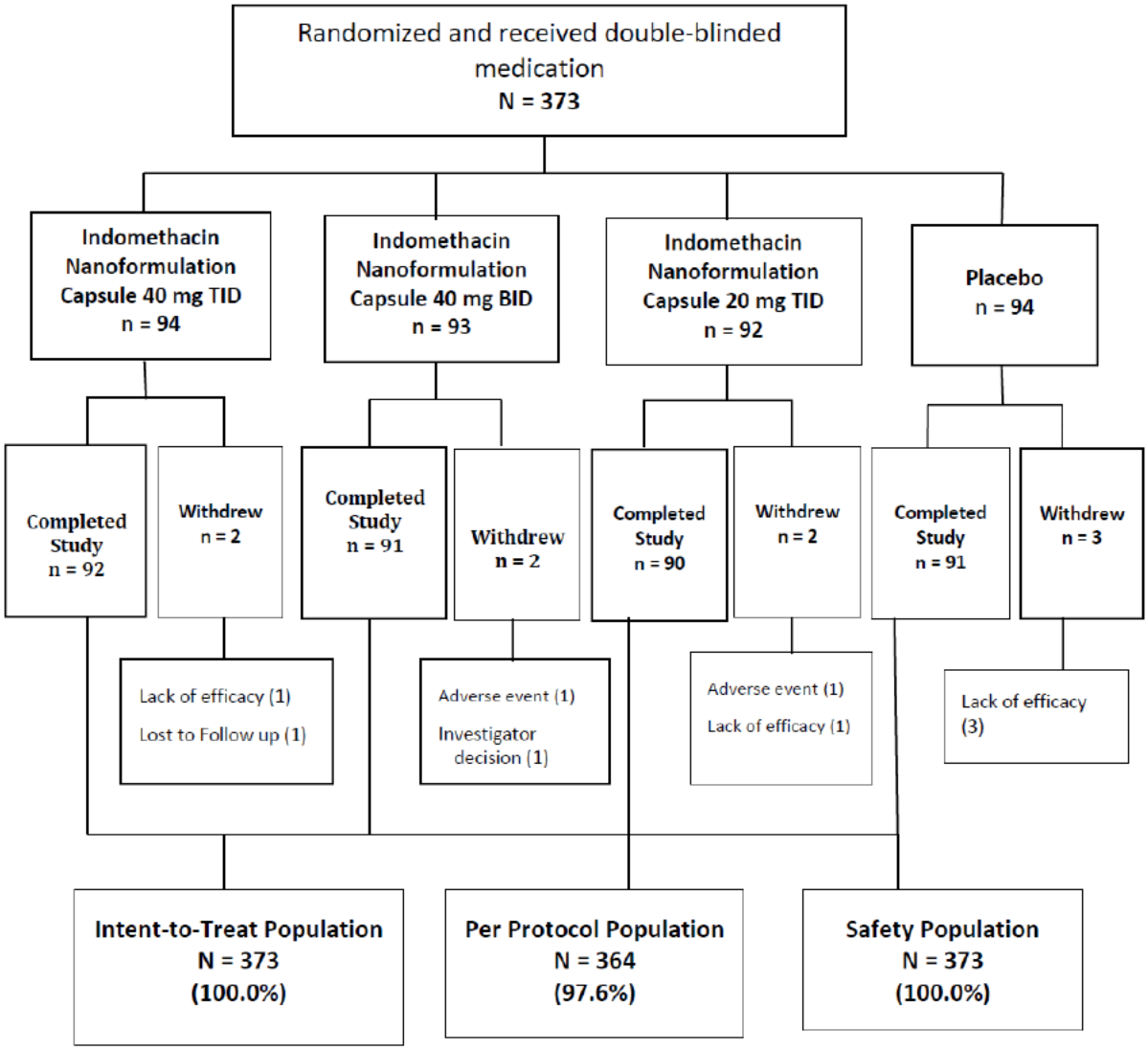
A major protocol deviation was reported for one subject who met the exclusion criteria (surgical procedure consisted of osteotomy without internal fixation) and was excluded from the per-protocol population. It is unlikely that this single case would impact the primary efficacy results.

Enrollment/ Subject disposition

A total of 516 potential subjects were screened, and 373 subjects were randomized into the trial. There were 364 subjects who completed the trial. A small number of subjects, total of 9, were discontinued from the trial. Placebo patients discontinued due to lack of efficacy. Discontinuations due to AEs occurred in the Indomethacin groups. The enrollment/disposition for the randomized subjects is presented on the figure below.

Figure 4: Subject disposition (IND3-10-06)

Figure 10-1 Subject Disposition Flowchart



(Source: Applicant's Figure 10-1 from Study Report, p. 51)

Extent of exposure

All 373 subjects received trial drug according to their randomization assignment and were included in the safety analysis population.

Demographics

The trial population was predominantly female 85%. (384 subjects [83.1%]) and this is expected for bunionectomy surgery. The demographic characteristics were balanced across the treatment groups (see table below).

Table 13: Demographic Characteristics (IND3-10-06)

Table 11-1 Summary of Demographic Characteristics — Safety Population

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

(Source: Applicant's table from Study Report, p. 53)

Baseline medical characteristics and concomitant therapy

The mean baseline VAS pain intensity was 72.1 mm, and was similar across the treatment groups. The mean duration of the surgical procedure was 27 minutes and consistent across treatment groups. The minimum duration of surgery in all treatment groups was 13 minutes and the maximum was 82 minutes.

Medical history and concomitant diseases were similar between the treatment groups.

Applicant's Efficacy Analysis

Primary Efficacy Variable

The primary efficacy endpoint was the VAS SPID calculated as a time-weighted average over 0 to 48 hours (VAS SPID-48). The statistical analysis plan (SAP) for this trial was finalized prior to unblinding any study data, and defined two different methodological approaches for analyzing the primary efficacy parameter.

Original protocol-defined analysis

The original protocol-defined 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). The model used a baseline observation carried forward (BOCF) approach to impute missing efficacy assessments for subjects who withdrew due to lack of efficacy or for reasons related to AE/tolerability to study medication, and last observation carried forward (LOCF) for subjects who withdrew for any other reason. Additionally, efficacy data from all time points following the subjects' initial dose of rescue medication were imputed using BOCF in this analysis.

Using the original protocol-defined primary analysis, the Applicant found that both 40 mg Indomethacin treatment groups demonstrated statistically significant efficacy compared to placebo with the largest difference in Least Squares means (SE) for the 40 mg BID treatment group. The difference compared with placebo was not statistically significant for the Indomethacin 20 mg TID treatment group.

SAP-defined analysis with limited BOCF imputation

In response to an FDA Advice Letter from August 2012, the primary efficacy variable (VASSPID-48) was also analyzed using a mixed-model repeated-measure (MMRM) model that was prospectively included in the SAP prior to finalization. The model used all available data from all subjects to derive an estimate of pain intensity scores for subjects following study withdrawal, rather than "imputing" a score for individual subjects. In addition, rather than using the BOCF technique to impute efficacy assessment values for all time points following the first dose of rescue medication, the MMRM model limited application of the BOCF technique to only those efficacy assessments collected within 4 hours following receipt of rescue medication.

In the MMRM analysis, the treatment differences in the VASSPID-48 were calculated as the time weighted average of VAS Pain Intensity Difference Least Squares Mean estimates at each time point based on a MMRM model and included hour-by-treatment interaction as the main effect and baseline pain intensity as a covariate with no intercept. A compound symmetry covariance matrix was used to model the within-subject correlation.

Using the MMRM analysis model, the Applicant found that all three Indomethacin treatment groups demonstrated statistically significantly superior efficacy (P<0.001) compared to placebo.

Post-hoc analyses

1. ANCOVA with limited BOCF imputation.

A re-analysis of the primary efficacy parameter (VASSPID-48) was performed using the original protocol-specified ANCOVA methodology, but limiting BOCF to only those efficacy assessments collected within 4 hours after a dose of rescue medication. This approach produced results similar to those seen in the SAP-defined MMRM analysis. Differences in the LS means from this post-hoc analysis for all Indomethacin treatment groups demonstrated statistically significantly superior efficacy compared to placebo.

2. MMRM with penalized efficacy scores for early withdrawal.

The results of this analysis were consistent with those of the main MMRM model.

Table 14: Analysis of VASSPID48, ITT (IND3-10-06)

Parameter[a]	(b) (4) Capsules			Placebo
	40 mg tid n=94	40 mg bid n=93	20 mg tid n=92	n=94
VASSPID-48 (ANCOVA)[b]	598.47 (105.69) *P*=0.034	622.99 (106.24) *P*=0.023	342.83 (106.77) *P*=0.680	280.85 (105.79) --
VASSPID-48 (MMRM)[c, d]	2141.31 (74.90) *P*<0.001	2087.23 (75.33) *P*<0.001	1873.93 (75.74) *P*<0.001	1391.72 (75.11) --
VASSPID-48 (ANCOVA-posthoc)[b, c]	2152.01 (87.49) *P*<0.001	2106.94 (88.42) *P*<0.001	1880.73 (88.88) *P*<0.001	1392.60 (88.53) --

(Source: Applicant's table from 2.7.3 Summary of Clinical Efficacy, page 16, amendment submission date August 30, 2013)

Secondary Efficacy Variables

- Pain Intensity Difference Over 0 to 4 Hours, Over 0 to 8 Hours, and Over 0 to 24 Hours

As secondary analyses, the SPID were assessed for various time periods following trial entry: 0 to 4 hours, VAS SPID-4; 0 to 8 hours, VAS SPID-8; and 0 to 24 hours, VAS SPID-24. Statistically significant difference for Indomethacin versus placebo was observed for the 40 mg TID and 40 mg BID groups for VASSPID-8 and VASSPID-24 (see table below).

Table 15: VAS SPID at scheduled time points (IND3-10-06)

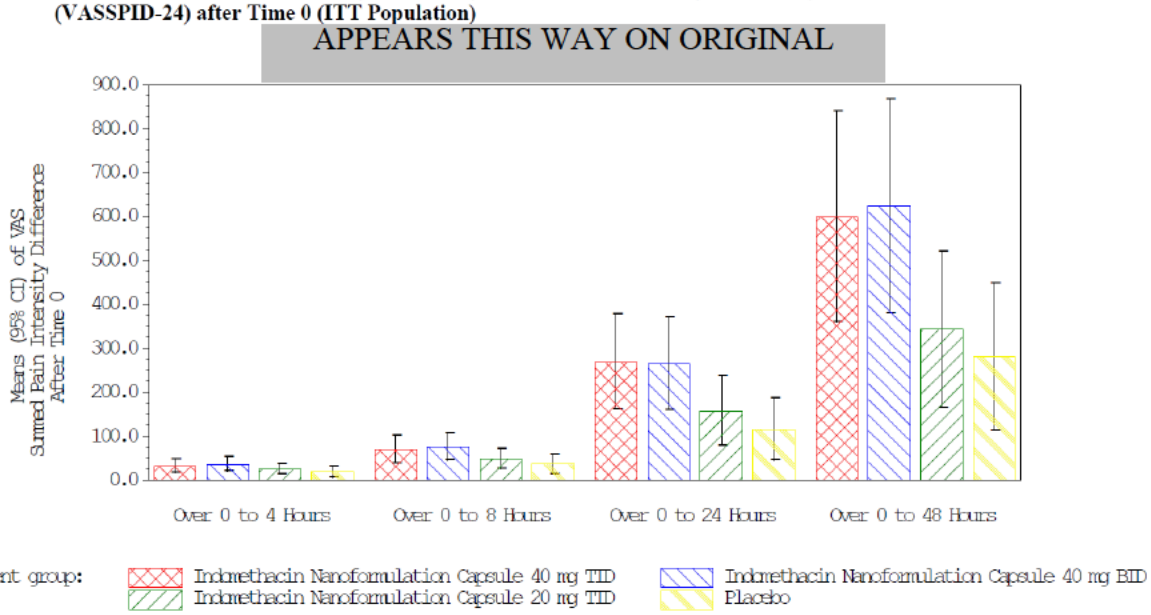
Table 11-4 Analysis of the Visual Analogue Scale Summed Pain Intensity Difference Over 0 to 4 Hours, 0 to 8 Hours, and 0 to 24 Hours—Intent-to-Treat Population

Statistic	Indomethacin Nanoformulation Capsule 40 mg TID (n = 94)	Indomethacin Nanoformulation Capsule 40 mg BID (n = 93)	Indomethacin Nanoformulation Capsule 20 mg TID (n = 92)	Placebo (n = 94)
VASSPID-4				
n	94	93	92	94
Mean (SD)	31.5 (74.4)	35.3 (79.6)	24.78 (54.6)	18.4 (62.1)
Median	3.3	0.50	4.05	0.8
Minimum, maximum	(-54.0, 277. 7)	(-89.8, 322.0)	(-62. 7, 250.0)	(-67.3, 312.5)
Comparison vs placebo[a]				
P value for difference	0.191	0.108	0.461	
VASSPID-8				
n	94	93	92	94
Mean (SD)	69.7 (151.7)	75.5 (152.5)	47.6 (109.9)	35.8 (107.9)
Median	3.3	2.8	4.1	0.8
Minimum, maximum	(-91.9, 559.6)	(-103.7, 688.0)	(-76.5, 559.3)	(-67.3, 710.8)
Comparison vs placebo[a]				
P value for difference	0.079	0.041	0.458	
VASSPID-24				
n	94	93	92	94
Mean (SD)	268.4 (526.9)	265.2 (516.2)	156.8 (384.0)	115.5 (346.5)
Median	2.8	2.8	7.8	0.8
Minimum, maximum	(-91.9, 1787.2)	(-171. 5, 2085. 8)	(-76.5, 1835.3)	(-67.3, 2291.5)
Comparison vs placebo[a]				
P value for difference	0.020	0.021	0.441	

(Source: Applicant's table from Study Report, page 60, August 30, 2013 amendment submission)

Figure 5: VAS SPID at scheduled time points (IND3-10-06)

Figure 11-1 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 (ITT Population)



(Source: Applicant's figure from Study Report, page 61, August 30, 2013 amendment submission)

The Applicant found that with re-analysis using post-hoc methods that limited data imputation, the Indomethacin 20 mg TID treatment group as well as both 40 mg treatment groups demonstrated statistically significant differences compared with placebo over 0-24 hours (VASSPID-24).

- Total Pain Relief Over 0 to 4 Hours. Over 0 to 8 Hours, Over 0 to 24 Hours, and Over 0 to 48 Hours

The patterns for total pain relief for the periods 0 to 4 hours, 0 to 8 hours and 0 to 24 hours were similar to the pattern observed for the analysis of VAS SPID scores noted above.

- Time to onset of analgesia

The mean time to onset of analgesia occurred approximately 1.5 hours post dose in the active treatment groups. Substantial (ranging from 60% to 80%) numbers of subjects were censored.

There were no meaningful differences for the different Indomethacin groups.

Figure 6: Time to onset of analgesia (IND3-10-06)

Figure 11-3 Time to Onset of Analgesia After Time 0 — Intent-to-Treat Population

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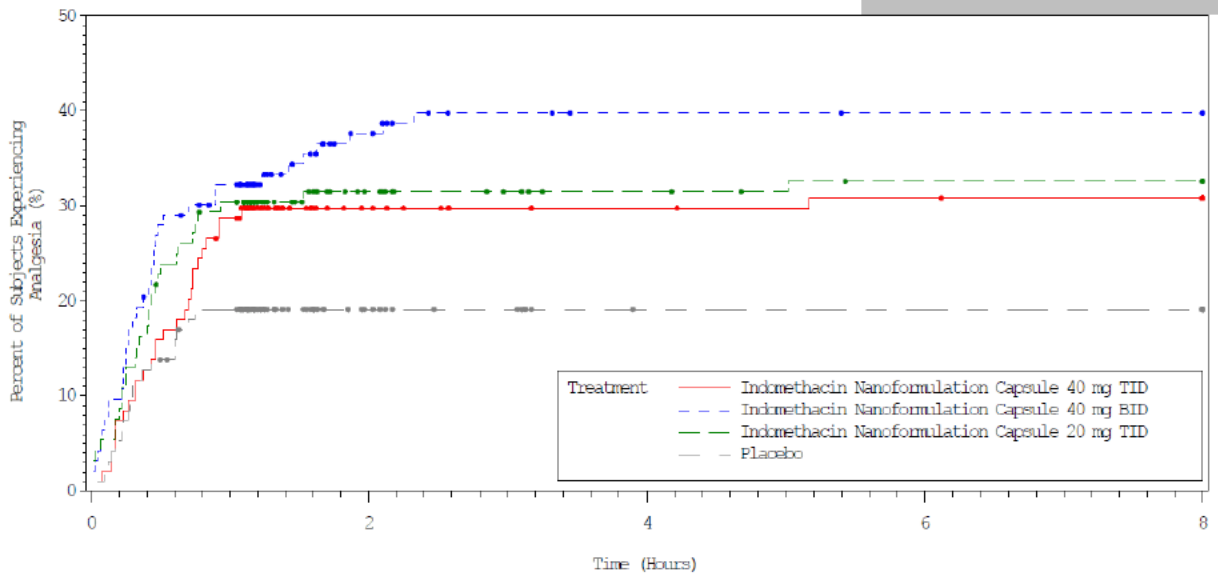

(Source: Applicant's figure from Study Report page 71, August 30, 2013 amendment submission)

- Peak Pain Relief (PR)

The Applicant found that more subjects in the Indomethacin treatment groups had higher peak PR than subjects in the placebo group. The Indomethacin 40 mg BID group had the most subjects achieve "a lot" or "complete" PR compared with the placebo group (32% versus 17%, respectively). Each of the active treatment arms achieved peak PR at a faster rate than placebo.

In a post-hoc analysis of peak PR that limited BOCF imputation to the 4 hours following rescue, there was higher number of subjects in all treatment groups reporting "a lot" or "complete" PR: Indomethacin 40 mg TID (90%), 40 mg BID (94%) and 20 mg TID (94%), and placebo (85%).

- Use of Rescue Medication

The Applicant found high rates for use of rescue medication in all of the treatment groups: Indomethacin Nanoformulation 40 mg BID treatment group (76%), Indomethacin Nanoformulation 40 mg TID treatment group (80%), Indomethacin Nanoformulation 20 mg TID treatment group (87%), and placebo group (89%).

Table 16: Use of rescue medication by treatment group (IND3-10-06)

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Statistics	Indomethacin Nanoformulation Capsule 40 mg TID (N=94)	Indomethacin Nanoformulation Capsule 40 mg BID (N=93)	Indomethacin Nanoformulation Capsule 20 mg TID (N=92)	Placebo (N=94)
Rescue medication usage				
Yes	75 (79.8%)	71 (76.3%)	80 (87.0%)	84 (89.4%)
No	19 (20.2%)	22 (23.7%)	12 (13.0%)	10 (10.6%)
Missing	0	0	0	0
Odds Ratio (95% C.I.)[1]	0.493 (0.214, 1.135)	0.400 (0.177, 0.906)	0.815 (0.332, 2.002)	
P value [1]	0.096	0.028	0.655	

(Source: Applicant's table 14.2.9 from Study Report, Section 14, page 217, August 30, 2013 amendment submission)

Mean (SE) time to first use of rescue medication was 10 hours for the Tivorbex 40 mg TID group, 6 hours for the Tivorbex 40 mg BID group, 8 hours for the Tivorbex 20 mg TID group, and 7 hours for the placebo group.

- Subjects' Global Evaluation of Study Drug

The Applicant found that 27% (P<0.001) of the subjects in the Indomethacin Nanoformulation BID 40 mg treatment group reported "excellent" or "very good" pain control, followed by the Indomethacin Nanoformulation 40 mg TID treatment group (23%, P=0.038). The number of subjects (16%]) in the Indomethacin Nanoformulation 20 mg TID treatment group reporting "excellent" or "very good" pain management was approximately twice that of those reporting the same in the placebo group (9%), but no statistical significance was reached.

Table 17: Subject's Global Evaluation of Study Drug – ITT (IND3-10-06)

	IND3-08-04b						IND3-10-06				
	(b) (4) Capsules			Celecoxib Capsules	Placebo	Total	(b) (4) Capsules			Placebo	Total
Global Evaluation Response	40 mg tid n=93	40 mg bid n=91	20 mg tid n=91	200 mg[a] bid n=93	n=94	N=462	40 mg tid n=94	40 mg bid n=93[b]	20 mg tid n=92	n=94[c]	N=373
Excellent	16 (17.2)	8 (8.8)	6 (6.6)	2 (2.2)	1 (1.1)	33 (7.2)	15 (16.0)	15 (16.3)	7 (7.6)	4 (4.3)	41 (11.1)
Very good	6 (6.5)	6 (6.6)	5 (5.5)	9 (9.8)	2 (2.1)	28 (6.1)	7 (7.4)	10 (10.9)	8 (8.7)	4 (4.3)	29 (7.8)
Good	3 (3.2)	7 (7.7)	8 (8.8)	7 (7.6)	5 (5.3)	30 (6.5)	1 (1.1)	10 (10.9)	7 (7.6)	7 (7.5)	25 (6.7)
Fair	13 (14.0)	15 (16.5)	6 (6.6)	17 (18.5)	16 (17.0)	67 (14.5)	14 (14.9)	10 (10.9)	13 (14.1)	16 (17.2)	53 (14.3)
Poor	55 (59.1)	55 (60.4)	66 (72.5)	57 (62.0)	70 (74.5)	303 (65.7)	57 (60.6)	47 (51.1)	57 (62.0)	62 (66.7)	223 (60.1)
P value[d]	<0.001	0.003	0.060	0.018	--	--	0.038	<0.001	0.185	--	--

(Source: Applicant's table from Summary of clinical efficacy, 2.7.3, p. 74, August 30, 2013 amendment submission)

5.3.3. Protocol IND2-08-03

This was a Phase 2 efficacy and safety trial of a single dose of Tivorbex in subjects with acute postsurgical pain following removal of impacted third molars. This trail evaluated efficacy over a period of 8 hours following a single dose of trial drug. At the EOP2

meeting in June 2010, the Applicant was informed that results from this trial would be considered only supportive.

An earlier formulation of Tivorbex Capsules, the POC Formulation, was used in this trial. Changes in the drug product manufacturing process led to the Commercial Formulation, which was used in the Phase 3 trials and is the formulation intended for commercialization. The Sponsor states that the results from in-process dissolution testing and Phase 1 bioavailability trials (IND1-08-01 and IND1-12-07) demonstrated that these formulations have similar in vitro and in vivo performance.

Eligible subjects for this trial (PI VAS ≥50 mm VAS within 6 hours after surgery) were randomized to receive a single oral dose of Tivorbex 20 mg, Tivorbex 40 mg, celecoxib 400 mg, or placebo. Efficacy was assessed during the 8 hours following Time 0 and included measures of pain, PR, time to onset of PR, use of rescue medication, and subject's global assessment. Acetaminophen (1000 mg) was permitted as the initial rescue medication. Subjects were encouraged to wait at least 60 minutes after receiving trial drug prior to taking rescue medication.

The primary efficacy endpoint was total pain relief (TOTPAR), calculated as time-weighted averages of each PR assessment over 0 to 8 hours (TOTPAR-8) after Time 0. The Applicant found that the LS mean difference from the placebo group was statistically significant for each of the active treatment groups (P<0.001).

Table 18: TOTPAR-8, TOTPAR-4, ITT (IND2-08-03)

Parameter[a]	(b) (4) Capsules 40 mg n=51	(b) (4) Capsules 20 mg n=50	Celecoxib 400 mg n=51	Placebo n=51
TOTPAR-8	12.564 (1.3368) *P*<0.001	10.794 (1.3501) *P*<0.001	14.822 (1.3376) *P*<0.001	3.019 (1.3375) --
TOTPAR-4	6.159 (4.7793) *P*<0.001	5.465 (4.6065) *P*<0.001	7.152 (4.1791) *P*<0.001	1.632 (2.8268) --

(Source: Applicant's table from 2.7.3 Summary of Clinical Efficacy, page 19, amendment submission date August 30, 2013)

The secondary endpoints were similar to the endpoints of the Phase 3 trials.

- VASSPID-4 and VASSPID-8, demonstrated statistically significant difference for all active treatment groups compared to placebo.

Table 19: VASSPID over 0 to 4 and 0 to 8 hours, ITT (IND2-08-03)

Parameter	(b) (4) Capsules 40 mg n=51	(b) (4) Capsules 20 mg n=50	Celecoxib 400 mg n=51	Placebo n=51
VASSPID-4				
n	51	50	51	51
Mean (SD)	102.769 (99.0290)	87.275 (98.0901)	127.971 (99.1934)	14.272 (43.5216)
P value (difference vs placebo)[a]	<0.001	<0.001	<0.001	--
VASSPID-8				
n	51	50	51	51
Mean (SD)	228.425 (218.3931)	189.575 (215.5225)	284.265 (229.4447)	35.664 (102.9965)
P value (difference vs placebo)[a]	<0.001	<0.001	<0.001	--

(Source: Applicant's table from Summary of clinical efficacy, 2.7.3, p. 76)

- Time to onset of analgesia. Subjects who achieved analgesia, measured as time to perceptible PR confirmed by meaningful PR, by 8 hours after trial entry were included in the analysis. Subjects who received rescue medication before achieving analgesia were censored. The applicant found that fewer subjects in this trial were censored compared with the number of subjects censored in the Phase 3 trials. The mean (SE) times to onset of analgesia were 0.9 (0.08) hours for the Tivorbex Capsules 40 mg treatment group, 1.0 (0.07) hours for the Tivorbex Capsules 20 mg treatment group, 0.9 (0.08) hours for the celecoxib 400 mg treatment group, and 0.8 (0.03) hours for the placebo group (P<0.001 for all four treatment groups).
- Use of rescue medication. The Applicant found that fewer subjects in the Tivorbex Capsules 40 mg (51%, 26 subjects), Tivorbex Capsules 20 mg (62%, 31 subjects), and celecoxib 400 mg (41%, 21 subjects) treatment groups used rescue medication compared with the placebo group (90%, 46 subjects). The mean (SE) times to first use of rescue medication were 4.8 (0.39) hours for the Tivorbex Capsules 40 mg treatment group, 4.5(0.39) hours for the Tivorbex Capsules 20 mg treatment group, 4.7 (0.27) hours for the celecoxib 400 mg treatment group, and 2.1 (0.23) hours for the placebo group.
- Subject's global evaluation of study drug.

Table 20: Subject's global evaluation of study drug, ITT (IND2-08-03)

Response	(b) (4) Capsules 40 mg n=51	(b) (4) Capsules 20 mg n=50	Celecoxib 400 mg n=51	Placebo n=51
Poor	17 (33.3)	19 (38.0)	6 (11.8)	39 (76.5)
Fair	1 (2.0)	7 (14.0)	9 (17.6)	7 (13.7)
Good	4 (7.8)	15 (30.0)	10 (19.6)	5 (9.8)
Very Good	23 (45.1)	6 (12.0)	18 (35.3)	0
Excellent	6 (11.8)	3 (6.0)	8 (15.7)	0
P value[a]	<0.001	<0.001	<0.001	--

(Source: Applicant's table from Summary of clinical efficacy, 2.7.3, p. 86)

6 Review of Efficacy

Efficacy Summary

To support the indication for the treatment of mild to moderate acute pain with Tivorbex Capsules, the Applicant performed two Phase 3 trials in postoperative bunionectomy pain populations. For inclusion into the trials, a minimum VAS pain score of 40mm was required. The efficacy of multiple Tivorbex Capsules doses (40 mg tid, 40 mg bid, and 20 mg tid) was evaluated over a 48 hour treatment period.

The Division agreed with the primary efficacy endpoint for the Phase 3 trials, the sum of pain intensity differences assessed by visual analogue scale (VAS) over 0 to 48 hours (VASSPID-48). The original protocol-defined primary analysis in both trials used an ANCOVA model. The pre-specified imputation for missing data applied baseline carried forward (BOCF) for dropouts due to lack of efficacy, intolerance, or adverse events, and last observation carried forward (LOCF) for dropouts due to other reasons.

In response to a request by the Division to follow the NAS recommendations for imputation of missing data, the following additional analyses of the primary endpoint were performed:

1) A mixed-model repeated measure (MMRM), where all available data were used without imputation for drop outs and BOCF was limited to efficacy assessments within 4 hours after rescue use.
2) Posthoc ANCOVA with BOCF limited to the 4 hours following receipt of rescue medication.

Based on the review of the Applicant's analyses and results and Dr. Yan Zhou's additional efficacy analyses, there is evidence of efficacy for all studied Tivorbex

Capsules doses and dosing regiments. Using the original protocol-defined ANCOVA for the primary efficacy variable (VASSPID-48), Tivorbex Capsules 20 mg tid and 40 mg bid and tid in trial IND3-08-04b and Tivorbex Capsules 40 mg bid and tid in trial IND3-10-06 demonstrated significant reductions in pain intensity compared to placebo. In both trials, all Tivorbex Capsules dosing regimens demonstrated significantly greater reductions in pain compared to placebo using the MMRM analysis and the post-hoc ANCOVA with imputation of efficacy assessments limited to 4 hours following use of rescue medication.

In the Phase 3 trials there was a high percentage of rescue medication use in all treatment groups, including placebo. However, the proportion of subjects using rescue medication was lower and the mean time to first use of rescue medication was longer in each active treatment group than in the placebo group.

As described in Sections 1 and 2, the Applicant hypothesized that their formulation of indomethacin 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, Indocin, therefore, no comparative conclusions can be made with regard to efficacy or safety.

Celebrex was used in one of the Phase 3 trials as an active comparator, but the trial was not designed to evaluate comparative efficacy between Tivorbex Capsules and Celebrex.

6.1 Indication

The Applicant seeks approval of Tivorbex Capsules for the treatment of mild to moderate acute pain.

6.1.1 Methods

Efficacy data contained in this submission were generated from the following placebo-controlled trials:

- Phase 3 trials in subjects following bunionectomy surgery
    - IND3-08-04b, n=275 Tivorbex capsules all treatment groups, n=93 Celecoxib, n=94 Placebo
    - IND3-10-06, n= 279 Tivorbex Capsules all treatment groups, n= 94PBO
- Phase 2 supportive trial
    - IND2-08-03, n=101 Tiforbax Capsules treatment groups, n=51 Celecoxib, n=51 Placebo

All trials followed the guidelines for Good Clinical Practice. Analysis of the primary and secondary efficacy endpoints were conducted for the Phase 3 placebo-controlled trials.

Trials IND3-08-04b and IND3-10-06 were presented as having positive results and therefore intended to provide the primary basis of efficacy.

For detailed description of trial designs, see Section 5.3.

6.1.2 Demographics

Based on patient baseline disease characteristics, the patients enrolled in the Phase 3 trials had mean baseline PI score of 72 on a 100 mm VAS scale indicating moderate to severe pain. Of note, the Applicant seeks approval of Tivorbex for the treatment of mild to moderate acute pain. For enrollment, a PI of ≥ 40 mm VAS was required. The mean baseline PI score was similar among the treatment groups.

Tivorbex capsules, Celecoxib, and placebo treatment groups were generally balanced within trials, with no significant treatment group differences in patients' gender, age, race, and baseline severity of illness. For more details refer to Section 7.2.1 of this review.

6.1.3 Subject Disposition

A total of 735 subjects received at least 1 dose of Tivorbex Capsules, including 554 subjects in the Phase 3 trials, 101 subjects in the Phase 2 trial, and 80 subjects in the Phase 1 trials. The rate of trial completion was high and discontinuations due to AEs were infrequent. A small number of discontinuations due to lack of efficacy occurred in Tivorbex Capsules treatment at all dose levels and in the placebo group.

In the Phase 3 trials, more than 97% of subjects in all treatment groups completed the trials, with only 5 subjects (0.9%) from Tivorbex Capsules treatment groups discontinuing due to AEs. Given the low number of premature discontinuations, missing data are not expected to impact the efficacy results.

Table 21: Disposition of subjects in Phase 3 clinical trials (IND3-08-05b and IND3-10-06)

Table 2.7.4.2.1-1 Disposition of Subjects in Tiforbex Capsules Clinical Trials

	Integrated Safety Population (Phase 3)					
	(b) (4) Capsules					
	40 mg tid n=187	40 mg bid n=184	20 mg tid n=183	Combined n=554	Celecoxib 200 mg bid[a] n=93	Placebo n=188
Number Randomized, n	187	184	183	554	93	188
Number Completed, n (%)	182 (97.3)	179 (97.3)	179 (97.8)	540 (97.5)	93 (100.0)	181 (96.3)
Withdrew Trial, n (%)	5 (2.7)	5 (2.7)	4 (2.2)	14 (2.5)	0	7 (3.7)
Withdrawn due to AE(s), n (%)	2 (1.1)	2 (1.1)	1 (0.5)	5 (0.9)	0	2 (1.1)

	Phase 3 Clinical Trials								
	IND3-08-04b					IND3-10-06			
	(b) (4) Capsules			Celecoxib 200 mg bid[a]	Placebo	(b) (4) Capsules			Placebo
	40 mg tid n=93	40 mg bid n=91	20 mg tid n=91	n=93	n=94	40 mg tid n=94	40 mg bid n=93	20 mg tid n=92	n=94
Number Enrolled, n	93	91	91	93	94	94	93	92	94
Number Completed, n (%)	90 (96.8)	88 (96.7)	89 (97.8)	93 (100.0)	90 (95.7)	92 (97.9)	91 (97.8)	90 (97.8)	91 (96.8)
Withdrew Trial, n (%)	3 (3.2)	3 (3.3)	2 (2.2)	0	4 (4.3)	2 (2.1)	2 (2.2)	2 (2.2)	3 (3.2)
Withdrawn due to AE(s), n (%)	2 (2.2)	1 (1.1)	0	0	2 (2.1)	0	1 (1.1)	1 (1.1)	0

(Source: Applicant's table from 2.7.4 Summary of clinical safety, page 19)

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Measure and Endpoint

For drugs intended to treat acute pain, and that will likely be used for several days, the evaluation of efficacy over the first 48 hours is often used. The primary efficacy measure must assess pain intensity. The primary efficacy endpoint VASSPID-48, calculated as a time-weighted average used in the Tivorbex Phase 3 trials, is acceptable. The Division also recommends calculation of response rates in analgesic trials, considering the proportion of treatment responders at the end of treatment. A comparison of response across all levels of response [i.e. a cumulative (continuous) responder analysis] is encouraged, with patients who dropout for any reason counted as non-responders. With regard to the strategy for imputation of missing data, the Division follows the recommendations from the 2010 National Academy of Sciences NAS report. The NAS does not favor single imputation methods for imputing missing values due to discontinuation from the study. In addition, the report recommends explicit specification of the causal estimand.

For Tivorbex Capsules, to support the indication for the treatment of mild to moderate acute pain, the Applicant relied on positive results from two Phase 3 trials in bunionectomy patients (IND3-08-04b and IND3-10-06). Results from a Phase 2 trial in dental pain model (IND2-08-03) are included as supportive of efficacy. Supportive efficacy findings are also presented from a literature search performed by the Applicant from relevant published trials.

The Phase 3 trials were randomized, double-blind, placebo-controlled in patients with acute pain following bunionectomy surgery. Pain intensity rating of ≥40 mm VAS during the 9-hour period after discontinuation of the regional anesthetic block was required for randomization. Tivorbex Capsules 20 mg tid, 40 mg bid, and 40 mg tid dosing regimens were compared to placebo. Trial IND3-08-04b included an additional active comparator arm: celecoxib 200 mg. The efficacy was assessed during the 48-hour treatment period and included measures of pain intensity VAS, pain relief (5-point categorical scale), time to onset of relief, use of rescue medication, and subject's global assessment. Hydrocodone/acetaminophen 10 mg/325 mg was permitted as rescue medication every 4 to 6 hours as needed.

The Phase 2 trial was performed with the POC formulation in subjects following surgical removal of impacted third molars. Single oral dose of Tivorbex Capsules 20 mg and 40 mg, celecoxib 400 mg, and placebo were administered. The primary endpoint was total pain relief (TOTPAR), calculated as time-weighted averages of each pain relief assessment over 0 to 8 hours (TOTPAR-8). This trial does not meet the requirements for supporting an efficacy for an acute pain indication and will not be discussed in this section of the NDA review.

The Applicant's choice for the primary efficacy variable in the Phase 3 trials was the sum of pain intensity differences measured by visual analogue scale (VASSPID-48). The original protocol-defined primary analysis in both trials used ANCOVA model with treatment effect as factor and baseline pain intensity as covariate. The ITT population included all subjects who received at least one dose of study drug. To account for the multiple comparisons, sequential testing was performed: 40mg TID compared to placebo, then 40 mg BID compared to placebo, then 20 mg TID compared to placebo. The pre-specified imputation for missing data applied BOCF for dropouts due to lack of efficacy, intolerance, or adverse events, and LOCF for dropouts due to other reasons. All scheduled assessments after the first dose of rescue medication were disregarded and imputed using BOCF.

In response to the August 2012 FDA Advice Letter that included the NAS recommendations for imputation of missing data, the Applicant performed the following sensitivity analysis:

- MMRM model (post-hoc for Study IND3-08-04b) where:
  - for dropouts: all available data were used without imputation
  - for rescue use: BOCF limited to efficacy assessments within 4 hours after rescue use
- ANCOVA model (post-hoc for both studies) where:
  - for dropouts: same as in the primary analyses
  - for rescue use: BOCF limited to efficacy assessments within 4 hours after rescue use

Applicant's Efficacy Results of the primary endpoint from the Phase 3 trials
For the analysis of the primary efficacy variable (VASSPID-48), the Applicant found the following:

- Using the original protocol-defined ANCOVA analysis: Tivorbex Capsules 20 mg and 40 mg in trial IND3-08-04b and Tivorbex Capsules 40 mg bid and tid in trial IND3-10-06 demonstrated statistically significant reductions in PI compared with placebo. The differences compared with placebo for the Tivorbex Capsules 20 mg tid were not statistically significant in trial IND3-10-06.
- Using the MMRM with limited BOCF imputation: In both Phase 3 trials, all Tivorbex Capsules dosing regimens and the celecoxib demonstrated statistically significantly reductions in pain compared to placebo.
- Post-hoc ANCOVA with limited BOCF imputation: Statistically significant reductions in pain intensity were demonstrated for Tivorbex 20 mg and 40 mg dosing regimens and for celecoxib.

Table 22: Analyses of VASSPID-48 – ITT Population (IND3-08-04b and IND3-10-06)

	IND3-08-04b					IND3-10-06			
	(b) (4) Capsules			Celecoxib Capsules 200 mg bid[a]		(b) (4) Capsules			
	40 mg tid n=93	40 mg bid n=91	20 mg tid n=91		Placebo n=94	40 mg tid n=94	40 mg bid n=93	20 mg tid n=92	Placebo n=94
VASSPID-48 by ANCOVA (Protocol-defined analysis method)[b]									
n	93	91	91	93	94	94	93	92	94
Least squares mean	509.6	328.0	380.5	279.4	67.8	598.47	622.99	342.83	280.85
SE	91.9	92.9	92.9	91.9	91.4	105.69	106.24	106.77	105.79
95% CI	329.0, 690.2	145.4, 510.6	198.0, 563.1	98.8, 459.9	-111.8, 247.4	390.64, 806.29	414.08, 831.89	132.87, 552.78	72.83, 488.87
P value (difference vs placebo)	<0.001	0.046	0.017	0.103	--	0.034	0.023	0.680	--
VASSPID-48 by MMRM (limited BOCF approach)[c, d]									
n	93	91	91	93	94	94	93	92	94
Least squares mean	2025.4	2135.5	1930.9	1840.4	1195.7	2141.31	2087.23	1873.93	1391.72
SE	69.1	69.9	69.9	68.8	68.9	74.90	75.33	75.74	75.11
95% CI	1889.7, 2161.1	1998.2, 2272.9	1793.6, 2068.1	1705.1, 1975.6	1060.4, 1331.0	1994.11, 2288.50	1939.20, 2235.27	1725.09, 2022.77	1244.10, 1539.32
P value (difference vs placebo)	<0.001	<0.001	<0.001	<0.001	--	<0.001	<0.001	<0.001	--
VASSPID-48 by ANCOVA (posthoc analysis with limited BOCF imputation)[b, c]									
n	90	88	88	93	90	93	91	90	91
Least squares mean	2056.5	2127.4	1928.6	1838.2	1197.3	2152.01	2106.94	1880.73	1392.60
SE	86.7	87.7	87.7	85.3	86.7	87.49	88.42	88.88	88.53
95% CI	1886.1, 2226.9	1955.1, 2299.7	1756.3, 2101.0	1670.6, 2005.8	1026.9, 1367.7	1979.96, 2324.06	1933.05, 2280.83	1705.95, 2055.52	1218.50, 1566.69
P value (difference vs placebo)	<0.001	<0.001	<0.001	<0.001	--	<0.001	<0.001	<0.001	--

(Source: Applicant's table from Summary of Clinical Efficacy, August 30, 2013 Amendment submission, page 23)

During the review cycle the Applicant has discovered an error made by the CRO in the programming used for some of the sensitivity analyses performed on the primary and multiple secondary endpoints. The table above reflects the corrected results. Minor changes to the clinical output values have been observed in the revised analyses. The results from the corrected analysis continue to support the Applicant's efficacy conclusions.

Division's efficacy analyses of the primary endpoint
The statistical reviewer, Dr. Yan Zhou, performed analyses of the primary endpoint in both Phase 3 trials that supported the Applicant's efficacy conclusions that all three Tivorbex Capsules treatment groups (20 mg TID, 40 mg bid, and 40 mg tid) demonstrated statistically significant reductions in pain intensity compared to placebo.

Trial IND3-08-04b – results from analyses performed by Dr. Yan Zhou

Analysis of SPID 48 using ANCOVA model with BOCF after the first use of rescue demonstrated statistically significant reductions in pain intensity compared to placebo for all Tivorbex Capsules treatment groups.

Table 23: SPID48 by ANCOVA (BOCF after the first use of rescue medication) – IND3-08-04b

	Reviewer's Analyses				
	Indomethacin			Celecoxib	Placebo
	40 mg tid	40 mg bid	20 mg tid		
N	93	91	91	93	94
LS Mean (SE)	510 (92)	328 (93)	380 (93)	279 (92)	67 (91)
Difference in LS mean	443	261	313	212	
95% CI for diff. in LS mean	(188, 697)	(5, 517)	(57, 569)	(-43, 466)	
p-value for treatment effect	0.0007	0.046	0.017	0.103	

(Source: Table created by Dr. Yan Zhou)

Analysis of SPID 48 using ANCOVA model with BOCF within 4 hours after the first use of rescue demonstrated statistically significant superiority for all Tivorbex Capsules treatment groups compared to placebo.

Table 24: SPID48 by ANCOVA (BOCF within 4 hours after rescue use) – IND3-08-04b

	Reviewer's Analyses				
	Indomethacin			Celecoxib	Placebo
	40 mg tid	40 mg bid	20 mg tid		
N	93	91	91	93	94
LS Mean (SE)	1988 (89)	2052 (90)	1905 (90)	1837 (89)	1149 (89)
Difference in LS mean	839	903	756	687	
95% CI for diff. in LS mean	(592, 1086)	(654, 1151)	(507, 1004)	(440, 934)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001	< 0.001	

(Source: Table created by Dr. Yan Zhou)

A sensitivity analysis where pre-rescue score was carried forward to the next assessment for the 1st rescue use and observed pain scores were used for other rescue uses confirmed that each Tivorbex Capsule treatment group was statistically superior compared to placebo.

Table 25: SPID48 by ANCOVA (pre-rescue score carried forward to the next assessment for the 1st rescue use and observed pain scores used for other rescue uses) - IND3-08-04b

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

(Source: Table created by Dr. Yan Zhou)

The results from the following series of additional sensitivity analysis consistently showed superiority of all Tivorbex Capsules treatment groups compared to placebo:

- BOCF for 6 hours after any rescue use
- Pre-rescue carried forward for 4 hours (for the 1st rescue use)
    - For other rescue uses: BOCF for 4 hours

- Pre-rescue carried forward for 4 hours (for the 1st rescue use)
    - For other rescue uses: using observed pain scores
- Pre-rescue carried forward for 6 hours (for the 1st rescue use)
    - For other rescue uses: BOCF for 6 hours
    - Pre-rescue carried forward for 6 hours (for the 1st rescue use)
    - For other rescue uses: using observed pain scores

Trial IND3-10-06 – results from analyses performed by Dr. Yan Zhou
Analysis of SPID 48 using ANCOVA model with BOCF after the first use of rescue demonstrated statistically significant reductions in pain intensity compared to placebo for the Tivorbex Capsules 40 mg bid and 40 mg tid treatment groups.

Table 26: SPID48 by ANCOVA (BOCF after the first use of rescue medication) – IND3-10-06

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

(Source: Table created by Dr. Yan Zhou)

Analysis of SPID 48 using ANCOVA model with BOCF within 4 hours after the first use of rescue demonstrated statistically significant superiority for all Tivorbex Capsules treatment groups compared to placebo.

Table 27: SPID48 by ANCOVA (BOCF within 4 hours after rescue use) – IND3-10-06

	Reviewer's Analyses			
	Indomethacin			Placebo
	40 mg tid	40 mg bid	20 mg tid	
N	94	93	92	94
LS Mean (SE)	2093 (93)	2068 (93)	1841 (94)	1352 (93)
Difference in LS mean	742	717	489	
95% CI for diff. in LS mean	(483, 1000)	(458, 975)	(230, 748)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001	

(Source: Table created by Dr. Yan Zhou)

A sensitivity analysis where pre-rescue score was carried forward to the next assessment for the 1st rescue use and observed pain scores were used for other rescue uses confirmed that each Tivorbex Capsule treatment group was statistically superior compared to placebo.

Table 28: SPID48 by ANCOVA (pre-rescue score carried forward to the next assessment for the 1st rescue use and observed pain scores used for other rescue uses) - IND3-10-06

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

(Source: Table created by Dr. Yan Zhou)

The same series of additional sensitivity analysis as for Study IND3-08-04b were conducted and confirmed the positive results for all Tivorbex Capsules treatment groups.

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant evaluated multiple secondary endpoints none of which was identified as a key secondary endpoint. The Applicant's analyses of the secondary endpoints are presented in Section 5.3.

Because it was noted that high percentage of patients from all treatment groups used rescue medication, this section will focus on the analyses performed by Dr. Yan Zhou to investigate the impact of rescue use on the primary efficacy outcome.

Trial IND3-08-04b – results from analyses performed by Dr. Yan Zhou

In this trial, the highest incidence of rescue use was observed in the placebo group (97%). The lowest incidence of rescue use was observed in the Tivorbex capsule 40 mg tid treatment group (82%).

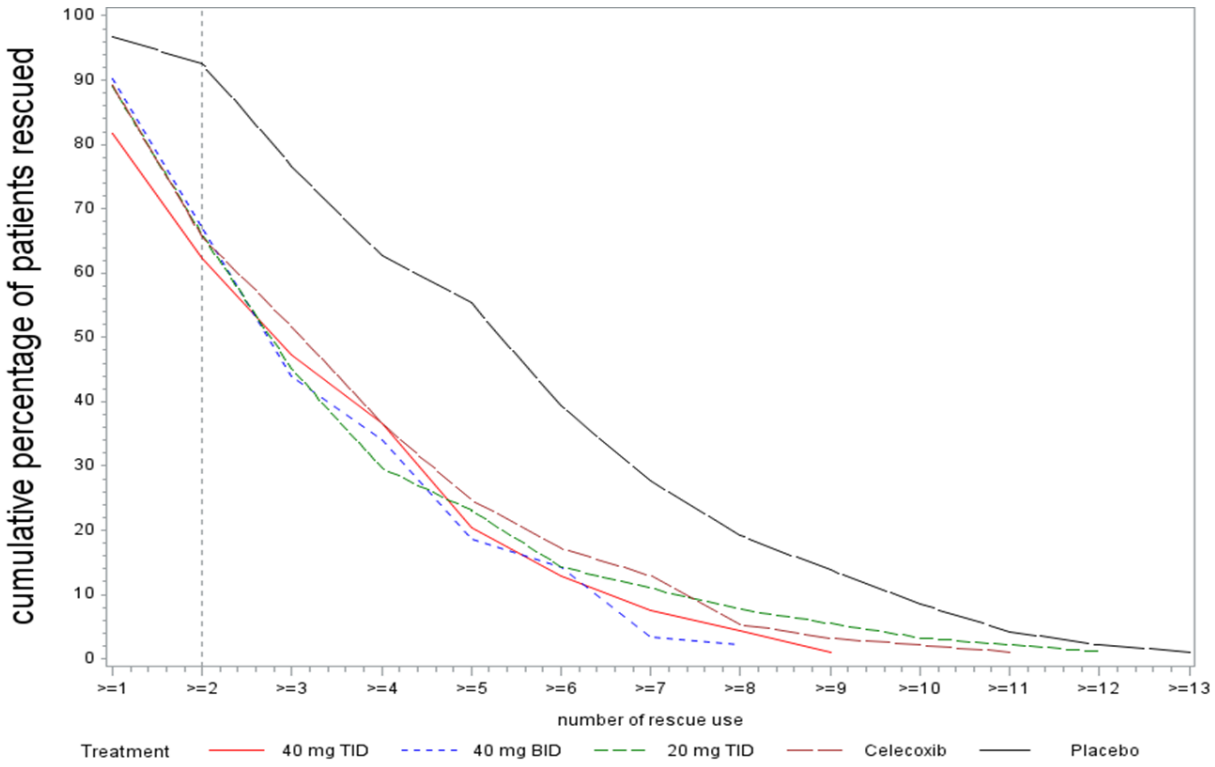
Table 29: Use of rescue medication – IND3-08-04b

	Indomethacin			Celecoxib	Placebo
	40 mg tid	40 mg bid	20 mg tid		
Randomized	93	91	91	93	94
Subjects who took rescue within 48 hours	76 (82%)	82 (90%)	81 (89%)	83 (89%)	91 (97%)
Subjects who took rescue within first 8 hours	73 (78%)	78 (86%)	77 (85%)	81 (87%)	91 (97%)
Number of rescue use within first 24 hours					
mean (SD)	2.3 (1.7)	2.2 (1.4)	2.3 (1.7)	2.4 (1.6)	3.6 (1.7)
median	2.0	2.0	2.0	2.0	4.0
min, max	(0, 6)	(0, 5)	(0, 7)	(0, 6)	(0, 7)
Number of rescue use within 48 hours					
mean (SD)	2.7 (2.3)	2.7 (2.0)	3.0 (2.6)	3.1 (2.5)	5.0 (2.9)
median	2.0	2.0	2.0	3.0	5.0
min, max	(0, 9)	(0, 8)	(0, 12)	(0, 11)	(0, 13)

(Source: Table created by Dr. Yan Zhou)

Fewer subjects in the Tivorbex Capsules treatment groups used rescue medication and used less tablets of rescue medication compared with placebo.

Figure 7: Cumulative percentage of patients taking rescue medication - IND3-08-04b



(Source: Figure created by Dr. Yan Zhou)

The time to first use of rescue medication was similar across the Tivorbex Capsules treatment groups and occurred later than in the placebo group.

Figure 8: Time to first use of rescue medication – IND3-08-04b

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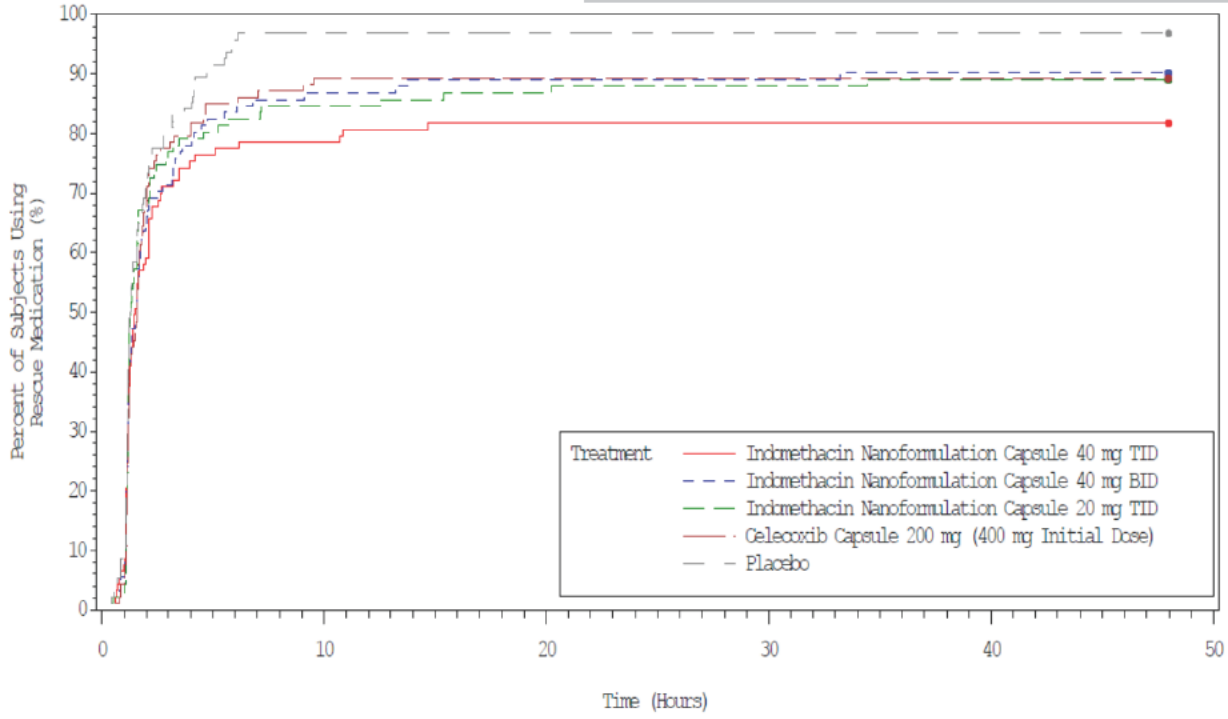
Figure 11-6 Time to First Use of Rescue Medication



Note: symbols represent censored cases.

(Source: Figure created by Dr. Yan Zhou)

Trial IND3-10-06 – results from analyses performed by Dr. Yan Zhou

In this trial, the use of rescue medication was very similar for the placebo and Tivorbex Capsule 20 mg tid group, 89% and 87%, respectively.

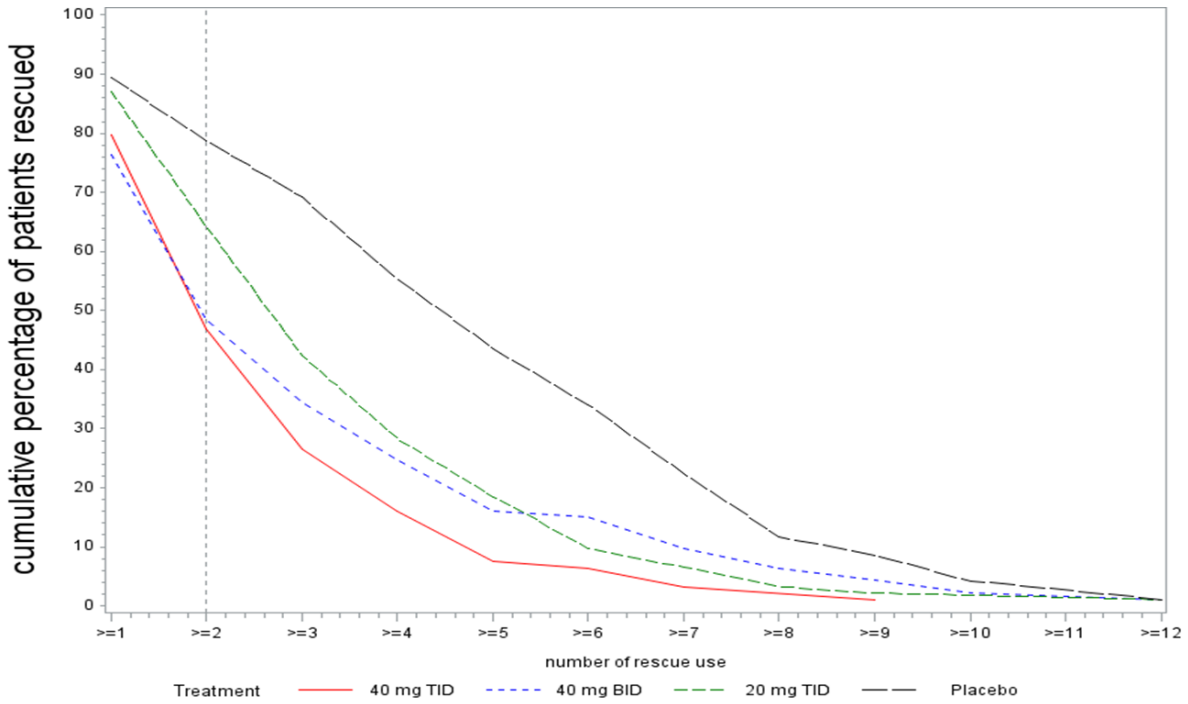
Table 30: Use of rescue medication – IND3-10-06

	Indomethacin			Placebo
	40 mg tid	40 mg bid	20 mg tid	
Randomized	94	93	92	94
Subjects who took rescue within 48 hours	75 (80%)	71 (76%)	80 (87%)	84 (89%)
Subjects who took rescue within first 8 hours	69 (73%)	67 (72%)	75 (82%)	81 (86%)
Number of rescue use within first 24 hours				
mean (SD)	1.6 (1.4)	1.9 (1.7)	2.1 (1.4)	3.0 (1.8)
median	1.0	1.0	2.0	3.0
min, max	(0, 6)	(0, 8)	(0, 6)	(0, 7)
Number of rescue use within 48 hours				
mean (SD)	1.9 (1.8)	2.4 (2.6)	2.7 (2.2)	4.2 (2.9)
median	1.0	1.0	2.0	4.0
min, max	(0, 9)	(0, 12)	(0, 12)	(0, 12)

(Source: Table created by Dr. Yan Zhou)

However, when a cumulative percentage of patients using rescue analysis was performed, a separation of the curves was noted for the placebo and all Tivorbex Capsules treatment groups.

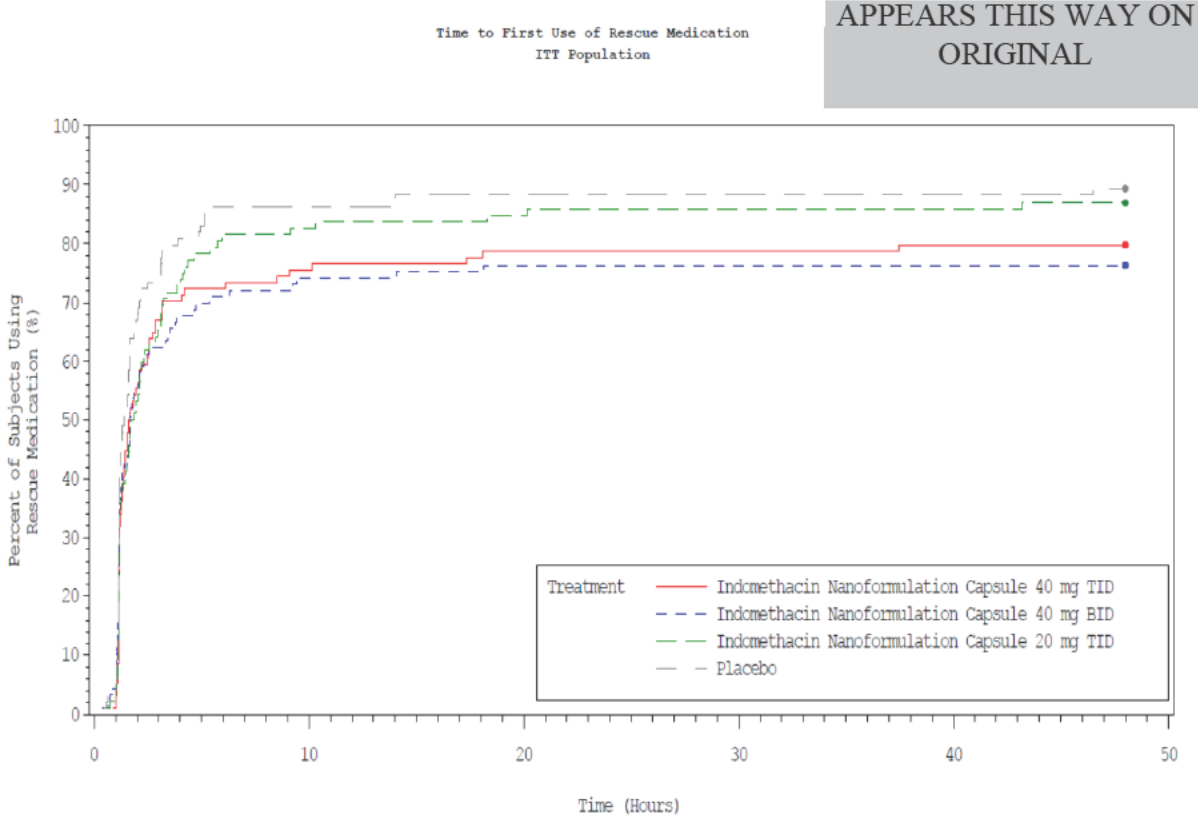
Figure 9: Cumulative percentage of patients taking rescue medication - IND3-10-06



(Source: Figure created by Dr. Yan Zhou)

The time to first use of rescue medication occurred later in the Tivorbex Capsules treatment groups than in the placebo group.

Figure 10: Time to first use of rescue medication – IND3-10-06



(Source: Figure created by Dr. Yan Zhou)

Based on the results from these analyses, Dr. Yan Zhou concluded that there was a high percentage of rescue medication use in the Phase 3 trials. Majority of the patients rescued within 8 hours. The placebo group used rescue more often than the Tivorbex Capsule treatment groups.

6.1.6 Other Endpoints

There were no requests for additional analyses.

6.1.7 Subpopulations

The applicant conducted subgroup analyses of the primary endpoint by age, race and gender using the per-protocol population (PP). Dr. Zhou conducted subgroup analyses by age (≤ 45 or > 45 years old) for all the randomized subjects that did not reveal any concerns. Subgroup analysis for gender was not conducted because the majority of the study population was female (83% in Study IND3-08-04b and 85% in study IND3-10-06). Race was also not included in the assessment of subgroups because the majority of the study population was white (72% in Study IND3-08-04b and 76% in Study IND3-10-06).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Tivorbex Capsules 20 mg and 40 mg are recommended by the Applicant for the treatment of mild to moderate acute pain to provide therapeutic options and allow for treatment with the lowest effective dose.

The primary endpoints were met for both Phase 3 clinical trials. Tivorbex Capsules 40 mg were associated with numerically higher levels of efficacy than Tivorbex Capsules 20 mg. Tivorbex Capsules 20 mg tid demonstrated analgesic efficacy in the protocol-defined primary endpoint analysis for the IND3-08-04b Phase 3 trial and in the prospectively-defined analysis for the IND3-10-06 Phase 3 trial, which limited the imputation of missing data.

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 IND3-08-04b Phase 3 trial to show a direct comparison in efficacy between Tivorbex and celecoxib. Therefore, comparative claims cannot be made between these treatment groups.

7 Review of Safety

Safety Summary

The emphasis in the safety review for this application was to determine whether the safety profile of Tivorbex capsules differed from the already-established safety profile of indomethacin and the overall safety profile of the NSAID class.

The size of the analysis population was adequate to assess the safety for the intended use of Tivorbex to treat mild to moderate acute pain. A total of 735 subjects received at least one dose of Tivorbex Capsules in completed trials, including 80 healthy subjects in Phase 1 trials, 101 subjects in the Phase 2 trial, and 554 subjects in the Phase 3 trials

Tivorbex Capsules were well tolerated when administered in single and repeated doses for up to 48 hours. No new safety concerns beyond those addressed in NSAID class labeling were identified. The overall percentages of subjects who experienced at least one TEAE were similar across treatment groups for all trials. The gastrointestinal, central nervous system, and post-procedural events were the most frequent. No severe

cardiovascular (CV), gastrointestinal (GI), or renal TEAEs of the type reported in class labeling for NSAIDs (myocardial infarction, stroke, acute coronary syndrome, ulcers, GI bleeding, hypertension, renal failure, or renal insufficiency) were observed across the Tivorbex Capsules clinical trials.

There were no deaths. Withdrawals from the trials were infrequent and only one SAE of calf deep vein thrombosis occurred in one Phase 3 trial.

Vital sign and physical examination abnormalities were also uncommon. Clinical laboratories were collected only at baseline.

In conclusion, no new safety concerns specific to Tivorbex were identified during the review of the safety data included in this application. The overall safety profile of Tivorbex resembled the established safety profile for other indomethacin products and described in the product label.

7.1 Methods

In support of this New Drug Application, the applicant provided safety data for duloxetine from two Phase 3 trials (IND3-08-04b and IND3-10-06) in subjects with acute bunionectomy pain, one Phase 2 trial (IND2-08-03) in subjects with acute dental pain and two the Phase 1 trials (IND1-08-01 and IND1-12-07) in healthy subjects. The Safety Population for each trial was defined as all subjects who received at least 1 dose of trial drug.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Trial design, treatment groups and dosing for the primary chronic pain trials are summarized in Table 3, Section 5.1 of this review.

7.1.2 Categorization of Adverse Events

TEAEs were defined as AEs with onset at the time of or following the start of treatment with trial drug, or AEs starting before the start of treatment but increasing in severity at the time of or following the start of treatment. TEAEs were coded and grouped by System Organ Class (SOC) and/or preferred term using currently-available versions of the Medical Dictionary for Regulatory Activities (MedDRA; version 10.0 or higher). Summaries of TEAEs by SOC and preferred term were tabulated for each treatment group, including summaries of TEAE by severity and relationship to trial drug of individual TEAEs. For the Integrated Safety Population, summaries were also tabulated for the combined Tivorbex Capsules treatment groups and overall. Review of the coding of adverse events, comparing the verbatim terms to the preferred terms used by investigators and patients, showed that it was performed correctly.

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

For the Phase 3 trials, safety data were pooled, and safety analyses were performed on the integrated population. Safety data from the Phase 2 trial and the Phase 1 trials were presented separately for each trial.

7.2 Adequacy of Safety Assessments

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

Exposure to Drug
A total of 735 subjects received at least 1 dose of Tivorbex Capsules in completed trials, including 80 healthy subjects in Phase 1 trials, 101 subjects in the Phase 2 trial, and 554 subjects in the Phase 3 trials.

Extent of exposure to Tivorbex Capsules in the Integrated Safety Population (IND3-08-04b and IND3-10-06) is summarized by time of exposure and cumulative dose in table below. The majority of subjects (98%) randomized to Tivorbex Capsules groups in the Phase 3 trials received drug for 24 hours or longer. The majority of subjects randomized to the 40 mg tid and bid groups received 240 mg (98%) or 160 mg (97%) of Tivorbex Capsules, respectively, during the course of the trials. The majority of subjects (98%) randomized to the 20 mg tid group received 120 mg of Tivorbex Capsules during the course of the trials.

Table 31: Extent of exposure by time and cumulative dose (Integrated safety population, the two Phase 3 trials)

Exposure	(b) (4) Capsules 40 mg tid n=187	40 mg bid n=184	20 mg tid n=183	Combined n=554
Time of Exposure, n (%)				
0 to 24 hours	3 (1.6)	4 (2.2)	4 (2.2)	11 (2.0)
≥24 hours	184 (98.4)	180 (97.8)	179 (97.8)	543 (98.0)
Cumulative Dose, n (%)				
<120 mg	3 (1.6)	4 (2.2)	4 (2.2)	11 (2.0)
120 mg	0	1 (0.5)	179 (97.8)	180 (32.5)
160 mg	1 (0.5)	179 (97.3)	0	180 (32.5)
240 mg	183 (97.9)	0	0	183 (33.0)

(Source: Applicant's table from 2.7.4 Summary of clinical safety, page 21)

Extent of exposure in single-dose Tivorbex Capsules clinical trials (IND1-08-01, IND1-12-07, and IND2-08-03) is summarized in table below. A total of 80 healthy subjects received one dose of Tivorbex Capsules in Phase 1 trials during each of the Tivorbex Capsules treatment periods (40 mg Tivorbex Capsules Fasted, 20 mg Tivorbex Capsules Fasted, and 40 mg Tivorbex Capsules Fed). A total of 101 subjects received at least one dose of Tivorbex Capsules in the completed Phase 2 trial in subjects following third molar extraction (n=100).

Table 32: Extent of exposure in single-dose clinical trials (Phase 1 and Phase 2)

Clinical Trial	(b) (4) Capsules Dose Group	n	Duration of Exposure Days
IND1-08-01[a]	40 mg Fasted	40	1
	20 mg Fasted	40	1
	40 mg Fed	40	1
IND1-12-07[b]	40 mg Fasted	36	1
	20 mg Fasted	38	1
	40 mg Fed	38	1
IND2-08-03	40 mg	51	1
	20 mg	50	1

(Source: Applicant's table from 2.7.4 Summary of clinical safety, page 22)

Demographics

For the Integrated Safety Population (N= 835), across all five treatment groups, the demographic characteristics were generally balanced. The population consisted of male and female subjects of diverse race and ethnicity, ranging in age from 18 to 68 years.

As expected for bunionectomy procedures, the trial population was predominantly female (84%). The majority of subjects were White (74%) and not Hispanic or Latino (81%); the mean age was 41 years. The mean body weight was 74 kg.

Prior medications included all medications administered prior to trial drug administration and excluded all preoperative and intraoperative medications. Medications received at any time during the trial by at least 5% of subjects included the following: mepivacaine (98%); Vicodin® (55%); Oxycocet® (28%); ibuprofen (27%); multivitamins (16%); paracetamol (7%), and fish oil (6%).

7.2.2 Explorations for Dose Response

Iroko Pharmaceuticals has used a proprietary SoluMatrix™ manufacturing technology to reduce indomethacin drug substance particle sizes in Tivorbex Capsules and to enhance rates of dissolution (b) (4) Tivorbex Capsules contain either 20 mg or 40 mg of indomethacin, representing a 20% reduction in dosage compared with currently available oral indomethacin products (Indomethacin 25 mg and 50 mg capsules). In Phase 1, relative bioavailability trials (IND1-08-01 and IND1-12-07), the Cmax was similar for the Tivorbex Capsules 40 mg and the Indomethacin 50 mg. However, the extent of indomethacin exposure was lower and the tmax was earlier for Tivorbex Capsules 40 mg compared with Indomethacin 50 mg capsules.

In the Phase 2 dental pain trial, single doses of two dose strengths, 20 mg and 40 mg Tivorbex, were evaluated. In the Phase 3 bunionectomy trials, three dose regimens of Tivorbex Capsules were evaluated, 20 mg TID, 40 mg BID, and 40 mg TID.

7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3 of this review.

7.2.4 Routine Clinical Testing

The safety testing for the dental pain and bunionectomy trials was adequate. The primary safety concerns for indomethacin including GI and cardio-embolic events were appropriately covered. Safety assessments included vital signs, physical examination, general hematology and chemistry testing, urinalysis, and questioning about adverse events. Safety was assessed at pre-specified time points with acceptable frequency.

7.2.5 Metabolic, Clearance, and Interaction Workup

Trials IND1-08-01 and IND1-12-07, conducted by the Applicant, determined the relative bioavailability of Tivorbex Capsules and Indomethacin 50 mg capsules. In these trials, the rate (Cmax and tmax) of indomethacin absorption from Indomethacin 50 mg capsules was comparable with the known rate of absorption for. Following administration of Tivorbex Capsules 40 mg, Cmax values were comparable and tmax was achieved faster in both trials compared with Indomethacin 50 mg capsules. The overall extent of indomethacin exposure (as measured by AUC0-inf and AUC0-t) was lower following Tivorbex Capsules 40 mg administration compared with Indomethacin 50 mg capsules administration, which probably reflects the 20% dosage reduction in Tivorbex Capsules of active ingredient. Based on the similarities of indomethacin absorption from Tivorbex Capsules and Indomethacin 50 mg capsules, it is expected that the known PK and PD characteristics of indomethacin will also apply to Tivorbex Capsules.

For more details, see Section 4.4 of this review.

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

See Section 2.4 of this review.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in any of the clinical trials.

7.3.2 Nonfatal Serious Adverse Events

One SAE of deep vein thrombosis in the left calf was reported in a subject in the Tivorbex Capsules 40 mg bid treatment group in clinical trial IND3-08-04b.

Subject 003-092
A 40-year-old white female, with medical history of right foot bunion, intermittent tension headaches, and removal of left breast benign cyst in 1999 was randomized to trial IND3-08-04b (b) (6) On (b) (6) (trial Day 6), the subject experienced the beginning of pain in her left calf. The following day, she presented for her first postoperative follow-up visit with complaints of left calf pain. The subject was taking Reclipsen® (ethinyl estradiol and desogestrel) and clindamycin at the time of onset of the event. A deep vein thrombosis in the popliteal vein was confirmed on venous Doppler ultrasound (b) (6) She was treated with subcutaneous Lovenox®

(enoxaparin sodium) and oral Coumadin (warfarin). The investigator considered the event to be not related to administration of the trial medication.

My review of the narrative provided by the applicant for this SAE concurs with the conclusion of the investigators regarding the relation of the SAE and study drug administration. In this case, the oral contraceptive and immobility after the surgery are the most likely the factors that led to the deep vein thrombosis.

7.3.3 Dropouts and/or Discontinuations

A total of seven TEAEs resulted in subject discontinuation from the Phase 3 trials: five events from the Tivorbex Capsules groups and two events from the placebo treatment group. From the seven TEAE that led to discontinuation, two events of urticaria and one of angioedema occurred in Tivorbex-treated patients. All events were non-serious and mild to moderate in intensity.

Table 33: Adverse events leading to trial withdrawal (Integrated safety population)

Clinical Trial	Subject Number Age (years) /Race/Sex	Treatment arm	Adverse Event Leading to Trial Withdrawal	
			Preferred Term	Relationship to Trial Drug
IND3-08-04b	Subject 002-041 48/White/Female	(b) (4) Capsules 40 mg tid	uvulitis	unlikely related
	Subject 004-058 60/White/Female	(b) (4) Capsules 40 mg tid	urticaria	unlikely related
	Subject 004-013 51/Other/Female	(b) (4) Capsules 40 mg bid	angioedema	possibly related
	Subject 002-157 53/Black/Male	Placebo	pyrexia	not related
	Subject 004-080 61/White/Female	Placebo	anxiety	possibly related
IND3-10-06	Subject 002-026 23/White/Female	(b) (4) Capsules 40 mg bid	nausea	not related
	Subject 004-020 56/White/Female	(b) (4) Capsules 20 mg tid	urticaria	probably (likely) related

(Source: Applicant's table from ISS, 2.7.4, page 37)

Study IND3-08-04b

- Subject 002-041: A 48-year-old female subject in the Tivorbex Capsules 40 mg tid group discontinued the trial after receiving five doses of trial drug due to moderate uvulitis. Concomitant medications included multivitamins. The subject was treated with diphenhydramine. The AE was considered by the investigator to be unlikely related to trial.
- Subject 004-058: A 60-year-old female subject in the Tivorbex Capsules 40 mg tid group discontinued the trial after receiving three doses of trial drug due to mild urticaria (verbatim term: hives on trunk). Concomitant medications included multivitamins and Caltrate. The subject was treated with diphenhydramine. The AE was considered by the investigator to be unlikely related tostudy drug.
- Subject 004-013: A 51-year-old female subject in the Tivorbex Capsules 40 mg bid group discontinued the trial after receiving one dose of trial drug due to moderate angioedema (verbatim term: angioedema of lips and right eye). Concomitant medications included lisinopril and Vicodin. The subject was treated with diphenhydramine and the event resolved. The AE was considered by the investigator to be possibly related to study drug.
- Subject 002-157: A 53-year-old male subject in the placebo group discontinued the trial after receiving one dose of trial drug due to moderate pyrexia. The event was reported to have started immediately prior to trial drug administration. The AE was considered by the investigator to be not related to study drug.
- Subject 004-080: A 61-year-old female subject in the placebo group discontinued the trial after receiving three doses of study drug due of mild anxiety. Concomitant medications included multivitamins, alendronate sodium, fish oil, and ondansetron. The AE was considered by the investigator to be possibly related to study drug.

Study IND3-10-06

- Subject 002-026: A 23-year-old female subject in the Tivorbex Capsules 40 mg bid group discontinued the trial after receiving three doses of study drug due to nausea, classified as mild. The event was reported to have started prior to trial drug administration. The AE was considered by the investigator to be not related to study drug.
- Subject 004-020: A 56-year-old female subject in the Tivorbex Capsules 20 mg tid group discontinued the trial after receiving four doses of study drug due urticaria (verbatim term: hives on trunk and bilateral arms) classified as mild. Concomitant medications included citalopram, levothyroxine, simvastatin, ibuprofen, and Vicodin. The subject was treated with diphenhydramine and the event resolved. The event was considered by the investigator to be probably related to study drug.

7.3.4 Significant Adverse Events

For this application, the one serious adverse event, the five adverse events leading to discontinuation from the trial, and the adverse events of severe intensity, were listed as significant adverse events.

A total of five subjects (0.6%) reported severe TEAEs across Phase 3 trials. One subject (0.5%) in the Tivorbex Capsules 40 mg tid group reported severe nausea. Four subjects (0.7%) in the combined Tivorbex Capsules (two subjects each in the 20 mg tid and 40 mg tid groups) experienced severe headaches.

Table 34: Severe treatment-related adverse events (Integrated safety population)

Preferred Term, n (%)	(b) (4) Capsules 40 mg tid n=187	40 mg bid n=184	20 mg tid n=183	Combined n=554	Celecoxib Capsule 200 mg[a] bid n=93	Placebo n=188	Total N=835
Any severe TEAE	3 (1.6)	0	2 (1.1)	5 (0.9)	0	0	5 (0.6)
Headache	2 (1.1)	0	2 (1.1)	4 (0.7)	0	0	4 (0.5)
Nausea	1 (0.5)	0	0	1 (0.2)	0	0	1 (0.1)

(Source: Applicant's table from ISS, 2.7.4, page 36)

7.3.5 Submission Specific Primary Safety Concerns

There were no events of clinical concern (cardio-embolic, GI bleeding, hepatic or renal) observed in the Tivorbex Capsule trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Integrated Safety Population (Phase 3 trials)
A total of 626 subjects (75%) in any treatment group experienced at least one TEAE in the Phase 3 clinical trials. The incidence of the TEAEs was similar across the treatment groups:

- 70% for Tivorbex Capsules 40 mg tid
- 80% for Tivorbex Capsules 40 mg bid
- 75% for Tivorbex Capsule 20 mg tid
- 73% for Celecoxib 200 mg bid
- 76% for placebo

An overall summary of adverse events is presented on the table below:

Table 35: Summary of Adverse Events (Integrated Safety Population)

Category, n (%)	(b) (4) Capsules 40 mg tid n=187	(b) (4) Capsules 40 mg bid n=184	(b) (4) Capsules 20 mg tid n=183	(b) (4) Capsules Combined n=554	Celecoxib Capsules 200 mg[a] bid n=93	Placebo n=188	Total N=835
Subjects with ≥1TEAEs	131 (70.1)	148 (80.4)	137 (74.9)	416 (75.1)	68 (73.1)	142 (75.5)	626 (75.0)
Subjects with ≥1 treatment-related TEAE	50 (26.7)	64 (34.8)	59 (32.2)	173 (31.2)	26 (28.0)	65 (34.6)	264 (31.6)
Subjects with ≥1 severe TEAE	3 (1.6)	0	2 (1.1)	5 (0.9)	0	0	5 (0.6)
Subjects with ≥1 serious TEAEs	0	1 (0.5)	0	1 (0.2)	0	0	1 (0.1)
Subject who terminated trial early due to AE	2 (1.1)	2 (1.1)	1 (0.5)	5 (0.9)	0	2 (1.1)	7 (0.8)
Subjects who died	0	0	0	0	0	0	0

(Source: Applicant's table from ISS, 2.7.4, page 32)

The most frequent TEAEs were nausea, post procedural edema, headache, dizziness, vomiting, post procedural hemorrhage, and constipation. Nausea was the most frequently reported event (282 subjects, 34%), with similar frequency across treatment groups. A slightly higher incidence of headache (16%) was reported in the Tivorbex Capsules 40 mg tid treatment group compared with placebo (11%). The incidence of headache in the Tivorbex Capsules 40 mg bid and 20 mg tid groups was comparable to that in the placebo group.

The most frequent TEAEs (those that occurred in ≥1% of subjects in any treatment group) are summarized by preferred term in the table below:

Table 36: TEAEs occurring in more than 1% of combined Tivorbex Capsule subjects (Integrated safety Population)

Preferred Term, n (%)	(b) (4) 40 mg tid n=187	(b) (4) 40 mg bid n=184	(b) (4) 20 mg tid n=183	(b) (4) Capsule Combined n=554	Celecoxib Capsule 200 mg[a] bid n=93	Placebo n=188	Total N=835
Any TEAE	131 (70.1)	148 (80.4)	137 (74.9)	416 (75.1)	68 (73.1)	142 (75.5)	626 (75.0)
Nausea	62 (33.2)	60 (32.6)	63 (34.4)	185 (33.4)	30 (32.3)	67 (35.6)	282 (33.8)
Post procedural edema	44 (23.5)	40 (21.7)	48 (26.2)	132 (23.8)	25 (26.9)	60 (31.9)	217 (26.0)
Headache	29 (15.5)	25 (13.6)	20 (10.9)	74 (13.4)	5 (5.4)	21 (11.2)	100 (12.0)
Dizziness	28 (15.0)	26 (14.1)	18 (9.8)	72 (13.0)	7 (7.5)	32 (17.0)	111 (13.3)
Vomiting	14 (7.5)	19 (10.3)	21 (11.5)	54 (9.7)	3 (3.2)	21 (11.2)	78 (9.3)
Post procedural hemorrhage	9 (4.8)	20 (10.9)	9 (4.9)	38 (6.9)	8 (8.6)	11 (5.9)	57 (6.8)
Constipation	7 (3.7)	9 (4.9)	11 (6.0)	27 (4.9)	3 (3.2)	9 (4.8)	39 (4.7)
Pruritus	4 (2.1)	5 (2.7)	8 (4.4)	17 (3.1)	4 (4.3)	0	21 (2.5)
Diarrhea	4 (2.1)	6 (3.3)	4 (2.2)	14 (2.5)	0	1 (0.5)	15 (1.8)
Dyspepsia	6 (3.2)	3 (1.6)	1 (0.5)	10 (1.8)	3 (3.2)	1 (0.5)	14 (1.7)
Post procedural swelling	2 (1.1)	5 (2.7)	2 (1.1)	9 (1.6)	0	1 (0.5)	10 (1.2)
Presyncope	3 (1.6)	5 (2.7)	1 (0.5)	9 (1.6)	2 (2.2)	3 (1.6)	14 (1.7)
Rash	4 (2.1)	2 (1.1)	3 (1.6)	9 (1.6)	0	0	9 (1.1)
Abdominal pain upper	3 (1.6)	2 (1.1)	3 (1.6)	8 (1.4)	0	1 (0.5)	9 (1.1)
Somnolence	4 (2.1)	3 (1.6)	1 (0.5)	8 (1.4)	3 (3.2)	1 (0.5)	12 (1.4)
Erythema	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)	1 (1.1)	10 (5.3)	17 (2.0)
Pruritus generalized	1 (0.5)	3 (1.6)	2 (1.1)	6 (1.1)	1 (1.1)	0	7 (0.8)

(Source: Applicant's table from ISS, 2.7.4, page 33)

The majority of the TEAEs were mild (61%) or moderate (13%) in intensity. A total of 13 subjects reported severe TEAEs across all trials and 5 (0.6%) across the Phase 3 trials. The reported severe TEAEs included nausea, vomiting, alveolar osteitis, muscle tightness, and headache. No severe CV, GI, or renal TEAEs of the type reported in class labeling for NSAIDs (myocardial infarction, stroke, acute coronary syndrome, ulcers, GI bleeding, hypertension, renal failure, or renal insufficiency) were observed across the Tivorbex Capsules clinical trials.

Phase 2 trial

A total of 93 subjects (46%) experienced at least one TEAE in clinical trial IND2-08-03. Across treatment groups, TEAEs were reported most frequently in the placebo group (29 subjects, 57%) followed by the Tivorbex Capsules 40 mg (26 subjects, 51%), Tivorbex Capsules 20 mg (19 subjects, 38%), and celecoxib (19 subjects, 37%) groups. There were no deaths, SAEs, or AEs that led to trial discontinuation. The most frequent TEAEs occurring in more than 5% of subjects in any treatment group were nausea, headache, alveolar osteitis, post procedural swelling, vomiting, oropharyngeal pain, and dizziness. Nausea was reported in 12% of subjects in the Tivorbex Capsules 40 mg group, 16% of subjects in the Tivorbex Capsules 20 mg group, 10% of subjects in the celecoxib 400 mg group, and 24% of subjects in the placebo group.

Phase 1 trials

- IND1-08-01

A total of 17 subjects (43%) experienced at least one TEAE. The frequency of TEAEs was similar across the treatment groups (range of 15% to 18%). Somnolence was the most frequently reported TEAE, reported by 6 subjects (15%) who received Tivorbex Capsules (40 mg and 20 mg Fasted; 40 mg Fed) and 4 subjects (10%) who received Indomethacin 50 mg (Fasted and Fed) capsules. No deaths, SAEs, or AEs that led trial discontinuation were reported.

- IND1-12-07

A total of 10 subjects (25%) reported 14 AEs during the trial. The percentage of subjects reporting TEAEs were generally similar across the treatment periods. No deaths, SAEs, or TEAEs that led to trial discontinuation were reported.

7.4.2 Laboratory Findings

In the Phase 2 and 3 clinical trials, laboratory evaluations were performed only at Screening. No evaluations of laboratory parameters over time or for individual subject changes were performed at any other time during the trials.

Clinical laboratory evaluations were monitored over time during the Phase 1 clinical trials (IND1-12-07 and IND1-08-01). By subject listings were provided for the laboratory

results by the Applicant. Review of the information provided did not reveal any clinically significant abnormalities.

7.4.3 Vital Signs

There were no clinically significant vital signs (VS) abnormalities observed in Phase 1 trials.

There were no clinically meaningful changes from baseline in mean vital signs at any time point in the Phase 2 trial, and only one individual change in vital signs was reported as a TEAE (increased body temperature) during the trial.

In the Phase 3 trials VS, including blood pressure (BP), heart rate (HR), respiratory rate (RR), and oral body temperature, were recorded at the following times: at Screening and before surgery on Day 0. From Day 1 through discharge from the trial site on Day 3, VS were measured immediately before and 1 hour after the first dose of study drug each day. Vital signs were also measured at the Follow-up Visit (or Early Termination Visit).

Abnormally high and abnormally low VS measurements of potential clinical concern (systolic BP, diastolic BP, HR, RR, and oral body temperature) were identified based on criteria presented in the table below:

Table 37: Criteria for identification of VS measurements of potential clinical concern

Vital Sign	Normal Values	Potentially Clinically Significant	
		Abnormally Low	Abnormally High
Blood pressure (mmHg)[a]	Systolic: <120 Diastolic: <80	Systolic: <90 Diastolic: <60	Systolic:>140 Diastolic: >90
Respiratory rate (breaths/minute at rest)	12 to 16	<12	>16
Oral temperature (°F [°C])	97.8 (36.5) to 99 (37.2)	<97.7 (36.5)	>99 (37.2)
Pulse rate (beats/minute at rest)	50 to 90	<50	>90

(Source: Applicant's table from ISS, 2.7.4, page 58)

A slightly higher proportion of subjects in the Tivorbex Capsules and celecoxib treatment groups had at least one value of potential clinical concern (low and high) for diastolic BP compared with the placebo group. A summary of subjects with VS measurements of potential clinical concern is provided in the table below:

Table 38: Summary of subjects with VS measurements of potential clinical concern (Phase 3 trials)

Category, n (%)	(b) (4) Capsules 40 mg tid n=187	(b) (4) Capsules 40 mg bid n=184	(b) (4) Capsules 20 mg tid n=183	(b) (4) Capsules Combined n=554	Celecoxib Capsules 200 mg[a] bid n=93	Placebo n=188	Total N=835
Systolic blood pressure							
High	62 (33.2)	52 (28.3)	51 (27.9)	165 (29.8)	27 (29.0)	48 (25.5)	240 (28.7)
Low	3 (1.6)	14 (7.6)	10 (5.5)	27 (4.9)	3 (3.2)	7 (3.7)	37 (4.4)
Diastolic blood pressure							
High	49 (26.2)	49 (26.6)	47 (25.7)	145 (26.2)	23 (24.7)	35 (18.6)	203 (24.3)
Low	40 (21.4)	50 (27.2)	44 (24.0)	134 (24.2)	26 (28.0)	35 (18.6)	195 (23.4)
Heart rate							
High	38 (20.3)	32 (17.4)	35 (19.1)	105 (19.0)	18 (19.4)	51 (27.1)	174 (20.8)
Low	15 (8.0)	9 (4.9)	8 (4.4)	32 (5.8)	5 (5.4)	9 (4.8)	46 (5.5)
Respiratory rate							
High	136 (72.7)	117 (63.6)	121 (66.1)	374 (67.5)	71 (76.3)	128 (68.1)	573 (68.6)
Low	0	0	1 (0.5)	1 (0.2)	0	1 (0.5)	2 (0.2)
Oral body temperature							
High	52 (27.8)	46 (25.0)	43 (23.5)	141 (25.5)	17 (18.3)	75 (39.9)	233 (27.9)
Low	125 (66.8)	124 (67.4)	116 (63.4)	365 (65.9)	56 (60.2)	116 (61.7)	537 (64.3)

(Source: Applicant's table from ISS, 2.7.4, page 59)

7.4.4 Electrocardiograms (ECGs)

In Phase 3 clinical trials, ECGs were only collected at baseline and thus no analyses were conducted and submitted to the Agency for ECGs. Some ECG data were collected for safety assessments but no abnormalities of ECG were reported by the Investigator in any of the trials.

Indomethacin and NSAIDs are not reported to be associated with prolongation of the measure between Q wave and T wave in the heart's electrical cycle (QT interval). Definitive studies on the effect of Tivorbex Capsules on QT prolongation have not been conducted. Potential effects of indomethacin on the QT interval are not described in the prescribing information for approved indomethacin products and have not been noted in the literature.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed during the development program.

7.4.6 Immunogenicity

No new data regarding the immunogenic potential of Tivorbex were included in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to Section 7.2.2

7.5.2 Time Dependency for Adverse Events

Refer to Section 7.2.2

7.5.3 Drug-Demographic Interactions

Subgroup analyses by gender, age, race, ethnicity, BMI, and concomitant medications were performed on the Integrated Safety Population. There were no safety findings to suggest a need for dose adjustment in older patients. There were no safety concerns related to gender, BMI, or race and the use of Tivorbex Capsules.

7.5.4 Drug-Disease Interactions

Tivorbex Capsules clinical trials enrolled generally healthy subjects undergoing short-term treatment. Analyses of TEAEs and vital sign measurements by specific medical histories that could be associated with an increased risk of AEs did not reveal any safety concerns with the use of Tivorbex Capsules in these subjects.

7.5.5 Drug-Drug Interactions

Class labeling for NSAIDs includes a list of medications that when taken with NSAIDs have the potential to increase AEs. These medications include the following: aspirin, ACE-inhibitors, angiotensin II antagonists, beta-blockers, digoxin, furosemide or other diuretics, warfarin or other oral anticoagulants, antiplatelet medications, lithium, methotrexate, cyclosporine, and CYP929 inducers or inhibitors.

Clinically significant drug interactions were not reported as TEAEs in Tivorbex Capsules clinical trials. Few subjects in Tivorbex Capsules clinical trials were concomitantly administered trial drug and medications of interest (ACE inhibitors, angiotensin II antagonists, beta blockers, platelet aggregation inhibitors, and thiazides). Although the subgroup sizes are small, analyses of TEAEs and vital sign measurements by

concomitant medications of interest in the Integrated Safety Population did not reveal safety concerns related to the use of Tivorbex Capsules and these medications.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new carcinogenicity studies were performed for Tivorbex Capsule. For indomethacin, no carcinogenic potential was identified in an 81-week study in rats at oral doses of ≤1 mg/kg/day, or in mice or rats given oral doses of ≤1.5 mg/kg/day for 62 to 88 weeks or 73 to 110 weeks, respectively. Indomethacin has not been shown to be a tumor promoter or inhibitor in vivo.

7.6.2 Human Reproduction and Pregnancy Data

The pharmacokinetics, efficacy, and safety of Tivorbex Capsules were not studied in women who were pregnant or lactating. However, Tivorbex Capsules are expected to have similar risks associated with administration during pregnancy and lactation as has been previously demonstrated for other indomethacin drug products. Starting at 30 weeks gestation, indomethacin, as with other NSAIDs, if used by pregnant women may cause premature closure of the ductus arteriosus in the fetus.

NSAIDs, including indomethacin, are labeled as Pregnancy Category C drugs. Indomethacin is known to cross the placenta and is excreted in breast milk. Its use is not recommended during pregnancy due to an increased risk of fetal side effects.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of Tivorbex Capsules in subjects 17 years of age and younger has not been studied.

The Division outlined the requirements for the Applicant's pediatric plan during the end-of-Phase 2 meeting. In summary, the Division stated that the proposed acute pain indication exists throughout the entire pediatric population. Therefore, Applicant's proposal for a waiver for pediatric subjects (b) (4) and deferral for pediatric subjects (b) (4) was not acceptable. The Applicant was informed that they must develop an age appropriate formulation to dose the younger age patients. If it would be unsafe to use Tivorbex in patients under a particular age, the Applicant was asked to submit supporting scientific justification. The Applicant was informed that in the spirit of the Pediatric Research Equity Act (PREA), it is preferable if pediatric studies are commenced during development in adults, and if possible, completed studies submitted

with the NDA. The studies are expected to inform appropriate dose, dose interval, pharmacokinetics, efficacy, and safety in different age pediatric strata.

At the pre-NDA meeting the Applicant informed the Division that they are working with experts to develop a pediatric plan that satisfies the requirements of PREA and that they plan to submit the Pediatric Plan to the IND in advance of the scheduled NDA submission. Nevertheless, Pediatric Plan was not submitted prior to the NDA application.

The Pediatric Plan submitted with the NDA was not consistent with the advice provided by the Division during discussions in the past. The Applicant requests waivers for ages birth to <12 months (b) (4) and a deferral for ages (b) (4)

Input regarding the appropriate lower age limit for PREA PMR studies of NSAIDs indicated for acute pain was requested from the Pediatric and Maternal Health Stuff (PMHS). Their conclusion was that each NSAID must be evaluated independently based on the available safety data and the review of use data in the pediatric population.

Literature review did not suggest that indomethacin is typically used for the treatment of acute pain in the pediatric population. The Division of Epidemiology II (DEPI II) review of use data of indomethacin in the pediatric population confirmed that use of indomethacin in pediatric patients is extremely low.

DEPI II evaluated the extent of oral indomethacin use in pediatric patients aged less than 1, 1, 2-5, 6-11, and 12-16, and 17+ years, for years 2008 through 2012, and year-to-date August 2013. (b) (4)

In November 2013, the Division sent an information request to the Applicant outlining updated requirements for the indomethacin pediatric plan. As with NSAIDs in general, efficacy findings for patients ages 2 to 17 years can be extrapolated from adults because the underlying condition (pain) and the response to treatment is expected to be the same in this age group compared to adults. The Division agreed on a partial waiver for pediatric patients ages birth to less than one year because the product does not

represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of patients in this pediatric age group, and a deferral for pediatric patients ages 1 to less than 17 years because the product is ready for approval in adults.

Agreement was reached with the Sponsor for a pediatric plan that includes the following clinical studies:

Table 39: Planned Pediatric Trials

Age Group	Type of Trial	Comments	Deferral request planned, Y/N
1 year to < 2 years	Efficacy/Safety/PK trial	Endpoints to be determined Use of rescue medication will be included in trial design	Y
2 years to < 6 years	Safety/PK trial (Open-label)	Evaluate safety and tolerability in acute pain Determine single dose PK	Y
6 years to < 18 years	Safety/PK trial (Open-label)	Evaluate safety and tolerability in acute pain Determine single dose PK	Y

(Source: Adapted from Sponsor's amendment submission from November 21, 2013)

The proposed timeline for the pediatric studies is as follow:

Table 40: Timeline for pediatric trials

Clinical Trials	Final Protocol Submission Date	Trial Start Date	Final Report Submission
6 years to < 18 years (Trial 1)	April 1, 2015	October 1, 2015	October 2, 2017
2 years to < 6 years (Trial 2)	November 2, 2015	June 1, 2016	June 1, 2018
1 year to < 2 years (Trial 3)	June 1, 2018	December 31, 2018	December 31, 2020

(Source: Adapted from Sponsor's amendment submission from November 21, 2013)

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on January 15, 2014. The PeRC agreed with the Division to grant 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 and is unlikely to be used in a substantial number of patients in this pediatric age group. 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. PeRC requested a revised timeline to accelerate the protocol submissions. A request was sent to Sponsor to provide a new timeline that includes earlier dates for all protocol submissions, and adjusted study conduct dates and report submissions to align with those dates.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to class labeling for NSAIDs, symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. GI bleeding can also occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic doses of NSAIDs, and may also occur following an overdose.

There have been no instances of overdose in Tivorbex Capsules clinical trials.

Indomethacin does not have abuse potential or evidence for withdrawal symptoms.

7.7 Additional Submissions / Safety Issues

All safety data were provided in the original NDA submission. No additional safety data were collected following completion of the clinical trials.

8 Postmarket Experience

Tivorbex Capsules have not been registered in any country and there are no postmarketing data.

9 Appendices

9.1 Literature Review/References

Published studies of indomethacin reported in the literature were reviewed by the Applicant to provide information on AEs. The incidence and pattern of AEs were consistent with the known safety profile of indomethacin. The incidence, pattern, and severity of AEs observed in the Tivorbex Capsules clinical trials were also consistent with the known safety profile of indomethacin. The most common AEs across the Tivorbex Capsules treatment groups and the published trials consisted of GI effects (such as nausea and vomiting) and CNS effects (such as headache and dizziness). In the Phase 3 Tivorbex Capsules trials, the most common TEAEs were reported at similar rates in the published literature.

9.2 Labeling Recommendations

Based on the review of the proposed labeling provided in the submission, the following changes are recommended from the clinical perspective. 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 6 Clinical Trials Experience
The table of adverse reactions provided in this section does not reflect the correct number of Tivorbex exposures from the Phase 3 trials and needs to be revised. In addition, (b) (4) needs to be deleted (b) (4)

The adverse events table in this section must include the reported events of urticaria and angioedema as well as all events with higher incidence rate for the Tivorbex treatment group compared to placebo.

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
The Applicant included information (b) (4) in this section, and *I recommend it be removed* (b) (4)

I also recommend adding more detail about the Phase 3 clinical trials to give prescribers a better idea of the study population, including a brief description of the study population and baseline pain characteristics, and use of rescue medication.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for this NDA application.

9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review

Application Number: 204-768

Submission Date(s): April 30, 2013

Applicant: Iroko Pharmaceuticals, LLC

Product: Tivorbex™ (indomethacin submicron particle), Capsules 20 mg and 40 mg

Reviewer: Anjelina Pokrovnichka, M.D.

Date of Review: April 29, 2013

Covered Clinical Study (Name and/or Number): IND 1-08-01, IND1-12-07, IND2—08-03, IND3-08-04b, IND3-10-06

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 40		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None identified		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (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 all investigators for the Phase 1, Phase 2, and Phase 3 clinical trials, certifying that they had no financial interests or arrangements to disclose.

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.

None of the investigators had financial interests or arrangements to disclose.

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

/s/

ANJELINA POKROVNICHKA
01/15/2014

ELLEN W FIELDS
01/15/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204-768 **Applicant:** Iroko Pharmaceuticals, LLC **Stamp Date:** April 30, 2013

Drug Name: (b) (4) Capsules **NDA/BLA Type:** 505 (b)(2)

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			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			During the Pre-NDA Meeting, the FDA agreed that efficacy data from the Ph3 and Ph2 trials would not be pooled. Since there is no data integration, the summary information on effectiveness is located in 2.7.3 Summary of Clinical Efficacy. Results from the two Ph3 trials (IND3-08-04b and IND3-10-06) are presented separately. The Ph2 trial (IND2-08-03) is also presented separately.
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			**For safety and efficacy data**: Indocin® 25 mg and 50 mg capsules application

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

	Content Parameter	Yes	No	NA	Comment
					(iCeutica Operations, LLC), NDA 016059 - discontinued for reasons not related to safety or efficacy **For biolinking purposes**: Ph1 trials against Indomethacin 50 mg capsules (Mylan Pharmaceuticals, Inc., ANDA 070-624)
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)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	X			Indication: Treatment of mild to moderate acute pain. The Sponsor conducted two Ph3 efficacy studies(**IND3-08-04b** and **IND3-10-06**) that evaluated the efficacy and safety of (b) (4) in patients with postoperative pain following bunionectomy.
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			• ITT to include all subjects who received at least one dose of study drug • Comparisons of onset of analgesia without data regarding analgesic potency are not meaningful • Recommend calculating the VAS SPID-48 as a time-weighted average • Follow the NAS report

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					recommendations to handle missing data • For claims of efficacy for all 3 doses (b) (4) studied (40mg TID, 40 mg BID, and 20 mg BID) based on comparisons to placebo, strategy to handle multiplicity must be included
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			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
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			At the EOP2, the Division agreed that safety data base of 500 subjects is acceptable, barring unexpected safety signal.
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					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			

[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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
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			
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			SAS-transformed format
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
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			
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____

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

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

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NA

Anjelina Pokrovnichka, M.D.	
Reviewing Medical Officer	Date
Ellen Fields, MD	June 28, 2013
Clinical Team Leader	Date

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

/s/

ELLEN W FIELDS
06/28/2013