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MEDICAL REVIEW

CLINICAL REVIEW

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Reviewer Name Christina Fang, M.D., M.P.H.
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Established Name Ibuprofen IV injection
(Proposed) Trade Name Caldolor™ (ibuprofen) IV injection
Therapeutic Class NSAID
Applicant Cumberland Pharmaceuticals Inc.

Priority Designation 3P

Formulation Solution for injection containing 100 mg/mL ibuprofen
Dosing Regimen (b) (4)
Indication Fever; pain (supplemental to morphine treatment)
Intended Population Adult (b) (4) patients

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

IV ibuprofen injection is recommended for a regulatory action of approval.

The recommendation for approval is based on an acceptable benefit/risk ratio according to my review of clinical efficacy and safety data submitted in NDA 22-348.

The antipyretic efficacy of IV ibuprofen injection for treating fever in hospitalized patients is supported by replicable positive findings from the two fever studies (Study 004 and 006) in addition to the consideration of similar bioavailability between the IV and oral formulations of ibuprofen. The strength of evidence in support of antipyretic efficacy of IV ibuprofen injection was indicated by the statistically significant treatment differences by primary analyses and clinically meaningful effect sizes of treatment differences in the percentage of patients with temperature reduction, the length of time to lower the temperature, and the degrees of temperature reduction.

The therapeutic benefit of IV ibuprofen injection for use as supplemental analgesia to opioid treatment is supported by the statistically significant treatment difference by primary analysis in Study 008b associated with combined effects on reduction of morphine use, reduction of morphine-related adverse events, and reduction of pain as shown in the two pain studies (Study 008a and 008b).

The use of IV ibuprofen is considered reasonably safe based on the lack of new safety signals or unexpected events in clinical trial database, the known safety profile of the ibuprofen moiety, and the anticipated short-term use of the IV formulation and close safety monitoring in a hospital setting.

1.2 Risk Benefit Analysis

The benefits of treating fever with IV ibuprofen 100 mg, 200 mg, and 400 mg in hospitalized patients have been shown in terms of clinically meaningful treatment differences from placebo in the percentage of patients with temperature reduction, the length of time to lower the temperature, and the degree of temperature reduction.

In comparison to placebo, treatment with IV ibuprofen 400 mg resulted in 45% more patients with fever reduced to a temperature of <101.0°F in four hours, 5-hour earlier temperature reduction to <101.0°F and 7-hour earlier temperature reduction to <100.0°F in 24 hours, and a mean temperature reduction by 2.0 more degrees (°F) in four hours and 1.4 more degrees in 24 hours. Treatment with IV ibuprofen 200 mg resulted in 41% more patients with fever reduced to a temperature of <101.0°F in four hours, 4-hour earlier temperature reduction to <101.0°F and 6-hour earlier temperature reduction to <100.0°F in 24 hours, and a mean temperature reduction by 1.5 more degrees in four hours and 1.0 more degree in 24 hours. Treatment with IV ibuprofen 100 mg resulted in 33% more patients with fever reduced to a temperature of <101.0°F in four hours, 5-hour earlier temperature reduction to <101.0°F as well as to <100.0°F in 24 hours, and a mean temperature reduction by 1.3 more degrees in four hours and 1.0 more degrees in 24 hours. Statistically significant treatment differences have been demonstrated in analyses of the primary endpoint and several of the key secondary endpoints for the three IV ibuprofen doses studied.

The benefits of using IV ibuprofen injection 800 mg to supplement opioid analgesia in treating pain have been shown in combined effects on reduction of morphine use, reduction of morphine-related adverse events, and reduction of pain.

In comparison to the morphine-alone treatment group the addition of IV ibuprofen 800 mg to morphine analgesia resulted in 10-20% reduction in the amount of morphine use in 24 hours, about 10% reduction in any or combined known morphine-related adverse events, differences in mean PI by 0.5-1.2 units on a 11-point scale and difference in median PI by about 10 to 40% for about 24 hours. The addition of IV ibuprofen 400 mg to morphine analgesia resulted in 2-5% reduction in the amount of morphine use in 24 hours, about 10% reduction in any and 20% reduction in combined known morphine-related adverse events, differences in mean PI by 0.5-1.0 units on a 11-point scale and difference in median PI by about 10 to 20% for about 12 hours. Statistically significant treatment difference has been demonstrated in the reduction of 24-hour morphine use for the IV ibuprofen 800 mg dose in Study 008b based on primary analysis of the untransformed data and reanalysis of the data excluding Dr. Snow's site.

Because ibuprofen is indicated for mild to moderate pain and morphine is indicated for moderately severe pain, ibuprofen is not expected of capable of treating post-operative pain that is severe in nature, when used alone. The use of ibuprofen in patients already on opioid analgesic treatment is not expected to provide additional pain reduction to the extent comparable to the effect size commonly seen when a placebo is compared to NSAID drugs in treating dental pain or compared to opioid drugs in treating post-operative pain. However, the combined effects of the relatively small reduction in morphine use, pain reduction, and reduction of morphine-related AEs are considered therapeutically beneficial to patients who might not be able to use larger doses of opioid analgesics.

In evaluation of the safety of IV ibuprofen in sick patient populations, ibuprofen-induced toxicities might overlap with clinical abnormalities associated with end-stage disease, concurrent illness, and concomitant medication, making it difficult to assess the causal relationship between study drug and adverse events.

Of the safety data in more than 600 subjects exposed to IV ibuprofen for up to 1-2 days in most patients and up to 4 days in a few, there were no new safety signal or unexpected events identified. Local irritancy with undiluted ibuprofen solution was greatly reduced when the preparation was diluted before IV administration.

The use of IV ibuprofen in a hospital setting is considered reasonably safe as supported by the safety data collected from the six clinical studies and known safety profile of ibuprofen established from extensive clinical studies and 35 years of use on the U.S. market. The duration of use is anticipated to be limited to two to three days when IV access is still available. Close monitoring of the amount of IV infusion and drug safety with the use of IV ibuprofen will be available around the clock in the hospital setting.

The benefit/risk ratio is considered acceptable in my opinion.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendation for other Postmarketing Study Commitments

Pediatric studies are recommended to be conducted in accordance to the Pediatric Written Request and pediatric plan. The recommended pediatric studies include pharmacokinetic study in hospitalized pediatric patients ages from birth to <16 years who are in need for IV treatment of fever, fever efficacy study in hospitalized pediatric patients aged <6 months who are in need for IV treatment of fever, and safety study in pediatric patients with fever or pain (if additional exposure is required).

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

IV ibuprofen injection (IVib) is an IV formulation containing 100 mg/mL ibuprofen packaged in 400 mg/4 mL and 800 mg/8 mL vials to be diluted in 5% dextrose or 0.9 % sodium chloride solution prior to administration for the management of fever and pain.

The established name of the product is ibuprofen IV injection and the proposed trade name was originally Amelior™, which was changed to Caldolor™ after receiving comments from DMEPA. The active ingredient of the product, ibuprofen, is a propionic acid derivative and a member of the non-steroidal anti-inflammatory drug (NSAID) class. The proposed dosage for ibuprofen IV injection is 400 mg every four to six hours for fever and (b) (4)g every six hours for pain.

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Several drugs of the NSAID class are currently available for treating fever and mild to moderate pain. There has been no market approval of IV formulation for a fever indication in the U.S.

2.3 Availability of Proposed Active Ingredient in the United States

There are many ibuprofen containing products currently available in the United States. The information on these products is summarized in the table below by the proprietary name, active ingredient, strength of formulation, NDA number, and application approval date.

Table 2-1 Products Containing Ibuprofen Approved for the U.S. market

Proprietary Name	Active Ingredient	Strength	NDA#	Approval date
Rx				
Neoprofen	Ibuprofen lysine	EQ 20mg base/2mL (EQ 10mg base/mL)	<u>021903</u>	Apr 13, 2006
Combunox	Ibuprofen; oxycodone hydrochloride	400mg;5mg	<u>021378</u>	Nov 26, 2004
Vicoprofen	Hydrocodone bitartrate; ibuprofen	7.5mg;200mg	<u>020716</u>	Sep 23, 1997
Generic	Ibuprofen suspension	100mg/5mL	Multiple	
Generic	Ibuprofen tablet	400mg, 600mg, 800mg	Multiple	
OTC				
Advil PM	Diphenhydramine citrate; ibuprofen	38mg;200mg	<u>021394</u>	Dec 21, 2005
Advil PM	Diphenhydramine hydrochloride; ibuprofen capsule	25mg;EQ 200mg free acid and potassium salt	<u>021393</u>	Dec 21, 2005
Children's Advil Allergy Sinus	Chlorpheniramine maleate; ibuprofen; pseudoephedrine hydrochloride	1mg/5mL; 100mg/5mL; 15mg/5mL	<u>021587</u>	Feb 24, 2004
Advil Allergy Sinus	Chlorpheniramine maleate; ibuprofen; pseudoephedrine hydrochloride	2mg;200mg;30mg	<u>021441</u>	Dec 19, 2002
Advil Cold and Sinus	Ibuprofen; pseudoephedrine hydrochloride	EQ 200mg free acid and potassium salt; 30mg capsule	<u>021374</u>	May 30, 2002
Children's Advil Cold	Ibuprofen; pseudoephedrine hydrochloride	100mg/5mL;15mg/5mL suspension	<u>021373</u>	Apr 18, 2002
Children's Motrin Cold	Ibuprofen; pseudoephedrine hydrochloride	100mg/5ml;15mg/5mL suspension	<u>021128</u>	Aug 1, 2000
Sine-Aid IB	Ibuprofen; pseudoephedrine hydrochloride	200mg;30mg tablet	<u>019899</u>	Dec 31, 1992
Advil Cold and Sinus	Ibuprofen; pseudoephedrine hydrochloride	200mg;30mg tablet	<u>019771</u>	Sep 19, 1989
Children's Elixsure	Ibuprofen suspension	100mg/5mL	<u>021604</u>	Jan 7, 2004

Children's Advil	Ibuprofen suspension	100mg/5mL	020589	Jun 27, 1996
Children's Motrin	Ibuprofen suspension	100mg/5mL	020516	Jun 16, 1995
Midol Liquid Gels	Ibuprofen capsule	Capsule 200MG	021472	Oct 18, 2002
Advil Migraine Liqui-Gels & Advil Liqui-Gels	Ibuprofen capsule	EQ 200mg free acid and potassium salt	020402	Apr 20, 1995
Children's & Junior Strength Advil	Ibuprofen chewable tablet	50mg, 100mg	020944	Dec 18, 1998
Children's & Junior Strength Motrin	Ibuprofen chewable tablet	50mg, 100mg	020601	Nov 15, 1996
Pediatric Advil	Ibuprofen suspension/drops	100mg/2.5mL	020812	Jan 30, 1998
Children's Motrin	Ibuprofen suspension/drops	40mg/mL	020603	Jun 10, 1996
Junior Strength Advil	Ibuprofen tablet	100mg	020267	Dec 13, 1996
Junior Strength Motrin	Ibuprofen tablet	100mg	020602	Jun 10, 1996
Motrin Migraine Pain	Ibuprofen tablet	200mg	019012	Dec 17, 1990
Advil	Ibuprofen tablet	200mg	018989	May 18, 1984

Source: Orange book, 2009 edition.

Major safety concerns with the use of ibuprofen, especially at higher doses for a prolonged exposure, are risks of cardiovascular, gastrointestinal, and renal toxicities.

2.4 Important Issues with Consideration to Related Drugs

The most recent safety findings concerning the use of NSAID drugs are their cardiovascular toxicities, for which all NSAID drugs are now required to have cardiovascular box warnings in their labels.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

In response to the Applicant's request for comments on their General Investigational Plan the Division recommended the proposed studies of safety and antipyretic efficacy to include critically ill patients and the future pediatric studies to have sufficient exposure, in a letter sent to the Sponsor on September 10, 2001. A follow up letter from the Division dated October 2, 2001 recommended the inclusion of adequate number of dose levels for studying dose response in order to determine the minimum effective dose in the fever study (004). The Division emphasized the importance of enrolling hemodynamically compromised patients in pain and PK studies and studying high risk groups to provide data for formulating dosage recommendations in patients with renal insufficiency according to the meeting minutes dated October 30, 2003. The Division recommended deferral of pediatric studies until results of adult studies were available, requested the Sponsor to address safety concerns with renal and GI toxicities and bleeding potential in patients after major surgeries, and commented on the lack of adequate design of the original (b) (4) trial conducted under a different IND, based on the meeting minutes dated February 3, 2004. The Division stated the need for a larger sample in using opioid sparing as the primary efficacy endpoint, asked the Sponsor for clinical interpretation of the primary endpoint, discussed the possibility of additional open-label drug exposure in order to obtain adequate safety database, and commented on pediatric study design, in the meeting minutes dated May 19, 2004. Comments about a pain study protocol submitted under Special Protocol Assessment (SPA) were sent to the Sponsor in the letter dated July 30, 2004. Follow up Divisional inputs on sample size, stratified randomization, timing of assessment, imputation methodology, and the need for a Statistical Analysis Plan (SAP) before agreement on SPA, were sent on September 30, 2004. Topics on sample size, stratification, and pediatric study requirements were discussed further as recorded in the meeting minutes dated October 4, 2004. Comments on missing data imputation and interim analysis in response to SAP, by the statistical review team, were forwarded to the Sponsor in a letter dated April 5, 2005. The Sponsor also received comments on data analysis plan for Study 004 and 008, and comments on pediatric fever study 005, according to the meeting minutes dated August 12, 2005. The content and format of NDA submission were discussed at the pre NDA meeting as recorded in the meeting minutes dated June 27, 2008. Fast track status was granted in the letter dated July 15, 2008. Pediatric Study Written Request was issued by the Division on March 30, 2009.

2.6 Other Relevant Background Information

Ibuprofen IV injection for fever or pain indication has not been approved in any country.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

There were a number of inconsistencies between different parts of the submission and between the original submission and subsequent submissions (sent in as the Applicant's response to the reviewer's request for more information and clarification of data). Some data and/or analyses commonly seen in most of the other NDA submissions were missing here, so that the reviewer had to either request or do the calculations and graphs for the review. The quality of the submission in terms of data organization, retrieval, and completeness could have been improved before NDA submission. Additional data/analysis queries from the reviewer included requests for information about distribution of dropouts and protocol violation/deviation per study site, detailed exposure data in multiple-dose studies, graphic presentation of time course of analgesic response, additional analyses of the percentage and the time to achieve lower temperatures, clarifications on protocol violation/deviation per treatment group for pain studies, the number of elderly patients enrolled per treatment group in Phase 3 studies, and clarification on cases with bone fractures.

3.2 Compliance with Good Clinical Practices

The steps to ensure compliance with Good Clinical Practices (GCP) included approval of protocols, informed consent forms, and all the amendments by the Institutional Review Boards (IRBs) before the initiation of the study, filing all study documents on-site in designated study file, requirement on recording all the data in the Case Report Forms (CRF) and signing of the CRFs by the Investigator, check for accuracy of the CRF data against source documents, dual record keeping of the CRFs by the study site and by the clinical monitor, timely report of protocol violation/deviation and reasons for violation/deviation, and pre defined monitoring function and responsibilities.

Rates of protocol violation/deviation were relatively high at about 40% to 60% in different studies. Major reasons for protocol violation/deviation were deviations from exclusion criteria in Study 004, missing laboratory tests and lack of double entry of data (data were double checked instead of double entered) in Study 006, study medication administration error and use of excluded medication in Study 008a, and use of excluded medication and missing or miss-timed assessments in Study 008b. The proportion of protocol violation/deviation in each category was roughly balanced between the treatment groups.

Four clinical sites lead by the Investigators Dr. Peter Morris (Study 004), Dr. John T. Promes (Study 004), Dr. Henry Frazer (Study 008b), and Dr. Lamar Snow (Study 008a and 008b), were selected for DSI inspection based on the number of patients enrolled, the percentage of protocol violation/deviations, the site's influence to the efficacy outcomes of the study, and the percentage of critically ill patients involved (fever study 004 only).

According to a preliminary review by Dr. Susan Leibenhaut dated May 19, 2009, the inspection of Dr. Peter Morris' site was performed as a data audit of selected patients and found no regulatory violations. The study appears to have been conducted adequately, and the data generated by the site may be used to support an efficacy conclusion.

The inspection of Dr. John Promes' site was performed as a data audit of 100% patient's records including informed consent forms, source documents, and case report forms. Inspection revealed a case of violation of the exclusion criteria of patients with severe head trauma. Another remarkable finding was that the Sponsor

was found to have advised the site not to enroll patients with fractures under the exclusion criteria in terms of the patients being "otherwise unsuitable for the study in the opinion of the investigator", as a precaution after two cases of bone fractures were reported by the site (refer to the safety Review Section 7.3.2 for detail). The overall conclusion from the inspection was that the study appears to have been conducted adequately, and the data generated by the site may be used to support an efficacy conclusion.

The inspection of Dr. Henry Frazer's site was performed as a data audit of selected patients and found no regulatory violations. The study appears to have been conducted adequately, and the data generated by the site may be used to support an efficacy conclusion.

The inspection of Dr. Lamar Snow's site was performed as a data audit of all patients for the primary efficacy endpoint and selected patients (10 of the 31 patients enrolled in Study 008a and 10 of the 39 patients enrolled in Study 008b) for their records involving informed consent forms, source documents, and case report forms. The inspection revealed discrepancies between the source documents and the NDA line listing in reporting 24-hour morphine use in four of the 70 patients (over reporting in two patients and underreporting in two patients). The other regulatory violations included not reporting a case of nausea and vomiting, unblinding study assignments of two patients by recording their treatment in the medication administration records, and enrolling two patients not eligible for the study because of receiving morphine before the start of study drug infusion. As stated in Dr. Leibenhaut's review, Dr. Snow "did not appear to have adequate oversight of the study". The overall conclusion from the inspection was that the data generated by the site for the patients other than the four mentioned above appear acceptable in support of an efficacy conclusion.

Due to the concern of data integrity the primary efficacy endpoint in Study 008b was reanalyzed without data from Dr. Snow's site by Dr. Norton. The reanalysis had the same statistical conclusion as the analyses of the original data set.

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in the six clinical studies was attached to the form) had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Ibuprofen IV injection is a clear sterile aqueous solution containing 100 mg/mL ibuprofen using arginine 78 mg/mL (b) (4). It is available in two strengths, 400 mg (4 mL in a (b) (4) vial) and 800 mg (8 mL in a (b) (4) vial). In-process controls, drug product specifications, and container/closure system are all considered acceptable according to the chemistry reviewer, Dr. Martin Haber's review of the original submission and the amendments dated March 11, 2009 and April 20, 2009, in which all chemistry deficiencies have been appropriately addressed by the Applicant (refer to Dr. Haber's review for detail).

CMC portion of the application is considered adequate and acceptable to support a market approval of the product by the chemistry review team, pending a satisfactory cGMP inspection report of the manufacture site in (b) (4)

4.2 Clinical Microbiology (if applicable)

Product quality microbiology control included sterilizing ibuprofen injection using a (b) (4) [redacted], are all considered acceptable according to the Microbiology Review by Dr. Vinayak Pawar (refer to the Microbiology Review for detail).

4.3 Preclinical Pharmacology/Toxicology

According to the review summary by Dr. Asoke Mukherjee major findings from the 28-day studies in dogs dosed at 5, 10 and 15 mg/kg tid or 15, 30 and 45 mg/kg/day, included liquid feces and kidney inflammation at all doses and GI erosions and ulcers at 45 mg/kg/day, consistent with known NSAID toxicities. NOEL was identified as 1 mg/kg/day and 5 mg/kg/day in different dog studies. Injection site inflammation and thrombosis observed in both the control and treated animals suggested that they were procedure-induced injection site reactions. Findings from local tolerance study of rabbit veins at 1.6, 20 and 100 mg/kg IV single dose included signs of irritancy, edema and erythema around the vein, which were considered vehicle (arginine) related. *In vitro* studies of human blood revealed no blood protein flocculation at 1:1 ratio between ibuprofen IV solution and human serum, red blood cell (RBC) hemolysis with undiluted ibuprofen solution at 100 mg/mL, and no RBC hemolysis with diluted solution at 4 mg/mL (dilution at 1:25 ratio).

In regard to issues with impurity (b) (4) detected at (b) (4) in drug substance and (b) (4) in drug product (versus 0.15% limit set by ICH guidelines), ibuprofen injection is considered reasonably safe to use in humans because of the anticipated maximum daily dose of impurity of (b) (4) in human within ICH limit of 0.08 mg/kg, lack of unexpected findings in repeat dose dog toxicity studies, and lack of any functional group in (b) (4) to pose a structural alert for mutagenicity according to Dr. Mukherjee's review (refer to Dr. Mukherjee's review for detail).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for ibuprofen is not completely understood but may be related to regulation of prostaglandin synthesis via prostaglandin synthetase. The mechanism involves an inhibition of cyclooxygenase (COX-1 and COX-2) pathways.

4.4.2 Pharmacodynamics

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models.

4.4.3 Pharmacokinetics

Pharmacokinetic (PK) data were obtained from two clinical studies, a single-dose relative bioavailability study (CPI-CL-001) comparing oral and IV formulations at 200, 400, and 800 mg levels and a Phase 3 fever study

(CPI-CL-004). According to the review summary by the PK reviewer, Dr. David Lee, findings from the single-dose study showed that the IV and oral formulations were bioequivalent at corresponding dose levels, except that mean C_{max} for the IV formulation was 78% of the oral formulation, falling slightly below the expected 90% confidence interval. Dose linearity was demonstrated for IV ibuprofen doses from 200 to 800 mg. In the fever study of IV ibuprofen in hospitalized patients including both critically ill and non-critically ill patients there was no critical drug accumulation after the 6th dose based on the comparison of PK profiles in 0 to 4-hour and 20 to 26-hour time intervals by Dr. Lee.

Based on cross study comparison of PK parameters obtained from Study 001 and 004 healthy subjects and ill-patients had similar observed C_{max} and $t_{1/2}$ values (AUC could not be compared because of the difference in time interval designated for AUC in the two studies).

Subpopulation comparison of PK data in Study 004 revealed that drug bioavailability was much lower in critically ill patients in comparison to non-critically ill patients, about 40% lower at 100 mg dose and 50% lower at 200 and 400 mg doses (refer to the PK Review for detail).

[Reviewer's comments:

For the critically ill subpopulation clinically meaningful treatment differences between IV ibuprofen and placebo were demonstrated in terms of the percentage of patients reaching temperature <101.0°F by the end of 4-hour period at 100, 200, and 400 mg doses and in terms of the degree of fever reduction during the 24-hour treatment period at 100 and 400 mg doses (refer to the Review Section 5.3.1.2 for detail) The greater variation of antipyretic response at 200 mg could be partially explained by the smaller number of critically ill patients in the 200 mg group. Lower mean baseline temperatures for critically ill treatment groups (101.7 to 102.0°F) than non-critically ill groups (102.2 to 102.9°F) might also be an important confounder. In this reviewer's opinion, the recommended antipyretic dose level for treating fever in critically ill patients should not be raised as proposed by the Applicant in the draft labeling. It is especially important to use the minimum effective dose in critically ill patients because they are at higher risk for ibuprofen toxicities due to concurrent illness and concomitant medication.]

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Study # Dates, Phase	Study Design	Sites	Treatments	N	Study Population Demographics	Use of Data	Review section
CPI-CL-001 1//01-2/01 Phase 1	Open-label, randomized, crossover (between IV and oral)	1 Australia	IVib 200 mg IVib 400 mg IVib 800 mg Single dose IV and Single dose oral	12 12 12 T: 36	Healthy Volunteers 24 M/ 12 F Mean age 29 yr (range 18-50)	ISS: single-dose exposure	4.4 7.5
CPI-CL-003 2//02-3/02 Phase 1	Randomized, double-blind, placebo- controlled, crossover	1 US	IVib 400 mg x 3 doses Placebo x 3 doses	12	Healthy Volunteers 11 M/ 1 F Mean age 28 yr (range 18-39)	ISS: three-dose exposure	7.5
CPI-CL-004 6//02-8/05 Phase 3	Randomized, double-blind, parallel, placebo- controlled	9 (7 US)	IVib 100 mg IVib 200 mg IVib 400 mg Placebo q4 hr x 6 doses	31 30 31 28 T: 120	Hospitalized febrile including critically ill 88 M/32 F Mean age 38 yr (range 18-89 yr)	Positive outcome in support of efficacy ISS: 1-day exposure	5.3 7.2-7.5
CPI-CL-006 4//02-7/02 Phase 3	Randomized, double-blind, parallel, placebo- controlled	1 Thailand	IVib 400 mg Placebo q6 hr x 3 days (12 doses)	30 30 T: 60	Hospitalized febrile with malaria 48 M/12 F Mean age 30 yr (range 18-54 yr)	Positive outcome in support of efficacy ISS: 3-day exposure	5.3 7.2-7.5
CPI-CL-008a 2//05-9/06 Phase 3	Randomized, double-blind, parallel, placebo- controlled	17 (8 US)	IVib 400 mg IVib 800 mg Placebo q6 hr x 2 days & then PRN x 3 days	134 138 134 T: 406	Post-operative pain 87 M/319 F Mean age 45 yr (range 18-69 yr)	Positive outcome in support of efficacy ISS: up to about 3- day exposure	5.3 7.2-7.5
CPI-CL-008b 2//05-9/06 Phase 3	Randomized, double-blind, parallel, placebo- controlled	10 US	IVib 800 mg Placebo q6 hr x 2 days & then PRN x 3 days	166 153 T: 319	Abdominal hysterectomy post-operative pain 319 F Mean age 42 yr (range 22-65 yr)	Positive outcome in support of efficacy ISS: up to about 2- day exposure	5.3 7.2-7.5

(b) (4)

*Studies conducted in Germany

5.2 Review Strategy

There were seven clinical studies submitted in the NDA 22-348, six studies of the current formulation (100 mg/mL in arginine (b) (4)) conducted under IND 62.605 (b) (4)

(b) (4) The original protocol submitted in (b) (4) was under an investigator's IND, which was exempted from Divisional review. Also, the study was not designed to study (b) (4)

Data from all six studies under IND 62,605 will be used for safety review. The four phase 3 studies will each be reviewed individually for efficacy.

5.3 Discussion of Individual Studies

5.3.1 Fever Study 004

5.3.1.1 Protocol

The study protocol described in Amendment 1 dated March 22, 2002 changed dramatically from the original protocol dated October 12, 2001. The study was initiated on June 11, 2002 and followed the Protocol Amendment 1. Therefore, Protocol Amendment 1, instead of the original protocol (or the difference between the two versions), is presented below.

Study CPI-CL-004 was planned as a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (6 doses in 24 hours), dose-ranging antipyretic study of Ibuprofen IV Injection (IVIb) 100 mg, 200mg, and 400mg in hospitalized febrile patients.

Eligible patients were to have been hospitalized adult patients with adequate intravenous access and a new onset (within last 7 days) of fever, documented by temperature greater than or equal to 101.0°F (38.3°C) (measured as core, tympanic, rectal, or urinary bladder catheter temperature). (Refer to the complete list of the eligibility criteria attached as the last item in the Appendix of the study review). The plan was to include at least 1/3 of the study population as critically ill patients defined as patients requiring mechanical ventilation for respiratory failure, pressor support for hypotension, or both, and at least 1/3 as non critically ill patients.

Of the eligible patients to be randomized to one of the four treatments IVIb 100 mg, 200 mg, and 400 mg and placebo, those with continued temperature elevation of $\geq 101.0^\circ\text{F}$ (38.3°C) at baseline within 15 minutes of the initial dose were to receive the 30-minute IV infusion of study drug every four hours for a total of six doses in 24 hours.

Rescue treatments were to have been allowed during post treatment period and in cases of treatment failures, where treatment failures were defined as temperature $\geq 103.0^\circ\text{F}$ (39.4°C) during the Treatment Period after a minimum of 2 hours after a dose of study medication. It was going to be up to the Investigator's discretion on the use of rescue treatment. Examples of planned rescue were acetaminophen or other antipyretic medication (other than aspirin or NSAIDs, which were not going to be allowed before Hour 168 from the start of the initial infusion) and cooling procedures such as cold packs, cooling blankets, and alcohol baths. All antipyretic treatments were planned to have been required to be documented.

Body temperature (core, tympanic, rectal, or urinary bladder catheter temperature with the same method of measurement for the same individual patient during the study) was planned to be measured before the start of infusion and every 30 minutes during the first four hours after the start of the initial infusion and then every 2 hours in the period of Hour 4 to Hour 24.

The planned primary efficacy endpoint was the percentage of patients on IVIb 400 mg (versus placebo), whose temperature was less than 101.0°F (38.3°C) at Hour 4 after the start of the initial dose. The planned secondary efficacy endpoints included the percentage of patients on IVIb 200 mg or 100 mg (versus placebo), whose temperature was less than 101.0°F (38.3°C) at Hour 4; percentage of treatment failures during the first 24 hours of treatment; time to temperature less than 101.0°F (38.3°C) during the first 24 hours of treatment. Other planned efficacy endpoints included area under the temperature versus time curve (AUC-T°) in the first four hours or first 24 hours of treatment; number and percentage of patients with a (1° x hour) per hour reduction in AUC-T°; change in temperature from Hour 0 to Hour 4 or from Hour 0 to Hour 24.

Plasma samples (1mL each) for ibuprofen concentrations were to have been collected at baseline and at 0.5, 1, 2, 3, 4, 20, 20.5, 22, and 24 hours after the beginning of the initial infusion to obtain PK profile on the initial and the last dose and to determine dose linearity.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study, where all AEs judged to be clinically significant (including laboratory abnormalities) would have been followed until resolution; vital signs at screening visit, prior to the initial dose, every two hours up to Hour 4 and every four hours up to 24 hours after the initial dose, and on Day 2, Day 3 and Day 7; transfusion monitoring at screening visit, 24 hours after the initial dose, and then daily up to Day 7; routine laboratory tests at screening visit, 24 hours after the initial dose, and on Day 3 and Day 7;

Statistical Analysis

Population for analysis

The planned intent-to-treat (ITT) population was to have included all treated patients with a baseline assessment and at least one post baseline evaluation of the primary endpoint.

The planned efficacy-evaluable population (EEP) was to have been a subset of the ITT population with no major protocol violations with regard to eligibility criteria or study conduct.

Efficacy analysis

- The planned primary efficacy parameter, the percentage of patients on IVIb 400 mg versus placebo who had a temperature reduction to <101.0°F (38.3°C) at Hour 4 after the start of the initial dose, was to be analyzed using the Cochran-Mantel-Haenszel (CMH) procedure adjusted for center using exact Chi-squared test statistic.
- All the other comparisons of percentages were to have been using the same CMH procedure.
- Planned time-to-event variables were to be analyzed by using the Logrank test, among which time to T <101.0°F (38.3°C) was going to be summarized using the Kaplan-Meier survival curves.
- Various comparisons of temperature changes were to be analyzed using an analysis of variance (ANOVA) model.
- Treatment effects were planned to be analyzed for the stratified groups: critically ill and non-critically ill patients.

Missing data management

Missing data were to have been imputed by the Last Observation Carried Forward (LOCF) when applicable. (This was not discussed in the protocol. Refer to Statistical Analysis Plan dated July 26, 2005 for detail)

Sample size

A sample size of 30 patients per treatment group in the ITT population was planned to provide 80% power for a χ^2 test to detect 37% treatment difference at the 5% level of significance based on the results of (b) (4) study.

Protocol Amendments

There were three additional protocol amendments. The amendment submitted on August 16, 2002 included addition of oral route for temperature measurements, shortening the time interval of restricting other antipyretic treatments prior to the initial dose of the study medication, from eight hours to four hours, and changing the post study assessment from Day 7 to Day 5. The amendment submitted on December 13, 2002 changed aspirin from being excluded to being restricted of use in four hours prior to and 24 hours after the initial dose of study medication. The amendment submitted on May 5, 2004 reduced the number of patients to provide PK samples from 120 to the first 98 patients.

The reviewer's brief summary of the major components of the protocol is presented in the table below.

Table 5.3.1-1 Reviewer's Summary of the Protocol

<i>Study #</i>	CPI-CL-004
<i>Objectives</i>	To study single-dose and multiple-dose antipyretic effects, tolerability and safety, and pharmacokinetic and pharmacodynamic relationship of IV ibuprofen given at 100, 200, and 400 mg doses to hospitalized patients with fever and dose response.
<i>Design</i>	Multiple-center (nine sites with 1/9 foreign), randomized, double-blind, placebo-controlled, parallel, multiple-dose (six doses in 24 hours), dose-ranging
<i>Sample population</i>	Hospitalized adult patients with adequate IV access and a new onset of fever (within 7 days of enrollment) of $\geq 101.0^{\circ}\text{F}$ (38.3°C), including $\geq 1/3$ of study population as critically ill patients (on mechanical ventilation for respiratory failure, pressor support for hypotension, or both) and $\geq 1/3$ as non critically ill patients
<i>Treatment</i>	30-minute IV infusion of ibuprofen 100 mg, 200 mg or 400 mg, or matching placebo q4 hours for a total of six doses in 24 hours
<i>Rescue medication</i>	Fever treatment such as acetaminophen or other antipyretic medication and cooling procedures such as cold packs, cooling blankets, and alcohol baths, were permitted only post treatment or during treatment in those with treatment failures [temperature $\geq 103.0^{\circ}\text{F}$ (39.4°C)]; aspirin or NSAIDs were only allowed after Hour 168
<i>Efficacy data</i>	Temperature at baseline, every 0.5 hours during Hours 0-4, and every 2 hours during Hours 4-24
<i>Efficacy parameter</i>	<p>Primary: Percentage of patients on IVIb 400 mg (versus placebo) with temperature $< 101.0^{\circ}\text{F}$ (38.3°C) at Hour 4 after the start of infusion</p> <p>Secondary:</p> <ul style="list-style-type: none"> • Percentage of patients on IVIb 200 mg and 100 mg (versus placebo, respectively) having temperature $< 101.0^{\circ}\text{F}$ (38.3°C) at Hour 4 after the start of infusion • Percentage of treatment failures [$T \geq 103.0^{\circ}\text{F}$ (39.4°C)] in Hours 0-24 • Time to temperature less than 101.0°F (38.3°C) during the 24-hour period <p>Other:</p> <ul style="list-style-type: none"> • Area under the temperature versus time curve (AUC-T$^{\circ}$) in Hours 0-4 • Area under the temperature versus time curve (AUC-T$^{\circ}$) in Hours 0-24 • Number and % of patients with degree per hour reduction in AUC-T$^{\circ}$ • Time-specific change in temperature during Hours 0-4 • Time-specific change in temperature during Hours 0-24
<i>Safety monitoring</i>	<ul style="list-style-type: none"> • Adverse events • Vital signs at screening, baseline, q2 hours in Hours 0-4, q4 hours in Hours 4-24, and on Days 2, 3 and 7; • Transfusion monitoring at screening, 24 hours after the initial dose, and daily up to Day 7; • Routine laboratory tests at screening visit, 24 hours after the initial dose, and on Days 3 and 7
<i>PK/PD</i>	Plasma samples at baseline and 0.5, 1, 2, 3, 4, 20, 20.5, 22, and 24 hours after starting initial infusion to obtain PK profile about the first and the last dose and to determine dose linearity.

5.3.1.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 120 patients enrolled who received the study medication, with an age range of 17 to 89 years and a mean of 38 years. Of the 120 patients, 48% were Caucasian, 11% were African American, 7% were Hispanic, 33% were Asian, and 27% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race (except the ratio of the Black and Hispanic in the 400 mg IVIb group), height, and weight. Critically ill patients accounted for 40% to 46% of the study population and the proportion was balanced between the treatment groups. Baseline temperature ranged from 38.9 to 39.2°C, or 102.0 to 102.5°F. There was a group mean difference of 0.27°C (39.16°C versus 38.89°C), or 0.5°F in baseline temperature between the IVIb 400mg and placebo group. No formal analysis of comparability of these demographic variables across treatment groups was performed by the Applicant.

Table 5.3.1-2 Demographics and Baseline Characteristics

Study 004 Baseline Characteristics	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)	Total (n=120)
Age (years)					
Mean (SD)	40.1 (19.0)	34.5 (15.0)	39.2 (17.2)	37.0 (19.1)	37.8 (17.5)
Median	35.0	28.0	36.0	31.0	33.5
Minimum, Maximum	18, 83	18, 68	17, 73	18, 89	17, 89
Gender, n (%)					
Male	23 (74.2)	22 (73.3)	22 (71.0)	21 (75.0)	88 (73.3)
Female	8 (25.8)	8 (26.7)	9 (29.0)	7 (25.0)	32 (26.7)
Race, n (%)					
Caucasian	13 (41.9)	15 (50.0)	16 (51.6)	14 (50.0)	58 (48.3)
Black	5 (16.1)	4 (13.3)	1 (3.2)	3 (10.7)	13 (10.8)
Hispanic	2 (6.5)	1 (3.3)	4 (12.9)	1 (3.6)	8 (6.7)
Asian	10 (32.3)	10 (33.3)	10 (32.3)	10 (35.7)	40 (33.3)
Other	1 (3.2)	0	0	0	1 (0.8)
Height (cm)					
Mean (SD)	170.3 (10.3)	170.1 (10.5)	168.2 (10.1)	168.8 (11.8)	169.4 (10.6)
Median	169.0	168.0	166.4	165.0	168.0
Minimum, Maximum	152.0, 188.0	147.0, 190.5	148.0, 188.0	153.0, 193.0	147.0, 193.0
Weight (kg)					
Mean (SD)	77.9 (32.6)	80.3 (29.2)	72.5 (23.4)	78.4 (26.6)	77.2 (28.0)
Median	69.5	69.8	67.1	68.2	69.2
Minimum, Maximum	42.0, 191.4	41.0, 150.0	42.5, 129.0	46.0, 129.9	41.0, 191.4
Baseline Temperature (°C)	39.07 (0.61)	39.07 (0.71)	39.16 (0.72)	38.89 (0.48)	
Baseline Temperature (°F)	102.3 (1.1)	102.3 (1.3)	102.5 (1.3)	102.0 (0.9)	
Highest Temp Prior to BL (°C)	39.4 (0.7)	39.4 (0.6)	39.4 (0.7)	39.2 (0.8)	39.4 (0.7)
Critically ill status n (%)					
Critically ill	14 (45%)	12 (40%)	14 (45%)	13 (46%)	53 (44%)
Non-Critically ill	17 (55%)	18 (60%)	17 (55%)	15 (54%)	67 (56%)
In ICU at BL	17 (55%)	15 (50%)	17 (55%)	16 (57%)	65 (54%)
On Mechanical Ventilation at BL	14 (45%)	12 (40%)	14 (45%)	13 (46%)	53 (44%)
On Pressor Support at BL	2(7%)	2 (7%)	0(0%)	0(0%)	4(3%)

SD = standard deviation; Min = minimum; Max = maximum; BL = baseline.

Source: Table 13 on pages 51 to 52 and Appendix Table 14.1.4 on page 110 of the report for Study 004.

Patient disposition

More than 90% of 120 treated patients completed the study. There were 11 cases of dropouts, four from the 100 mg IVIb group, two from the 400 mg IVIb group, and five from the placebo group. The reasons for dropouts included treatment failure in three cases, adverse events in three, using excluded concomitant medication in two, bleeding precaution in two, and inadequate IV access in one. The number of patient who dropped out was between none and two per treatment group for any particular reason listed as shown in the table below.

Table 5.3.1-3 Patient Disposition

Study 004 Patient Disposition	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)	Total (n=120)
All Treated Patients	31	30	31	28	120
Discontinued n (%)	4 (12.9)	0	2 (6.5)	5 (17.9)	11 (9.2)
Critically ill	3 (9.7)	0	1 (3.2)	4 (14.3)	8 (6.7)
Non-Critically ill	1 (3.2)	0	1 (3.2)	1 (3.6)	3 (2.5)
Reason for discontinuation					
Treatment failure	0	0	1 (3.2)	2 (7.1)	3 (2.5)
Adverse Event	2 (6.5)	0	0	1 (3.6)	3 (2.5)
Excluded Concomitant Medication	1 (3.2)	0	0	1 (3.6)	2 (1.7)
Bleeding Precaution	0	0	1 (3.2)	1 (3.6)	2 (1.7)
Inadequate IV Access	1 (3.2)	0	0	0	1 (0.8)

Source: Table 6 and 7 on pages 39 to 40 of the report for Study 004.

Protocol violations

The rate of protocol deviations ranged from 37% (200 mg IVIb) to 57% (placebo). About half of the cases in each treatment group were due to deviations from exclusion criteria. The rest were due to receiving excluded concomitant medication (9%), failure to discontinue CTM (clinical trial material or study medication) when rescue treatment initiated (8%), randomization error or randomization to wrong stratum (3%), and CTM administration error (3%) in the total sample population. The distribution of each type of these less frequent protocol deviations varied among the treatment groups, occurred more randomly, and did not appear to suggest a pattern of differences between the placebo and the active treatment groups. Therefore, differences in protocol deviations for less frequent reasons among treatment groups are not considered as having a major impact on study outcomes.

Table 5.3.1-4 Summary of Protocol Deviations

Study 004 Protocol deviations	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)	Total (n=120)
Total number of patients with protocol deviations	16 (52%)	11 (37%)	14 (45%)	16 (57%)	57 (46%)
Exclusion criteria	8 (26%)	7 (23%)	7 (23%)	7 (25%)	29 (24%)
Received excluded concomitant medication	5 (16%)	1 (3%)	3 (10%)	2 (7%)	11 (9%)
Failure to discontinue CTM when rescue treatment initiated	3 (10%)	2 (7%)	0	5 (18%)	10 (8%)
Randomization error, randomized to wrong stratum	0	1 (3%)	1 (3%)	2 (7%)	4 (3%)
CTM administration error	0	0	3 (10%)	0	3 (3%)

CTM = clinical trial material

Source: Table 9 on pages 41 to 42 of the report for Study 004.

Exposure

The exposure information is summarized in the table below. More than 80% (ranged from 82% to 100%) of patients in each treatment groups received all 6 doses. Drug exposure was similar between the treatment groups.

Table 5.3.1-5 Exposure

Study 004 Exposure	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
#Doses, n (%)	Distribution				Cumulative			
1	1 (3.2%)	0	1 (3.2%)	3 (10.7%)	31 (100%)	30 (100%)	31 (100%)	28 (100%)
2	0	0	0	0	30 (97%)	30 (100%)	30 (97%)	25 (89%)
3	1 (3.2%)	0	1 (3.2%)	0	30 (97%)	30 (100%)	30 (97%)	25 (89%)
4	0	0	0	1 (3.6%)	29 (94%)	30 (100%)	29 (94%)	25 (89%)
5	2 (6.5%)	0	1 (3.2%)	1 (3.6%)	29 (94%)	30 (100%)	29 (94%)	24 (86%)
6	27 (87%)	30 (100%)	28 (90%)	23 (82%)	27 (87%)	30 (100%)	28 (90%)	23 (82%)

Source: Appendix Table 14.3.5.10 on page 259 of the report for Study 004 and supplementary tables on pages 8 and 10 of the submission dated January 19, 2009.

Efficacy results

Primary efficacy endpoint:

Percentage of patients with fever reduced to T<101.0°F (38.3°C) at Hour 4 (400 mg IVIb versus placebo)

The treatment differences in terms of the percentage of patients with their fever reduced to a temperature <101.0°F during the first 4 hours after the initial dose are summarized in the table below. In comparing 400mg IVIb to placebo such differences were 45% (77% versus 32 %) in the ITT population, 49% (57% versus 8%) in the critically ill subpopulation, and 41% (94% versus 53%) in the non-critically ill subpopulation. All these treatment differences between IVIb 400 mg and placebo were statistically significant based on the Applicant's analyses.

Table 5.3.1-6a: Number (%) of Patients with Fever Reduced to T<101.0°F at Hour 4 in ITT Population

Study 004 Fever reduced to <101.0°F at Hour 4	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
Number (%) reached T<101.0°F, ITT population	20 (65%)	22 (73%)	24 (77%)	9 (32%)
Comparison against placebo, p-value of CMH test	p=0.0138	p=0.0018	p=0.0005	
Number (%) reached T<101.0°F, Critically ill	10 (71%)	6 (50%)	8 (57%)	1 (8%)
Comparison against placebo, p-value of CMH test	p=0.010	p=0.0211	p=0.0075	
Number (%) reached T<101.0°F, Non critically ill	10 (59%)	16 (89%)	16 (94%)	8 (53%)
Comparison against placebo, p-value of CMH test	p=0.7585	p=0.0245	p=0.0089	

T = temperature; ITT = intent-to-treat; CMH = Cochran-Mantel-Haenszel

Source: Appendix Table 14.2.3 on pages 129-130 of the report for Study 004.

Using T<38.3.0°C as a cut point the treatment differences between IVIb 400 mg and placebo for the entire sample population, critically ill subpopulation, and non-critically ill subpopulation, respectively, were statistically significant. The findings were confirmed by the statistical reviewer Dr. Jonathan Norton's analyses (refer to the Evaluation of Efficacy Section of the Statistical Review for detail).

Table 5.3.1-6b: Number (%) of Patients with Fever Reduced to T<38.3.0°C at Hour 4 in ITT Population

Study 004 Fever reduced to <38.3.0°C at Hour 4	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
Number (%) reached T<38.3.0°C, ITT population	19 (61%)	21 (70%)	24 (77%)	9 (32%)
Comparison against placebo by CMH test	p=0.0264	p=0.0043	p=0.0005	
<i>Asymptotic p based on statistical reviewer's analyses</i>	<i>p=0.0328</i>	<i>p=0.0079</i>	<i>p=0.0006</i>	
<i>Exact p based on statistical reviewer's analyses</i>	<i>p=0.0581</i>	<i>p=0.0147</i>	<i>p=0.0011</i>	
Number (%) reached T<38.3.0°C, Critically ill	9 (64%)	6 (50%)	8 (57%)	1 (8%)
Comparison against placebo, p-value of CMH test	p=0.028	p=0.0211	p=0.0075	
<i>Exact p based on statistical reviewer's analyses</i>	<i>p=0.064</i>	<i>p=0.0533</i>	<i>p=0.0175</i>	
Number (%) reached T<38.3.0°C, Non critically ill	10 (59%)	15 (83%)	16 (94%)	8 (53%)
Comparison against placebo, p-value of CMH test	p=0.7585	p=0.0660	p=0.0089	
<i>Exact p based on statistical reviewer's analyses</i>	<i>p=1.0000</i>	<i>p=0.1264</i>	<i>p=0.0220</i>	

T = temperature; ITT = intent-to-treat; CMH = Cochran-Mantel-Haenszel

Source: Appendix Table 14.2.4 on pages 131-132 of the report for Study 004 and Evaluation of Efficacy Section of Statistical Review.

Secondary efficacy endpoints:

Percentage of patients with fever reduced to T<101.0°F (38.3°C) at Hour 4 (200 mg IVIb versus placebo and 100 mg IVIb versus placebo)

The differences in percentage of patients with their fever reduced to a temperature <101.0°F during the first 4 hours, based on the comparison between 200 mg IVIb and placebo, were 41% (73% versus 32 %) in the ITT population, 42% (50% versus 8%) in the critically ill subpopulation, and 36% (89% versus 53%) in the non-critically ill subpopulation, and were all statistically significant based on the Applicant's analyses.

The differences in comparison between 100 mg IVIb and placebo were 33% (65% versus 32 %) in the ITT population, 63% (71% versus 8%) in the critically ill subpopulation, and 6% (59% versus 53%) in the non-critically ill subpopulation. Statistically significant differences were shown for the ITT population and the critically ill subpopulation but not for non-critically ill subpopulation based on the Applicant's analyses.

Using $T < 38.3.0^{\circ}\text{C}$ as a cut point one patient from each of the following study group/subgroup: IVIb 100 mg group, IVIb 100 mg critically ill group, and IVIb 200 mg group, switched from "treatment success" to "treatment failure" status. The results of statistical testing for the pairwise comparisons between each of the three groups and placebo had borderline significance based on Dr. Norton's reanalysis of data using $T < 38.3.0^{\circ}\text{C}$ as a cut point.

Secondary efficacy endpoints:

Percentage of patients identified as Treatment Failures and Time to Treatment Failure during the 24-hour treatment period

Patients with temperature reaching $\geq 103.0^{\circ}\text{F}$ (39.4°C) should have been recorded as treatment failure after a 2-hour waiting period following any dose according to the protocol and the 2-hour restriction was omitted in the Statistical Analysis Plan by error. The results for the percentage of treatment failure with and without 2-hour restriction are summarized in the table below. In either case about 30% placebo patients were identified as treatment failures, more than twice of the percentage recorded in the 400 mg IVIb group.

Table 5.3.1-7 Number (%) of Patients as Treatment Failures in 24 Hours in ITT Population

Study 004 Number (%) of treatment failure	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
$\geq 103.0^{\circ}\text{F}$ (39.4°C) at ≥ 2 hours post a dose*	8 (26%)	4 (13%)	4 (13%)	9 (32%)
Comparison against placebo, p-value of CMH test	p=0.595	p=0.089	p=0.078	
$\geq 103.0^{\circ}\text{F}$ (39.4°C) at any time post a dose (SAP)*	9 (29%)	7 (23%)	4 (13%)	10 (36%)
Comparison against placebo, p-value of CMH test	p=0.587	p=0.305	p=0.041	

T = temperature; CMH = Cochran-Mantel-Haenszel; SAP = Statistical Analysis Plan.

*Note: There was a two-hour waiting period after each dose for defining treatment failure in the original protocol, which was omitted in the Statistical Analysis Plan by error.

Source: Appendix Table 14.2.6 on page 134 of the report for Study 004.

The Time to Treatment Failure during the 24-hour treatment period was analyzed without 2-hour restriction applied in recording treatment failure and was twice as faster in the placebo group than the 400 mg IVIb and 200 mg IVIb groups.

Table 5.3.1-8 Time to Treatment Failures during the 24-Hour Period in ITT Population

Study 004 Time to treatment failure (hour)	100 mg IVIb (n=9 of 31)	200 mg IVIb (n=7 of 30)	400 mg IVIb (n=4 of 31)	Placebo (n=10 of 28)
Mean (SE)	7.39 (1.39)	10.29 (3.25)	10.75 (2.75)	5.70 (1.97)
Median	8.00	8.00	12.00	2.75
Comparison against placebo, p-value of CMH test	p=0.7544	p=0.2221	p=0.3899	

SE = standard error; CMH = Cochran-Mantel-Haenszel.

Source: Appendix Table 14.2.8 on page 136 of the report for Study 004.

Secondary efficacy endpoints:

Time to fever reduction reaching $T < 101.0^{\circ}\text{F}$ (38.3°C) during the 24-hour treatment period

A total of eight patients: one on 100mg IVIb, two on 200mg IVIb, one on 400mg IVIb, and four on placebo, never reached temperature $< 101.0^{\circ}\text{F}$ (38.3°C) by the end of 24 hours and therefore, were excluded from the analysis. The treatment differences in time to $T < 101.0^{\circ}\text{F}$ were 4.8 hours (3.7 hours versus 8.5 hours) in comparison of 100 mg IVIb to placebo, 4.1 hours (4.4 hours versus 8.5 hours) in comparison of 200 mg IVIb to placebo, and 4.9 hours (3.6 hours versus 8.5 hours) in comparison of 400 mg IVIb to placebo, and were all statistically significant as shown in the table below.

Table 5.3.1-9 Time to Temperature <101.0°F (38.3°C) in Hours 0-24 in ITT Population

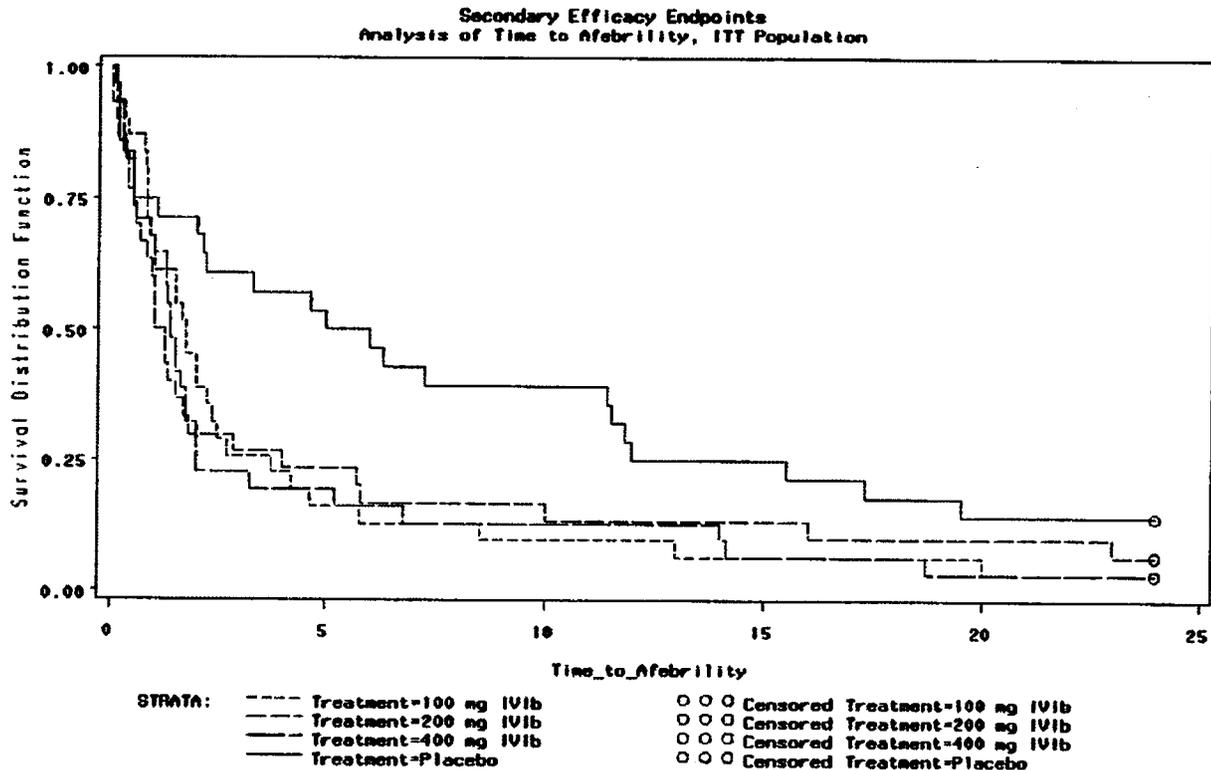
Study 004 Time to T<101.0°F (38.3°C) in 24 hours	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
Number (%) with T<101.0°F (38.3°C) at Hours 24	30 (97%)	28 (93%)	30 (97%)	24 (86%)
Time to T<101.0°F (38.3°C) by Hours 24				
Mean (SD) (hour)	3.67 (1.00)	4.40 (1.34)	3.61 (1.06)	8.47 (1.61)
Median (hour)	1.75	1.13	1.39	5.50
Comparison against placebo, p-value of Log-rank test	p=0.0187	p=0.0476	p=0.0137	

T = temperature; SD = standard deviation.

Source: Appendix Table 14.2.10 on page 138 of the report for Study 004.

Figure 5.3.1-1 Time to Temperature <101.0°F (38.3°C) in 24 hours, ITT

Figure 2. Time to Afebrility, ITT Population



Source: Figure 2 on page 59 of the report for Study 004.

Additional analysis requested by the reviewer:

Time to fever reduction reaching T<100.0°F (37.8°C) during the 24-hour treatment period

A majority of patients (83-87% in the active treatment groups and 64% in the placebo group) reached temperature <100.0°F (37.8°C) by the end of 24 hours. The treatment differences in time to T<100.0°F were 5.0 hours (8.3 hours versus 13.3 hours) in comparison of 100 mg IVIb to placebo, 5.6 hours (7.7 hours versus 13.3 hours) in comparison of 200 mg IVIb to placebo, and 7.2 hours (6.1 hours versus 13.3 hours) in comparison of 400 mg IVIb to placebo, and were all statistically significant as shown in the table below.

Table 5.3.1-10 Time to Temperature <100.0°F (37.8°C) in Hours 0-24 in ITT Population

Study 004 Time to T<100.0°F (37.8°C) in 24 hours	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
Number (%) with T<100.0°F (37.8°C) at Hours 24	27 (87%)	25 (83%)	27 (87%)	18 (64%)
Time to T<100.0°F (37.8°C) by Hours 24				
Mean (SD) (hour)	8.28 (1.37)	7.70 (1.45)	6.06	13.27 (1.70)
Median (hour)	4.67	2.75	3.63	13.24

Comparison against placebo, p-value of Log-rank test	0.0232	0.0295	0.0101	
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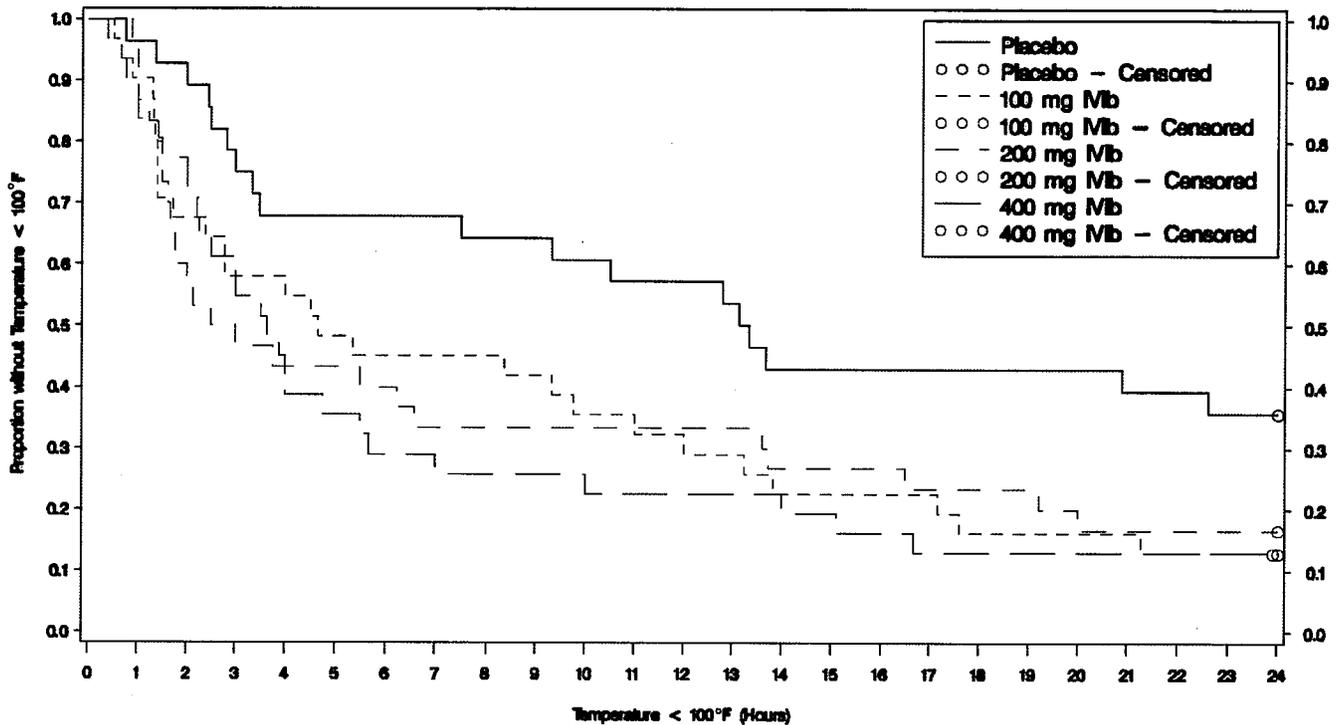
T = temperature; SD = standard deviation.

Source: Supplement Table on page 3 of the submission dated March 20, 2009.

Figure 5.3.1-2 Time to Temperature <100.0°F (37.8°C) in 24 hours, ITT

Figure 4.1.1

Time to Temperature < 100°F (37.8°C) in 24 hours
Intent-to-Treat Population



Source: Figure 4.1.1 on page 3 of the submission dated March 20, 2009.

Time to fever reduction reaching T<99°F (37.2°C) during the 24-hour treatment period

A majority of patients (61-77% in the active treatment groups and 61% in the placebo group) reached temperature <100.0°F (37.8°C) by the end of 24 hours. The treatment differences in time to T<100.0°F were 1.2 hours (15.1 hours versus 16.3 hours) in comparison of 100 mg IVIb to placebo, 5.2 hours (11.1 hours versus 16.3 hours) in comparison of 200 mg IVIb to placebo, and 5.0 hours (11.3 hours versus 16.3 hours) in comparison of 400 mg IVIb to placebo, and none were statistically significant as shown in the table below.

Table 5.3.1-11 Time to Temperature <99°F (37.2°C) in Hours 0-24 in ITT Population

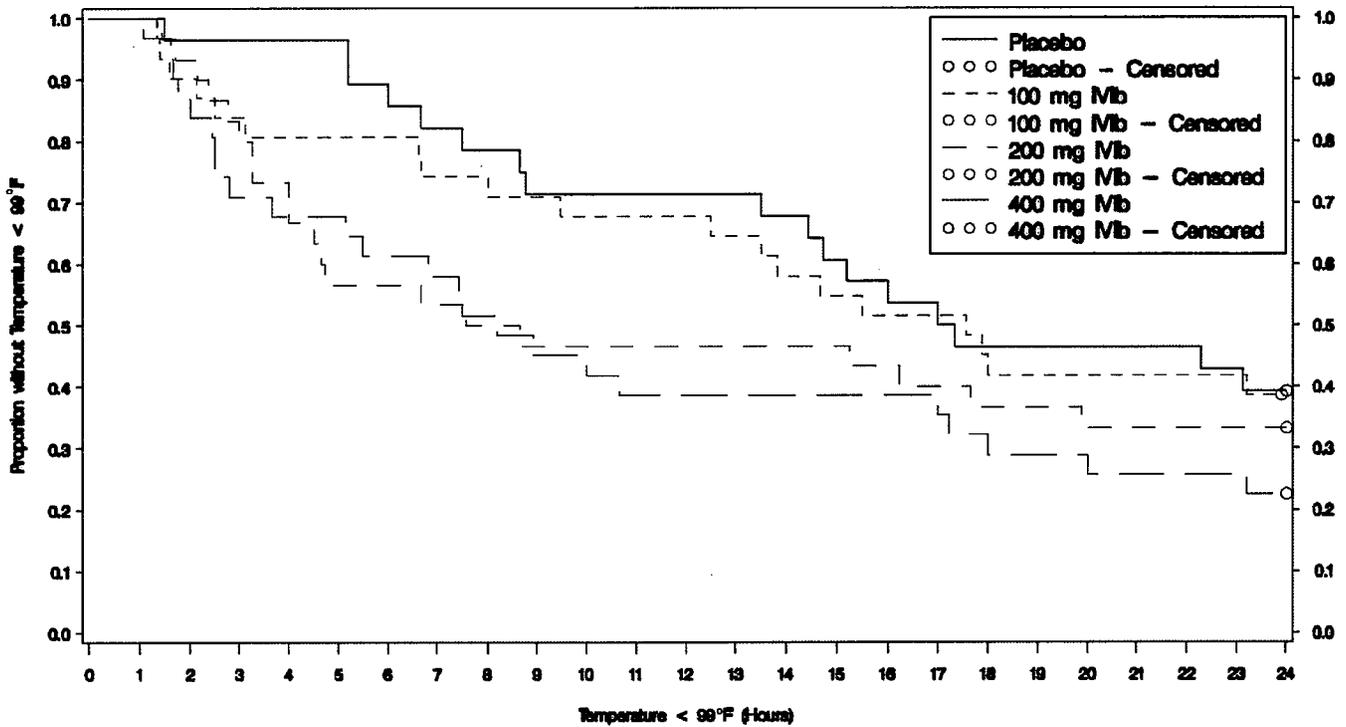
Study 004	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	Placebo (n=28)
Time to T<99°F (37.2°C) in 24 hours				
Number (%) with T<99°F (37.2°C) at Hours 24	19 (61%)	20 (67%)	24 (77%)	17 (61%)
Time to T<99°F (37.2°C) by Hours 24				
Mean (SD) (hour)	15.09 (1.53)	11.09 (1.45)	11.29 (1.58)	16.34 (1.41)
Median (hour)	17.55	8.11	8.18	17.17
Comparison against placebo, p-value of Log-rank test	0.8134	0.2444	0.0610	

T = temperature; SD = standard deviation.

Source: Supplement Table on page 4 of the submission dated March 20, 2009.

Figure 5.3.1-3 Time to Temperature <99°F (37.2°C) in 24 hours, ITT

Figure 4.1.2
Time to Temperature < 99°F (37.2°C) in 24 hours
Intent-to-Treat Population



Source: Figure 4.1.2 on page 4 of the submission dated March 20, 2009.

Additional analysis:

Temperature decreases in 4 hours after the initial dose and in 24 hours after one-day treatment

The mean temperature decreases were 1.9, 2.1, and 2.7°F in response to the initial dose of IV Ib 100 mg, 200 mg, and 400 mg versus 0.6°F for placebo in the first 4 hours and 3.1, 3.1, and 3.5°F for active treatments versus 2.1°F for placebo during the 24-hour period as patients being treated with 6 doses of IV infusions. The treatment differences between each of the three IV Ib doses and placebo were 1.3, 1.5 and 2.1°F, respectively, further temperature reduction in 4 hours and 1.0, 1.1, and 1.4°F further temperature reduction in 24 hours. All these results are considered clinically meaningful.

Table 5.3.1-12 Fever Reduction after the Initial Dose and One-Day Treatment in ITT Population

Study 004	100 mg IV Ib (n=31)	200 mg IV Ib (n=30)	400 mg IV Ib (n=31)	Placebo (n=28)
Fever reduction in 4 hours & in 24 hours				
Temperature decrease in 4 hours (°F)				
Mean (SD)	1.89 (1.30)	2.09 (1.49)	2.67 (1.61)	0.61 (1.77)
Median	1.98	2.16	2.70	0.35
Minimum	-0.1	-0.1	0.0	-2.9
Maximum	5.0	5.0	5.4	4.0
<i>Difference from Placebo</i>	<i>1.27</i>	<i>1.48</i>	<i>2.05</i>	
Dunnett's 95% Simultaneous Confidence Limits for comparison with Placebo	0.32, 2.23	0.51, 2.44	1.10, 3.01	
Temperature decrease in 24 hours (°F)				
Mean	3.07 (1.95)	3.12 (1.88)	3.45 (2.02)	2.07 (2.37)
Median	2.88	2.60	2.88	1.28
Minimum	-0.2	0.5	0.5	-1.0
Maximum	6.5	6.7	9.0	6.5
<i>Difference from Placebo</i>	<i>0.99</i>	<i>1.05</i>	<i>1.37</i>	
Dunnett's 95% Simultaneous Confidence Limits for	-0.28, 2.27	-0.24, 2.33	0.10, 2.65	

comparison with Placebo				
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Source: Appendix Table 14.2.13 on page 141 of the report for Study 004.

Additional analysis:

Time-specific response during the 24-hour treatment period in ITT population and critically ill patients

The mean temperatures over time in 24 hours for the ITT population are summarized in the table below and presented in the graph following the table. The treatment differences were basically consistent throughout the 24-hour evaluation period. Based on the end-of dosing (4, 8, 12, 16, 20, and 24 hours) temperature measurements, treatment differences were 1.6-1.9°F in the first 12 hours and 0.9 to 1.6°F in the second 12 hours between 400 mg IVIb and placebo, 1.1-1.2°F in the first 12 hours and 0.5 to 0.8°F in the second 12 hours between 200 mg IVIb and placebo, and 0.5-0.9°F during the 24-hour period between 100 mg IVIb and placebo. An end-of dosing treatment difference of at least 1°F from placebo was shown in the first 12 hours for 200 mg dose and during most of the 24 hour for 400 mg dose. Treatment differences between 400 mg and 200 mg IVIb were in a range of 0.5-0.9°F up to Hour 20, based on the end-of dosing temperature measurements.

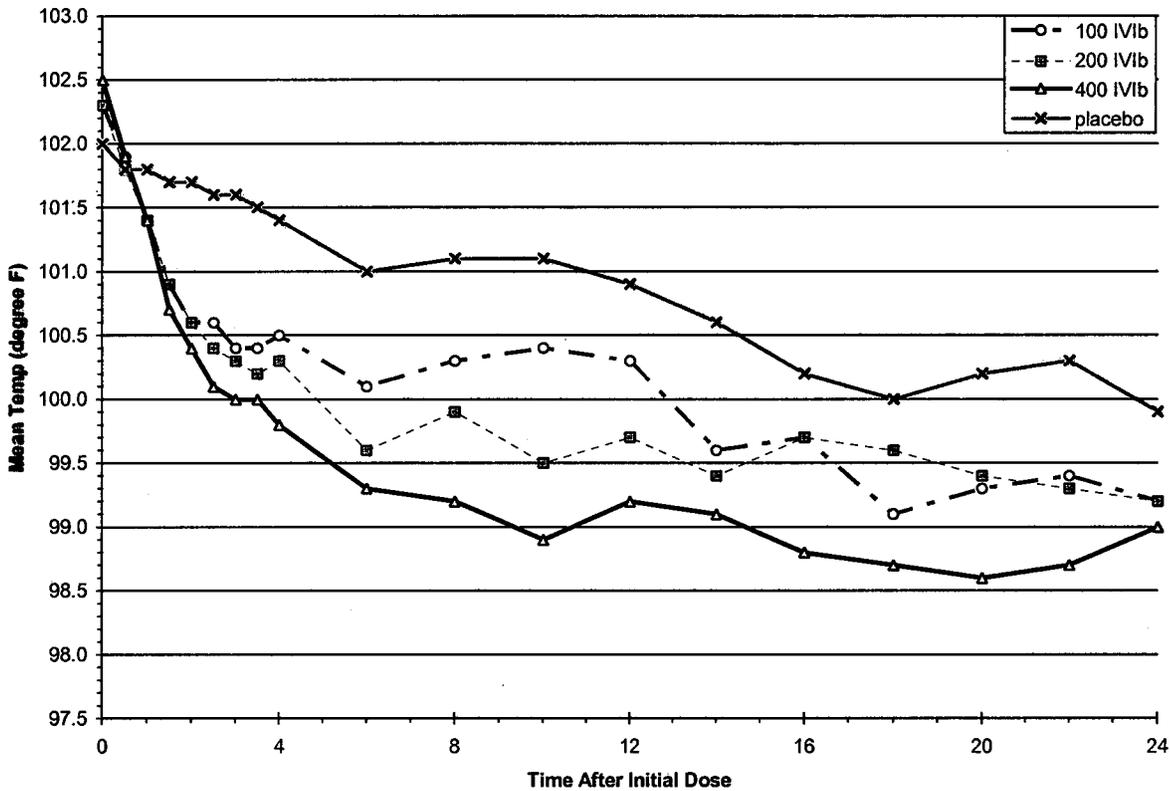
Table 5.3.1-13 Time-Specific Temperature Measurements (°F) in 1st 24 Hours, ITT

Temp (°F)	0	0.5	1	1.5	2	2.5	3	3.5	4	6	8	10	12	14	16	18	20	22	24
100 IVIb	102.3	101.9	101.4	100.9	100.6	100.6	100.4	100.4	100.5	100.1	100.3	100.4	100.3	99.6	99.7	99.1	99.3	99.4	99.2
200 IVIb	102.3	101.8	101.4	100.9	100.6	100.4	100.3	100.2	100.3	99.6	99.9	99.5	99.7	99.4	99.7	99.6	99.4	99.3	99.2
400 IVIb	102.5	101.9	101.4	100.7	100.4	100.1	100.0	100.0	99.8	99.3	99.2	98.9	99.2	99.1	98.8	98.7	98.6	98.7	99.0
placebo	102.0	101.8	101.8	101.7	101.7	101.6	101.6	101.5	101.4	101.0	101.1	101.1	100.9	100.6	100.2	100.0	100.2	100.3	99.9
Difference from placebo																			
100 IVIb					1.1				0.9	0.9	0.8	0.7	0.6	1	0.5	0.9	0.9	0.9	0.7
200 IVIb					1.1				1.1	1.4	1.2	1.6	1.2	1.2	0.5	0.4	0.8	1	0.7
400 IVIb					1.3				1.6	1.7	1.9	2.2	1.7	1.5	1.4	1.3	1.6	1.6	0.9
Difference between 400 mg and 200 mg doses																			
									0.5	0.3	0.7	0.6	0.5	0.3	0.9	0.9	0.8	0.6	0.2

Source: Appendix Tables 14.2.27-14.2.30 on pages 159 to 165 of the report for Study 004.

Figure 5.3.1-4 Time-Specific Temperature Measurements (°F) in 1st 24 Hours, ITT

Temperature by Treatment, ITT Population



The mean temperatures over time in 24 hours for critically ill patients are also summarized in the table below and presented in the graph following the table. There were greater variations in terms of the treatment differences from placebo in the critically ill patients. At the first end-of dosing time point (Hour 4) treatment differences from placebo were 1.3 to 1.5°F for the three IVib groups. An end-of dosing treatment difference of at least 1°F from placebo was shown more consistently in the first 12 hours for the 100 mg IVib dose and in the second 12 hours for the 400 mg IVib dose but not for the 200 mg IVib dose.

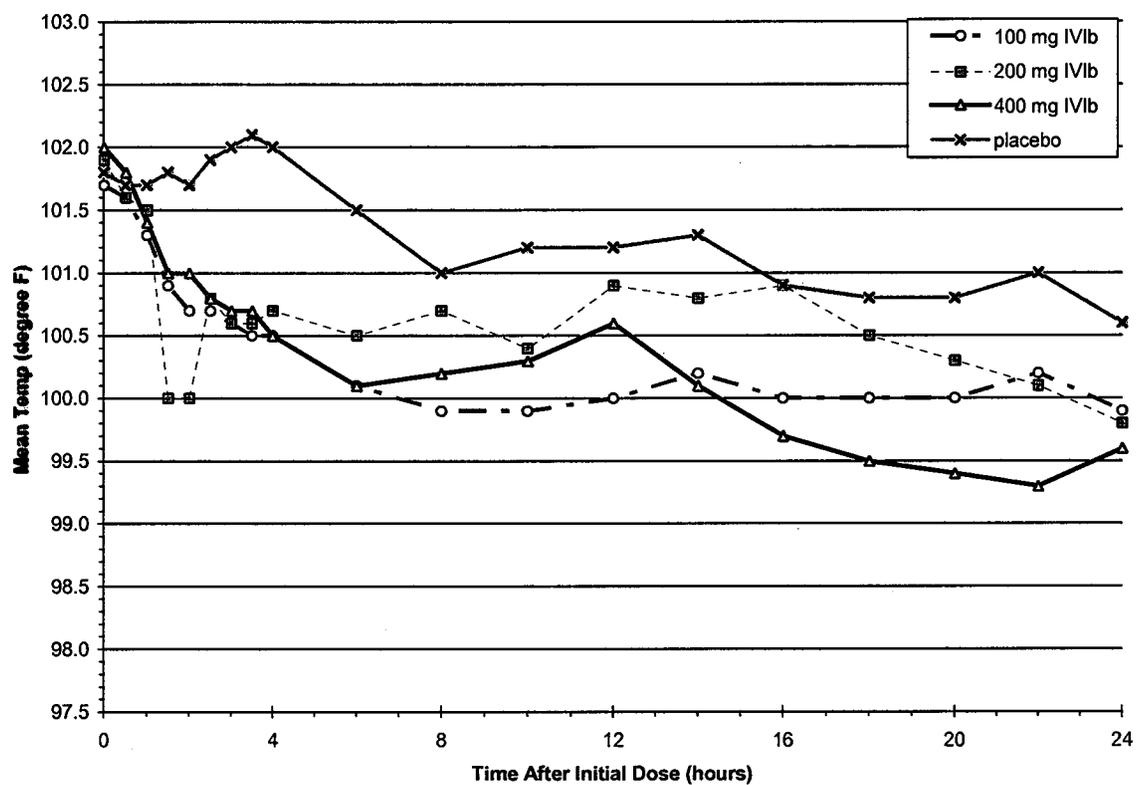
Table 5.3.1-14 Time-Specific Temperature Measurements (°F) in 1st 24 Hours, Critically Ill Patients

Temp (°F)	0	0.5	1	1.5	2	2.5	3	3.5	4	6	8	10	12	14	16	18	20	22	24
100 IVib	101.7	101.6	101.3	100.9	100.7	100.7	100.6	100.5	100.5	100.1	99.9	99.9	100.0	100.2	100.0	100.0	100.0	100.2	99.9
200 IVib	101.9	101.6	101.5	100.0	100.0	100.8	100.6	100.6	100.7	100.5	100.7	100.4	100.9	100.8	100.9	100.5	100.3	100.1	99.8
400 IVib	102.0	101.8	101.4	101.0	101.0	100.8	100.7	100.7	100.5	100.1	100.2	100.3	100.6	100.1	99.7	99.5	99.4	99.3	99.6
placebo	101.8	101.7	101.7	101.8	101.7	101.9	102.0	102.1	102.0	101.5	101.0	101.2	101.2	101.3	100.9	100.8	100.8	101.0	100.6
Difference from placebo																			
100 IVib					1				1.5	1.4	1.1	1.3	1.2	1.1	0.9	0.8	0.8	0.8	0.7
200 IVib					1.7				1.3	1	0.3	0.8	0.3	0.5	0	0.3	0.5	0.9	0.8
400 IVib					0.7				1.5	1.4	0.8	0.9	0.6	1.2	1.2	1.3	1.4	1.7	1
Difference between 400 mg and 200 mg doses																			
									0.2	0.4	0.5	0.1	0.3	0.7	1.2	1	0.9	0.8	0.2

Source: Appendix Tables 14.2.27-14.2.30 on pages 159 to 167 of the report for Study 004.

Figure 5.3.1-5 Time-Specific Temperature Measurements (°F) in 1st 24 Hours, Critically Ill Patients

Temperature by Treatment, Critically Ill



5.3.1.3 Summary of Findings and Discussion

Study conduct

The treatment groups in Study 004 were generally balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to the proportion of critically ill patients. Baseline temperature ranged from 38.9 to 39.2°C, or 102.0 to 102.5°F for the four treatment groups. There was a group mean difference of 0.73°C (39.16°C versus 39.89°C) between the IVIb 400mg and placebo group (pending test for statistical significance).

Dropouts (due to treatment failure, adverse events, using excluded medication, bleeding precaution, and inadequate IV access) accounted for <10% (11/120) of the study population. The number of patient dropped out for any specific reason ranged between none and two per treatment group.

The rate of protocol deviation was close to 50% on the average. About half of the cases in each treatment group were due to deviations from the exclusion criteria. The distribution of the rates of occurrence for other types of protocol deviations varied among the treatment groups and did not suggest a pattern of association with the active treatments versus placebo. Therefore, they are not considered as having a differential impact on study outcomes.

Efficacy

The efficacy results are summarized in the table below in terms of treatment differences from placebo to examine the effect sizes for clinical significance.

Treatment differences between IVIb 400 mg and placebo were shown in terms of 40-50% (statistically significant differences by primary analyses, which were confirmed by Dr. Norton's analyses) more patients, including those who were identified as critically ill, reaching a fever reduction to temperature <101.0°F (38.3°C) in the first 4 hours; about 5 hours earlier on the average to reach T<101.0°F and 7 hours earlier to reach T<100.0°F (37.8°C) during 24 hours; a mean temperature reduction by 2 more degrees (°F) in the first 4 hours and by 1.4 more degrees (°F) during 24 hours; time-specific end-of-dosing temperature reductions by 1-2 more degrees (°F) in the 400 mg group and by 0.5-1.5 more degrees (°F) in the critically ill patients on IVIb 400 mg during 24 hours.

Treatment differences between IVIb 200 mg and placebo were shown in terms of 41% more patients (42% in the critically ill subgroup and 36% in the none critically ill subgroup) reaching a fever reduction to temperature <101.0°F (38.3°C) in the first 4 hours; about 4 hours earlier on the average to reach T<101.0°F and 6 hours earlier to reach T<100.0°F (37.8°C) during 24 hours; a mean temperature reduction by 1.5 (°F) more degrees in the first 4 hours and by 1.0 (°F) more degree during 24 hours. The differences in the time-specific end-of-dosing temperature reductions were 0.5 to 1.2°F in comparison of the 200 mg treatment to placebo and 0-1.3°F in comparison of the critically ill patients in the two treatment groups.

Treatment differences between IVIb 100 mg and placebo were shown in terms of 33% more patients (63% more in the critically ill sub group and only 6% more in the none critically ill patients) reaching a fever reduction to temperature <101.0°F (38.3°C) in the first 4 hours; about 5 hours earlier on the average to reach T<101.0°F and T<100.0°F (37.8°C) during 24 hours; a mean temperature reduction by 1.3 (°F) more degrees in the first 4 hours and by 1.0 (°F) more degree during 24 hours. The differences in the time-specific end-of-dosing temperature reductions were 0.5 to 0.9°F in comparison of the 200 mg treatment to placebo and 0.7-1.5°F in comparison of the critically ill patients in the two treatment groups.

Table 5.3.1-13 Summary of Efficacy Findings

Study 004 Efficacy summary	Effect size of treatment differences from placebo		
	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)
% with T<101.0°F by Hour 4, ITT	33%**	41%*	45%*
% with T<101.0°F by Hour 4, critically ill	63%**	42%**	49%*
% with T<101.0°F by Hour 4, non critically ill	6%	36%*	41%*
% with T<101.0°F (38.3°C) by Hour 24	11%	7%	11%
Time to T<101.0°F (38.3°C) by Hour 24 (h)	4.80*	4.07*	4.86*
% with T<100.0°F (37.8°C) by Hour 24	23%	19%	23%
Time to T<100.0°F (37.8°C) by Hour 24 (h)	4.99*	5.57*	7.21*
% with T<99°F (37.2°C) by Hour 24	0	6%	16%
Time to T<99°F (37.2°C) by Hour 24 (h)	1.25	5.25	5.05
Mean temperature reduction in Hours 0-4 (°F)	1.27	1.48	2.05
Mean temperature reduction in Hours 0-24 (°F)	0.99	1.05	1.37
Time-specific end-of dosing temperature in Hours 0-24 (°F), ITT	0.6-0.9 (Hr 4-12) 0.5-0.9 (Hr 16-24)	1.1-1.2 (Hr 4-12) 0.5-0.8 (Hr 16-24)	1.6-1.9 (Hr 4-12) 0.9-1.7 (Hr 16-24)
Time-specific end-of dosing temperature in Hours 0-24 (°F), critically ill	1.2-1.5 (Hr 4-12) 0.7-0.9 (Hr 16-24)	0.3-1.3 (Hr 4-12) 0.0-0.8 (Hr 16-24)	0.6-1.5 (Hr 4-12) 1.0-1.4 (Hr 16-24)

* Statistically significant difference.

** Statistically significant difference by the Applicant's analyses and borderline significant difference by Dr. Norton's analyses using T<38.3.0°C as a cut point.

Refer to all the efficacy tables in this section.

Dosing interval

The end-of-dosing assessments of the initial dose and time-specific end-of-dosing assessments in 24 hours combined with overall multiple-dose efficacy results support a dosing interval of every 4 hours for fever indication.

5.3.1.4 Conclusion

Ibuprofen injection at 400 mg, 200 mg, and 100 mg given every four hours is considered effective in treating fever in hospitalized patients, including critically ill patients, based on the demonstration of statistically significant and clinically meaningful treatment differences in Study 004.

5.3.1.5 Appendix

Eligibility Criteria in Study 004

Inclusion Criteria

Patients were going to be required to meet all of the following criteria to be eligible for this study:

1. Were hospitalized
2. Had new (not chronic, within last 7 days) onset of fever, documented by temperature greater than or equal to 101.0°F (38.3°C) (The method of temperature measurement could be core, tympanic, rectal, or urinary bladder catheter temperature; the route of temperature measurement used immediately before randomization should have been used immediately before dosing and for all temperature measurements during the Treatment Period.)
3. Had adequate intravenous access
4. Had the ability to understand the requirements of the study, were willing to provide written informed consent (as evidenced by signature on an informed consent document approved by an Institutional Review Board [IRB]), and agreed to abide by the study restrictions and to return for the required assessments (If the patient was incapacitated, informed consent would have been sought from a legally acceptable representative.)

Exclusion Criteria

Patients were going to be excluded from this study if they had met any of the following criteria:

1. Were less than 18 years of age
2. Had received antipyretic drug therapy (*e.g.*, aspirin, other NSAIDs, or acetaminophen) within 8 hours before dosing
3. Had any history of allergy or hypersensitivity to any component of IVIb, NSAIDs (including aspirin), or COX-2 inhibitors
4. Were pregnant or nursing
5. Had a history of severe head trauma that required current hospitalization, intracranial surgery, or stroke within the previous 30 days, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesions
6. Weighed less than 40 kg
7. Had a history of congenital bleeding diatheses (*e.g.*, hemophilia) or any active clinically significant bleeding, or had underlying platelet dysfunction, including (but not limited to) idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, or congenital platelet dysfunction
8. Had gastrointestinal bleeding that had required medical intervention within the previous 6 weeks (unless definitive surgery has been performed)
9. Had a platelet count less than 30,000/mm³
10. Were receiving full dose anticoagulation therapy or Activated Protein C within 6 hours before dosing (Prophylaxis with subcutaneous heparin IS acceptable.)
11. Had fever secondary to blood or drug reaction
12. Had an expected life span of less than 14 days because of imminent withdrawal of life support or severity of illness
13. Were receiving treatment with corticosteroids (Patients who were expected to receive corticosteroids during the Treatment Period or through Hour 168 of the Post-treatment Period were not eligible.)
14. Had neurogenic fever
15. Were on dialysis, had oliguria or creatinine greater than 3.0 mg/dL, or were receiving nephrotoxic drugs
16. Had major surgery within the past 12 hours, unless adequate hemostasis had been achieved
17. Had received another investigational drug within the past 30 days
18. Became afebrile (temperature below 101.0°F [38.3°C]) before dosing and had not redeveloped fever entry criteria during this hospitalization
19. Were otherwise unsuitable for the study, in the opinion of the Investigator

5.3.2 Fever Study 006

5.3.2.1 Protocol

Study CPI-CL-006 was planned as a single-center (in Thailand), randomized, double-blind, placebo-controlled, parallel, multiple-dose (every 6 hours for up to 5 days), antipyretic study of Ibuprofen IV Injection (IVIb) 400mg in adult febrile patients hospitalized for the treatment of uncomplicated malaria.

Eligible patients were to have been hospitalized adult patients with a clinical diagnosis of uncomplicated malaria confirmed by laboratory testing, who experienced fever greater than 38.0°C (100.4°F) by tympanic temperature measurement within 12 hours prior to receiving the study drug (refer to the complete list of the eligibility criteria attached as the last item in the Appendix of the study review).

Eligible patients were to have been randomly assigned to receive either IVIb 400 mg or placebo 30-minute IV infusion every six hours for the first three days (12 doses) followed by q6-hour treatment as needed for temperature > 38.0°C (100.4°F) for two more days.

Rescue treatments were to have been allowed during the post treatment period and in cases of treatment failure, during the study, where treatment failures were defined as temperature $\geq 106.0^{\circ}\text{F}$ (41.1°C) ≥ 2 hours after the initial dose or $\geq 103.0^{\circ}\text{F}$ (39.4°C) ≥ 2 hours after the subsequent doses in patients with uncomplicated malaria. It was going to be up to the Investigator's discretion on the use of rescue treatment. Examples of planned rescue listed in the protocol were cold packs, cooling blankets, and alcohol baths. All antipyretic treatments were to have been required to be documented.

Body temperature by tympanic measurement was planned to be recorded before the start of infusion, hourly during the first four hours after the start of the initial dose, and every four hours during the rest of the treatment period.

The planned primary efficacy endpoint was the fever reduction measured by area under the temperature curve [above the temperature line of 37.0°C (98.6°F)] within the first 24 hours of treatment. The planned secondary efficacy endpoints included fever reduction measured by area under the temperature curve within the first 4 hours of treatment and area under the curve in the treatment period of 24 to 72 hours, respectively; the number and percentage of treatment failures; parasite clearance time defined as the time from the initial treatment to the time of the first negative result.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study, where all AEs judged to be clinically significant (including laboratory abnormalities) were to have been followed until resolution; vital signs at baseline, every four hours during the treatment period, and on Days 7, 14, and 21; routine laboratory tests at screening visit, daily during the treatment period, and on Days 7, 14, and 21.

Statistical Analysis

Population for analysis

The planned intent-to-treat (ITT) population was to have included all treated patients with a baseline assessment and at least one post baseline evaluation of the primary endpoint.

The planned efficacy-evaluable population (EEP) was to have been a subset of the ITT population with no major protocol violations with regard to eligibility criteria or study conduct and no two (or more) consecutive temperature measurements missing within the first 24 hours of the treatment period. Only EEP was planned to have been used in the primary and secondary efficacy analyses

Efficacy analysis

- The planned primary efficacy parameter, the area under the temperature curve within the first 24 hours of treatment, was to be analyzed using the linear trapezoidal rule.
- All the other efficacy parameters defined by area under the temperature curves were to have been using the same linear trapezoidal rule.
- The number and percentages of treatment failure were to be analyzed using the CMH procedure.
- The comparison of parasite clearance time was planned to use the rank test.

Missing data management

Missing data were to have been imputed by the Last Observation Carried Forward (LOCF).

Sample size

A sample size of 30 patients per treatment group in the ITT population was planned to provide 90% power for detecting an estimated difference of 12°C x hour in AUC-T° for the first 24 hours at the 5% level of significance.

Protocol Amendments

There were no protocol amendments.

The reviewer's brief summary of the major components of the protocol is presented in the table below.

Table 5.3.2-1 Reviewer's Summary of the Protocol

<i>Study #</i>	CPI-CL-006
<i>Objectives</i>	To study single-dose and multiple-dose antipyretic effects, and tolerability and safety of IV ibuprofen 400 mg in treating fever in hospitalized patients with uncomplicated malaria.
<i>Design</i>	Single-center (Thailand), randomized, double-blind, placebo-controlled, parallel, multiple-dose (five-day: four doses per day for three days and as needed for two more days)
<i>Sample population</i>	Hospitalized adult patients with a clinical diagnosis of uncomplicated malaria confirmed by laboratory testing, who experienced fever > 38.0°C (100.4°F) within 12 hours prior to initial dosing
<i>Treatment</i>	30-minute IV infusion of ibuprofen 400 mg or matching placebo q6 hours first 3 days (12 doses) followed by q6-hour as needed for temperature >38.0°C (100.4°F) for two more days
<i>Rescue medication</i>	Fever treatment such as cold packs, cooling blankets, and alcohol baths were permitted only post treatment or during treatment in those with treatment failures [temperature ≥106.0°F (41.1°C) ≥2 hours after the initial dose or ≥103.0°F (39.4°C) ≥2 hours after the subsequent doses];
<i>Efficacy data</i>	Temperature before the start of infusion, hourly in first four hours of treatment and then every four hours thereafter
<i>Efficacy parameter</i>	Primary: Area under the temperature curve [above 37.0°C (98.6°F)] in Hours 0-24 Secondary: <ul style="list-style-type: none">• Area under temperature curve in Hours 0-4• Area under temperature curve in Hours 24-72• Area under temperature curve in Hours 0-72 (post hoc)• Number and % of treatment failures (T≥106.0°F (41.1°C) ≥2 hours after initial dose or ≥103.0°F (39.4°C) ≥2 hours after any subsequent dose)• Parasite clearance time (time from initial treatment to time of first negative result)
<i>Safety monitoring</i>	Vital signs at screening, baseline, and 0.5, 1, 2, 4, and 6 hours post dose; adverse events (AEs) report

5.3.2.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 60 patients enrolled who received the study medication, with an age range of 18 to 54 years and a mean of 30 years. All 60 patients were Asians and 20% were female. The two treatment groups were balanced with regard to demographic characteristics such as age, gender, and weight. Baseline temperature was 38.65°C (101.6°F) in the IVIb 400 mg group and 38.82°C (101.9°F) in the placebo group and was not considered clinically significantly different between the two groups.

Table 5.3.2-2 Demographics and Baseline Characteristics

Study 006 Baseline Characteristics	400 mg IVIb (n=30)	Placebo (n=30)	Total (n=60)
Age (years)			
Mean (SD)	32.4 (9.4)	27.8 (9.4)	30.1 (9.4)
Median	31.5	25.5	
Minimum, Maximum	18, 54	18, 52	18, 54
Gender, n (%)			
Male	24 (80%)	24 (80%)	48 (80%)
Female	6 (20%)	6 (20%)	12 (20%)
Race, n (%)			
Asian	30 (100%)	30 (100%)	60 (100%)
Weight (kg)			
Mean (SD)	55.4 (5.5)	53.2 (8.6)	54.3
Median	55.2	51.0	
Minimum, Maximum	45.0, 67.0	43.0, 83.0	43.0, 83.0
Baseline Temperature (°C)			
Mean (SD)	38.65 (0.53)	38.82 (0.71)	
Minimum, Maximum	38.2, 39.5	38.2, 40.0	38.2, 40.0
Baseline Temperature (°F)			
Mean (SD)	101.6 (0.95)	101.9 (1.28)	

SD = standard deviation; Min = minimum; Max = maximum

Source: Section 11.2 on pages 37-38 and Tables 1.2 -1.3 on pages 56-57 of the report for Study 006.

Patient disposition

All 60 patients completed the 3-day fixed dosing treatment period. Only one patient on IVIb 400 mg dropped out of the study for not returning to 21-day assessment.

Table 5.3.2-3 Patient Disposition

Study 006 Patient Disposition	400 mg IVIb (n=30)	Placebo (n=30)	Total (n=60)
All Treated Patients	30	30	60
Discontinued n (%)	1 (3.3)	0	1 (1.7)
Reason for discontinuation			
Lost to follow up (missed 21 day assessment)	1 (3.3)	0	1 (1.7)

Source: Page 35 of the report for Study 006.

Protocol violations

There were two major systematic protocol deviations. First deviation involved all 60 patients that the data were not double-entered as specified in the original protocol, but were single-entered and double-checked. Second deviation involved first 38 patients enrolled that their laboratory tests to be collected daily during the first five treatment days were missing. Other less frequent protocol deviations included miss-timed (n=7) or missing (n=1) post treatment assessments on Days 7, 14, or 21 in eight patients, four in each treatment group; rescue medication in one placebo patient when temperature (39.2°C) did not meet the criteria of receiving rescue; rescue medication not provided to one placebo patient when temperature (39.6°C) met the criteria of rescue

treatment. These protocol deviations in general were balanced between the treatment groups. None was considered as having a differential impact on efficacy outcomes. Missing daily safety laboratory tests in more than 50% of the sample population would shrink the size of the safety database in both treatment groups.

Table 5.3.2-4 Summary of Protocol Deviations

Study 006 Protocol deviations	400 mg IVIb (n=30)	Placebo (n=30)	Total (n=60)
Total number of patients with protocol deviations other than data entry	22 (73.3%)	24 (80%)	46 (76.7%)
Missing laboratory tests (daily labs for first 5 days)	18 (60%)	20 (66.7%)	38 (63.3%)
Miss-timed or missing post treatment assessments (D7, D14, D21)	4 (13.3%)	4 (13.3%)	8 (13.3%)
Rescue given prematurely	0	1 (3.3%)	1 (1.7%)
Rescue not given	0	1 (3.3%)	1 (1.7%)

D = days

Source: Pages 35 to 36 and Table 3 on page 36 of the report for Study 006.

Exposure

All 60 patients received 12 doses or three days of treatments.

Efficacy results

Primary and secondary efficacy endpoints based on area under the temperature curve measurements

The area under the temperature curve [above 37.0°C (98.6°F)] refers to the total number of degrees accumulating over the number of hours of specified time interval and was reported as (°C x hours) in the submission. To better interpret what it means the unit (°C x hours) is converted to (°F x hours) and then changed to °F per hour (hourly AUC, which is considered equivalent to the mean temperature change in the time interval) by dividing the corresponding number of hours in each time interval. As shown in the table below, for the time interval of Hours 0-24 and 0-4, the hourly AUC was on a magnitude of 0.5 to 2.5°F. For the time interval of Hours 24-72 and 0-72, the hourly AUC was too small to be clinically meaningful. AUC over extended time period does not appear to be an appropriate choice for evaluation of multiple-dose antipyretic effects of this type of antipyretic agent (short dosing interval) in this particular fever model (relatively low baseline temperature and rapid fever reduction by natural course of disease). The treatment difference in terms of hourly AUC was 1.25°F (1.08°F for IVIb versus 2.33°F for placebo), i.e., IVIb treated patients were 1.25°F closer to the temperature of 98.6°F than placebo treated patients on an average during the first four hours of treatment. Underestimate of treatment difference by AUC₀₋₂₄ was reflected in the reduction of effect size to about one-half (0.67 versus 1.25°F) when AUC was calculated from 0 to 24 hours since most patients no longer had fevers after the first 12 hours as shown by the time-specific temperature measurements presented below.

Table 5.3.2-5a Area under the Temperature Curve Measurements

Study 006 Area under the temperature curve endpoint	400 mg IVIb (n=30)			Placebo (n=30)		
	Mean (SD), °C·hr	Mean °F·hr	°F/hr	Mean (SD), °C·hr	Mean °F·hr	°F/hr
AUC-T° Hours 0-24, primary endpoint	7.49 (7.94)	13.48	0.56	16.44 (11.60)	29.59	1.23
Comparison against placebo		16.11	0.67			
p-value	P=0.0019					
AUC-T° Hours 0-4, secondary endpoint	2.40 (1.54)	4.32	1.08	5.18 (2.97)	9.32	2.33
Comparison against placebo		5.00	1.25			
p-value	P<0.0001					
AUC-T° Hours 24-72, secondary endpoint	1.36 (4.00)	2.45	0.051	0.50 (1.51)	0.90	0.02
AUC-T° Hours 0-72, endpoint not pre-defined	8.85 (11.03)	15.93	0.12	16.94 (12.23)	30.49	0.42

AUC-T° = area under the temperature curve

Note: The effect of baseline temperature on AUC-T° (0-24) was statistically significant (p=0.024)

Source: Table 5 on page 39 and Table 6 on page 41 of the report for Study 006.

The treatment differences for AUC-T°₀₋₂₄ and AUC-T°₀₋₄ were statistically significant. The findings were confirmed by Dr. Norton's analyses as summarized in the table below (refer to the Evaluation of Efficacy Section of the Statistical Review for detail).

Table 5.3.2-5b AUC₀₋₂₄ and AUC₀₋₄ Based on Statistical Reviewer Dr. Norton's Analyses

Study 006 Area under the temperature curve endpoint	400 mg IVIb (n=30)			Placebo (n=30)		
	Mean (SD), °C·hr	Mean °F·hr	°F/hr	Mean (SD), °C·hr	Mean °F·hr	°F/hr
AUC-T° Hours 0-24, primary endpoint	<i>7.99 (7.96)</i>	14.38	0.60	<i>16.94 (11.69)</i>	30.49	1.27
Comparison against placebo		16.11	0.67			
p-value	<i>P=0.002</i>					
AUC-T° Hours 0-4, secondary endpoint	<i>2.56 (1.52)</i>	4.61	1.15	<i>5.30 (2.94)</i>	9.54	2.39
Comparison against placebo		4.93	1.24			
p-value	<i>P<0.0001</i>					

AUC-T° = area under the temperature curve; SD = standard deviation

Source for the means and p values: The Evaluation of Efficacy Section of the Statistical Review.

Time-specific response during the 24-hour treatment period in ITT population

The mean temperatures over time in 24 hours for the ITT population are summarized in the table below and presented in the graph following the table. As shown in Figure 5.3.2-1 below the mean temperature was reduced to <100°F in about 1.3 hours in the IVIb 400 mg group and in about 6 hours in the placebo group. All the temperature readings in the time period after 24 hours were below 98°F as shown in Figure 5.3.2-2. The data suggested that the time period for efficacy evaluation should not be beyond 12 hours.

In the first 4 hours after the initial dose the treatment differences were in a range of 1 to 2°F between the IVIb 400 mg and placebo. The data were not collected at the end of the first dosing interval at Hour 6. The treatment difference at Hour 8 (2 hours after the second dose representing peak effect of the second dose) was 1.8°F and became 0.2°F at the end of the second dosing interval.

Table 5.3.2-6 Time-Specific Temperature Measurements in the First 24 Hours in the ITT Population

Study 006	0	1	2	3	4	8	12	16	20	24
T (°C)										
400 IVIb	38.65	37.86	37.31	36.85	36.81	36.75	37.31	36.79	36.71	36.78
placebo	38.82	38.39	38.28	38.03	37.89	37.75	37.40	37.22	36.96	36.70
T (°F)										
400 IVIb	101.6	100.1	99.2	98.3	98.3	98.2	99.2	98.2	98.1	98.2
placebo	101.9	101.1	100.9	100.5	100.2	100.0	99.3	99.0	98.5	98.1
	0.3	1.0	1.7	2.1	1.9	1.8	0.2	0.8	0.4	-0.1

T = temperature

Source: Table 2.1 on page 59 of the report for Study 006

Figure 5.3.2-1 Time-Specific Temperature Measurements in Hours 0-24, ITT Population

Temperature by Treatment, ITT population

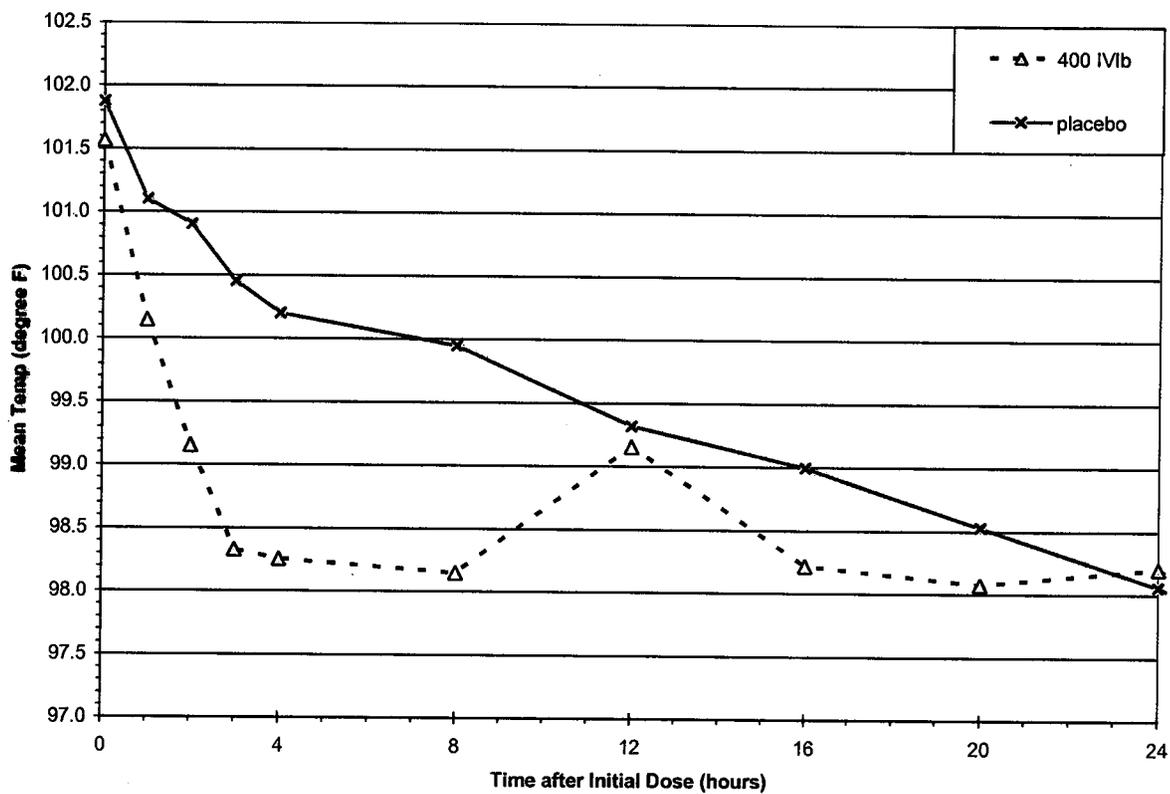
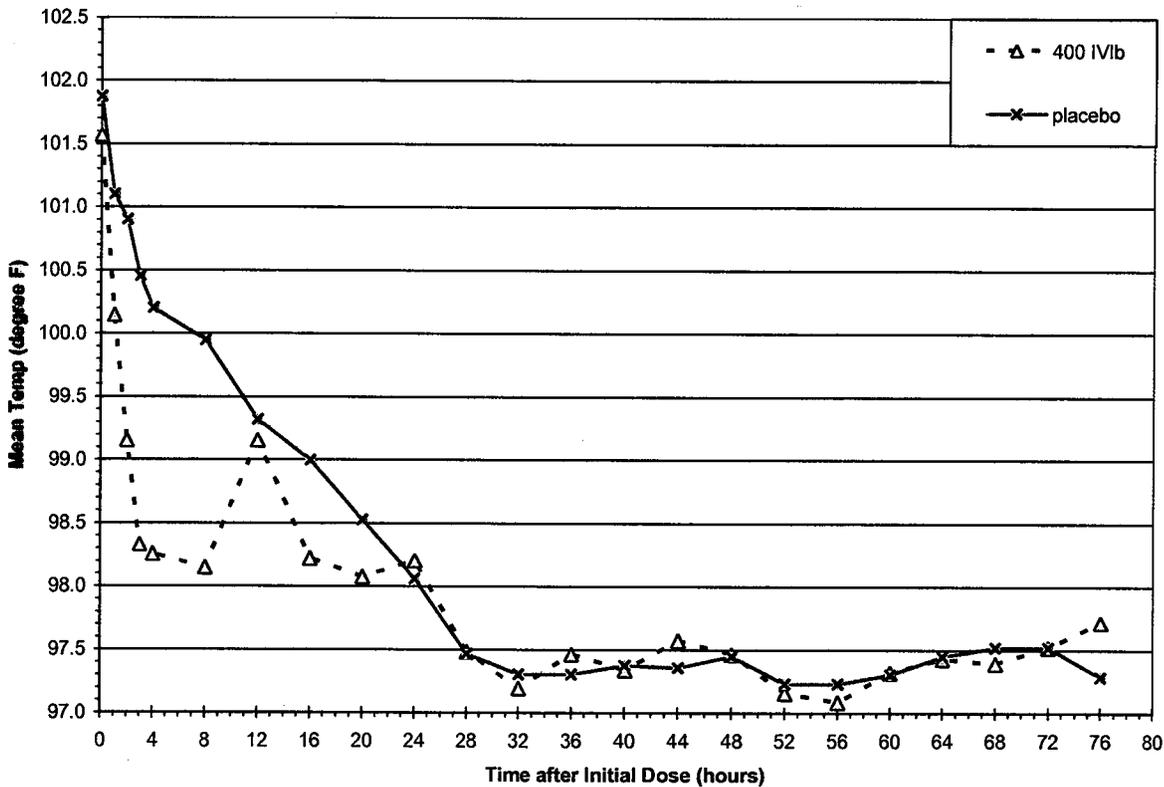


Figure 5.3.2-2 Time-Specific Temperature Measurements in Hours 0-72, ITT Population

Temperature by Treatment, ITT population



Number of patients identified as Treatment Failures

Only two patients on IVIb 400 mg and three patients on placebo were identified as treatment failures.

Parasite clearance time

The range for the parasite clearance time was 14 to 50 hours in both treatment groups. This endpoint was not considered an adequate measurement of fever reduction.

Additional analysis requested by the reviewer:

Time to fever reduction reaching T<100.0°F (37.8°C) during the 24-hour treatment period

Except one placebo patient all patients reached temperature <100.0°F (37.8°C) by the end of 24 hours. The treatment difference in time to T<100.0°F was about 5 hours (1.7 hours versus 6.6 hours) in comparison of 400 mg IVIb to placebo and was statistically significant as shown in the table below. The effect size of treatment difference is illustrated by the separation of survival curves in the graph following the table.

Table 5.3.2-7 Time to Temperature <100.0°F (37.8°C) in Hours 0-24 in ITT Population

Study 006	400 mg IVIb (n=30)	Placebo (n=30)
Time to T<100.0°F (37.8°C) in 24 hours		
Number (%) with T<100.0°F (37.8°C) at Hours 24	30 (100%)	29 (97%)
Time to T<100.0°F (37.8°C) by Hours 24*		
Mean (SD) (hour)	1.70 (0.43)	6.56 (1.06)
Median (hour)	1.18	3.33
Comparison against placebo, p-value of Log-rank test	<0.0001	

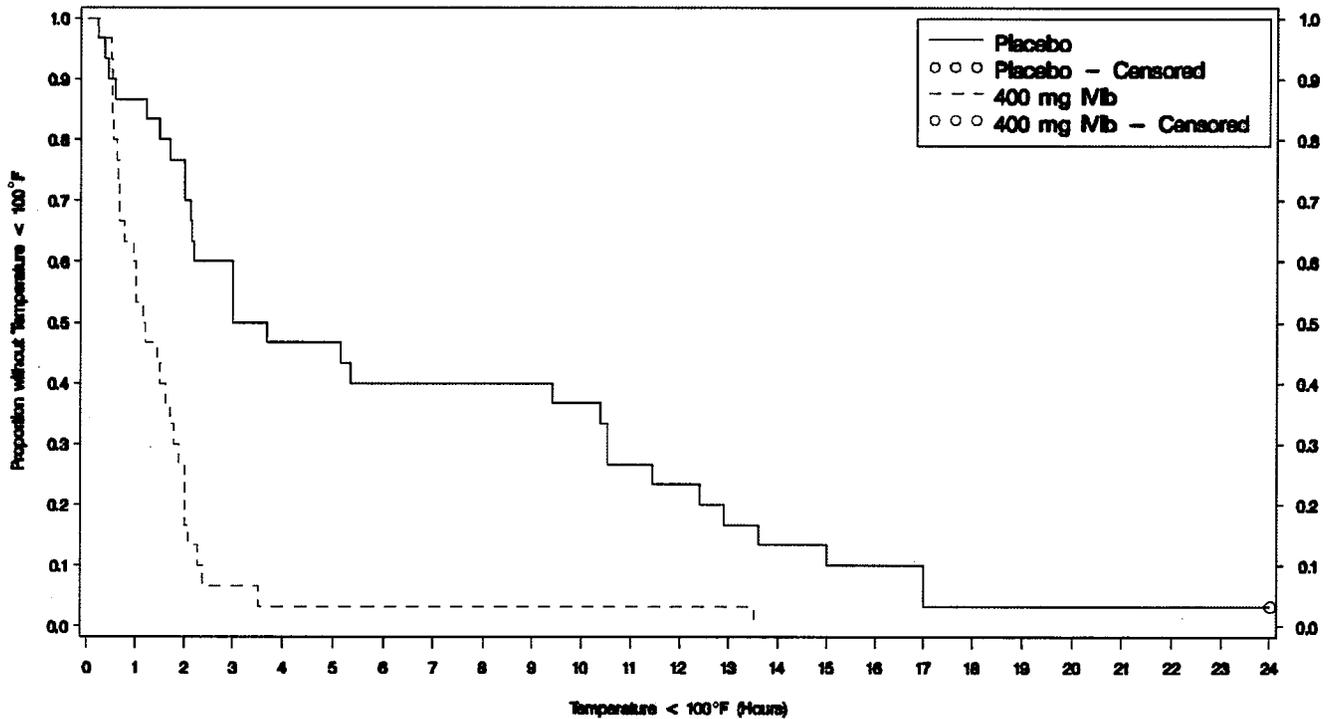
T = temperature; SD = standard deviation

Source: Supplement Table on page 5 of the submission dated March 20, 2009.

Figure 5.3.2-3 Time to Temperature <100.0°F (37.8°C) in 24 Hours, ITT

Final Analysis

Figure 6.1.1
Time to Temperature < 100°F (37.8°C) in 24 hours
Intent-to-Treat Population



Source: Figure 6.1.1 on page 5 of the submission dated March 20, 2009.

Time to fever reduction reaching T<99°F (37.2°C) during the 24-hour treatment period

All patients reached temperature <99°F (37.2°C) by the end of 24 hours. The treatment difference in time to T<99.0°F was about 6 hours (4.0 hours versus 10.4 hours) in comparison of 400 mg IVIb to placebo and was statistically significant as shown in the table below. The effect size of treatment difference is illustrated by the separation of survival curves in the graph following the table.

Table 5.3.1-8 Time to Temperature <99°F (37.2°C) in Hours 0-24 in ITT Population

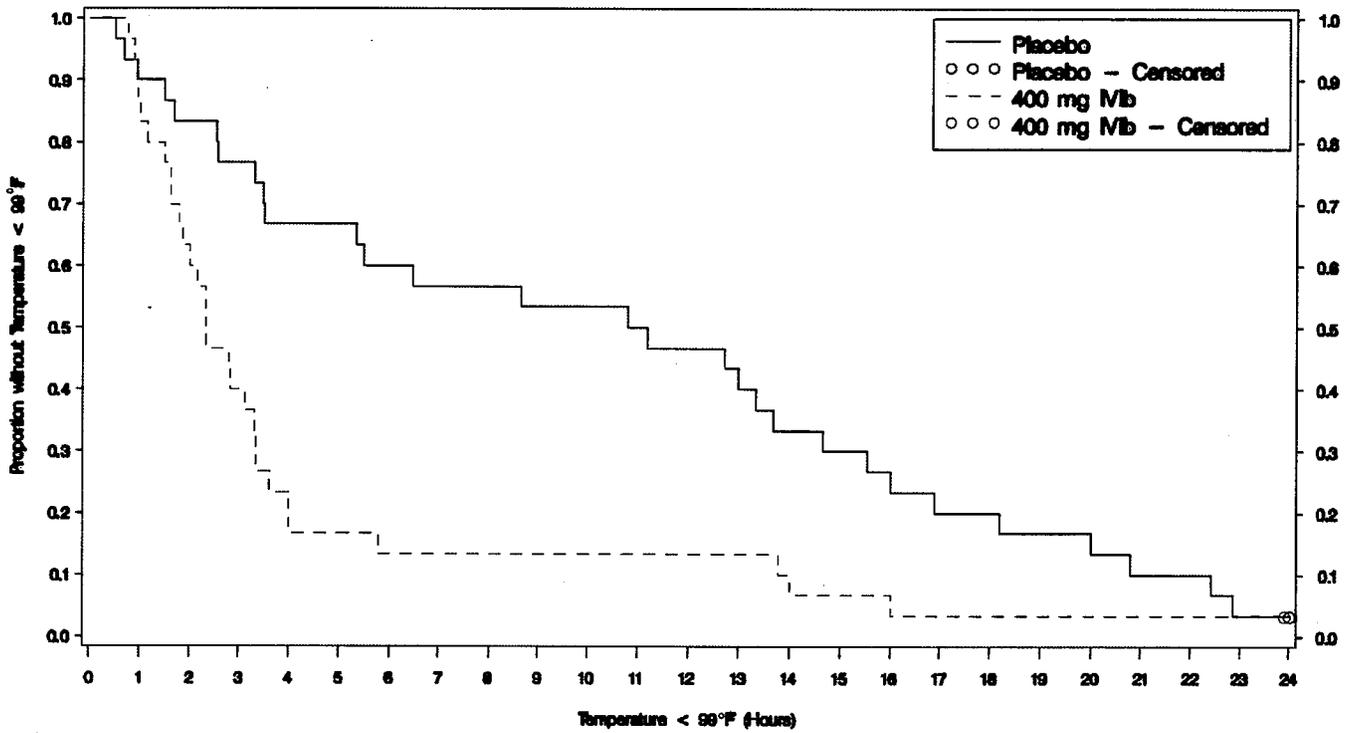
Study 006	400 mg IVIb (n=30)	Placebo (n=30)
Time to T<99°F (37.2°C) in 24 hours		
Number (%) with T<99°F (37.2°C) at Hours 24	29 (97%)	29 (97%)
Time to T<99°F (37.2°C) by Hours 24		
Mean (SD) (hour)	4.03 (0.82)	10.39 (1.37)
Median (hour)	2.33	11.01
Comparison against placebo, p-value of Log-rank test	0.0038	

T = temperature; SD = standard deviation

Source: Table on page 6 of the submission dated March 20, 2009.

Figure 5.3.1-4 Time to Temperature <99°F (37.2°C) in 24 Hours, ITT

Figure 6.1.2
Time to Temperature < 99°F (37.2°C) in 24 hours
Intent-to-Treat Population



Source: Figure 6.1.2 on page 6 of the submission dated March 20, 2009.

5.3.2.3 Summary of Findings and Discussion

Study conduct

The treatment groups in Study 006 were basically balanced with regard to demographic characteristics such as age, gender, race, and weight. Baseline temperature was 38.65°C (101.6°F) in the IVIb 400 mg group and 38.82°C (101.9°F) in the placebo group and was not considered significantly different between the two groups.

There were no dropouts during treatment. Only one patient in the IVIb 400 mg group dropped out of the study (not returning for 21-day visit).

Protocol deviations were mainly related to deviated method of data entry, missing laboratory tests, and missed or missing post treatment assessments, and were balanced between the two treatment groups.

Efficacy

The efficacy results are summarized in the table below in terms of treatment differences from placebo to examine the effect sizes for clinical significance.

Because of the rapid decrease in temperature back to normal range in both treatment groups as shown in the temperature response curve formed by time-specific measurements, efficacy end points defined by area under the temperature curve over an extended time period (beyond 12 hours) do not appear to adequately reflect the true treatment differences. Statistically significant treatment differences were shown in AUC-T° over four hours and over 24 hours, respectively, which were confirmed by Dr. Norton's analyses (refer to the Evaluation of Efficacy Section of the Statistical Review for detail). Statistically significant treatment differences were also shown in the time it took to reduce fever to a temperature <100.0°F and to a temperature <99.0°F. Clinically meaningful treatment differences between IVIb 400 mg and placebo were shown mainly in terms of a temperature reduction of 1.3°F more in hourly average AUC-T°₀₋₄; a reduction by 1-2 more degrees (°F) in time-specific measurements from 1 to 8 hours; about 5 hours earlier on the average to reach T<100.0°F and 6 hours earlier to reach T<99.0°F, in comparison of IVIb 400 mg to placebo.

Table 5.3.2-9 Summary of Efficacy Findings

Study 006 Efficacy summary	Effect size of treatment difference from placebo
	400 mg IVIb (n=30)
Primary efficacy endpoint	
AUC-T° ₀₋₂₄ (°F·hr)	16.11*
Hourly average AUC-T° ₀₋₂₄ (°F/hr)	0.67
Secondary and additional efficacy endpoints	
AUC-T° ₀₋₄ (°F·hr)	5.0*
Hourly average AUC-T° ₀₋₄ (°F/hr)	1.25
Time-specific q4 hour temperature measurements (q6 hour dosing) in Hours 0-24 (°F), ITT	1.0-2.1 (Hr 1-8) 0.2-0.8 (Hr 12-20)
Time to T<100.0°F (37.8°C) by Hour 24 (h)	4.9*
Time to T<99°F (37.2°C) by Hour 24 (h)	6.4*

*Note: Statistically significant difference.

Refer to all the efficacy tables in this section.

Dosing interval

Dosing interval was not adequately evaluated because fever was measured every 4 hours whereas study medication was given every 6 hours. The overall results suggested a positive outcome of antipyretic multiple-dose effects with the IVIb every 6-hour dosing.

5.3.2.4 Conclusion

Ibuprofen injection 400 mg given every six hours is considered effective in treating fever in hospitalized patients based on the demonstration of statistically significant and clinically meaningful treatment differences in Study 006.

5.3.2.5 Appendix

Eligibility Criteria in Study 006

Inclusion Criteria

Patients were going to be required to meet the following criteria for inclusion in the study if they:

1. Were hospitalized
2. Were clinically diagnosed with uncomplicated malaria, confirmed by laboratory testing
3. Were experiencing fever greater than 38.0°C (100.4°F) for which pharmacological treatment was appropriate, in the judgment of the attending physician. Temperature would be measured using the tympanic method for the duration of the study.
4. Were febrile within 12 hours prior to dosing
5. Were at least 18 years of age
6. Had the ability to understand the requirements of the study, were willing to provide written informed consent (as evidenced by signature on an informed consent document approved by an Institutional Ethics Committee [IEC]), and agreed to abide by the study restrictions and to return for the required assessments. If the patient was incapacitated, informed consent would be sought from a legally acceptable representative.

Exclusion Criteria

Patients were going to be excluded from this study if they:

1. Weighed less than 40 kg
2. Had inadequate intravenous access
3. Had received antipyretic drug therapy (e.g. aspirin, or other NSAIDs) within 8 hours before dosing
4. Had any history of allergy or hypersensitivity to any component of IVIb or NSAIDs, including aspirin
5. Were pregnant or nursing
6. Had a history of severe head trauma that required current hospitalization, intracranial surgery, or stroke within the previous 30 days or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesions
7. Had a history of congenital bleeding diatheses (e.g. hemophilia) or any active clinically significant bleeding, or had underlying platelet dysfunction, including (but not limited to) idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, or congenital platelet dysfunction
8. Had gastrointestinal bleeding that had required medical intervention within the previous 6 weeks (unless definitive surgery has been performed)
9. Had a platelet count less than 30,000/mm³
10. Were receiving full dose anticoagulation therapy (prophylaxis with subcutaneous heparin is acceptable)
11. Had fever secondary to blood or drug reaction
12. Had an expected life span of less than 14 days due to imminent withdrawal of life support or severity of illness
13. Were receiving treatment with corticosteroids (patients who are expected to receive corticosteroids during the course of the study were not eligible)
14. Had neurogenic fever
15. Were on renal dialysis or had serum creatinine of 3 mg/dL or higher
16. Had had major surgery within the past 12 hours, unless adequate hemostasis had been achieved
17. Had received another investigational drug within the past 30 days
18. Were otherwise unsuitable for the study, in the opinion of the Investigator

5.3.3 Post Surgical Pain Study 800a

5.3.3.1 Protocol

Study CPI-CL-008a was planned as a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (every six hours for up to five days), dose-ranging analgesic study of Ibuprofen IV Injection (IVIb) 400 mg and 800mg in hospitalized patients with post-operative pain requiring narcotic analgesia.

Eligible patients were to have been hospitalized adult patients scheduled for elective single-site orthopedic surgery (knee, hip or shoulder joint replacement or reconstruction) or gynecologic/abdominal (total abdominal hysterectomy, gall bladder, bowel or lower abdominal general investigative) surgery, with anticipated need for post-operative narcotic analgesia, who had adequate intravenous access and anticipated hospital stay for ≥ 24 hours.

Stratified randomization was to have been used to assign eligible patients to a strata based on their age (18 to 45 years and >45 to 70 years) and weight (≤ 75 Kg and >75 KG) to randomly receive one of the three treatments, IVIb 400 mg, IVIb 800 mg, or matching placebo. The initial dose of the study medication was planned to be administered approximately at the initiation of skin closure (about 30 minutes before the end of surgery). Seven subsequent doses were to be administered every six hours for two days, followed by PRN dosing for three more days.

Concomitant narcotic use was to have been limited to fentanyl to be given by anesthesiologist in the 15-minute time window: about 45 minutes prior to the end of surgical procedure before the initiation of study medication, and morphine to be given (1-2 mg or more if needed) every 5 minutes upon request or as patient-controlled analgesia (PCA). Concurrent morphine use was planned to be started after the completion of the 30-minute infusion of the initial dose of ibuprofen (upon discharge from the operating room).

Study medication was to have been required to be discontinued if other narcotics or NSAIDs were needed and to have been allowed to discontinue when patients were able to tolerate oral pain medication, had no more pain or no IV access, and were discharged from the hospital.

Pain intensity (PI) at rest and with movement were to have been measured by the 11-point (0-10) visual analog scale (VAS) at 1 and 3 hours and every 3 hours thereafter up to Hour 48, and then daily through Day 5 if the study medication was to be continued on a PRN basis.

The planned primary efficacy endpoint was the reduction in total morphine usage in the first 24 hours post surgery as compared to placebo. The planned secondary efficacy endpoints included PI at rest and with movement in 48 hours; time to first subsequent narcotic analgesia for breakthrough pain (or time to treatment failure); nocturnal awakenings due to pain. Reduction of opioid-related side effects was also planned as a secondary endpoint and was defined by time to GI motility as measured by return of bowel sounds, resumption of ambulation, resumption of liquid intake and solid diet, length of hospital stay, and each individual and combined assessment of the following (each counted as a score of one): diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter (after initial removal of surgical catheter), incidence of post-operative vomiting or need for anti-emetic medication, and Richmond Agitation Sedation Scale (≤ 3).

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study, where all treatment-related AEs would have been followed until resolution; vital signs at 1, 2, 3, 6, 9, 12, and 24 hour after the initial dose and then daily up to Day 7; routine laboratory tests (clinical chemistry, hematology, and

coagulation) at baseline and 24, 48, 72, 120, and 172 hours (Days 1, 2, 3, 5, and 7) after the start of study medication; monitoring of transfusion requirements.

Statistical Analysis (refer to statistical review for detail)

Population for analysis

The planned intent-to-treat (ITT) population was to have included all treated patients with at least one dose of study medication.

The planned efficacy-evaluable population (EEP) was to have been a subset of the ITT population with no major protocol violations with regard to eligibility criteria or study conduct and with primary efficacy assessments.

Efficacy analysis

The planned primary efficacy parameter, the amount of morphine use in 24 hours in comparison to placebo, was to be analyzed using the analysis of variance and covariance adjusted for center and using Dunnett's test for multiple comparisons.

The plan for secondary efficacy analyses included analysis of variance and covariance for continuous variables, Life-table and Cox's Proportional Hazard Model for time to events, and Chi-square, Cochran-Mantel-Haenszel test, and Logistic Regression for categorical variables.

Missing data management

In terms of morphine use, missing data in between two adjacent assessments would have been replaced by the average of the two assessments if there were no more than two consecutive missing time points. Treatment group mean was planned to be used to replace either missing data for more than two consecutive time points or missing data due to dropout.

Sample size

The planned sample size was 75 patients per treatment group based on an estimated effect size of 65.2 mg (SD=35 mg) in 24-hour morphine use for the active treatment groups to provide 80% power to detect a treatment difference of 25% (16.3 mg) reduction from placebo at the 5% level of significance. An administrative analysis was planned under the condition of not breaking the blind or dividing data by groups, after enrollment of at least 75% of patients (56 per treatment group) to estimate the overall standard deviation in order to adjust sample size accordingly.

Protocol Amendments

There were six protocol amendments and most were mainly for clarification purpose. Amendment 1 (dated December 6, 2004) included change of fentanyl use from until 30 minutes before skin closure to until 30 minutes before the end of surgical procedure, addition of flatulence and bowel movement as evidence of GI motility, addition of "24 hours" as the time limit for exclusion of concomitant medication, addition of exceptions to the exclusion by allowing muscle relaxant to be used for intubation procedure and paracetamol and/or tramadol to be used until midnight prior to surgery, deletion of baseline pain assessment because patients were still unconscious at the start of study medication, deletion of naloxone as a specific treatment for respiratory depression to also capture other treatments used for respiratory depression, and addition of Investigator's designee as an alternative signer for informed consent. Amendment 2 (dated March 7, 2005) specified the time frame of post-operative need for morphine analgesia to be ≥ 24 hours in the inclusion criteria. Amendment 3 (dated May 12, 2005) tightened exclusion criteria for calculated creatinine clearance from 70 mL/min to 60 mL/min. Amendment 4 dated (June 9, 2005) changed the volume of normal saline from 200 mL to 250 mL for preparation of IV infusion. Amendment 5 (dated September 6, 2005) included change from central to by-site randomization, clarification of treatment failure to be requiring narcotics other than morphine or other NSAIDs due to inability to manage pain and no more efficacy assessment in patients identified as

treatment failures, further extension of time frame for use of paracetamol to six hours prior to surgery, expansion of the type of surgery to include also "dual site bone graft orthopedic procedures" in the inclusion criteria, deletion of pain assessment at 27, 33, 39, and 45 hours to minimize interruption to sleep, addition of solid food intake for recording GI motility if the exact time of motility was not captured by other means, and clarification of laboratory assessment at discharge to avoid duplication of lab tests on the same day. Amendment 6 (dated March 8, 2006) included an increase of sample size to 120 patients per group based on administrative analysis and allowing dropout replacement in case of dropouts occurred after the start of study medication to ensure a minimum total of 360 patients.

The reviewer's brief summary of the major components of the protocol is presented in the table below.

Table 5.3.3-1 Reviewer's Summary of the Protocol

<i>Study #</i>	CPI-CL-008a
<i>Objectives</i>	To study multiple-dose analgesic effects (targeted at reduced use of narcotics), tolerability and safety of IV ibuprofen 400 mg and 800 mg doses and dose response in hospitalized patients with postoperative pain.
<i>Design</i>	Multiple-center (8 domestic and 9 foreign), randomized, double-blind, placebo-controlled, parallel, multiple-dose (q6 hours for up to 5 days), dose-ranging
<i>Sample population</i>	Hospitalized adult patients scheduled for elective surgery (refer to the list below) with anticipated need for post-operative narcotic analgesia, who had adequate intravenous access and anticipated hospital stay for ≥ 24 hours <ul style="list-style-type: none"> • Orthopedic surgery - single surgical site at knee, hip or shoulder joint replacement or reconstruction • Gynecologic surgery - total abdominal hysterectomy • Abdominal surgery - gall bladder, bowel or lower abdominal general investigational surgery
<i>Treatment</i>	IVib 400 mg, 800 mg, or matching placebo, 30-minute IV infusion initiated about 30 minutes before the end of surgery, q6 hours for 2 days, and then PRN for 3 more days; Morphine 1-2 mg (or more based on need) q5 minutes upon request or PCA after surgery
<i>Treatment discontinuation</i>	Treatment required to be discontinued if in need of other narcotics or NSAIDs; Treatment allowed to be discontinued in the following cases: <ul style="list-style-type: none"> • Ability to tolerate oral pain medication • Resolution of pain • No IV Access • Discharge from the hospital
<i>Raw efficacy data</i>	Pain intensity at rest and with movement by 11-point (0-10) visual analog scale (VAS) at Hours 1 and 3 and q3 hours thereafter up to 48 hours from the start of the initial dose, and then daily through Day 5 during PRN dosing
<i>Efficacy parameter</i>	Primary: total morphine usage in 24 hours Secondary: <ul style="list-style-type: none"> • PI at rest and with movement: time-specific measurements up to H48 • Time to first subsequent narcotic analgesia for breakthrough pain (time to treatment failure) • Nocturnal awakenings due to pain • Reduction of opioid-related side effects defined by <ul style="list-style-type: none"> ○ Time to GI motility (q6 hours): return of bowel sounds, flatulence, or bowel movement ○ Resumption of ambulation ○ Resumption of liquid intake and solid diet ○ Length of hospital stay ○ Combined Safety Assessment: <ul style="list-style-type: none"> • Diffuse pruritus • Overt respiratory depression requiring treatment • Need for post-operative urinary indwelling catheter • Post-operative vomiting or need for anti-emetic medication • Richmond Agitation Sedation Scale (<-3)
<i>Safety monitoring</i>	<ul style="list-style-type: none"> • Adverse events • Vital signs at 1, 2, 3, 6, 9, 12, and 24 hour after the initial dose and then daily up to Day 7 • Routine lab tests at baseline and 24, 48, 72, 120, and 172 hours (Days 1, 2, 3, 5, and 7) • Transfusion monitoring

5.3.3.2 Results

Demographic and other baseline characteristics

The sample population consisted of 406 patients enrolled who received the study medication, with an age range of 18 to 69 years and a mean of 45 years. Of the 406 patients, 86% were Caucasian, 11% were African American, 2% were Asian, and 79% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight. Baseline pain intensity was not planned to be obtained.

Table 5.3.3-2 Demographics and Baseline Characteristics

Study 008a Baseline Characteristics	400 mg IVIb (n=134)	800 mg IVIb (n=138)	Placebo (n=134)	Total (n=406)
Age (years)				
Mean (SD)	45 (12.5)	46 (11.9)	45 (10.9)	45 (11.8)
Median	43.0	45.0	44.0	44
Minimum, Maximum	18, 69	20, 69	21, 69	18, 69
Gender, n (%)				
Male	35 (26%)	27 (20%)	25 (19%)	87 (21%)
Female	99 (74%)	111 (80%)	109 (81%)	319 (79%)
Race, n (%)				
Caucasian	112 (84%)	118 (86%)	118 (88%)	348 (86%)
Black	16 (12%)	15 (11%)	14 (10%)	45 (11%)
Asian	2 (1.6%)	3 (2%)	2 (1.6%)	7 (2%)
Hispanic	1 (0.8%)	0	0	
Other	3 (2%)	2 (1%)	0	6 (1%)
Height (cm)				
Mean (SD)	167.7 (9.22)	166.7 (9.34)	167.3 (9.00)	167.2 (9.17)
Median	167.0	165.1	165.1	165.6
Minimum, Maximum	147.3, 198.0	120.0, 192.0	147.0, 195.6	120.0, 198.0
Weight (kg)				
Mean (SD)	83.0 (18.16)	84.9 (20.83)	83.4 (18.15)	83.8 (19.08)
Median	79.8	81.8	81.8	81.0
Minimum, Maximum	44.0, 140.5	50.9, 150.0	54.0, 160.0	44.0, 160.0

SD = standard deviation; Min = minimum; Max = maximum

Source: Appendix Table 14.1.3 on page 172 of the report for Study 008a.

Patient disposition

Close to 90% of the 406 patients completed the study. There were 49 cases of dropouts, 11 from the 800 mg IVIb group and 19 from each of the 400 mg IVIb and placebo groups. The main reasons for dropouts were AE (5% on IVIb 800 mg, 7% on IVIb 400 mg, and 5% on placebo) and treatment failure (1% on IVIb 800 mg, 4% on IVIb 400 mg, and 5% on placebo). Very few patients per treatment group dropped out for the other reasons such as withdrawal at patient's request, noncompliance with protocol, protocol violation, inadequate IV Access, and concurrent illness as summarized in the table below.

Table 5.3.3-3 Patient Disposition

Study 008a Patient Disposition	400 mg IVIb (n=134)	800 mg IVIb (n=138)	Placebo (n=134)	Total (n=406)
All Treated Patients	134	138	134	406
Discontinued n (%)	19 (14%)	11 (8%)	19 (14%)	49 (12%)
Reason for discontinuation				
Adverse Event	10 (7%)	7 (5%)	7 (5%)	24 (6%)
Treatment failure	6 (4%)	2 (1%)	7 (5%)	15 (4%)
Withdrawal at patient's request	1 (<1%)	0	3 (2%)	4 (1%)
Noncompliance with protocol	2 (1%)	1 (<1%)	0	3 (<1%)
Protocol violation	0	1 (<1%)	0	1 (<1%)
Inadequate IV Access	0	0	1 (<1%)	1 (<1%)
Concurrent illness	0	0	1 (<1%)	1 (<1%)

Source: Tables on page 7 of the March 20, 2009 submission.

Protocol violations

Major protocol deviations were reported in 41% patients, mainly as CTM (clinical trial material or study medication) administration error (24%), taking excluded medication (18%), meeting exclusion criteria (4%), and miss timed consent (3%). Minor protocol deviations were reported in 77% patients, mainly as missed assessment (76%), CTM administration error (18%), and Day 14 follow up error (6%). The specific types of protocol deviations were balance between the treatment groups and were not expected to have differential impact on study outcomes.

Table 5.3.3-4 Summary of Protocol Deviations

Study 008a Protocol deviations	400 mg IVIb (n=134)		800 mg IVIb (n=138)		Placebo (n=134)		Total (n=406)	
	cases	N (%)	cases	N (%)	cases	N (%)	cases	N (%)
Total number of patients with major protocol deviations, n (%)								
Major protocol deviations: #cases and patients (%)	88	55 (41%)	94	57 (41%)	84	55 (41%)	266	167 (41%)
CTM administration error (outside ±60 min window)	47	30 (22%)	45	32 (23%)	49	36 (27%)	141	98 (24%)
Received excluded medication	28	25 (19%)	37	26 (19%)	24	22 (16%)	89	73 (18%)
Exclusion criteria	6	6 (4%)	5	5 (4%)	6	5 (4%)	17	16 (4%)
Consenting error (timing)	3	3 (2%)	6	6 (4%)	5	5 (4%)	14	14 (3%)
Randomization error (to wrong strata)	3	3 (2%)	1	1 (<1%)	0	0	4	4 (<1%)
Missed assessment	1	1 (<1%)	0		0	0	1	1 (<1%)
Minor protocol deviations: #cases and patients (%)	397	108 (81%)	433	104 (75%)	399	102 (76%)	1229	314 (77%)
Missed assessment	373	105 (78%)	417	103 (75%)	380	99 (74%)	1170	307 (76%)
CTM administration error	13	25 (19%)	7	26 (19%)	7	22 (16%)	27	73 (18%)
Day 14 follow up error	9	9 (7%)	8	8 (6%)	8	8 (6%)	25	25 (6%)
Not meeting inclusion criteria	2	1 (<1%)	1	1 (<1%)	0	0	3	2 (<1%)
Randomization error	0	0	0	0	3	3 (2%)	3	3 (<1%)
Screening error	0	0	0	0	1	1 (<1%)	1	1 (<1%)

CTM = clinical trial material

Source: Tables 14.1.5 on page 9 of the March 20, 2009 submission.

Exposure

The exposure information is summarized in the table below. At least 90% of patients in each treatment group (90% on IVIb 400 mg, 93% on IVIb 800 mg, and 94% on placebo) received one day or four doses of treatment. Less than one third of the study population (28% on IVIb 400 mg, 30% on IVIb 800 mg, and 23% on placebo) received two days or eight doses of treatment. A total of 17 patients (less than 10%), including four subjects on IVIb 400 mg, 12 on IVIb 800 mg, and one on placebo, received more than eight doses.

Table 5.3.3-5 Exposure

Study 008a Exposure	400 mg IVIb (n=134)	800 mg IVIb (n=138)	Placebo (n=134)	400 mg IVIb (n=134)	800 mg IVIb (n=138)	Placebo (n=134)
#Doses, n (%)	Distribution			Cumulative		
1	11 (8%)	7 (5%)	6 (4%)	134 (100%)	138 (100%)	134 (100%)
2	3 (2%)	1 (1%)	0	123 (92%)	130 (94%)	128 (96%)
3	0	1 (1%)	2 (1%)	120 (90%)	130 (94%)	128 (96%)
4 (Day 1)	15 (11%)	21 (15%)	28 (21%)	120 (90%)	129 (93%)	126 (94%)
5	48 (36%)	50 (36%)	54 (40%)	105 (78%)	108 (78%)	98 (73%)
6	7 (5%)	11 (8%)	8 (6%)	57 (43%)	59 (43%)	45 (34%)
7	12 (9%)	6 (4%)	6 (4%)	50 (37%)	47 (34%)	37 (28%)
8 (Day 2)	34 (25%)	29 (21%)	30 (22%)	38 (28%)	41 (30%)	31 (23%)
9	1 (1%)	6 (4%)	1 (1%)	4 (3%)	12 (9%)	1 (1%)
10	0	0	0	3 (2%)	6 (4%)	0
11	1 (1%)	1 (1%)	0	3 (2%)	6 (4%)	0
12 (Day 3)	1 (1%)	3 (2%)	0	2 (1%)	5 (4%)	0
13	1 (1%)	1 (1%)	0	1 (1%)	2 (1%)	0

14	0	0	0	0	1 (1%)	0
15	0	0	0	0	1 (1%)	0
16 (Day 4)	0	0	0	0	1 (1%)	0
17	0	1 (1%)	0	0	1 (1%)	0

Source: Appendix Table 14.1.4 on page 174 of the report for Study 008a and supplementary table on pages 8 to 9 of the submission dated January 19, 2009.

Efficacy results

Primary efficacy endpoint: morphine usage during the first 24 hours following surgery

The total amount of morphine used in the first 24 hours after surgery is summarized in the table below. The difference between IVIb 800 mg and placebo were 5.1 mg (43.8 mg versus 48.9 mg) representing a 10.4% reduction in mean and 9.8 mg (35.5 mg versus 45.3 mg) representing a 21.6% reduction in median. The differences between IVIb 400 mg and placebo were 2.6 mg (46.3 mg versus 48.9 mg) representing a 5.3% reduction in mean and 1.3 mg (44 mg versus 45.3 mg) representing only a 2.9% reduction in median. Therefore, 24-hour use of morphine was reduced by 10-22% with IVIb 800 mg treatment and reduced by less than 6% with IVIb 400 mg treatment. Treatment differences in LS-means based on pairwise comparison between each active treatment and placebo were not statistically significant. Treatment difference in LS-means of data derived by rank transformation (non-parametric testing model for not violating assumptions for normality) was statistically significant between the IVIb 800 mg and placebo groups. The results were confirmed by Dr. Norton's analyses. The statistical review team preferred untransformed data for the reasons that the departure from normality was not too large and the sample size was not too small (refer to Dr. Dionne Price's review for detail).

Table 5.3.3-6 Reduction in Morphine Use in First 24 Hours Post Surgery

Study 008a 1 ^o efficacy endpoint morphine use in 1 st 24 hours	400 mg IVIb (n=134)	800 mg IVIb (n=138)	Placebo (n=134)
Morphine Requirement (mg)			
Mean (SD)	46.3 (29.4)	43.8 (33.7)	48.9 (27.7)
<i>Difference (mg) from placebo & % of reduction</i>	<i>2.6 (5.3%)</i>	<i>5.1 (10.4%)</i>	
Median	44.0	35.5	45.3
<i>Difference (mg) from placebo & % of reduction</i>	<i>1.3 (2.3%)</i>	<i>9.8 (21.6)</i>	
Min, Max	3.0, 198.25	0.0, 221.3	0.0, 144.0
Morphine Requirement (mg)			
LSMeans (SE) ¹	46.3 (3.5)	43.8 (3.4)	48.9 (3.6)
LSMean difference from placebo	2.6	5.1	
p-value ²	0.667	0.287	
Transformed Morphine Requirement (mg)			
LSMeans (SE) ³	208.5 (13.6)	190.6 (13.1)	223.0 (13.8)
LSMean difference from placebo	14.5	32.4	
p-value ²	0.458	0.030	

SD = standard deviation; LSMeans = least square means; SE = standard error;

1. LS means are adjusted for age group, weight group, randomization center, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

3. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, and treatment group.

Source: Table 21 on page 66 and Table 14.2.1.1.1 on page 178 of the report for Study 008a.

Secondary efficacy endpoints:

PI for pain with movement

Mean PI with Movement during the 48-hour fixed-dosing treatment period in ITT population

The mean pain intensity scores for pain with movement (PI) recorded on a scale of 0 to 10 are summarized in the table below and presented in the graph following the table. Treatment differences in LS-means of transformed morphine requirement (refer to statistical review for discussion on data transformation) for pain with movement were **statistically significant** between the IVIb 800 mg group and placebo from 9 to 48 hours

and between the IVIb 400 mg group and placebo at Hours 9, 15 to 21, 30, and 36 to 48. In the time interval of 9-48 hours with demonstration of statistically significant treatment differences, the effect sizes of treatment differences on a magnitude of 0.5 to 1.1 units were noticed in Hours 9 to 36 for comparison between IVIb 800 mg and placebo and in Hours 9 to 21 for comparison between IVIb 400 mg and placebo

Table 5.3.3-7 Time-Specific Mean PI with Movement in 48 Hours (Fixed-Dosing) in ITT population

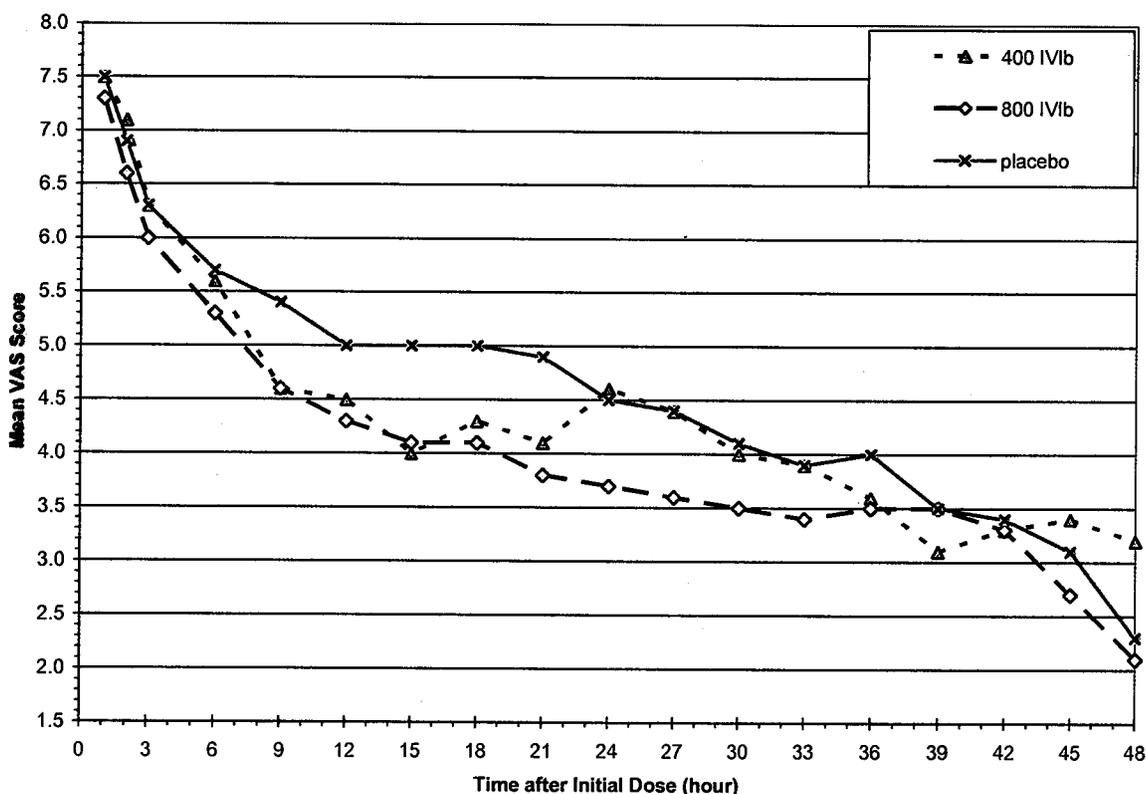
Hours	0	1	2	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Mean PI with movement																			
400 IVIb		7.5	7.1	6.3	5.6	4.6	4.5	4.0	4.3	4.1	4.6	4.4	4.0	3.9	3.6	3.1	3.3	3.4	3.2
800 IVIb		7.3	6.6	6.0	5.3	4.6	4.3	4.1	4.1	3.8	3.7	3.6	3.5	3.4	3.5	3.5	3.3	2.7	2.1
placebo		7.5	6.9	6.3	5.7	5.4	5.0	5.0	5.0	4.9	4.5	4.4	4.1	3.9	4.0	3.5	3.4	3.1	2.3
Difference in mean from placebo																			
400 IVIb		0	-0.2	0	0.1	0.8	0.5	1	0.7	0.8	-0.1	0	0.1	0	0.4	0.4	0.1	-0.3	-0.9
800 IVIb		0.2	0.3	0.3	0.4	0.8	0.7	0.9	0.9	1.1	0.8	0.8	0.6	0.5	0.5	0	0.1	0.4	0.2
Statistically significant treatment differences versus placebo in LS-means of transformed data																			
400 IVIb						x		x	x	x			x		x	x	x	x	x
800 IVIb						x	x	x	x	x	x	x	x	x	x	x	x	x	x

PI = pain intensity

Source: Table 25 on pages 68 to 70 of the report for Study 008a (also included in the Appendix at the end of the review of this study).

Figure 5.3.3-1 Time-Specific Mean PI with Movement in 48 Hours in ITT population

Study 008a - PI with Movement, ITT



Median PI with movement in 48 hours in ITT population

Time-specific median pain intensity scores for pain with movement are summarized in the table below. Treatment differences in terms of reduction in median PI of at least 10% (about 10 to 22%) were shown in Hours 9 to 30, 36, and 45 when comparing IVIb 800 mg treatment to placebo and in Hours 9 to 21 when comparing IVIb 400 mg treatment to placebo.

Table 5.3.3-8 Time-Specific Median PI with Movement in 48 Hours (Fixed-Dosing) in ITT population

Study 008a Median PI	400 mg IVIb (N=134)		800 mg IVIb (N=138)		Placebo (N=134)
	Median	% Reduction vs placebo	Median	% Reduction vs placebo	Median
1-Hour	7.5	6.2	7.3	8.8	8.0
2-Hour	7.4	-1.4	6.8	6.8	7.3
3-Hour	6.3	0.0	6.0	4.8	6.3
6-Hour*	5.7	0.0	5.3	7.0	5.7
9-Hour	4.7	9.6	4.6	11.5	5.2
12-Hour*	4.5	10.0	4.3	14.0	5.0
15-Hour	3.9	22.0	4.2	16.0	5.0
18-Hour*	4.3	14.0	4.0	20.0	5.0
21-Hour	4.1	16.3	3.8	22.4	4.9
24-Hour*	4.6	-2.2	3.7	17.8	4.5
27-Hour	4.6	-4.5	3.6	18.2	4.4
30-Hour*	4.0	0.0	3.5	12.5	4.0
33-Hour	3.8	0.0	3.5	7.9	3.8
36-Hour*	3.6	10.0	3.5	12.5	4.0
39-Hour	3.1	11.4	3.7	-5.7	3.5
42-Hour*	3.3	2.9	3.3	2.9	3.4
45-Hour	3.3	-6.5	2.7	12.9	3.1
48-Hour*	3.2	-39.1	2.1	8.7	2.3

*End of dose interval, assessment just prior to next scheduled dose.

Source: Table 27 on page 71 of the report for Study 008a.

Summary of PI with movement by AUC in ITT population

The analyses of the area under the pain intensity curve (AUC) were not pre specified in the original protocol or Statistical Analysis Plan. Nevertheless, the treatment differences between IVIb 400 mg and placebo and between IVIb 800 mg and placebo, respectively, in AUC from 1-24 hours, 6-24 hours and 12-24 hours, were all statistically significant. The p values of the statistical tests for comparisons of 24-hour AUC were confirmed by the Dr. Norton's analyses (refer to the Evaluation of Efficacy Section of the Statistical Review for detail).

Table 5.3.3-9 Summary of PI with Movement by AUC in ITT population

Study 008a Summary of PI with movement by AUC	400 mg IVIb (N=134)	800 mg IVIb (N=138)	Placebo (N=134)
AUC_{1-24 hr}			
Mean ± SD	111.9 ± 40.66	106.3 ± 43.87	123.3 ± 45.98
Median	113.1	107.5	124.8
Transformed VAS Score: LSMeans (SE) ¹	212.0 (13.19)	201.9 (12.70)	240.0 (13.40)
LSMeans Difference (95% CI)	28.0 (53.8, 2.3)	38.2 (63.8, 12.6)	
p-value vs Placebo ²	0.033	0.004	
AUC_{6-24 hr}			
Mean ± SD	80.0 ± 32.70	76.2 ± 35.53	91.5 ± 37.59
Median	80.0	76.2	91.5
Transformed VAS Score: LSMeans (SE) ¹	204.0 (13.29)	193.6 (12.80)	239.4 (13.51)
LSMeans Difference (95% CI)	35.4 (61.3, 9.4)	45.8 (71.6, 20.0)	
p-value vs Placebo ²	0.008	<0.001	
AUC_{12-24 hr}			
Mean ± SD	51.0 ± 22.22	47.9 ± 23.98	59.2 ± 25.29
Median	50.7	47.9	59.1
Transformed VAS Score: LSMeans (SE) ¹	194.5 (13.16)	183.0 (12.67)	230.6 (13.37)
LSMeans Difference (95% CI)	36.0 (61.7, 10.4)	47.6 (73.1, 22.1)	
p-value vs Placebo ²	0.006	<0.001	

AUC = area under the pain intensity curve; hr = hours; SD = standard deviation; VAS = Visual Analogue Scale; LSMeans = least square means; SE = standard error; CI = confidence interval.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.
 2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.
- Source: Table 26 on pages 70 to 71 of the report for Study 008a.

PI for pain at rest

Mean PI at rest in 48 hours in ITT population

The mean PI for pain at rest recorded on a scale of 0 to 10 are summarized in the table below and presented in the graph following the table. Treatment differences in LS-means of transformed morphine requirement (refer to statistical review for discussion on data transformation) for pain at rest were **statistically significant** between the IVIb 800 mg group and placebo from 9 to 48 hours and between the IVIb 400 mg group and placebo at Hours 15, 21, and 30 to 48. In the time interval of 9-48 hours with demonstration of statistically significant treatment differences, the effect sizes of treatment differences on a magnitude of 0.5 to 1.2 units were noticed in Hours 9 to 33 for comparison between IVIb 800 mg and placebo and in Hours 9, 15 to 21, 30 to 33 for comparison between IVIb 400 mg and placebo.

Table 5.3.3-10 Time-Specific Mean PI at Rest in 48 Hours (Fixed-Dosing) in ITT population

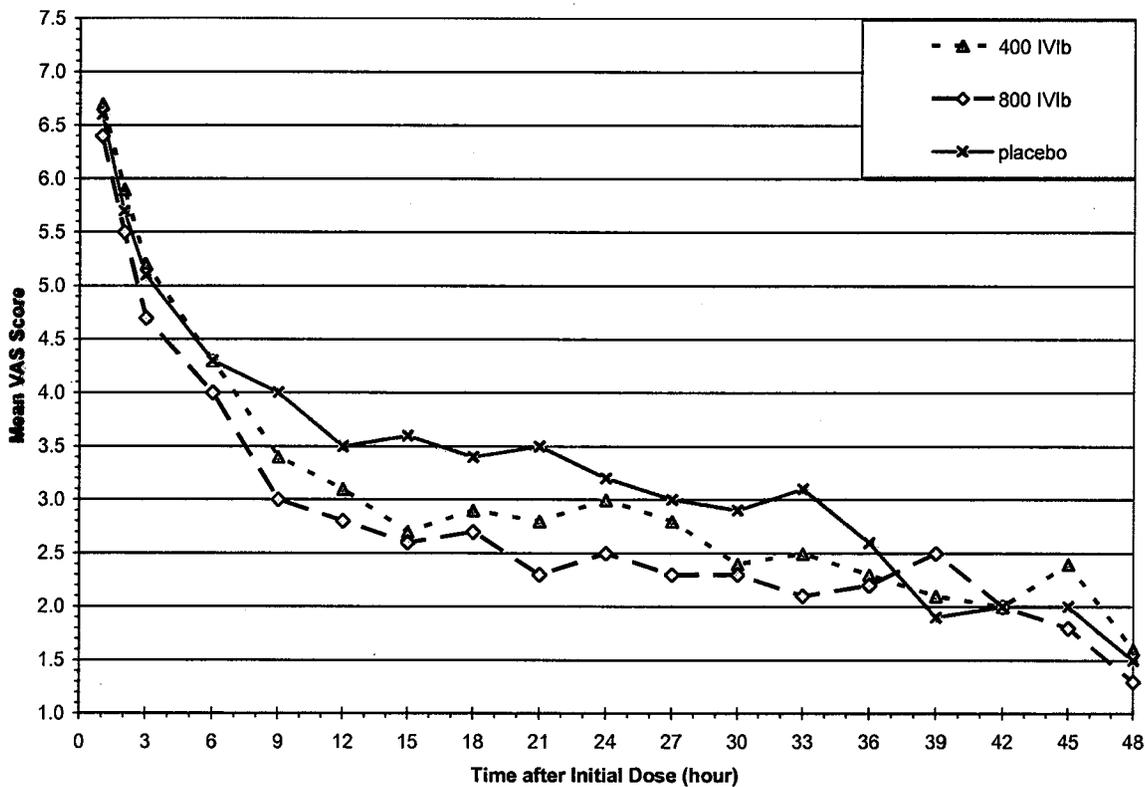
Hours	0	1	2	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Mean PI at rest																			
400 IVIb		6.7	5.9	5.2	4.3	3.4	3.1	2.7	2.9	2.8	3.0	2.8	2.4	2.5	2.3	2.1	2.0	2.4	1.6
800 IVIb		6.4	5.5	4.7	4.0	3.0	2.8	2.6	2.7	2.3	2.5	2.3	2.3	2.1	2.2	2.5	2.0	1.8	1.3
Placebo		6.6	5.7	5.1	4.3	4.0	3.5	3.6	3.4	3.5	3.2	3.0	2.9	3.1	2.6	1.9	2.0	2.0	1.5
Difference from placebo																			
400 IVIb		-0.1	-0.2	-0.1	0	0.6	0.4	0.9	0.5	0.7	0.2	0.2	0.5	0.6	0.3	-0.2	0	-0.4	-0.1
800 IVIb		0.2	0.2	0.4	0.3	1	0.7	1	0.7	1.2	0.7	0.7	0.6	1	0.4	-0.6	0	0.2	0.2
Statistically significant Treatment differences versus placebo in LS-means of transformed data																			
400 IVIb								x		x			x	x	x	x	x	x	x
800 IVIb						x	x	x	x	x	x	x	x	x	x	x	x	x	x

PI = pain intensity

Source: Table 31 on pages 75 to 77 of the report for Study 008a (also included in the Appendix at the end of the review of this study).

Figure 5.3.3-2 Time-Specific Mean PI at Rest in 48 Hours in ITT population

Study 008a - PI at Rest, ITT



Median PI at rest in 48 hours in ITT population

Time-specific median pain intensity scores for pain at rest are summarized in the table below. Treatment differences in median PI of at least 10% were shown as the following: 13-43% reduction in median PI comparing IVib 800 mg treatment to placebo in Hours 9 to 30, 36, and 45 and 11-21% reduction in median PI comparing IVib 400 mg treatment to placebo at Hours 9, 15, and 21 (all three were at mid-dosing interval) and Hours 30 to 36.

Table 5.3.3-11 Time-Specific Median PI at Rest in 48 Hours (Fixed-Dosing) in ITT population

Study 008a Median PI	400 mg IVib (N=134)		800 mg IVib (N=138)		Placebo (N=134)
	Median	% Reduction vs placebo	Median	% Reduction vs placebo	Median
1-Hour	7.0	0.0	7.0	0.0	7.0
2-Hour	6.3	-3.3	5.7	6.6	6.1
3-Hour	5.1	-2.0	5.0	0.0	5.0
6-Hour*	4.3	-7.5	4.0	0.0	4.0
9-Hour	3.5	12.5	3.0	25.0	4.0
12-Hour*	3.1	-3.3	2.9	3.3	3.0
15-Hour	2.6	21.2	2.6	21.2	3.3
18-Hour*	2.9	3.3	2.0	33.3	3.0
21-Hour	2.8	20.0	2.0	42.9	3.5
24-Hour*	3.0	0.0	2.0	33.3	3.0
27-Hour	3.1	-3.3	2.2	26.7	3.0
30-Hour*	2.4	11.1	2.3	14.8	2.7
33-Hour	2.7	15.6	2.3	28.1	3.2
36-Hour*	2.3	11.5	2.2	15.4	2.6
39-Hour	2.1	-16.7	2.7	-50.0	1.8
42-Hour*	2.1	-5.0	1.9	5.0	2.0

45-Hour	2.4	-20.0	1.9	5.0	2.0
48-Hour*	1.6	-6.7	1.3	13.3	1.5

*End of dose interval, assessment just prior to next scheduled dose.

Source: Table 33 on page 78 of the report for Study 008a

Summary of PI at rest by AUC in ITT population

The analyses of the area under the pain intensity curve (AUC) were not pre specified in the original protocol or Statistical Analysis Plan. Nevertheless, the treatment differences between IVIb 400 mg and placebo and between IVIb 800 mg and placebo, respectively, in AUC from 1-24 hours, 6-24 hours and 12-24 hours were all statistically significant.

Table 5.3.3-12 Summary of PI at Rest by AUC in ITT population

Study 008a Summary of PI at rest by AUC	400 mg IVIb (N=134)	800 mg IVIb (N=138)	Placebo (N=134)
AUC_{1-24 hr}			
Mean ± SD	81.7 ± 41.70	73.9 ± 39.59	91.0 ± 46.01
Median	82.1	70.6	88.1
Transformed VAS Score: LSMeans (SE) ¹	224.3 (12.62)	207.7 (12.15)	245.2 (12.82)
LSMeans Difference (95% CI)	20.9	37.5	
p-value vs Placebo ²	0.095	0.003	
AUC_{6-24 hr}			
Mean ± SD	55.6 ± 32.60	49.8 ± 31.41	65.3 ± 37.06
Median	55.6	48.0	65.0
Transformed VAS Score: LSMeans (SE) ¹	217.8 (12.88)	201.2 (12.41)	246.0 (13.09)
LSMeans Difference (95% CI)	28.2	44.9	
p-value vs Placebo ²	0.028	<0.001	
AUC_{12-24 hr}			
Mean ± SD	34.3 ± 21.25	30.6 ± 21.47	41.7 ± 24.66
Median	34.0	29.3	41.1
Transformed VAS Score: LSMeans (SE) ¹	208.8 (13.04)	191.3 (12.56)	241.2 (13.25)
LSMeans Difference (95% CI)	32.4	49.9	
p-value vs Placebo ²	0.013	<0.001	

AUC = area under the pain intensity curve; hr = hours; SD = standard deviation; VAS = Visual Analogue Scale; LSMeans = least square means; SE = standard error; CI = confidence interval.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 32 on pages 77 to 78 of the report for Study 008a.

Secondary efficacy endpoints:

Treatment failure and time to treatment failure

Patients in need of narcotics other than morphine or in need of other NSAIDs were recorded as treatment failures. Only 14 of 406 patients were identified as treatment failures, including 7 (5%) patients on IVIb 400 mg, 4 (3%) patients on IVIb 800 mg, and 10 (7%) on placebo. Time to treatment failure could not be adequately compared because of the small number of treatment failures.

Secondary efficacy endpoints:

Reduction of morphine side effects

The Applicant grouped all the following secondary endpoints together with the term opioid-related side effect: time to GI motility, time to ambulation, time to resumption of liquid intake and solid diet, time to discharge from hospital, and Combined Safety Assessment (diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter, incidence of post-operative vomiting or need for anti-emetic medication, and scores of ≤3 on Richmond Agitation Sedation Scale). The items listed under the Combined Safety

Assessments are considered morphine-related AEs and the rest are considered assessments of function reflecting post-operative recovery status in the reviewer's opinion.

The combined and individual morphine-related AEs are summarized in the table below. Treatment differences of $\geq 10\%$ from placebo were shown in the percentage of patients with post-operative vomiting or need for anti-emetic medication, the percentage of patients with at least one morphine-related AE, and the Combined Safety Assessment. The differences from placebo were $\leq 5\%$ for the other individual morphine-related AEs listed.

Table 5.3.3-13 Reduction of Morphine Side Effects

Study 008a Morphine side effects	400 mg IVIb (N=134)	800 mg IVIb (N=138)	Placebo (N=134)
Combined safety assessment of morphine-related AEs¹			
Mean (SD)	0.8 ± 0.63	0.9 ± 0.78	1.0 ± 0.71
Median	1.0	1.0	1.0
Difference from placebo in mean	0.2 (20%)	0.1 (10%)	
p-value ²	0.011	0.154	
\geqone morphine-related side effects³, n (%)	87 (65%)	91 (66%)	102 (76%)
Difference from placebo (%)	11%	10%	
p-value ⁴	0.054	0.078	
Diffuse pruritus, n (%)	7 (5%)	6 (4%)	11 (8%)
Difference from placebo (%)	3%	4%	
p-value ⁴	0.337	0.199	
Overt respiratory depression, n (%)	1 (<1%)	7 (5%)	3 (2%)
Difference from placebo (%)	~1%	-3%	
p-value ⁴	0.317	0.206	
Need for post-operative urinary indwelling catheter, n (%)	9 (7%)	9 (7%)	10 (7%)
Difference from placebo (%)	0	0	
p-value ⁴	0.825	0.773	
Post-operative vomiting or need for anti-emetic medication, n (%)	70 (52%)	76 (55%)	89 (66%)
Difference from placebo (%)	14%	11%	
p-value ⁴	0.022	0.076	
Worst Richmond Agitation Sedation Score of ≤ -3 in 48 Hours, n (%)	14 (10%)	22 (16%)	19 (14%)
Difference from placebo (%)	4%	-2%	
p-value ²	0.377	0.629	

1. The combined safety endpoint is defined as the sum of the binary occurrences of any of the following events during the 48 hour treatment period: diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter (after initial removal of surgical catheter), incidence of post-operative vomiting or need for anti-emetic medication, or Richmond Agitation Sedation Scale (RASS) value of ≤ -3 .

2. The p-values are based on a Wilcoxon-Rank Sum Test.

3. Morphine side effects included in the count: diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter (after initial removal of surgical catheter), incidence of post-operative vomiting or need for anti-emetic medication, or Richmond Agitation Sedation Scale (RASS) value of ≤ -3 .

4. The p-values are based on a Chi-square test.

Source: Table 14.3.1 on pages 295 to 296 of the report for Study 008a.

Differences in mean and median time to all the endpoints indicating post operation recovery are summarized in the table below. Treatment differences in means of $\geq 10\%$ from placebo were shown in time to GI motility, time to resumption of liquid intake and solid diet, and time to ambulation, but not in length of hospital stay. In another words the differences represented 3- to 5-hour earlier return of GI motility, resumption of liquid intake, and resumption of ambulation, and 14- to 17-hour earlier resumption of solid food. Treatment differences in medians from placebo were about 10% for time to GI motility and time to resumption of solid diet and $\leq 2\%$ for all the other parameters listed.

Table 5.3.3-14 Functional Assessments Reflecting Post-Operation Recovery Status

Study 008a Functional assessment	400 mg IVIb (N=134)	800 mg IVIb (N=138)	Placebo (N=134)
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Time to GI Motility¹ (hrs)			
Number Censored (%)	3 (2%)	2 (1%)	2 (1%)
Mean (SD)	20.1 (1.27)	21.6 (1.50)	24.6 (1.78)
Median (95% CI)	21.1 (15.0, 23.1)	21.0 (17.3, 23.3)	23.1 (21.0, 24.6)
Difference in means from placebo	4.5 (18.3%)	3 (12.2%)	
Difference in medians from placebo	2 (8.7%)	2.1 (9.1%)	
p-value ²	0.039	0.220	
Time to Resumption of Liquid Intake¹ (hrs)			
Number Censored (%)	5 (4%)	2 (1%)	0
Mean (SD)	17.7 (1.24)	19.0 (1.74)	22.7 (5.55)
Median (95% CI)	15.8 (11.7, 20.3)	15.8 (13.6, 19.3)	16.1 (13.3, 18.1)
Difference in means from placebo	5 (22.0%)	3.7 (16.3%)	
Difference in medians from placebo	0.3 (1.9%)	0.3 (1.9%)	
p-value ²	0.982	0.930	
Time to Resumption of Solid Diet¹ (hrs)			
Number Censored (%)	9 (7%)	3 (2%)	4 (3%)
Mean (SD)	36.8 (2.62)	34.1 (2.42)	51.2 (9.80)
Median (95% CI)	28.9 (24.7, 33.2)	28.8 (26.2, 31.8)	32.0 (28.7, 35.8)
Difference in means from placebo	14.4 (28.1%)	17.1 (33.4%)	
Difference in medians from placebo	3.1 (9.7%)	3.2 (10.0%)	
p-value ²	0.397	0.065	
Time to Resumption of Ambulation¹ (hrs)			
Number Censored (%)	6 (4%)	1 (<1%)	1 (<1%)
Mean (SD)	30.4 (1.31)	29.0 (1.32)	33.9 (6.16)
Median (95% CI)	25.8 (23.9, 29.5)	24.6 (23.4, 26.5)	23.7 (22.4, 25.7)
Difference in means from placebo	3.5 (10.3%)	4.9 (14.5%)	
Difference in medians from placebo	-2.1 (-8.9%)	-0.9 (-3.8%)	
p-value ²	0.322	0.996	
Length of Hospital Stay¹ (hrs)			
Mean (SD)	77.5 (47.70)	83.4 (57.89)	81.9 (52.87)
Median	69.6	71.4	69.5
Min, Max	23.6, 335.6	23.5, 534.3	22.5, 334.9
Difference in means from placebo	4.4 (5.4%)	-1.5 (-1.8%)	
Difference in medians from placebo	-0.1 (-0.1%)	-1.9 (-2.7%)	
p-value ²	0.469	0.644	

GI = gastrointestinal; SD = standard deviation; CI = confidence interval

1. All the time to event was counted from the start of the initial infusion. Patients who did not have the specified event are censored at the last study visit.

2. The p-values are based on the log-rank statistic.

Source: Tables 14.2.5 to 14.2.9 on pages 287 to 291 and section 11.4.1.9 on page 84 of the report for Study 008a.

5.3.3.3 Summary of Findings and Discussions

Study conduct

The treatment groups in Study 008a were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight.

Dropouts accounted for 12% (49/406) of the study population, mainly due to AEs and treatment failure. Dropouts due to AEs were balanced between the treatment groups. Noticeably fewer patients dropped out due to treatment failure in the IVIb 800 mg group than the IVIb 400 mg and placebo groups (1% versus 4% and 5%, respectively).

Major and minor protocol deviations were 41% and 77%, respectively, and were mainly due to study medication administration error, taking excluded medication, and missed assessments. Protocol deviations were balanced between the treatment groups and were not considered as having differential impact on study outcomes.

Efficacy

The efficacy results are summarized in the table below in terms of treatment differences from placebo to examine the effect sizes for clinical interpretation of the findings. The reduction of morphine use in the first 24 hours post surgery was about 10% (difference in means) to 20% (22% difference in medians), representing a reduction of morphine use by 5-10 mg in 24 hours for the IVIb 800 mg group and less than 6% (5% difference in mean and 2% difference in median) for the IVIb 400 mg group. The treatment differences between the active treatments and placebo based on comparison of LSMeans of the original data were not statistically significant according to the Applicant's and Dr. Norton's analyses.

Time-specific PI measured at mid-dosing interval and end-of-dosing interval during the first 48 hours showed noticeable separations of mean PI from placebo pain curve in a range of 0.5 to 1.0 units (on a 0-10 point scale) from 9 to 21 hours for the 400 mg dose and 0.5 to 1.2 units from 9 to 33 hours for the 800 mg doses and sizable separation of median PI from placebo in a range of approximately 10-20% from 9 to 21 hours for the 400 mg dose and 10-40% from 9 to 36 hours for the 800 mg dose.

In comparison of active treatments (IVIb 400 and 800 mg) to placebo the noticeable treatment differences in morphine-related AEs included 10-11% reduction in any morphine-related AE among those listed in the table below, 11-14% reduction in post-operative vomiting or need for anti-emetic medication, and 10-20% reduction in Combined Safety Assessment (CSA) of morphine-related AEs. In assessment of functional recovery (time to GI activity, ambulation, and hospital discharge) that might be affected by morphine treatments, the noticeable reduction in means from placebo included 12-18% reduction in time to GI motility, 16-22% reduction in time to resumption of liquid intake, 28-33% reduction in time to resumption of solid diet, and 10-15% reduction in time to ambulation. Treatment differences in means from placebo in functional recovery could also be summarized as 3-5 hours of reduction in time to GI motility and resumption of liquid intake and ambulation. The noticeable reduction in medians from placebo included about 10% reduction in time to GI motility and time to resumption of solid diet.

Table 5.3.3-15 Summary of Efficacy Findings

Study 008a Efficacy summary	Effect size of treatment differences from placebo	
	400 mg IVIb (n=134)	800 mg IVIb (n=138)
Primary efficacy endpoint		
Reduction in mean morphine use in 24 hours, mg (%↓)	2.6 (5.3%)	5.1 (10.4%)
Reduction in median morphine use in 24 hours, mg (%↓)	1.3 (2.3%)	2.8 (21.6)
Difference in LSMeans (original data)	2.6 (5.3%)	5.1 (10.4%)

Difference in LSMMeans (transformed data)		14.5 (6.5%)	32.4 (14.5%)*
Secondary efficacy endpoints: PI (mid- & end-of-dosing)			
<i>Time-specific PI for pain with movement</i>			
Stat. significant difference in LSMMeans (transformed data)		*Hours 9, 15-21, 30, 36-48	*Hours 9-48
Reduction in mean PI of ≥ 0.5 units		0.5-1.0 units ↓ in Hours 9-21	0.5-1.1 units ↓ in Hours 9-36
Reduction in median PI of $\geq 10\%$		10-22% ↓ in Hours 9-21	12-22% ↓ in Hours 9-30, 36, 45
<i>Time-specific PI for pain at rest</i>			
Stat. significant difference in LSMMeans (transformed data)		*Hours 15, 21, 30-48	*Hours 9-48
Reduction in mean PI of ≥ 0.5 units		0.5-0.9 units ↓ in Hours 9, 15-21, 30-33	0.6-1.2 units ↓ in Hours 9-33
Reduction in median PI of $\geq 10\%$		11-21% ↓ in Hours 9, 15, 21, 30-36	13-43% ↓ in Hours 9, 15-36, 48
Secondary efficacy endpoints: morphine-related AEs			
Difference in mean score of CSA for morphine-related AEs		0.2 (20%)*	0.1 (10%)
Difference in \geq one morphine-related AE (%)		11%	10%
Difference in diffuse pruritus (%)		3%	4%
Difference in overt respiratory depression (%)		~1%	-3%
Difference in need for post-operative urinary catheter (%)		0	0
Post-op vomiting or need for anti-emetic medication (%)		14%*	11%
Richmond Agitation Sedation Score of ≤ -3 in 48 hrs (%)		4%	-2%
Secondary efficacy endpoints: functional assessments			
Difference in time to GI motility	Mean	4.5 (18.3%)*	3 (12.2%)
	Median	2 (8.7%)	2.1 (9.1%)
Difference time to resumption of liquid intake	Mean	5 (22.0%)	3.7 (16.3%)
	Median	0.3 (1.9%)	0.3 (1.9%)
Difference in time to resumption of solid diet	Mean	14.4 (28.1%)	17.1 (33.4%)
	Median	3.1 (9.7%)	3.2 (10.0%)
Difference in time to resumption of ambulation	Mean	3.5 (10.3%)	4.9 (14.5%)
	Median	-2.1 (-8.9%)	-0.9 (-3.8%)
Difference in length of hospital stay	Mean	4.4 (5.4%)	-1.5 (-1.8%)
	Median	-0.1 (-0.1%)	-1.9 (-2.7%)

*Note: Statistically significant difference.
Refer to all the efficacy tables in this section.

5.3.3.4 Conclusion

Taking all the effects into consideration, 10-20% reduction of 24-hour morphine use (treatment difference was not statistically significant based on analyses of untransformed data) coupled with noticeable pain curve separation in means (0.5-1.1 units on a 0-10 scale) and sizable pain reduction in medians (12-22%) by time-specific measurements, about 10% or more reduction in selected, any, or combined morphine-related AEs, and 3-5 hours earlier return of GI motility and resumption of fluid intake and ambulation, supplementing ibuprofen to morphine analgesia have relatively small additional therapeutic benefit.

The IVIb 400 mg dose was shown to have smaller effects on morphine reduction and analgesia than 800 mg dose and similar effects on reduction of morphine-related AEs and functional recovery as the 800 mg dose.

5.3.3.5 Appendix

Eligibility criteria

Inclusion Criteria

Patients were going to be required to meet the following criteria for inclusion in the study if they:

1. Were scheduled for elective single surgical site orthopedic surgery (knee, hip or shoulder joint replacement or reconstruction) or gynecologic/abdominal (total abdominal hysterectomy, gall bladder, bowel or lower abdominal general investigative surgery) with anticipated need for post-operative narcotic analgesia
2. Had adequate IV access
3. Had anticipated hospital stay ≥ 24 hours

Exclusion Criteria

Patients were going to be excluded from this study if they had any of the following:

1. Were unable to make a reliable self-report of pain intensity to pain relief
2. Were less than 18 years of age
3. Were greater than 70 years of age
4. Used NSAIDs within 12 hours prior to dosing
5. Were taking warfarin, lithium, combination of ACE-inhibitors and furosemide.
6. Had anemia and/or a history or evidence of asthma or heart failure.
7. Had history of allergy or hypersensitivity to any component of IVIb, aspirin (or aspirin related products), NSAIDs, or COX-2 inhibitors
8. Were pregnant or nursing
9. Had history of severe head trauma that required current hospitalization, intracranial surgery or stroke within the previous 30 days, or any history of intracerebral arteriovenous malformation, cerebral aneurism or CNS mass lesion
10. Weighed less than 30kg
11. Had a history of congenital bleeding diathesis (e.g., hemophilia) or any active clinically significant bleeding, or have underlying platelet dysfunction including (but not limited to) idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, or congenital platelet dysfunction
12. Had GI bleeding that required medical intervention within the previous 6 weeks (unless definitive surgery has been performed)
13. Had a platelet count less than 30,000/mm³ determined within the 28 days prior to surgery
14. Had pre-existing dependence on narcotics or known tolerance to opioids.
15. Were not able to understand the requirements of the study, not willing to provide written informed consent (as evidenced by signature on an informed consent document approved by an Institutional Review Board [IRB]), to abide by the study restrictions, or to return for the required assessments
16. Refused to provide written authorization for use and disclosure of protected health information

Time-specific measurements of pain intensity

Appendix Table 5.3.3-A1 Mean PI Score Measured with Movement (48 Hours), ITT

Study 008a PI with movement	VAS Score by Treatment Group	400 mg IVib (N=134)	800 mg IVib (N=138)	Placebo (N=134)
1 Hour Post-dose	VAS Score Mean ± SD	7.5 ± 2.61	7.3 ± 2.67	7.5 ± 2.48
	Transformed VAS Score: LS Means (SE) ¹	234.7 (12.71)	216.5 (12.24)	224.1 (12.92)
	LS Means Difference	10.6	-7.6	
	p-value vs Placebo ²	0.401	0.547	
2 Hour Post-dose	VAS Score Mean ± SD	7.1 ± 2.33	6.6 ± 2.53	6.9 ± 2.34
	Transformed VAS Score: LS Means (SE) ¹	240.3 (12.98)	208.5 (12.50)	224.6 (13.19)
	LS Means Difference	15.6	-16.2	
	p-value vs Placebo ²	0.226	0.207	
3 Hour Post-dose	VAS Score Mean ± SD	6.3 ± 2.65	6.0 ± 2.72	6.3 ± 2.63
	Transformed VAS Score: LS Means (SE) ¹	236.6 (12.83)	220.5 (12.36)	233.6 (13.04)
	LS Means Difference	3.1	-13.1	
	p-value vs Placebo ²	0.811	0.301	
6 Hour Post-dose*	VAS Score Mean ± SD	5.6 ± 2.67	5.3 ± 2.59	5.7 ± 2.76
	Transformed VAS Score: LS Means (SE) ¹	229.5 (13.65)	219.3 (13.15)	230.7 (13.87)
	LS Means Difference	-1.2	-11.3	
	p-value vs Placebo ²	0.931	0.401	
9 Hour Post-dose	VAS Score Mean ± SD	4.6 ± 2.39	4.6 ± 2.47	5.4 ± 2.63
	Transformed VAS Score: LS Means (SE) ¹	207.5 (13.63)	207.6 (13.13)	246.6 (13.85)
	LS Means Difference	-39.1	-39.0	
	p-value vs Placebo ²	0.004	0.004	
12 Hour Post-dose*	VAS Score Mean ± SD	4.5 ± 2.30	4.3 ± 2.41	5.0 ± 2.67
	Transformed VAS Score: LS Means (SE) ¹	215.2 (13.46)	206.1 (12.96)	239.9 (13.67)
	LS Means Difference	-24.8	-33.9	
	p-value vs Placebo ²	0.065	0.011	
15 Hour Post-dose	VAS Score Mean ± SD	4.0 ± 2.14	4.1 ± 2.21	5.0 ± 2.55
	Transformed VAS Score: LS Means (SE) ¹	189.1 (13.51)	206.9 (13.01)	240.9 (13.73)
	LS Means Difference	-51.8	-34.0	
	p-value vs Placebo ²	<0.001	0.011	
18 Hour Post-dose*	VAS Score Mean ± SD	4.3 ± 2.06	4.1 ± 2.38	5.0 ± 2.39
	Transformed VAS Score: LS Means (SE) ¹	187.2 (13.62)	174.6 (13.12)	216.3 (13.84)
	LS Means Difference	-29.1	-41.7	
	p-value vs Placebo ²	0.032	0.002	
21 Hour Post-dose	VAS Score Mean ± SD	4.1 ± 2.21	3.8 ± 2.40	4.9 ± 2.45
	Transformed VAS Score: LS Means (SE) ¹	193.3 (13.55)	175.5 (13.05)	222.8 (13.77)
	LS Means Difference	-29.5	-47.3	
	p-value vs Placebo ²	0.029	<0.001	
24 Hour Post-dose*	VAS Score Mean ± SD	4.6 ± 2.22	3.7 ± 2.41	4.5 ± 2.45
	Transformed VAS Score: LS Means (SE) ¹	214.7 (13.05)	161.8 (12.57)	205.6 (13.27)
	LS Means Difference	9.2	-43.8	
	p-value vs Placebo ²	0.481	<0.001	
27 Hour Post-dose	VAS Score Mean ± SD	4.4 ± 1.80	3.6 ± 1.82	4.4 ± 1.94
	Transformed VAS Score: LS Means (SE) ¹	230.2 (13.64)	150.6 (13.13)	206.4 (13.86)
	LS Means Difference	23.8	-55.8	
	p-value vs Placebo ²	0.080	<0.001	
30 Hour Post-dose*	VAS Score Mean ± SD	4.0 ± 1.99	3.5 ± 1.81	4.1 ± 2.01
	Transformed VAS Score: LS Means (SE) ¹	225.5 (14.00)	164.3 (13.49)	195.5 (14.23)
	LS Means Difference	29.9	-31.2	
	p-value vs Placebo ²	0.032	0.025	
33 Hour Post-dose	VAS Score Mean ± SD	3.9 ± 1.59	3.4 ± 1.84	3.9 ± 1.68
	Transformed VAS Score: LS Means (SE) ¹	223.3 (13.41)	149.7 (12.92)	217.6 (13.63)
	LS Means Difference	5.7	-67.9	
	p-value vs Placebo ²	0.667	<0.001	
36 Hour Post-dose*	VAS Score Mean ± SD	3.6 ± 1.51	3.5 ± 1.80	4.0 ± 1.66

	Transformed VAS Score: LS Means (SE) ¹	188.4 (13.76)	163.2 (13.25)	233.6 (13.98)
	LS Means Difference	-45.2	-70.4	
	p-value vs Placebo ²	0.001	<0.001	
39 Hour Post-dose	VAS Score Mean ± SD	3.1 ± 1.49	3.5 ± 1.44	3.5 ± 1.50
	Transformed VAS Score: LS Means (SE) ¹	150.3 (13.55)	231.9 (13.05)	189.1 (13.77)
	LS Means Difference	-38.9	42.7	
	p-value vs Placebo ²	0.004	0.002	
42 Hour Post-dose*	VAS Score Mean ± SD	3.3 ± 1.51	3.3 ± 1.68	3.4 ± 1.57
	Transformed VAS Score: LS Means (SE) ¹	197.4 (13.83)	160.8 (13.32)	227.8 (14.06)
	LS Means Difference	-30.4	-66.9	
	p-value vs Placebo ²	0.027	<0.001	
45 Hour Post-dose	VAS Score Mean ± SD	3.4 ± 1.33	2.7 ± 1.50	3.1 ± 1.43
	Transformed VAS Score: LS Means (SE) ¹	272.3 (12.20)	127.0 (11.75)	193.5 (12.40)
	LS Means Difference	78.9	-66.5	
	p-value vs Placebo ²	<0.001	<0.001	
48 Hour Post-dose*	VAS Score Mean ± SD	3.2 ± 1.12	2.1 ± 1.30	2.3 ± 0.98
	Transformed VAS Score: LS Means (SE) ¹	287.8 (11.18)	118.7 (10.77)	183.4 (11.36)
	LS Means Difference	104.4	-64.7	
	p-value vs Placebo ²	<0.001	<0.001	

*Note: End of dose interval, assessment just prior to next scheduled dose.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 25 on pages 68 to 70 of the report for Study 008a.

Appendix Table 5.3.3-A2 Mean PI Score Measured at Rest (48 Hours), ITT

Study 008b PI at rest	VAS Score by Treatment Group	400 mg IVib (N=134)	800 mg IVib (N=138)	Placebo (N=134)
1 Hour Post-dose	VAS Score Mean ± SD	6.7 ± 2.91	6.4 ± 3.10	6.6 ± 2.74
	Transformed VAS Score: LS Means (SE) ¹	230.2 (12.32)	222.5 (11.87)	219.3 (12.52)
	LS Means Difference	10.8	3.2	
	p-value vs Placebo ²	0.376	0.793	
2 Hour Post-dose	VAS Score Mean ± SD	5.9 ± 2.70	5.5 ± 2.72	5.7 ± 2.34
	Transformed VAS Score: LS Means (SE) ¹	236.2 (12.57)	220.6 (12.11)	220.9 (12.78)
	LS Means Difference	15.3	-0.3	
	p-value vs Placebo ²	0.220	0.982	
3 Hour Post-dose	VAS Score Mean ± SD	5.2 ± 2.76	4.7 ± 2.66	5.1 ± 2.73
	Transformed VAS Score: LS Means (SE) ¹	234.6 (12.98)	218.2 (12.50)	230.1 (13.19)
	LS Means Difference	4.5	-11.8	
	p-value vs Placebo ²	0.728	0.356	
6 Hour Post-dose*	VAS Score Mean ± SD	4.3 ± 2.57	4.0 ± 2.46	4.3 ± 2.66
	Transformed VAS Score: LS Means (SE) ¹	232.0 (13.09)	226.4 (12.61)	229.3 (13.30)
	LS Means Difference	2.7	-3.0	
	p-value vs Placebo ²	0.836	0.819	
9 Hour Post-dose	VAS Score Mean ± SD	3.4 ± 2.36	3.0 ± 2.24	4.0 ± 2.59
	Transformed VAS Score: LS Means (SE) ¹	223.0 (12.96)	202.2 (12.48)	244.9 (13.17)
	LS Means Difference	-22.0	-42.8	
	p-value vs Placebo ²	0.089	<0.001	
12 Hour Post-dose*	VAS Score Mean ± SD	3.1 ± 2.17	2.8 ± 2.19	3.5 ± 2.57
	Transformed VAS Score: LS Means (SE) ¹	227.6 (12.97)	213.7 (12.50)	240.1 (13.18)
	LS Means Difference	-12.5	-26.4	
	p-value vs Placebo ²	0.333	0.040	
15 Hour Post-dose	VAS Score Mean ± SD	2.7 ± 2.02	2.6 ± 1.98	3.6 ± 2.48
	Transformed VAS Score: LS Means (SE) ¹	205.5 (13.28)	204.9 (12.80)	243.6 (13.50)
	LS Means Difference	-38.1	-38.7	
	p-value vs Placebo ²	0.004	0.003	
18 Hour Post-dose*	VAS Score Mean ± SD	2.9 ± 1.91	2.7 ± 2.19	3.4 ± 2.15
	Transformed VAS Score: LS Means (SE) ¹	197.1 (13.55)	183.2 (13.05)	222.1 (13.77)

	LS Means Difference	-25.0	-38.9	
	p-value vs Placebo ²	0.064	0.004	
21 Hour Post-dose	VAS Score Mean ± SD	2.8 ± 2.11	2.3 ± 2.05	3.5 ± 2.42
	Transformed VAS Score: LS Means (SE) ¹	198.3 (13.22)	173.3 (12.74)	232.5 (13.44)
	LS Means Difference	-34.3	-59.2	
	p-value vs Placebo ²	0.009	<0.001	
24 Hour Post-dose*	VAS Score Mean ± SD	3.0 ± 1.99	2.5 ± 2.28	3.2 ± 2.36
	Transformed VAS Score: LS Means (SE) ¹	211.9 (13.44)	178.9 (12.94)	224.5 (13.66)
	LS Means Difference	-12.6	-45.6	
	p-value vs Placebo ²	0.345	<0.001	
27 Hour Post-dose	VAS Score Mean ± SD	2.8 ± 1.65	2.3 ± 1.69	3.0 ± 1.73
	Transformed VAS Score: LS Means (SE) ¹	236.1 (13.69)	166.7 (13.19)	221.4 (13.91)
	LS Means Difference	14.7	-54.7	
	p-value vs Placebo ²	0.279	<0.001	
30 Hour Post-dose*	VAS Score Mean ± SD	2.4 ± 1.76	2.3 ± 1.60	2.9 ± 1.75
	Transformed VAS Score: LS Means (SE) ¹	195.2 (13.82)	177.0 (13.31)	234.2 (14.04)
	LS Means Difference	-39.1	-57.2	
	p-value vs Placebo ²	0.005	<0.001	
33 Hour Post-dose	VAS Score Mean ± SD	2.5 ± 1.38	2.1 ± 1.60	3.1 ± 1.50
	Transformed VAS Score: LS Means (SE) ¹	194.4 (12.83)	148.0 (12.35)	264.8 (13.03)
	LS Means Difference	-70.4	-116.8	
	p-value vs Placebo ²	<0.001	<0.001	
36 Hour Post-dose*	VAS Score Mean ± SD	2.3 ± 1.49	2.2 ± 1.67	2.6 ± 1.59
	Transformed VAS Score: LS Means (SE) ¹	196.3 (13.41)	160.8 (12.91)	239.1 (13.62)
	LS Means Difference	-42.9	-78.4	
	p-value vs Placebo ²	0.001	<0.001	
39 Hour Post-dose	VAS Score Mean ± SD	2.1 ± 1.37	2.5 ± 1.46	1.9 ± 1.43
	Transformed VAS Score: LS Means (SE) ¹	199.5 (13.21)	239.0 (12.72)	144.0 (13.42)
	LS Means Difference	55.5	95.0	
	p-value vs Placebo ²	<0.001	<0.001	
42 Hour Post-dose*	VAS Score Mean ± SD	2.0 ± 1.26	2.0 ± 1.50	2.0 ± 1.40
	Transformed VAS Score: LS Means (SE) ¹	240.0 (13.69)	157.0 (13.19)	204.1 (13.91)
	LS Means Difference	35.9	-47.1	
	p-value vs Placebo ²	0.009	<0.001	
45 Hour Post-dose	VAS Score Mean ± SD	2.4 ± 1.17	1.8 ± 1.41	2.0 ± 1.35
	Transformed VAS Score: LS Means (SE) ¹	272.7 (12.16)	125.8 (11.71)	204.1 (12.35)
	LS Means Difference	68.6	-78.3	
	p-value vs Placebo ²	<0.001	<0.001	
48 Hour Post-dose*	VAS Score Mean ± SD	1.6 ± 1.04	1.3 ± 1.20	1.5 ± 0.80
	Transformed VAS Score: LS Means (SE) ¹	271.0 (11.89)	127.6 (11.46)	209.0 (12.09)
	LS Means Difference	62.0	-81.4	
	p-value vs Placebo ²	<0.001	<0.001	

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 31 on pages 75 to 77 of the report for Study 008a.

5.3.4 Post Surgical Pain Study 008b

5.3.4.1 Protocol

Study CPI-CL-008b shared the same protocol and six amendments and had mostly the same components of the study design as Study CPI-CL-008a. The features of the study unique to Study 008b were summarized in Amendment 7 (dated December 8, 2006), which included selecting 800 mg dose to be the active treatment, increasing sample size to 145 patients per treatment group, and limiting the type of surgery to abdominal hysterectomy.

The reviewer's brief summary of the major components of the protocol is presented in the table below.

Table 5.3.4-1 Reviewer's Summary of the Protocol

<i>Study #</i>	CPI-CL-008b
<i>Objectives</i>	To study multiple-dose analgesic effects (targeted at reduced use of narcotics), tolerability and safety of IV ibuprofen 800 mg in hospitalized patients with postoperative pain after abdominal hysterectomy.
<i>Design</i>	Multiple-center (10 USA sites), randomized, double-blind, placebo-controlled, parallel, multiple-dose (q6 hours for up to 5 days)
<i>Sample population</i>	Hospitalized adult patients scheduled for elective abdominal hysterectomy with anticipated need for post-operative narcotic analgesia, who had adequate intravenous access and anticipated hospital stay for ≥ 24 hours
<i>Treatment</i>	IV Ib 800 mg, or matching placebo, 30-minute IV infusion initiated about 30 minutes before the end of surgery, q6 hours for 2 days, and then PRN for 3 more days; Morphine 1-2 mg (or more based on need) q5 minutes upon request or PCA after surgery
<i>Treatment discontinuation</i>	Treatment required to be discontinued if in need of other narcotics or NSAIDs; Treatment allowed to be discontinued in the following cases: <ul style="list-style-type: none"> • Ability to tolerate oral pain medication • Resolution of pain • No IV Access • Discharge from the hospital
<i>Raw efficacy data</i>	Pain intensity at rest and with movement by 11-point (0-10) visual analog scale (VAS) at Hours 1 and 3 and q3 hours thereafter up to 48 hours from the start of the initial dose, and then daily through Day 5 during PRN dosing
<i>Efficacy parameter</i>	<i>Primary:</i> total morphine usage in 24 hours <i>Secondary:</i> <ul style="list-style-type: none"> • PI at rest and with movement: time-specific measurements up to H48 • Time to first subsequent narcotic analgesia for breakthrough pain (time to treatment failure) • Nocturnal awakenings due to pain • Reduction of opioid-related side effects defined by <ul style="list-style-type: none"> ○ Time to GI motility (q6 hours): return of bowel sounds, flatulence, or bowel movement ○ Resumption of ambulation ○ Resumption of liquid intake and solid diet ○ Length of hospital stay ○ Combined Safety Assessment: <ul style="list-style-type: none"> ◆ Diffuse pruritus ◆ Overt respiratory depression requiring treatment ◆ Need for post-operative urinary indwelling catheter ◆ Post-operative vomiting or need for anti-emetic medication ◆ Richmond Agitation Sedation Scale (<-3)
<i>Safety monitoring</i>	<ul style="list-style-type: none"> • Adverse events • Vital signs at 1, 2, 3, 6, 9, 12, and 24 hour after the initial dose and then daily up to Day 7 • Routine lab tests at baseline and 24, 48, 72, 120, and 172 hours (Days 1, 2, 3, 5, and 7) • Transfusion monitoring

5.3.4.2 Results

Demographic and other baseline characteristics

The sample population consisted of 319 patients enrolled who received the study medication, with an age range of 22 to 65 years and a mean of 43 years. Of the 319 female patients, 39% were Caucasian, 55% were African American, and 6% were Hispanic. The treatment groups were approximately balanced with regard to demographic characteristics such as age, race, height, and weight. Baseline pain intensity was not planned to be obtained.

Table 5.3.4-2 Demographics and Baseline Characteristics

Study 008b Baseline Characteristics	800 mg IVIb (n=166)	Placebo (n=153)	Total (n=319)
Age (years)			
Mean (SD)	42 (7.0)	42 (7.2)	42 (7.1)
Median	43	42	43
Minimum, Maximum	22, 62	22, 65	22, 65
Gender, n (%)			
Male	0	0	0
Female	166 (100%)	153 (100%)	319 (100%)
Race, n (%)			
Caucasian	71 (43%)	52 (34%)	123 (39%)
Black	84 (51%)	91 (59%)	175 (55%)
Hispanic	11 (7%)	8 (5%)	19 (6%)
Other	0	2 (1%)	2 (<1%)
Height (cm)			
Mean (SD)	163.8 (8.22)	163.0 (7.56)	163.4 (7.91)
Median	162.6	165.0	162.6
Minimum, Maximum	106.7, 180.3	142.2, 180.3	106.7, 180.3
Weight (kg)			
Mean (SD)	83.9 (18.67)	83.0 (19.07)	83.5 (18.83)
Median	83.7	82.7	82.7
Minimum, Maximum	45.9, 150.9	48.2, 147.7	45.9, 150.9

SD = standard deviation; Min = minimum; Max = maximum

Source: Appendix Table 14.1.3 on page 129 of the report for Study 008b.

Patient disposition

Close to 90% of the 319 patients completed the study. There were 37 cases of dropouts, 15 from the 800 mg IVIb group and 22 from the placebo group. The main reasons for dropouts were treatment failure (5% in the IVIb 800 mg group and 8% in the placebo group) and AE (3% in each of the two groups). Very few patients per treatment group dropped out for the other reasons such as protocol violation, withdrawal at patient's request, and noncompliance with protocol as summarized in the table below.

Table 5.3.4-3 Patient Disposition

Study 008b Patient Disposition	800 mg IVIb (n=166)	Placebo (n=153)	Total (n=319)
All Treated Patients	166	153	319
Discontinued n (%)	15 (9%)	22 (14%)	37 (12%)
Reason for discontinuation			
Treatment failure	8 (5%)	12 (8%)	20 (6%)
Adverse Event	5 (3%)	5 (3%)	10 (3%)
Protocol violation	1 (<1%)	2 (1%)	3 (1%)
Withdrawal at patient's request	1 (<1%)	1 (<1%)	2 (<1%)
Noncompliance with protocol	0	2 (1%)	2 (<1%)

Source: Tables on page 8 of the submission dated March 20, 2009.

Protocol violations

Protocol violations were reported in 21% patients mainly as taking excluded medication (20%). Protocol deviations were reported in 62% patients, mainly as missing or miss-timed assessments. The specific types of protocol violations and deviations were balance between the treatment groups and were not expected to have differential impact on study outcomes.

Table 5.3.4-4 Summary of Protocol Violations and Deviations

Study 008b Protocol violation/deviation	800 mg IVIb (n=166)		Placebo (n=153)		Total (n=319)	
	cases	N (%)	cases	N (%)	cases	N (%)
Protocol violations: #cases and patients n (%)	42	32 (19%)	42	36 (24%)	84	68 (21%)
Restricted medication	34	30 (18%)	37	33 (22%)	71	63 (20%)
CTM administration error (outside ±60 min window)	7	5 (3%)	1	1 (<1%)	8	6 (2%)
Consenting error	1	1 (<1%)	3	3 (2%)	4	4 (1%)
Missing assessment of morphine use	0		1	1 (<1%)	1	1 (<1%)
Protocol deviations: #cases and patients n (%)	211	104 (63%)	205	95 (62%)	416	199 (62%)
Incomplete lab test	79	59 (36%)	86	51 (33%)	165	110 (34%)
Miss-timed lab test	34	26 (16%)	34	29 (19%)	68	55 (17%)
Miss-timed vital signs	40	30 (18%)	26	21 (14%)	66	51 (16%)
Miss-timed VAS (pain) and/or RASS (agitation/sedation)	19	12 (7%)	19	12 (8%)	38	24 (8%)
Missing or miss recorded assessments	8	7 (4%)	11	9 (6%)	19	16 (5%)
Miss-timed Day 14 contact	9	9 (5%)	8	8 (5%)	17	17 (5%)
Miss-timed assessment of morphine use	10	9 (5%)	6	6 (4%)	16	15 (5%)
Missing record of nocturnal awakenings	4	4 (2%)	6	6 (4%)	10	10 (3%)
Dosing deviations	4	4 (2%)	4	3 (2%)	8	7 (2%)
Miss-timed screening	2	2 (1%)	2	2 (1%)	4	4 (1%)
Randomization error	1	1 (<1%)	1	1 (<1%)	2	2 (<1%)
Use of restricted medication after 24 hours	1	1 (<1%)	1	1 (<1%)	2	2 (<1%)
Discharge vital not done at specified time	0	0	1	1 (<1%)	1	1 (<1%)

CTM = clinical trial material; lab = laboratory; VAS = Visual Analogue Scale; RASS = Richmond Agitation Sedation Score.
Source: Tables 14.1.5 on page 10 of the March 20, 2009 submission.

Exposure

The exposure information is summarized in the table below. More than 80% of patients in each treatment group (86% on IVIb 800 mg and 83% on placebo) received five doses of treatment. Only a few patients received six or more doses.

Table 5.3.4-5 Exposure

Study 008b Exposure	800 mg IVIb (n=166)	Placebo (n=153)	800 mg IVIb (n=166)	Placebo (n=153)
#Doses, n (%)	Distribution		Cumulative	
1	6 (4%)	13 (8%)	166 (100%)	153 (100%)
2	3 (2%)	2 (1%)	160 (96%)	140 (92%)
3	2 (1%)	1 (<1%)	157 (95%)	138 (90%)
4 (Day 1)	12 (7%)	10 (7%)	155 (93%)	137 (90%)
5	141 (85%)	123 (80%)	143 (86%)	127 (83%)
6	2 (1%)	2 (1%)	2 (1%)	4 (3%)
7	0	0	0	2 (1%)
8 (Day 2)	0	1 (<1%)	0	2 (1%)
>8	0	1 (<1%)	0	1 (<1%)

Source: Supplementary tables on pages 9 and 11 of the submission dated January 19, 2009.

Efficacy results

Primary efficacy endpoint: morphine usage during the first 24 hours following surgery

The total amount of morphine used in the first 24 hours after surgery is summarized in the table below. The differences between IVIb 800 mg and placebo were 8.6 mg (47.3 mg versus 55.9 mg) representing a 15.4%

reduction in mean and 10.5 mg (43.5 mg versus 54.0 mg) representing a 19.4% reduction in median. Therefore, the 24-hour use of morphine was reduced by 15-19% with IVIb 800 mg treatment. Treatment differences in LS-means of the original and transformed data were all statistically significant between the two treatments. The results were confirmed by the statistical reviewer Dr. Norton's analyses (refer to the Evaluation of Efficacy Section of Statistical Review for detail).

Table 5.3.4-6 Reduction in Morphine Use in First 24 Hours Post Surgery

Study 008b 1 ^o efficacy endpoint morphine use in 1 st 24 hours	800 mg IVIb (n=166)	Placebo (n=153)
Morphine Requirement (mg)		
Mean (SD)	47.3 (25.6)	55.9 (20.6)
<i>Difference (mg) from placebo & % of reduction</i>	<i>8.6 (15.4%)</i>	
Median	43.5	54.0
<i>Difference (mg) from placebo & % of reduction</i>	<i>10.5 (19.4%)</i>	
Min, Max	4.0, 143.3	14.5, 114.0
Morphine Requirement (mg)		
LSMeans (SE) ¹	48.7 (2.3)	57.0 (2.4)
LSMean difference from placebo	8.3	
p-value ²	<0.001	
Transformed Morphine Requirement (mg)		
LSMeans (SE) ³	12.1 (0.4)	13.6 (0.4)
LSMean difference from placebo	1.5	
p-value ²	<0.001	

SD = standard deviation; LSMeans = least square means; SE = standard error;

1. LS means are adjusted for age group, weight group, randomization center, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

3. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, and treatment group.

Source: Table 13 on page 55 and Table 14.2.1.1.1 on page 135 of the report for Study 008b.

Secondary efficacy endpoints:

PI for pain with movement

Mean PI with Movement in 48 hours in ITT population

The mean pain intensity (PI) scores for pain with movement recorded on a scale of 0 to 10 are summarized in the table below and presented in the graph following the table. Treatment differences in LS-means of transformed morphine requirement (refer to statistical review for discussion on data transformation) for pain with movement were statistically significant between the IVIb 800 mg group and placebo from 15 to 24 hours. The effect sizes of these statistically significant treatment differences were 0.9 to 1.2 units. Treatment differences on a magnitude of 0.5 to 1.2 units were noticed from 9 to 24 hours.

Table 5.3.4-7 Time-Specific Mean PI with Movement in 24 Hours in ITT population

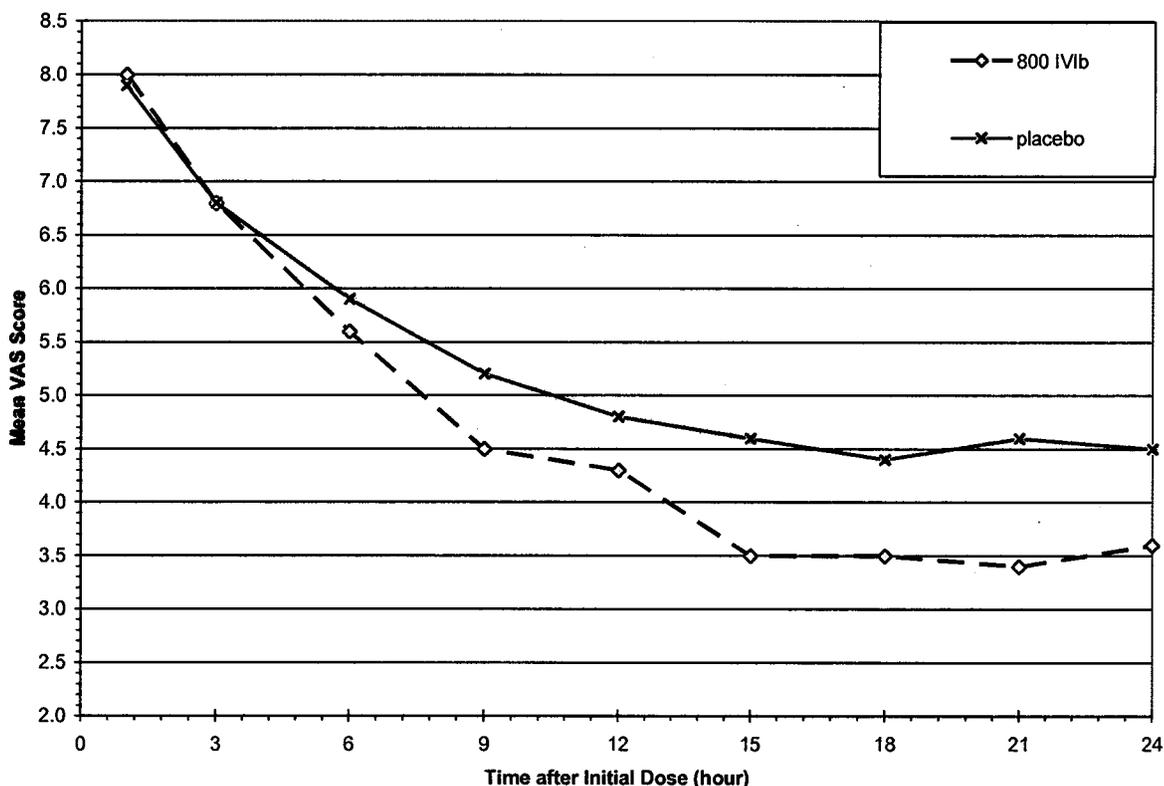
Hours	0	1	3	6	9	12	15	18	21	24
Mean PI with movement										
800 IVIb		8.0	6.8	5.6	4.5	4.3	3.5	3.5	3.4	3.6
placebo		7.9	6.8	5.9	5.2	4.8	4.6	4.4	4.6	4.5
Difference in mean from placebo										
		-0.1	0	0.3	0.7	0.5	1.1	0.9	1.2	0.9
Statistically significant treatment differences versus placebo in LS-means of transformed data										
							x	x	x	X

PI = pain intensity

Source: Table 15 on pages 56 to 57 of the report for Study 008b (also included in the Appendix at the end of the review of this study).

Figure 5.3.4-1 Time-Specific Mean PI with Movement in 24 Hours in ITT population

Study 008b - PI with Movement, ITT



Median PI with movement in 48 hours in ITT population

Time-specific median pain intensity scores for pain with movement are summarized in the table below. Treatment differences in terms of reduction in median PI of at least 10% (about 10 to 35%) were shown from 12 to 24 hours.

Table 5.3.4-8 Time-Specific Median PI with Movement in 24 Hours in ITT population

Study 008b Median PI	800 mg IVlb (n=166)		Placebo (n=153)
	Median	% Reduction vs placebo	Median
1-Hour	9.0	-12.5	8.0
3-Hour	7.0	0.0	7.0
6-Hour*	6.0	0.0	6.0
9-Hour	5.0	3.8	5.2
12-Hour*	4.3	10.4	4.8
15-Hour	3.4	22.7	4.4
18-Hour*	3.0	30.2	4.3
21-Hour	3.0	34.8	4.6
24-Hour*	3.6	20.0	4.5

*End of dose interval, assessment just prior to next scheduled dose.

Source: Table 17 on page 58 of the report for Study 008b

Summary of PI with movement by AUC in ITT population

The analyses of the area under the pain intensity curve (AUC) were not pre specified in the original protocol or Statistical Analysis Plan. Nevertheless, the treatment differences in AUC from 1-24 hours, 6-24 hours and 12-

24 hours, were all statistically significant. The p value for the 24-hour AUC was confirmed by Dr. Norton's analyses.

Table 5.3.4-9 Summary of PI with Movement by AUC in ITT population

Study 008b Summary of PI with movement by AUC	800 mg IVIb (N=166)	Placebo (N=153)
AUC_{1-24 hr}		
Mean ± SD	104.6 ± 45.48	120.0 ± 46.33
Median	103.5	121.0
Transformed VAS Score: LSMeans (SE) ¹	160.8 (7.78)	183.0 (8.01)
LSMeans Difference (95% CI)	22.2	
p-value vs Placebo ²	0.009	
AUC_{6-24 hr}		
Mean ± SD	71.4 ± 37.43	86.2 ± 38.04
Median	68.3	85.4
Transformed VAS Score: LSMeans (SE) ¹	157.8 (7.94)	186.9 (8.17)
LSMeans Difference (95% CI)	29.0	
p-value vs Placebo ²	<0.001	
AUC_{12-24 hr}		
Mean ± SD	42.9 ± 25.51	54.5 ± 25.49
Median	41.0	53.8
Transformed VAS Score: LSMeans (SE) ¹	157.4 (8.03)	195.8 (8.26)
LSMeans Difference (95% CI)	38.4	
p-value vs Placebo ²	<0.001	

AUC = area under the pain intensity curve; hr = hours; SD = standard deviation; VAS = Visual Analogue Scale; LSMeans = least square means; SE = standard error; CI = confidence interval.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 16 on pages 57 to 58 of the report for Study 008b.

PI for pain at rest

Mean PI at rest in 48 hours in ITT population

The mean PI for pain at rest recorded on a scale of 0 to 10 are summarized in the table below and presented in the graph following the table. Treatment differences in LS-means of transformed morphine requirement (refer to statistical review for discussion on data transformation) for pain with movement were statistically significant between the IVIb 800 mg group and placebo from 9 to 24 hours. The effect sizes of these statistically significant treatment differences were 0.6 to 1.0 units.

Table 5.3.4-10 Time-Specific Mean PI at Rest in 24 Hours in ITT population

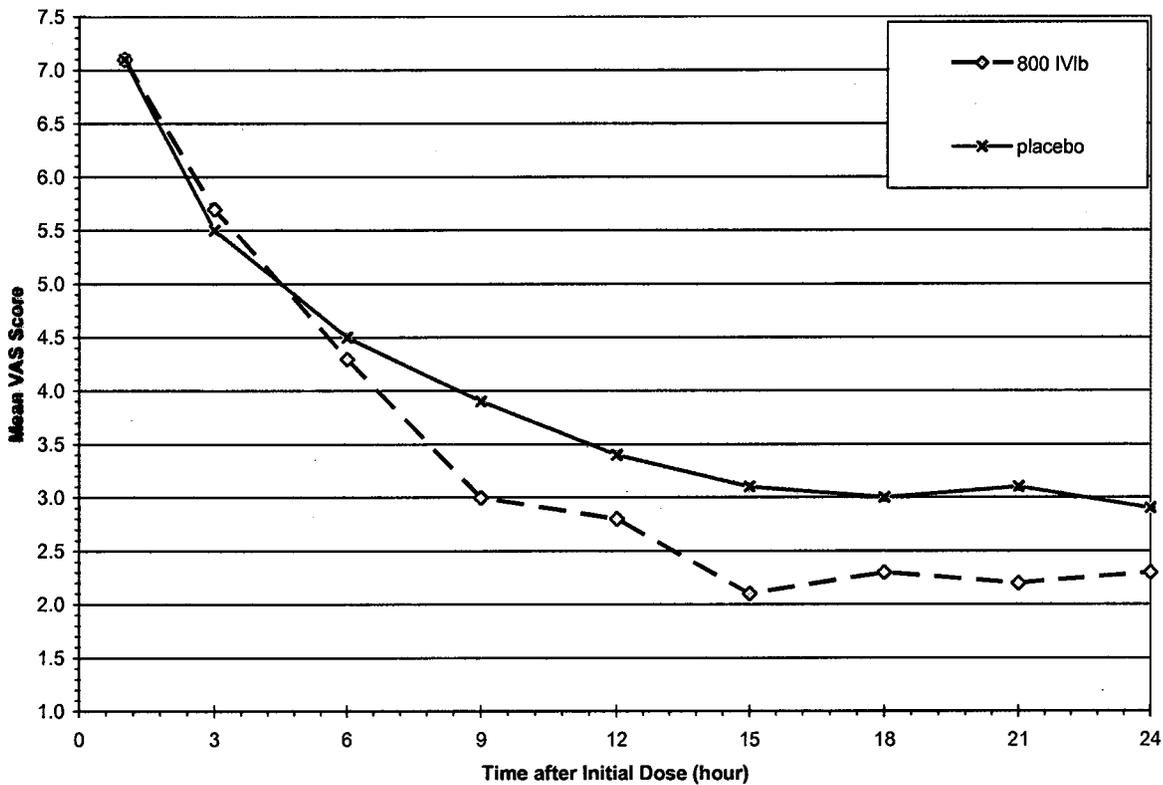
Hours	0	1	3	6	9	12	15	18	21	24
Mean PI at rest										
800 IVIb		7.1	5.7	4.3	3.0	2.8	2.1	2.3	2.2	2.3
placebo		7.1	5.5	4.5	3.9	3.4	3.1	3.0	3.1	2.9
Difference in mean from placebo										
		0	-0.2	0.2	0.9	0.6	1	0.7	0.9	0.6
Statistically significant treatment differences versus placebo in LS-means of transformed data										
					X	X	X	X	X	X

PI = pain intensity

Source: Table 21 on pages 61 to 62 of the report for Study 008b (also included in the Appendix at the end of the review of this study).

Figure 5.3.4-2 Time-Specific Mean PI at Rest in 24 Hours in ITT population

Study 008b - PI at Rest, ITT



Median PI at rest in 48 hours in ITT population

Time-specific median pain intensity scores for pain with movement are summarized in the table below. Treatment differences in terms of reduction in median PI of at least 10% (about 11 to 33%) were shown from 6 to 24 hours.

Table 5.3.4-11 Time-Specific Median PI at Rest in 24 Hours in ITT population

Study 008b Median PI	800 mg IVib (n=166)		Placebo (n=153)
	Median	% Reduction vs placebo	Median
1-Hour	8.0	0.0	8.0
3-Hour	5.7	5.0	6.0
6-Hour*	4.0	11.1	4.5
9-Hour	3.0	25.0	4.0
12-Hour*	2.7	20.6	3.4
15-Hour	2.0	31.0	2.9
18-Hour*	2.0	31.0	2.9
21-Hour	2.0	33.3	3.0
24-Hour*	2.0	31.0	2.9

*End of dose interval, assessment just prior to next scheduled dose.

Source: Table 23 on page 63 of the report for Study 008b

Summary of PI at rest by AUC in ITT population

The analyses of the area under the pain intensity curve (AUC) were not pre specified in the original protocol or Statistical Analysis Plan. Nevertheless, the treatment differences in AUC from 1-24 hours, 6-24 hours and 12-24 hours, were all statistically significant.

Table 5.3.4-12 Summary of PI at Rest by AUC in ITT population

Study 008b Summary of PI at rest by AUC	800 mg IVIb (N=166)	Placebo (N=153)
AUC_{1-24 hr}		
Mean ± SD	74.7 ± 38.68	88.2 ± 39.38
Median	70.1	88.5
Transformed VAS Score: LSMeans (SE) ¹	158.6 (8.08)	185.0 (8.31)
LSMeans Difference (95% CI)	26.4	
p-value vs Placebo ²	0.003	
AUC_{6-24 hr}		
Mean ± SD	46.9 ± 31.67	60.5 ± 32.04
Median	43.0	59.3
Transformed VAS Score: LSMeans (SE) ¹	154.4 (8.24)	191.3 (8.48)
LSMeans Difference (95% CI)	36.9	
p-value vs Placebo ²	<0.001	
AUC_{12-24 hr}		
Mean ± SD	27.3 ± 22.02	37.0 ± 21.53
Median	22.5	36.0
Transformed VAS Score: LSMeans (SE) ¹	156.1 (8.36)	198.3 (8.61)
LSMeans Difference (95% CI)	42.2	
p-value vs Placebo ²	<0.001	

AUC = area under the pain intensity curve; hr = hours; SD = standard deviation; VAS = Visual Analogue Scale; LSMeans = least square means; SE = standard error; CI = confidence interval.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 22 on page 62 of the report for Study 008b.

Secondary efficacy endpoints:

Treatment failure and time to treatment failure

Patients in need of narcotics other than morphine or in need of other NSAIDs were recorded as treatment failures. Only 18 of 319 patients were identified as treatment failures, including 7 (4%) patients on IVIb 800 mg and 11 (7%) on placebo. Time to treatment failure could not be adequately compared because of the small number of treatment failures.

Secondary efficacy endpoints:

Reduction of morphine side effects

The Applicant grouped all the following secondary endpoints together with the term opioid-related side effect: time to GI motility, time to ambulation, time to resumption of liquid intake and solid diet, time to discharge from hospital, and Combined Safety Assessment (diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter, incidence of post-operative vomiting or need for anti-emetic medication, and scores of ≤3 on Richmond Agitation Sedation Scale). The items listed under the Combined Safety Assessment are considered morphine-related AEs and the rest are considered assessments of function reflecting post-operative recovery status in the reviewer's opinion.

The combined and individual morphine-related AEs are summarized in the table below. Treatment difference of >10% from placebo was shown only in the Combined Safety Assessment. Treatment difference from placebo was 7% for at least one morphine-related AE and ≤3% for the individual morphine-related AEs listed in the table.

Table 5.3.4-13 Reduction of Morphine Side Effects

Study 008b Morphine side effects	800 mg IVIb (N=166)	Placebo (N=153)
Combined safety assessment of morphine-related AEs ¹		

Mean (SD)	0.7 ± 0.71	0.8 ± 0.73
Median	1.0	1.0
Difference from placebo in mean	0.1 (12.5%)	
p-value ²	0.228	
≥one morphine-related side effects³, n (%)	92 (55%)	95 (62%)
Difference from placebo (%)	7%	
p-value ⁴	0.223	
Diffuse pruritus, n (%)	17 (10%)	20 (13%)
Difference from placebo (%)	3%	
p-value ⁴	0.429	
Overt respiratory depression, n (%)	0	2 (1%)
Difference from placebo (%)	1%	
p-value ⁴	0.206	
Need for post-operative urinary indwelling catheter, n (%)	1 (<1%)	2 (1%)
Difference from placebo (%)	<1%	
p-value ⁴	0.514	
Post-operative vomiting or need for anti-emetic medication, n (%)	74 (45%)	73 (48%)
Difference from placebo (%)	3%	
p-value ⁴	0.571	
Worst Richmond Agitation Sedation Score of ≤-3 in 48 Hours, n (%)	22 (13%)	22 (14%)
Difference from placebo (%)	1%	
p-value ²	0.769	

1. The combined safety endpoint is defined as the sum of the binary occurrences of any of the following events during the 48 hour treatment period: diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter (after initial removal of surgical catheter), incidence of post-operative vomiting or need for anti-emetic medication, or Richmond Agitation Sedation Scale (RASS) value of ≤-3.

2. The p-values are based on a Wilcoxon-Rank Sum Test.

3. Morphine side effects included in the count: diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter (after initial removal of surgical catheter), incidence of post-operative vomiting or need for anti-emetic medication, or Richmond Agitation Sedation Scale (RASS) value of ≤-3.

4. The p-values are based on a Chi-square test.

Source: Table 14.3.1 on pages 204 to 205 of the report for Study 008b.

Differences in mean and median time to achieve all the endpoints indicating functional status of post operation recovery are summarized in the table below. Treatment difference in means of ≥10% from placebo was shown in time to GI motility and resumption of liquid intake (about 10%), representing at most a 2-hour shorter time interval. Treatment differences in means from placebo were about 8% in time to resumption of ambulation and ≤4% for the rest of the endpoints listed. Treatment differences in medians from placebo were >10% for time to resumption of liquid intake and ≤5% for all the other endpoints listed.

Table 5.3.4-14 Functional Assessments Reflecting Post-Operation Recovery Status

Study 008b Functional assessment	800 mg IV1b (n=166)	Placebo (n=153)
Time to GI Motility¹ (hrs)		
Number Censored (%)	2 (1%)	0
Mean (SD)	9.4 (0.87)	11.2 (1.40)
Median (95% CI)	3.6 (3.1, 4.8)	3.2 (2.8, 4.8)
Difference in means from placebo	1.8 (16.1%)	
Difference in medians from placebo	-0.4 (-12.5%)	
p-value ²	0.512	
Time to Resumption of Liquid Intake¹ (hrs)		
Number Censored (%)	0	1 (<1%)
Mean (SD)	12.1 (0.83)	13.4 (0.75)
Median (95% CI)	8.6 (6.5, 9.4)	10.4 (9.2, 15.4)
Difference in means from placebo	1.3 (9.7%)	
Difference in medians from placebo	1.8 (17.3%)	
p-value ²	0.520	

Time to Resumption of Solid Diet¹ (hrs)		
Number Censored (%)	10 (6%)	10 (7%)
Mean (SD)	41.0 (2.46)	41.1 (1.75)
Median (95% CI)	38.6 (33.1, 42.4)	34.7 (33.0, 42.5)
Difference in means from placebo	0.1 (0.2%)	
Difference in medians from placebo	-3.9 (-11.2%)	
p-value ²	0.397	
Time to Resumption of Ambulation¹ (hrs)		
Number Censored (%)	0	0
Mean (SD)	23.4 (0.50)	25.3 (0.94)
Median (95% CI)	24.1 (23.1, 25.0)	24.8 (24.0, 25.4)
Difference in means from placebo	1.9 (7.5%)	
Difference in medians from placebo	0.7 (2.8%)	
p-value ²	0.009	
Length of Hospital Stay¹ (hrs)		
Mean (SD)	62.4 (21.01)	64.9 (19.57)
Median	55.3	57.9
Min, Max	25.6, 191.4	25.7, 142.8
Difference in means from placebo	2.5 (3.9%)	
Difference in medians from placebo	2.6 (4.5%)	
p-value ²	0.142	

GI = gastrointestinal; SD = standard deviation; CI = confidence interval

1. All the time to event was counted from the start of the initial infusion. Patients who did not have the specified event are censored at the last study visit.

2. The p-values are based on the log-rank statistic.

Source: Appendix Tables 14.2.5 to 14.2.9 on pages 196 to 200 and section 11.4.1.9 on page 67 of the report for Study 008b.

5.3.4.3 Summary of Findings and Discussions

Study conduct

The treatment groups in Study 008b were approximately balanced with regard to demographic characteristics such as age, race, height, and weight.

Dropouts accounted for 12% (37/319) of the study population and were mainly due to treatment failure (6%) and AEs (3%). Dropouts due to AEs were balanced between the treatment groups. Fewer patients dropped out due to treatment failure in the IVIb 800 mg group than the placebo group (5% versus 8%).

Protocol violations and deviations were 20% and 62%, respectively, and were mainly due to taking excluded medication, missing assessments, and miss timed assessments. Protocol violation/deviations were balance between the treatment groups and were not considered as having differential impact on study outcomes.

Efficacy

The efficacy results are summarized in the table below in terms of treatment differences from placebo to examine the effect sizes for clinical interpretation of the findings. The reduction of morphine use in the first 24 hours post surgery was about **15%** (difference in **means**) to **20%** (difference in **medians**), representing a reduction of **morphine** use by **9-11 mg** in 24 hours. The treatment difference between IVIb 800 mg and placebo was statistically significant at $p < 0.05$ based on the comparison of LSMeans of the original. The findings were confirmed by the statistical review team (refer to the reviews by Dr. Norton and Dr. Price for detail). Reanalysis using the dataset without Dr. Snow's site yielded the same statistical conclusion (refer to the Review Section 3.2 for the issues with data integrity at Dr. Snow's site).

Time-specific PI measured at mid-dosing interval and end-of-dosing interval during the first 24 hours showed noticeable separations of **mean PI** from placebo pain curve in a range of **0.5 to 1.2 units** (on a 0-10 point scale) from **9-24 hours** and sizable separation of **median PI** from placebo in a range of **10-35%** from **9-24 hours**.

In comparison of IVIb 800 mg to placebo the noticeable treatment differences in morphine-related AEs included **7%** reduction in **any morphine-related AE** and **12.5%** reduction in **Combined Safety Assessment (CSA)** of morphine-related AEs. In assessment of functional recovery (time to GI activity, ambulation, and hospital discharge) that might be affected by morphine treatments, the noticeable reduction in means from placebo included **16%** reduction in time to **GI motility** and **8%** reduction in **time to ambulation**, representing a reduction in of time to GI motility and ambulation by less than 2 hours. The noticeable treatment differences in **medians** from placebo were **17%** reduction in time to **resumption of liquid intake**, representing also a reduction of less than 2 hours.

Table 5.3.4-15 Summary of Efficacy Findings

Study 008b Efficacy summary	Effect size of treatment differences from placebo
	800 mg IVIb (n=166)
Primary efficacy endpoint	
Reduction in mean morphine use in 24 hours, mg (%↓)	<i>8.6 (15.4%)</i>
Reduction in median morphine use in 24 hours, mg (%↓)	<i>10.5 (19.4%)</i>
Difference in LSMeans (original data)	8.3 (14.6%)* ($p < 0.001$)
Difference in LSMeans (transformed data)	1.5 (11.0%)* ($p < 0.001$)
Secondary efficacy endpoints: PI (mid- & end-of-dosing)	
<i>Time-specific PI for pain with movement</i>	
Stat. significant difference in LSMeans (transformed data)	*Hours 15-24
Reduction in mean PI of ≥ 0.5 units	0.5-1.2 units in Hours 9-24
Reduction in median PI of $\geq 10\%$	10-35% in Hours 12-24
<i>Time-specific PI for pain at rest</i>	

Stat. significant difference in LSMeans (transformed data)		*Hours 9-24
Reduction in mean PI of ≥ 0.5 units		0.6-1.0 units in Hours 9-24
Reduction in median PI of $\geq 10\%$		11-33% in Hours 6-24
Secondary efficacy endpoints: morphine-related AEs		
Difference in mean score of combined morphine-related AEs (CAS)		0.1 (12.5%)
Difference in \geq one morphine-related AE (%)		7%
Difference in diffuse pruritus (%)		3%
Difference in overt respiratory depression (%)		1%
Difference in need for post-operative urinary indwelling catheter (%)		<1%
Difference in post-op vomiting or need for anti-emetic medication (%)		3%
Difference in Richmond Agitation Sedation Score of ≤ -3 in 48 hrs (%)		1%
Secondary efficacy endpoints: functional assessments		
Difference in time to GI motility	Mean	1.8 (16.1%)
	Median	-0.4 (-12.5%)
Difference time to resumption of liquid intake	Mean	1.3 (9.7%)
	Median	1.8 (17.3%)
Difference in time to resumption of solid diet	Mean	0.1 (0.2%)
	Median	-3.9 (-11.2%)
Difference in time to resumption of ambulation	Mean	1.9 (7.5%)*
	Median	0.7 (2.8%)
Difference in length of hospital stay	Mean	2.5 (3.9%)
	Median	2.6 (4.5%)

*Note: Statistically significant difference.
Refer to all the efficacy tables in this section.

5.3.4.4 Conclusion

Taking all the effects into consideration: 15-20% (statistically significant) reduction of 24-hour morphine use coupled with noticeable pain curve separation in means (0.5-1.1 units on a 0-10 scale) and sizable pain reduction in medians (11-33%) by time-specific measurements, about 10% reduction in the combined morphine-related AEs, and a shorter time interval (less than 2 hours) for time to GI motility and ambulation, supplementing ibuprofen to morphine analgesia have relatively small additional therapeutic benefit.

5.3.4.5 Appendix

Eligibility criteria

Inclusion Criteria

Patients were going to be required to meet the following criteria for inclusion in the study if they:

1. Were scheduled for elective abdominal hysterectomy surgery with anticipated need for post-operative I.V. morphine analgesia with anticipated use of > 24 hours.
2. Had adequate IV access
3. Had anticipated hospital stay \geq 24 hours

Exclusion Criteria

Patients were going to be excluded from this study if they had any of the following:

1. Were unable to make a reliable self-report of pain intensity to pain relief
2. Were less than 18 years of age
3. Were greater than 70 years of age
4. Used NSAIDs within 12 hours prior to CTM administration
5. Used analgesics, muscle relaxants and sedatives less than 24 hours prior to CTM administration with the following exceptions: paracetamol (acetaminophen) could be administered until 6 hours prior to surgery, tramadol could be administered until midnight the evening prior to surgery, muscle relaxants working at the neuromuscular junction could be used for intubation and/or anesthesia administration for the surgical procedure prior to CTM administration, and sedatives (i.e., midazolam) used as a co-induction agent for the surgical procedure prior to CTM administration
6. Were taking warfarin, lithium, combination of ACE-inhibitors and furosemide.
7. Had anemia (active, clinically significant anemia) and/or a history or evidence of asthma or heart failure.
8. Had history of allergy or hypersensitivity to any component of IVIb, aspirin (or aspirin related products), NSAIDs, or COX-2 inhibitors
9. Were pregnant or nursing
10. Had history of severe head trauma that required current hospitalization, intracranial surgery or stroke within the previous 30 days, or any history of intracerebral arteriovenous malformation, cerebral aneurism or CNS mass lesion
11. Weighed less than 30kg
12. Had a history of congenital bleeding diathesis (e.g., hemophilia) or any active clinically significant bleeding, or have underlying platelet dysfunction including (but not limited to) idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, or congenital platelet dysfunction
13. Had GI bleeding that required medical intervention within the previous 6 weeks (unless definitive surgery has been performed)
14. Had a platelet count less than 30,000mm³ determined within the 28 days prior to surgery
15. Had pre-existing dependence on narcotics or known tolerance to opioids.
16. Were not able to understand the requirements of the study, not willing to provide written informed consent (as evidenced by signature on an informed consent document approved by an Institutional Review Board [IRB]), to abide by the study restrictions, or to return for the required assessments
17. Refused to provide written authorization for use and disclosure of protected health information
18. Were on dialysis, have oliguria or calculated creatinine clearance of less than 60 mL/min (calculated using the Cockcroft and Gault formula) determined within the 28 days prior to surgery
19. Were not able to achieve hemostasis or inability to close surgical incision, prior to Operating Room discharge
20. Had operative procedure including organ transplant
21. Had pre or intra-operative procedure utilized for the prevention of pre- or post-operative pain (i.e. epidural or nerve blocks)
22. Were receiving full dose anticoagulation therapy or Activated Protein C within 6 hours before dosing (Prophylaxis with subcutaneous heparin is acceptable)
23. Had received another investigational drug within the past 30 days
24. Were otherwise unsuitable for the study in the opinion of the investigator

Time-specific measurements of pain intensity

Appendix Table 5.3.4-A1 Mean PI Score Measured with Movement (24 Hours), ITT

Study 008b PI with movement	VAS Score by Treatment Group	800 mg IVIb (n=166)	Placebo (n=153)
1 Hour Post-dose	VAS Score Mean ± SD	8.0 ± 2.56	7.9 ± 2.45
	Transformed VAS Score: LS Means (SE) ¹	170.2 (8.63)	154.5 (8.88)
	LS Means Difference	15.7	
	p-value vs Placebo ²	0.094	
3 Hour Post-dose	VAS Score Mean ± SD	6.8 ± 2.57	6.8 ± 2.43
	Transformed VAS Score: LS Means (SE) ¹	173.0 (8.53)	166.4 (8.78)
	LS Means Difference	6.6	
	p-value vs Placebo ²	0.478	
6 Hour Post-dose*	VAS Score Mean ± SD	5.6 ± 2.67	5.9 ± 2.56
	Transformed VAS Score: LS Means (SE) ¹	161.9 (8.34)	162.6 (8.58)
	LS Means Difference	-0.7	
	p-value vs Placebo ²	0.937	
9 Hour Post-dose	VAS Score Mean ± SD	4.5 ± 2.57	5.2 ± 2.67
	Transformed VAS Score: LS Means (SE) ¹	153.2 (8.34)	170.0 (8.58)
	LS Means Difference	-16.9	
	p-value vs Placebo ²	0.063	
12 Hour Post-dose*	VAS Score Mean ± SD	4.3 ± 2.53	4.8 ± 2.34
	Transformed VAS Score: LS Means (SE) ¹	160.9 (8.38)	172.8 (8.62)
	LS Means Difference	-11.9	
	p-value vs Placebo ²	0.189	
15 Hour Post-dose	VAS Score Mean ± SD	3.5 ± 2.34	4.6 ± 2.27
	Transformed VAS Score: LS Means (SE) ¹	153.6 (8.21)	191.5 (8.44)
	LS Means Difference	-37.9	
	p-value vs Placebo ²	<0.001	
18 Hour Post-dose*	VAS Score Mean ± SD	3.5 ± 2.40	4.4 ± 2.31
	Transformed VAS Score: LS Means (SE) ¹	160.9 (8.40)	192.3 (8.65)
	LS Means Difference	-31.4	
	p-value vs Placebo ²	<0.001	
21 Hour Post-dose	VAS Score Mean ± SD	3.4 ± 2.37	4.6 ± 2.48
	Transformed VAS Score: LS Means (SE) ¹	161.5 (8.37)	201.5 (8.62)
	LS Means Difference	-40.0	
	p-value vs Placebo ²	<0.001	
24 Hour Post-dose*	VAS Score Mean ± SD	3.6 ± 2.49	4.5 ± 2.42
	Transformed VAS Score: LS Means (SE) ¹	153.6 (8.40)	186.8 (8.65)
	LS Means Difference	-33.2	
	p-value vs Placebo ²	<0.001	

*Note: End of dose interval, assessment just prior to next scheduled dose.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.

2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 15 on pages 56 to 57 of the report for Study 008b.

Appendix Table 5.3.4-A2 Mean PI Score Measured at Rest (24 Hours), ITT

Study 008b PI at rest	VAS Score by Treatment Group	800 mg IVIb (n=166)	Placebo (n=153)
1 Hour Post-dose	VAS Score Mean ± SD	7.1 ± 2.68	7.1 ± 2.79
	Transformed VAS Score: LS Means (SE) ¹	166.8 (9.07)	157.2 (9.33)
	LS Means Difference	9.6	
	p-value vs Placebo ²	0.329	
3 Hour Post-dose	VAS Score Mean ± SD	5.7 ± 2.52	5.5 ± 2.44
	Transformed VAS Score: LS Means (SE) ¹	176.1 (8.84)	163.4 (9.09)
	LS Means Difference	12.7	

	p-value vs Placebo ²	0.184	
6 Hour Post-dose*	VAS Score Mean ± SD	4.3 ± 2.61	4.5 ± 2.31
	Transformed VAS Score: LS Means (SE) ¹	156.0 (8.87)	154.3 (9.12)
	LS Means Difference	1.6	
	p-value vs Placebo ²	0.866	
9 Hour Post-dose	VAS Score Mean ± SD	3.0 ± 2.19	3.9 ± 2.35
	Transformed VAS Score: LS Means (SE) ¹	146.6 (8.64)	170.8 (8.89)
	LS Means Difference	-24.2	
	p-value vs Placebo ²	0.010	
12 Hour Post-dose*	VAS Score Mean ± SD	2.8 ± 2.10	3.4 ± 2.19
	Transformed VAS Score: LS Means (SE) ¹	155.7 (8.86)	177.1 (9.12)
	LS Means Difference	-21.4	
	p-value vs Placebo ²	0.027	
15 Hour Post-dose	VAS Score Mean ± SD	2.1 ± 1.94	3.1 ± 2.06
	Transformed VAS Score: LS Means (SE) ¹	157.4 (8.57)	195.2 (8.81)
	LS Means Difference	-37.8	
	p-value vs Placebo ²	<0.001	
18 Hour Post-dose*	VAS Score Mean ± SD	2.3 ± 2.16	3.0 ± 2.10
	Transformed VAS Score: LS Means (SE) ¹	159.2 (8.77)	188.1 (9.03)
	LS Means Difference	-28.9	
	p-value vs Placebo ²	0.003	
21 Hour Post-dose	VAS Score Mean ± SD	2.2 ± 2.09	3.1 ± 2.08
	Transformed VAS Score: LS Means (SE) ¹	159.5 (8.53)	204.1 (8.78)
	LS Means Difference	-44.5	
	p-value vs Placebo ²	<0.001	
24 Hour Post-dose*	VAS Score Mean ± SD	2.3 ± 2.32	2.9 ± 1.99
	Transformed VAS Score: LS Means (SE) ¹	155.4 (8.71)	183.5 (8.96)
	LS Means Difference	-28.1	
	p-value vs Placebo ²	0.003	

*Note: End of dose interval, assessment just prior to next scheduled dose.

1. Data are transformed using the rank transformation. LS means are adjusted for age group, weight group, randomization center, total morphine, and treatment group.
2. The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group.

Source: Table 21 on pages 61 to 62 of the report for Study 008b.

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

There were four Phase 3 efficacy studies of randomized, double-blind, placebo-controlled design: one antipyretic dose ranging study of IVIb 100 mg, 200 mg, and 400 mg dosed every 4 hours for 24 hours in a hospitalized population including critically ill patients; one fever study of 400 mg at every 6-hour dosing in patients with malaria in tropical area; two analgesic studies of almost identical design in hospitalized patients with post-operative pain, who were on morphine treatment in addition to receiving ibuprofen injection every 6 hours at a fixed dosing regimen for 2 days followed by PRN dosing. The studies enrolled representative sample populations with treatment groups approximately balanced in demographic characteristics.

Only a very small proportion of patients dropped out from the studies, in a range of 2% to 12%, mainly due to adverse events (AEs) and treatment failure. Dropouts due to AEs were approximately evenly distributed across treatment groups per study and dropouts due to treatment failure were generally dose-related.

The key clinically significant evidence in support of multiple-dose antipyretic efficacy for ibuprofen IV 100, 200, and 400 mg included the demonstration of a 4- to 5-hour earlier fever reduction to a temperature (T) <101.0°F (from mean baseline T of ≥102°F) and 33-45% more patients reaching T <101.0°F, 5 to more than 7 hours earlier fever reduction to temperature <100.0°F, 1.0-1.4°F more degrees of mean fever reduction in 24 hours, and the effect size of fever reduction by end-of-dosing measurements during the 24-hour period in Study 004. The positive outcomes were replicated in Study 006, which was targeted at the 400 mg dose level. The key clinically significant evidence in Study 006 included a 5-hour earlier fever reduction to T <100.0°F (from mean baseline T of >101.5°F), more than 6 hours earlier fever reduction to T <99.0°F, and 1-2°F more degrees of fever reduction by time-specific measurements in the first eight hours (temperature returned to near normal at Hour 12 in the placebo group).

The treatment differences from placebo were statistically significant for IVIb 400 mg in both studies and the findings were confirmed by Dr. Norton's analyses. The treatment difference from placebo was statistically significant for IVIb 200 mg by both the Applicant's and Dr. Norton's analyses, statistically significant for IVIb 100 mg by the Applicant's analysis and borderline significant by Dr. Norton's analysis using a temperature <38.3°C instead of 101°F as a cut point in Study 004.

The key findings in support of therapeutic benefits of ibuprofen IV 800 mg as supplements to opioid analgesia were 15 to 20% reduction in 24-hour morphine use (a statistically significant treatment difference based on analyses of data with and without Dr. Snow's site) as shown in Study 008b, associated with 12.5% reduction in combined known morphine-related adverse events, noticeable treatment differences in mean PI by 0.5-1.2 units on a 11-point scale and sizable difference in median PI by 10 to 35% for about 24 hours in comparison to placebo (the morphine only) treatment. Study 008a had similar findings in terms of effect size of treatment differences between IVIb 800 mg and placebo as those of Study 008b though the treatment difference for the primary endpoint was not statistically significant for the untransformed data. The key findings for the IVIb 400 mg dose in comparison to 800 mg dose were of smaller effect sizes in morphine reduction (2-5%) and pain reduction (10-20% reduction of median PI for about 12 hours) and similar effects on reduction of morphine-related adverse events.

The sample sizes of subpopulations were too small to allow subpopulation analyses with regard to age, gender, or race. The trend of increasing effect size in some of the key efficacy parameters in the two dose-ranging studies suggested a dose response at the dose levels tested (100 mg, 200 mg, and 400 mg) for fever indication and a dose response between 400 mg and 800 mg doses for pain indication. The efficacy data are considered

supportive of the proposed dosing interval of every 4-6 hours for fever indication and every 6 hours for pain indication.

Ibuprofen IV treatments have been shown to be efficacious in treating fever in hospitalized patients, including critically ill patients, and is considered beneficial in use as adjunctive to narcotic analgesia in treating post-operative pain in a hospital setting based on the results of the four efficacy studies.

6.1 Proposed Indication

The proposed indication for ibuprofen IV injection is for management of mild to severe pain and reduction of fever.

6.2 Methods/Study Design

The four Phase 3 studies were randomized, double-blind, placebo-controlled efficacy studies of fever (Study 004 and 006) and pain (Study 008a and 008b) in hospitalized patients. Study 004 was an antipyretic dose-ranging study of IVIb 100 mg, 200 mg, and 400 mg with a dosing regimen of every 4 hours for 24 hours in hospitalized patients including critically ill patients. Study 006 was a fever study of IVIb 400 mg dosed every 6 hours in patients with malaria in Thailand. Study 008a was an analgesic study of IVIb 400 and 800 mg with a dosing regimen of every 6 hours at a fixed interval for 2 days followed by PRN dosing for 3 days in patients with anticipated need for post-operative narcotic analgesia for treating pain associated with either orthopedic or abdominal surgery. Study 008b was an analgesic study of IVIb 800 mg in patients with anticipated need for post-operative narcotic analgesia for treating pain associated with abdominal hysterectomy and had almost an identical design as Study 008a. The protocol designs of these studies are discussed in detail in each individual study review in Section 5.3.

The focus of the efficacy review for the fever indication is to evaluate antipyretic effects of ibuprofen IV injection in hospitalized population, especially the critically ill subpopulation, and to assess the proposed every 4 to 6-hour dosing interval. The focus of the efficacy review for the pain indication is to evaluate additional therapeutic benefit by adding ibuprofen IV injection to morphing analgesia in treating postoperative pain.

The primary efficacy parameter defined in the original protocol was the percentage of patients on IVIb 400 mg reaching temperature <101.0°F (38.3°C) 4 hours after the start of infusion in Study 004; the area under the temperature curve [above 37.0°C (98.6°F)] during the first 24 hours in Study 006; the amount of morphine reduction in the first 24 hours post-surgery in both Study 008a and 008b.

The efficacy parameters considered by the reviewer as key endpoints for evaluation of antipyretic efficacy are the amount of temperature reduction, the percentage of patients and the time to achieve temperature reduction to lower degrees, and the end of dosing assessments during the course of treatment of persistent fever. The key parameters considered in the efficacy review of therapeutic benefit for use ibuprofen injection in addition to narcotic analgesia are the amount of morphine reduction, the amount of pain reduction, the reduction of morphine-related adverse effects, and the combination of the three factors.

6.3 Demographics

Demographic and baseline characteristics of the sample population in each study are tabulated and described in detail in the individual study reviews in Section 5.3. The two fever studies had less than 30% female patients and the two pain studies had mostly (about 80% in 008a and 100% in 008b) female patients, because of the involvement of abdominal hysterectomy. There were either a few or no elderly patients in each of the studies. Asian patients accounted for a larger proportion in fever studies (33% in Study 004 and 100% in study 006) from the enrollment in Thailand. Majority of patients (55%) in Study 008b were African American. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, Clinical Review of NDA 22-348 N000 (IV Ibuprofen) by Christina Fang

race, height, and weight in all the studies. Baseline temperature was in a range of 102-102.5°F in Study 004 and 101.6-101.9°F in Study 006, among the treatment groups. Baseline pain intensity could not be obtained because patients were still unconscious at the start of study medication injection and thus was no longer required in the study.

6.4 Patient Disposition

Patient disposition in each study is presented and discussed in details in Section 5.3. Dropouts accounted for a relatively small proportion of the study population in each of the studies (9% in Study 004, 2% in Study 006, and 12% each in Studies 008a and 008b), mostly due to treatment failure and adverse events. In general, dropouts due to treatment failure were reported less in the active treatment groups than the placebo group and less with the increase of dose levels (e.g., 5% on placebo, 4% on IVIb 400 mg, and 1% on IVIb 800 mg in Study 008a and 8% on placebo and 5% on IVIb 800 mg in Study 008b). Dropouts due to adverse events were approximately evenly distributed across the treatment groups (e.g., 5% on placebo, 7% on IVIb 400 mg, and 5% on IVIb 800 mg in Study 008a and 3% in each group in Study 008b). The AE-related dropouts will be discussed in detail in Section 7.3.

6.5 Analysis of the Primary Endpoint(s)

Antipyretic effects

The primary efficacy endpoint in Study 004 was the comparison between IVIb 400 mg and placebo in terms of the percentage of patients with fever reduced to temperature less than 101.0°F (38.3°C) during the first 4 hours. The effect sizes of treatment differences were 45% (77% versus 32 %) in the ITT population, 49% (57% versus 8%) in the critically ill subpopulation, and 41% (94% versus 53%) in the non-critically ill subpopulation and were all statistically significant.

The primary efficacy endpoint in Study 006 was the area under the temperature response curve on top of the 98.6°F (37.0°C) temperature line mark during the first 24 hours. The effect size of treatment difference was AUC-T₀₋₂₄ of 16.11 °F·hour (which is equivalent to an hourly AUC of 0.67°F for a clinical interpretation of what it means). Because the mean temperature for the placebo group returned to near normal after 12 hours, effect size of treatment difference was probably underestimated by the 24-hour AUC.

The statistical findings were confirmed by Dr. Norton's analyses.

Analgesic effects

The primary efficacy endpoint in both Study 008a and 008b was the amount of morphine reduction in the first 24 hours. In Study 008a the treatment differences were not statistically significant by analyses of untransformed data based on the Applicant's and Dr. Norton's analyses. The effect size of treatment difference in 24-hour morphine use between IVIb 800 mg and placebo was about 10 to 20% (considering both mean and median) or 5 to 10 mg. In Study 008b the treatment difference was statistically significant by analyses of untransformed data with and without Dr. Snow's site. The effect size of treatment difference in 24-hour morphine use between IVIb 800 mg and placebo was about 15 to 20% or 9 to 11 mg. The effect sizes of treatment differences in 24-hour morphine use between IVIb 400 mg and placebo were small, about 2 to 5% or 1 to 3 mg in Study 008a.

Table 6.1 Summary of Efficacy in Terms of Primary Endpoint for Pain Indication

Analgesic Studies 008a and 008b Efficacy summary	Effect size of treatment differences from placebo		
	Study 008a		Study 008b
	400 mg IVIb (n=134)	800 mg IVIb (n=138)	800 mg IVIb (n=166)
Primary efficacy endpoint			
Difference in mean morphine use in 24 hours, mg (% reduction)	2.6 (5.3%)	5.1 (10.4%)	8.6 (15.4%)

Difference in median morphine use in 24 hours, mg (% reduction)	1.3 (2.3%)	9.8 (21.6)	10.5 (19.4%)
Difference in LSMeans (original data)	2.6 (5.3%)	5.1 (10.4%)	8.3 (14.6%)*
Difference in LSMeans (transformed data)	14.5 (6.5%)	32.4 (14.5%)*	1.5 (11.0%)*

*Statistically significant treatment differences.

6.6 Secondary Endpoint(s)

Antipyretic effects

The results of secondary and additional endpoint measurements are summarized in the table below for the fever studies. In Study 004 the effect sizes of the treatment differences between IVIb 400 mg and placebo included a 5-hour reduction in time to reach T<101.0°F and 7-hour reduction in time to reach T<100.0°F, a mean temperature reduction by 2 (°F) more degrees in the first 4 hours and by 1.4 (°F) more degrees in the 24-hour period, a temperature reduction by 1-2 (°F) more degrees base on time-specific end-of-dosing measurements in the ITT population and by 0.5-1.5 (°F) more degrees in the critically ill subpopulation. The positive outcomes were replicated as shown by the results of Study 006, i.e., a temperature reduction by 1.3°F more in hourly average AUC-T₀₋₄, a temperature reduction by 1-2 (°F) more degrees base on time-specific measurements from 1 to 8 hours, and a 5-hour reduction in time to reach T<100.0°F and 6-hour reduction in time to reach T<99.0°F in comparison of IVIb 400 mg to placebo treatment.

The effect sizes of the treatment differences between IVIb 200 mg and placebo were shown in terms of 41% more patients (42% in the critically ill subgroup and 36% in the none critically ill subgroup) reaching a fever reduction to temperature <101.0°F (38.3°C) in the first 4 hours; about 4 hours earlier on the average to reach T<101.0°F and 6 hours earlier to reach T<100.0°F (37.8°C) during 24 hours; a mean temperature reduction by 1.5 (°F) more degrees in the first 4 hours and by 1.0 (°F) more degree during 24 hours. The differences in the time-specific end-of-dosing temperature reductions were 0.5 to 1.2°F in comparison of the 200 mg treatment to placebo and 0-1.3°F in comparison of the critically ill patients in the two treatment groups.

Treatment differences between IVIb 100 mg and placebo were shown in terms of 33% more patients (63% more in the critically ill sub group and only 6% more in the none critically ill patients) reaching a fever reduction to temperature <101.0°F (38.3°C) in the first 4 hours; about 5 hours earlier on the average to reach T<101.0°F and T<100.0°F (37.8°C) during 24 hours; a mean temperature reduction by 1.3 (°F) more degrees in the first 4 hours and by 1.0 (°F) more degree during 24 hours. The differences in the time-specific end-of-dosing temperature reductions were 0.5 to 0.9°F in comparison of the 200 mg treatment to placebo and 0.7-1.5°F in comparison of the critically ill patients in the two treatment groups.

Table 6.2 Summary of Efficacy Findings by Secondary Endpoints for Fever Indication

Antipyretic Studies 004 and 006 Efficacy summary	Effect size of treatment differences from placebo			
	Study 004			Study 006
	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)	400 mg IVIb (n=30)
% with T<101.0°F by Hour 4, ITT	33%**	41%*	45%*	
% with T<101.0°F by Hour 4, critically ill	63%**	42%**	49%*	
% with T<101.0°F by Hour 4, non critically ill	6%	36%*	41%*	
% with T<101.0°F (38.3°C) by Hour 24	11%	7%	11%	
Time to T<101.0°F (38.3°C) by Hour 24 (h)	4.80*	4.07*	4.86*	
% with T<100.0°F (37.8°C) by Hour 24	23%	19%	23%	3%
Time to T<100.0°F (37.8°C) by Hour 24 (h)	4.99*	5.57*	7.21*	4.9*
% with T<99°F (37.2°C) by Hour 24	0	6%	16%	0%
Time to T<99°F (37.2°C) by Hour 24 (h)	1.25	5.25	5.05	6.4*
Mean temperature reduction in Hours 0-4 (°F)	1.27	1.48	2.05	
Mean temperature reduction in Hours 0-24 (°F)	0.99	1.05	1.37	
Time-specific temperature (°F) in 24 hours, ITT	0.6-0.9 (Hr 4-12) 0.5-0.9 (Hr 16-24)	1.1-1.2 (Hr 4-12) 0.5-0.8 (Hr 16-24)	1.6-1.9 (Hr 4-12) 0.9-1.7 (Hr 16-24)	1.0-2.1 (Hr 1-8) 0.2-0.8 (Hr 12-20)
Time-specific temperature (°F) in 24 hours,	1.2-1.5 (Hr 4-12)	0.3-1.3 (Hr 4-12)	0.6-1.5 (Hr 4-12)	

critically ill	0.7-0.9 (Hr 16-24)	0.0-0.8 (Hr 16-24)	1.0-1.4 (Hr 16-24)	
AUC-T ₀₋₄ (°F·hr)	2.77	3.27	3.69	5.00*
Hourly average AUC-T ₀₋₄ (°F/hr)	0.69	0.82	0.92	1.25
AUC-T ₀₋₂₄ (°F·hr)	15.30	21.46	28.97	16.11*
Hourly average AUC-T ₀₋₂₄ (°F/hr)	0.64	0.89	1.21	0.67

*Statistically significant difference.

** Statistically significant difference by Applicant's analyses and borderline significant difference by Dr. Norton's analyses using T<38.3.0°C as a cut point.

Refer to all the efficacy tables in the Review Section 5 for fever studies.

Analgesic effects

The results of secondary endpoint assessments are summarized in the table below for the pain studies. In general, noticeable treatment differences in mean PI by 0.5-1.2 units on a 11-point scale and sizable difference in median PI by about 10 to 40% were shown starting after the second dose and lasting for about 24 hours for the IVIb 800 mg dose. Treatment differences between the IVIb 400 mg and placebo were slightly smaller than that from comparison of 800 mg and placebo and were shown for about 12 hours. PI in Study 008b was not measured beyond 24 hours because most patients had their IV removed after the fifth dose.

In comparison to placebo morphine-related unwanted effects were reduced by about 10% in terms of any or combined morphine-related AEs (CSA consisted of diffuse pruritus, overt respiratory depression requiring treatment, the need for post-operative urinary indwelling catheter, post-operative vomiting or need for anti-emetic medication, and a score of ≤3 on the Richmond Agitation Sedation Scale). Functional recovery in terms GI activity and resumption of ambulation was earlier by 3-5 hours for the 800 mg dose (by less than two hours in Study 008b). Morphine-related AEs were reduced by about 10% in any morphine-related AE and by 20% in combined morphine-related AEs for the 400 mg dose in comparison to placebo. Treatment differences from placebo in functional recovery were similar for the two active treatment groups.

Table 6.3 Summary of Efficacy Findings in Terms of Secondary Endpoints for Pain Indication

Analgesic Studies 008a and 008b Efficacy summary	Effect size of treatment differences from placebo		
	Study 008a		Study 008b
	400 mg IVIb (n=134)	800 mg IVIb (n=138)	800 mg IVIb (n=166)
Secondary efficacy endpoints – pain intensity			
<i>Time-specific PI for pain with movement</i>			
Stat. significant difference in LSM means (transformed data)	*Hours 9, 15-21, 30, 36-48	*Hours 9-48	*Hours 15-24
Reduction in mean PI of ≥0.5 units	0.5-1 units ↓ in Hours 9-21	0.5-1.1 units ↓ in Hours 9-36	0.5-1.2 units in Hours 9-24
Reduction in median PI of ≥10%	10-22% ↓ in Hours 9-21	12-22% ↓ in Hours 9-30, 36, 45	10-35% in Hours 12-24
<i>Time-specific PI for pain at rest</i>			
Stat. significant difference in LSM means (transformed data)	*Hours 15, 21, 30-48	*Hours 9-48	*Hours 9-24
Reduction in mean PI of ≥0.5 units	0.5-0.9 units ↓ in Hours 9, 15-21, 30-33	0.6-1.2 units ↓ in Hours 9-33	0.6-1.0 units in Hours 9-24
Reduction in median PI of ≥10%	11-21% ↓ in Hours 9, 15, 21, 30-36	13-43% ↓ in Hours 9, 15-36, 48	11-33% in Hours 6-24
Secondary efficacy endpoints – morphine-related AEs			
Difference in mean combined morphine-related AEs	0.2 (20%)*	0.1 (10%)	0.1 (12.5%)
Difference in ≥one morphine-related AE (%)	11%	10%	7%
Difference in diffuse pruritus (%)	3%	4%	3%
Difference in overt respiratory depression (%)	~1%	-3%	1%
Difference in need for post-operative urinary catheter (%)	0	0	<1%
Post-op vomiting or need for anti-emetic medication (%)	14%*	11%	3%
Richmond Agitation Sedation Score of ≤ -3 in 48 hrs (%)	4%	-2%	1%
Secondary efficacy endpoints – functional assessments			
Difference in time to GI motility	Mean	4.5 (18.3%)*	3 (12.2%)
			1.8 (16.1%)

	Median	2 (8.7%)	2.1 (9.1%)	-0.4 (-12.5%)
Difference time to resumption of liquid intake	Mean	5 (22.0%)	3.7 (16.3%)	1.3 (9.7%)
	Median	0.3 (1.9%)	0.3 (1.9%)	1.8 (17.3%)
Difference in time to resumption of solid diet	Mean	14.4 (28.1%)	17.1 (33.4%)	0.1 (0.2%)
	Median	3.1 (9.7%)	3.2 (10.0%)	-3.9 (-11.2%)
Difference in time to resumption of ambulation	Mean	3.5 (10.3%)	4.9 (14.5%)	1.9 (7.5%)*
	Median	-2.1 (-8.9%)	-0.9 (-3.8%)	0.7 (2.8%)
Difference in length of hospital stay	Mean	4.4 (5.4%)	-1.5 (-1.8%)	2.5 (3.9%)
	Median	-0.1 (-0.1%)	-1.9 (-2.7%)	2.6 (4.5%)

*Note: Statistically significant difference.

Refer to all the efficacy tables in the Review Section 5 for pain studies.

6.7 Subpopulations

Subpopulation analyses of efficacy are not applicable because of very small subpopulation size of the study groups divided by age, gender or race. For example, there were about 8 female patients per treatment group in fever Study 004 and 6 per group in Study 006, and ≤ 35 male patients per group in pain Study 008a and none in Study 008b. Two of the four studies had no patient aged >65 years and the other two had a few elderly patients. Only one of the four studies (Study 008b) had two major ethnic groups of noticeable size, 84 African American and 71 Caucasian in the IVIb 800 mg group and 91 African American and 52 Caucasian in the placebo group. Subgroup efficacy analysis with respect to race is still considered underpowered for evaluating racial influence on study outcomes.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dosing interval of 4-6 hours for fever indication was supported by results of the evaluation of every 4-hour dosing in Study 004, especially by demonstration of treatment differences in end-of-dosing temperature measurements during the multiple-dose period, and findings from evaluation of every 6-hour dosing in Study 006.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects for either fever or acute pain could not be adequately evaluated because of the rapid resolution of these signs/symptoms in a relatively short period that leaves only a small window of opportunity for demonstration of treatment effects.

6.10 Additional Efficacy Issues/Analyses

The time to fever reduction to temperature $<100.0^{\circ}\text{F}$ and $<99.0^{\circ}\text{F}$, respectively, and the percentage of patients with fever reduction to these degrees were the additional analyses requested by the reviewer and their results were summarized above.

7. INTEGRATED REVIEW OF SAFETY

Summary of Safety Results and Conclusions

The safety database contains safety data from six clinical studies including two Phase 1 studies in healthy volunteers and four Phase 3 studies in hospitalized patients with fever (Studies 004 and 006) and pain (Studies 008a and 008b).

About 600 subjects were exposed to IV ibuprofen, including about 200 hospitalized patients exposed to either 400 mg every 4-hour dosing for up to one day or every 6-hour dosing for up to three days, and about 300 hospitalized patients exposed to 800 mg every 6-hour dosing for up to four days (refer to the Review Section 7.2.1 for detail). Most patients had 1-2 days of exposure to IV ibuprofen.

The study population of the Phase 3 studies consisted of 95% non-elderly patients, about 75% female, and about 60% were Caucasian.

There were six reports of deaths. All deaths occurred in Study 004 in critically ill patients during the one-month post-treatment observation period. All were due to complications of underlying disease and none was considered study drug-related (refer to the Review Section 7.3.1 for detail).

There were 48 reports of nonfatal SAEs, 13 in patients (mostly critically ill) in Study 004 and 35 in post-operative patients in Study 008a and 008b. Twelve of the 13 SAEs in Study 004 were most likely caused by complications of underlying disease. One case of acute renal failure occurred in a young Asian male patient with malaria who had volume depletion associated with persistent vomiting and received six doses of IVIb 400 mg and had blood samples taken during the first day of the study. He was found to have hypotension and rapid elevation in BUN and creatinine at the 24-hour assessment and was diagnosed with acute renal failure. The SAE resolved with treatment with no sequela. Although the event was rated by the Investigator as unrelated to the IVIb treatment, ibuprofen with its known renal toxicity is suspected as having played an important role in the development of ARF in a patient who was at a higher risk for drug associated renal toxicity due to volume depletion by fever, vomiting, and blood sampling, and complication by potential renal damage with malarial infection. The 35 cases of SAEs reported in the pain studies were mostly complications of surgeries and were not considered study drug-related based on the nature of the event, the time of occurrence with respect to study drug administration, and the review of the individual Case Report Forms (refer to the Review Section 7.3.2 for detail).

The most commonly reported AEs were abnormal laboratory results, diarrhea, infections, and blood pressure abnormalities in Study 004, where close to half of the population was critically ill. The most commonly reported AEs in the pain studies were GI symptoms such as nausea, flatulence, vomiting, and constipation, and pruritus and headache with similar rates of reports between the IVIb 800 mg group and the placebo group (refer to the Review Section 7.4.1 for detail). There were remarkable increases of local irritation associated with IV administration of undiluted IVIb solutions in PK Study 001. After switching to diluted IV preparations in subsequent studies reports of local reactions became much less and not in trends to suggest IVIb association or dose response. In the tolerability Study 003 infusion pain was reported in more subjects receiving IVIb 400 mg than placebo.

Changes in laboratory test values and changes in vital signs were reported in all treatment groups with intra-group and inter-group variations. These changes could be associated with complications of medical conditions (such as post surgical complications or multi-organ failure in patients with severe sepsis), concurrent illness,

concomitant medication, and ibuprofen treatment. There were no clear patterns to suggest a dose dependent association of the changes with the use of IV ibuprofen.

Subpopulation safety analyses for drug-demographic interactions were not applicable due to the limited sizes of subpopulation by age, gender, or race for the treatment groups in each of the major disease populations.

Based on the review of safety data there were no new safety signals or major issues identified. Short-term use of IV ibuprofen at a dosage of up to 400 mg four times a day or six times a day and 800 mg four times a day for up to a few days, is considered relatively safe. Patients should be well hydrated before receiving IV ibuprofen to minimize the risks for acute renal toxicities. Minimum effective dosage should be targeted based on the individual response for better tolerance and safety.

7.1 Method

The safety of long-term use of ibuprofen up to 800 mg per dose and 3200 mg per day have been studied extensively with an established safety profile as described in the product labeling of approved ibuprofen oral formulations. Safety information applicable to some of the subsections of this safety review is referred to the approved product labeling. The IV formulation of ibuprofen is bioequivalent to the oral formulation and its use is limited to relatively short treatment duration at a hospital setting. The safety review is focused on severe reactions associated with short-term use of IV ibuprofen in a sicker population. The serious adverse events (SAEs) and common AEs were analyzed separately for each of the three main disease populations: patients with end-stage illness (Study 004), malaria (Study 006), and post operative status, because of the differences in clinical presentation of these medical conditions.

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

There were six clinical studies in the NDA submission including four efficacy studies discussed in the Review Sections 5 and 6 and two Phase 1 studies, a PK study and a study of multiple-dose tolerance. Safety data from all six studies were used to evaluate safety.

7.1.2 Adequacy of Data

The safety exposure included any exposure to ibuprofen in 608 subjects, exposure to the 400 mg dose in 219 subjects (195 of 219 were hospitalized patients) for up to 3 days in duration, and exposure to the 800 mg dose in 316 subjects (304 of 316 were hospitalized patients) for up to 4 days in duration. Deaths, SAEs, lists of all AEs, common AEs, dropouts due to AEs, abnormal laboratory tests and vital signs, and important Case Report Forms (CRF) were all available for review. Therefore, the database is considered adequate in general for this 505(b)(2) application.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Data on SAEs and common AEs are pooled from pain studies because of the similarity in study populations. Data on changes in laboratory tests and vital signs are pulled across Phase 3 studies. All safety data are presented by dose levels to assess dose response.

7.2 Adequacy of Safety Assessments

Safety assessments in the current submission are considered adequate based on information on relative bioavailability, size of database containing multiple-dose exposure in hospitalized patients including critically ill population, and the type and amount of safety monitoring during the study.

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

As summarized in the table below the overall exposure to at least one dose of ibuprofen IV injection was reported in 608 subjects (560 of 608 were hospitalized patients). Exposure by indication included 122 hospitalized patients with fever exposed to 100, 200, and 400 mg doses and 438 hospitalized patients with post-operative pain exposed to 400 and 800 mg doses. Exposure by dose level included 31 subjects exposed to IVIb 100 mg, 42 subjects exposed to IVIb 200 mg, 219 subjects exposed to IVIb 400 mg, and 316 subjects exposed to IVIb 800 mg in the six clinical studies. A total of 535 subjects (499 of 535 were hospitalized patients) had higher level exposure to IVIb 400 and 800 mg doses including 463 exposed to at least 4 doses, 175 to at least 6 doses, and 109 to at least 8 doses. Of the hospitalized patients on every 4-hour dosing regimen 85 fever patients completed one-day of IVIb treatments. Of the hospitalized patients on every 6-hour dosing regimen 434 patients completed at least one day, 148 completed at least 1.5 days, and 109 completed at least 2 days of IVIb treatments. The longest duration of exposure to IVIb was three days in fever patients in Study 006.

Table 7-1 Exposure by Dose Levels and Number of Doses

#Doses	Number of subjects exposed									
	Distribution					Cumulative distribution				
	Placebo	IV Ibuprofen				Placebo	IV Ibuprofen			
	100 mg	200 mg	400 mg	800 mg		100 mg	200 mg	400 mg	800 mg	
1	22	1	12	24	25	357	31	42	219	316
2	2	0	0	3	4	335	30	30	195	291
3	15	1	0	13	3	333	30	30	192	287
4	39	0	0	15	33	318	29	30	179	284
5	178	2	0	49	191	279	29	30	164	251
6	33	27	30	35	13	101	27	30	115	60
7	6			12	6	68			80	47
8	31			34	29	62			68	41
9	1			1	6	31			34	12
10	0			0	0	30			33	6
11	0			1	1	30			33	6
12	30			31	3	30			32	5
13	0			1	1				1	2
17	0				1					1

Reference: individual study reviews.

The demographic characteristics of patients in Phase 3 studies are pulled cross studies as summarized in the table below. About 95% (862/905) of the study population were non-elderly patients. Of the patients aged ≥ 60 years, 38 were in the age range of 60 to <65 and 43 were ≥ 65 years old. Female patients accounted for three quarters of the entire Phase 3 study population and represented an overwhelming majority in the post-operative pain studies. Subpopulation based on ethnic origin consisted of 59% Caucasian, 26% African American, 12% Asian, and 3% Hispanic.

Table 7-3 Demographics by Dose Level in Phase 3 Studies

	Placebo	100 mg	200 mg	400 mg	800 mg	Total
	N=345	N=31	N=30	N=195	N=304	905
Age (years)						
Mean	41	40	34	42	44	42
Min, Max	18, 89	18, 83	18, 68	17, 73	20, 69	17, 89
Age 17 to <60 years	320 (93%)	25 (81%)	28 (93%)	172 (88%)	279 (92%)	824 (91%)
Age 60 to <65 years	17 (5%)	2 (6%)	1 (3%)	6 (3%)	12 (4%)	38 (4%)
Age ≥ 65 years	8 (2%)	4 (13%)	1 (3%)	17 (9%)	13(4%)	43 (5%)
Gender, n (%)						

Male	70 (20%)	23 (74%)	22 (73%)	81 (42%)	27 (9%)	223 (25%)
Female	275 (80%)	8 (26%)	8 (27%)	114 (58%)	277 (91%)	682 (75%)
Race, n (%)						
Caucasian	184 (53%)	13 (42%)	15 (50%)	128 (66%)	189 (62%)	529 (59%)
Black	108 (31%)	5 (16%)	4 (13%)	17 (9%)	99 (32%)	233 (26%)
Asian	42 (12%)	10 (32%)	10 (33%)	42 (21%)	3 (1%)	107 (12%)
Hispanic	9 (3%)	2 (6%)	1 (3%)	5 (3%)	11 (4%)	28 (3%)
Other	2 (<1%)	1 (3%)	0	3 (1%)	2 (1%)	8 (1%)

Source: Table 2.7.4-6 on page 9 of the clinical safety summary report.

7.2.2 Explorations for Dose Response

Two of the four Phase 3 studies were dose ranging studies of the doses at 100, 200, and 400 mg in fever study (004) and dosed at 400 and 800 mg in pain study (008a). Safety data were pulled across studies by dose levels to explore dose response.

7.2.3 Special Animal and/or In Vitro Testing

Refer to Pharmacology/Toxicology Review.

7.2.4 Routine Clinical Testing

Safety monitoring consisted of mainly AE reporting, vital signs, transfusion monitoring, and routine laboratory tests and is considered adequate in studying short term (a few days) use of IV ibuprofen in hospitalized population.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to ibuprofen labeling approved for oral formulations.

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

The potential AEs associated with the NSAID drug class were measured by monitoring of GI events, measurement of blood pressure and heart rates, and laboratory tests of liver and renal function.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

Six cases of death were reported in Study 004 and none in the other studies. They included one case on IVIb 100 mg, two on IVIb 200 mg, two on IVIb 400 mg, and one on placebo. The key information about these fatal cases is summarized in the table below based on the narratives and individual Case Report Forms provided in the submission. All six cases occurred in critically ill patients who were already on mechanical ventilation or pressor support or both before receiving study drugs for fever management. None occurred during the 24-hour treatment period. The onset of the major SAEs leading to death ranged from 10 hours to one month after the last dose of the study drug. The deaths were all due to complications of underlying disease and not considered study drug-related based on the review of the individual Case Report Forms.

Table 7-4 Summary of Cases with Fatal Outcomes

Patient	Diagnosis at screening	Critically ill	Treatment	Cause of death	Onset wrt study drug
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#5058 WF age 67	Unresectable pancreatic cancer	Yes	IVIb 100 mg 6 doses	Respiratory failure due to pneumonia; withdrawal of ventilation support	~3 weeks after the 6 th dose of IVIb
#4058 WM age 60	Meningioencephalitis	Yes	IVIb 200 mg 6 doses	Hypotension, and cerebral edema, and multi-system organ failure; withdrawal of vasopressor support	10 hours after the 6 th dose of IVIb
#4075 WM age 58	Bacterial pneumonia	Yes	IVIb 200 mg 6 doses	Worsening sepsis and multi-system organ failure; withdrawal of life support	27 hours after the 6 th dose of IVIb
#4056 WF age 54	Acute respiratory distress syndrome	Yes	IVIb 400 mg 6 doses	Withdrawal of ventilation support	~1 month after the 6 th dose of IVIb
#4060 WM age 56	Hospital-acquired pneumonia	Yes	IVIb 400 mg 3 doses	Severe sepsis and multi-system organ failure; withdrawal of life support	11 days after the 3 rd dose of IVIb
#4053 WM age 43	Aspiration pneumonia	Yes	Placebo	Recurrence of pharyngeal cancer; refuse treatment	~3 weeks after the 6 th dose of placebo

WF = white female; WM = white male; wrt = with respect to;

Source: Section 12.3.2 on pages 91 to 94 and Appendix Table 16.2.7.1 on pages 1231-1245 of the report for Study 004, pages 27 to 29 of ISS, and individual Case Report Forms.

7.3.2 Nonfatal Serious Adverse Events

There were no reports of serious adverse events (SAEs) in Phase 1 studies and one of the phase 3 studies. The number and percentage of SAEs reported in Study 004, 008a, and 008b are summarized in the table below. There were several cases reported in each treatment group (7 to 16%) in Study 004, where critically ill patients were included in the study. In post-operative pain studies there was a trend of increasing rate of SAEs with increasing dosage (2% on placebo, 4% on IVIb 400 mg, and 7% on IVIb 800 mg in Study 008a and 3% on placebo versus 7% on IVIb 800 mg in Study 008b) suggested a dose response.

Table 7-5 Number and Percentage of Patients with SAEs in Phase 3 Studies

SAE	Placebo	100 mg	200 mg	400 mg	800 mg
004 nonfatal	3/28 (11%)	5/31 (16%)	3/30 (10%)	2/31 (6.5%)	
<i>004 fatal</i>	<i>1</i>	<i>1</i>	<i>2</i>	<i>2</i>	
SAE-nonfatal					
006	0			0	
008a	3/134 (2%)			6/134 (4%)	9/138 (7%)
008b	5/153 (3%)			NA	12/166 (7%)

Note: One patient might have several serious AEs; fatal cases in Study 004 were included as a separate row.

Source: Appendix table 16.2.7.1 on pages 1231-1245 of the report for Study 004 and table 2.1.3-2 on page 32 of ISS.

The 13 cases of nonfatal serious adverse events (SAEs) reported in Study 004 are summarized by treatment group, critically ill status, name of SAEs, time of occurrence with respect to study drug administration, and outcome of SAEs. Ten of 13 SAEs involved critically ill patients. Almost all the SAEs listed in the table were most likely due to complications of the medical conditions and are not considered to be related to the study drug based on the nature of the event, the time of occurrence with respect to study drug administration, and the review of the individual Case Report Forms.

There was one case of acute renal failure in a 25 years old Asian male hospitalized for treatment of severe malaria who presented with vomiting before study enrollment. He had "continued vomiting resulting in dehydration" while receiving all six doses of IV ibuprofen 400 mg for fever and had about 90 mL blood drawn for PK sampling during the first day of study. At 24-hour assessment he had hypotension and rapid elevation in BUN and creatinine. He was diagnosed as having "acute renal failure requiring intervention to prevent permanent damage." The SAE resolved in three weeks with treatments and was judged to be unrelated to the

study drug by the Investigator with the reason that "renal function may often be impacted by a malarial infection." In the reviewer's opinion contributing role of ibuprofen to acute renal failure could not be ruled out because of the known renal toxicity of ibuprofen in a case when patient was already at a higher risk due to volume depletion by fever, vomiting, and blood sampling complicated by malaria-related renal damage.

One SAE was reported as a recurrence of bone fracture in a placebo patient who was hospitalized for repair of a closed left distal humerus fracture and superior pubic rami fracture. The patient had re-fracture three weeks after the last dose of the study drug. The AE was thought to be due to premature weight bearing in his orthopedic surgeon's opinion. This was the second bone fracture case reported in the study. The first case was reported (not as a serious AE) in a critically ill patient, who had multiple bone fractures (including left humerus and right acetabular fractures) and chest trauma after being struck by a car and was hospitalized for emergency repair of pelvis and right hip. The patient received six doses of IVIb 100mg for fever due to pneumonia. About nine days after his last dose of the study drug he was reported as having loss of fixation on left posterior pelvis and on proximal humerus. The Investigator marked the relationship of the AEs to the study drug as unknown in this case.

Table 7-6 Nonfatal SAEs in Study 004

	Patient	Critically ill	Nonfatal serious events	Onset wrt study drug	Outcome
IVIb 100 mg	3056	Yes	Aspiration pneumonia	~2 weeks after 6 th dose	Resolved
	4055	Yes	Catheter-related infection	12 days after 6 th dose	Resolved
	4065	Yes	Bilateral tension pneumothoraces and multi-system organ failure due to worsening sepsis	After 5 th dose (dropped out of study)	Chronic
	4072	Yes	Dilated and fixed right pupil	2.5 hours after 1 st dose (dropped out of study)	Unknown
	5003	No	Pneumonia	3 days after 6 th dose	Resolved
IVIb 200 mg	4061	Yes	Bilateral lower extremity deep venous thrombosis	3.5 weeks after 6 th dose	Resolved
	5062	Yes	Sinus tachycardia	2.5 weeks after 6 th dose	Resolved
	1002	No	Headache	3.5 weeks after 6 th dose	Resolved
IVIb 400 mg	5063	Yes	i. punctate intraparenchymal hemorrhage; ii. Sepsis	i. 1.5 days after 6 th dose ii. 7 days after 6 th dose	Both resolved
	8015	No	Hypotension, vomiting, acute renal failure	One hour after 6 th dose	Resolved
Placebo	4078	Yes	Sepsis and multi-system organ failure	3 days after 6 th dose	Resolved
	5055	Yes	Left humerus fracture	3 weeks after 6 th dose	Resolved
	2003	No	i. Pulmonary embolism; ii. Sepsis; iii. Subconjunctival hemorrhage in left eye	i. 10 days after 6 th dose ii & iii. 3.5 weeks after 6 th dose	All resolved

Source: Section 12.3.2 on pages 91 to 94 and Appendix Table 16.2.7.1 on pages 1231-1245 of the report for Study 004, and individual Case Report Forms.

Nonfatal serious adverse events (SAEs) reported in the post-operative population in Studies 008a and 008b are summarized by treatment group, name of SAEs, time of occurrence with respect to study drug administration, and outcome of SAEs. Most of the SAEs listed in the table below were more consistent with complications of surgery and concurrent illness based on the nature of the event, the time of occurrence with respect to study drug administration, and the review of the individual Case Report Forms.

Table 7-6 Nonfatal SAEs in Post-Operative Pain Studies

	Patient	Nonfatal serious events	Onset wrt study drug	Outcome
IVIb 400 mg	2251	Pulmonary embolism	4 days after last dose	Resolved
Study 008a	2401	Pulmonary edema	28 hours after last dose	Resolved

	3017	Calf pain	7 hours after last dose	Resolved
	3251	Ileus	4 days after last dose	Resolved
	4009	Peritoneal hematoma		Resolved
	4015	Post operative abdominal pain	2 days after last dose	Resolved
IVIb 800 mg	1004	Post operative abdominal pain	3 days after last dose	Resolved
Study 008a	2023	Liver function tests increased	2 days after last dose	Resolved
	2023	Infection	3 days after last dose	Resolved
	2025	Post op infection	10 days after last dose	Ongoing
	2171	Vaginal hematoma	During & after treatment	Resolved
	2172	Hematoma	During & after treatment	Resolved
	4035	Knee pain	4 days after last dose	Resolved
	4051	Post op Ileus	2 days after last dose	Resolved
	4216	Trans ischemic attack	4 hours after 3 rd dose (then dropped out of study)	Resolved
		Trans ischemic attach	2 nd episode: 13 hours after 3 rd dose	Resolved
	4226	Ileus	During & after treatment	Resolved
IVIb 800 mg	5012	Ileus	3 days after last dose	Resolved
Study 008b	5154	Abdominal abscess	5 days after last dose	Resolved
	6018	Peritoneal abscess	7 days after last dose	Resolved
	6107	Wound drainage	8 days after last dose	Resolved
	6111	Tachycardia	Started after receiving 3 rd dose & lasted for 4 days	Resolved
	6207	Ileus	2 days after last dose	Resolved
	6251	Wound dehiscence	7 days after last dose	Resolved
	6315	Vaginal hemorrhage	6 hours after 1 st dose & treatment discontinued	Resolved
		Cellulitis	6 days after one dose	Resolved
	7004	Ileus	2 days after last dose	Resolved
		Hematuria	6 days after last dose	Ongoing
	8057	Pulmonary embolism	3 days after last dose	Resolved
	8061	Subdural hematoma	13 days after last dose	Resolved
	8604	Hematoma	14 hours after last dose	Resolved
Placebo	2038	Vomiting	1 day after last dose	Resolved
Study 008a	2155	Hematoma	days after last dose	Resolved
	4211	Pyrexia	days after last dose	Resolved
Placebo	5301	Oxygen saturation decreased	days after last dose	Resolved
Study 008b	6102	Atelectasis	days after last dose	Ongoing
	6209	Atelectasis	days after last dose	Resolved
		Ileus	days after last dose	Resolved
	6552	Peritoneal hemorrhage	days after last dose	Resolved
	6603	Cholecystitis	days after last dose	Resolved with sequelae

Source: Section 12.3.2 on pages 100 to 106, Table 40 on page 101, and Appendix Table 16.2.7.2 on pages 209-213 of the report for Study 008a; Section 12.3.2 on pages 78 to 85, Table 29 on page 79, and Appendix Table 16.2.7.2 on pages 123-126 of the report for Study 008a; Individual Case Report Forms.

7.3.3 Dropouts and/or Discontinuations

Dropouts due to AEs were reported in one of the Phase 1 studies (one case) and three of the Phase 3 studies. There were relatively small percentages of dropouts due to AEs, about 3-6% in Studies 004, 008a, and 008b (refer to the Patient Disposition section of the review of individual studies). The AEs leading to multiple dropouts in IVIb treated patients in Phase 3 studies included constipation, nausea, hypersensitivity, dizziness, headache, and pruritus as summarized in the table below.

Table 7-7 Type of AEs Leading to Dropouts in ≥Two Patients in Phase 3 Studies

AEs	Placebo	IV ibuprofen
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	(N=345)	<400 mg (N=61)	400 mg (N=195)	800 mg (N=304)	All dosage (N=560)
Constipation	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Nausea	4 (1%)	0	2 (1%)	1 (<1%)	3 (<1%)
Hypersensitivity	1 (<1%)	0	2 (1%)	0	2 (<1%)
Dizziness	0	0	3 (2%)	0	3 (<1%)
Headache	0	0	1 (<1%)	2 (1%)	3 (<1%)
Pruritus	7 (2%)	0	0 (0%)	5 (2%)	5 (<1%)

Source: Table 2.1.4-2 on page 37 of ISS.

7.3.4 Significant Adverse Events

No significant AEs other than known ibuprofen treatment-related AEs, have been identified in the safety database.

7.3.5 Submission Specific Primary Safety Concerns (optional)

None.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

Adverse events (AEs) reported in Phase 1 studies were generally minor in nature. The type and rate of AE reports were similar between the IV and oral formulations at the same dose levels. The major difference was the marked increase in local reactions such as contusion, catheter site hematoma/pain, infusion site anesthesia/bruising/inflammation/irritation/pain, and injection site bruising/irritation/pain associated with IV infusions, especially at higher doses of 400 and 800 mg, due to irritation potential of the undiluted IVIb solution. In tolerability Study 003 with the use of diluted solution, there were no reports of bruising and/or swelling and two reports of erythema, one in each treatment group. There were still more subjects reported infusion pain while receiving IV ibuprofen than they did while receiving placebo (33% versus 14%). Diluted IVIb solution was used in all subsequent clinical studies. The local reactions reported from these studies are summarized in the table below. There were no reports of local reactions in Study 006, a few in Study 004 and 008b, and more in Study 008a across treatment groups.

Table 7-8 Number of Local Reactions Reported in Phase 3 Studies

Local reaction	Placebo	IVIb 100 mg	IVIb 200 mg	IVIb 400 mg	
004					
Injection site extravasation	0	1	1	0	
Venipuncture site thrombosis	0	0	0	1	
006	0			0	
008a	Placebo			IVIb 400 mg	IVIb 800 mg
Infusion site swelling	1			1	3
Infusion site bruising	1			2	1
Infusion site pain	1			3	0
Infusion site inflammation	2			0	1
Injection site irritation	0			3	0
Infusion site coldness	0			1	0
Infusion site erythema	0			1	0
Infusion site phlebitis	0			0	1
Infusion site warmth	0			0	1
Injection site extravasation	1			0	0
008b	Placebo				IVIb 800 mg

Infusion site extravasation	2			0
Infusion site pain	0			2
Infusion site edema	0			1

Source: Table 14.3.1.1 on pages 27 to 28 of the addendum to report for Study 004, Table 8 on page 46 of the report for Study 006, Table 14.3.2.1 on pages 302 to 305 of the report for Study 008a, and Table 14.3.2.1 on pages 216 to 217 of the report for Study 008b.

AEs reported in patients with malaria in fever Study 006 were minor symptoms and most (7 of the 9 AEs listed for the IVIb group) had only one occurrence in the IVIb treatment group. The AEs reported in more than one patient in the IVIb group included nasal congestion in two patients on IVIb (versus none in the placebo group) and abdominal pain in five patients on IVIb (versus three in the placebo group).

For Study 004 involving critically ill patients, AEs reported by three or more patients ($\geq 10\%$) in any IVIb treatment group are summarized in the table below. There appeared to be more AEs in terms of anemia, neutropenia, blood urea increased, and hypertension in the IVIb 400 mg than the other three treatment groups. However, it would be difficult to single out which AEs were more likely to be related to IVIb treatment because of the small size of database (about 30 per treatment arm) and high proportion of patients being critically ill that most AEs listed in the table were the types of AEs generally seen in the sick populations with severe infections, multiple organ failures, and other end-stage medical conditions.

Table 7-8 Treatment Emergent AEs in ≥ 3 Patients in Any IVIb Treatment Group in Study 004

		Placebo (n=28)	IVIb 100 mg (n=31)	IVIb 200 mg (n=30)	IVIb 400 mg (n=31)
		Number (%) of patients with any AE			
	Any Treatment-Emergent AEs	25 (89%)	27 (87%)	25 (81%)	23 (74%)
Blood & lymphatic system disorder	Anemia	4 (14%)	5 (16%)	6 (19%)	11 (35%)
	Eosinophilia	7 (25%)	7 (23%)	7 (23%)	8 (26%)
	Neutropenia	2 (7%)	2 (6%)	2 (6%)	4 (13%)
	Thrombocythemia	0	3 (10%)	2 (6%)	1 (3%)
GI disorder	Diarrhea	2 (7%)	3 (10%)	3 (10%)	2 (6%)
Infections & infestations	Pneumonia bacterial	0	3 (10%)	1 (3%)	2 (6%)
	Bacteremia	0	4 (13%)	1 (3%)	0
Investigations	Blood lactate dehydrogenase increased	1 (4%)	3 (10%)	2 (6%)	1 (3%)
	Blood urea increased	0	0	0	3 (10%)
Metabolism & nutrition disorders	Hypokalemia	5 (18%)	4 (13%)	4 (13%)	6 (19%)
	Hypoproteinemia	2 (7%)	3 (10%)	0	4 (13%)
	Hypoalbuminemia	1 (4%)	3 (10%)	1 (3%)	3 (10%)
	Hypernatremia	0	2 (6%)	0	3 (10%)
Vascular disorders	Hypotension	1 (4%)	0	2 (6%)	3 (10%)
	Hypertension	0	0	0	3 (10%)

Source: Table 16 on pages 81 to 82 of the report for Study 004

The common AEs reported in $\geq 3\%$ post-operative patients in the two pain studies are summarized in the table below. The most common ($>10\%$) AEs had similar rates of occurrence between the IVIb 800 mg group and the placebo group. They included nausea (53% of patients on IVIb 800 mg versus 62% on placebo), flatulence (16% versus 15%), vomiting (15% versus 17%), constipation (13% versus 17%), pruritus (15% versus 16%), and headache (12% versus 11%).

Table 7-9 Treatment Emergent AEs in $\geq 3\%$ Patients on Any IVIb Treatment in Pain Studies

	System Organ Class Preferred Term	Placebo (N=287)	400 mg (N=134)	800 mg (N=304)
	Any Treatment-Emergent AEs	258 (90%)	118 (88%)	260 (86%)
Blood & lymphatic system disorders	Anemia	6 (2%)	5 (4%)	7 (2%)
Gastrointestinal disorders	Nausea	179 (62%)	77 (57%)	161 (53%)

	Flatulence	44 (15%)	10 (7%)	49 (16%)
	Vomiting	50 (17%)	30 (22%)	46 (15%)
	Constipation	49 (17%)	23 (17%)	38 (13%)
	Abdominal distension	10 (3%)	1 (<1%)	7 (2%)
	Dyspepsia	2 (<1%)	6 (4%)	4 (1%)
	Abdominal discomfort	0	4 (3%)	2 (<1%)
General disorders & administration site conditions	Pyrexia	32 (11%)	9 (7%)	16 (5%)
	edema peripheral	4 (1%)	1 (<1%)	9 (3%)
Investigations	Body temperature increased	8 (3%)	0	7 (2%)
	Hemoglobin decreased	3 (1%)	4 (3%)	6 (2%)
Metabolism & nutrition disorders	Hypokalemia	8 (3%)	5 (4%)	3 (<1%)
Nervous system disorders	Headache	31 (11%)	12 (9%)	35 (12%)
	Dizziness	5 (2%)	8 (6%)	13 (4%)
Psychiatric disorders	Insomnia	13 (5%)	4 (3%)	6 (2%)
Renal & urinary disorders	Urinary retention	10 (3%)	7 (5%)	10 (3%)
Reproductive system disorders	Vaginal hemorrhage	16 (6%)	13 (10%)	13 (4%)
Respiratory disorders	Cough	1 (<1%)	4 (3%)	2 (<1%)
Skin & subcutaneous tissue disorders	Pruritus	47 (16%)	10 (7%)	46 (15%)
Vascular disorders	Wound hemorrhage	4 (1%)	4 (3%)	4 (1%)
	Hypertension	8 (3%)	1 (<1%)	4 (1%)

Source: Table 2.1.1-6 on pages 26 to 27 of ISS.

7.4.2 Laboratory Findings

Shifts in laboratory test values from normal to abnormal in healthy volunteers in Phase 1 studies are summarized in the table below. Treatment-emergent shifts from normal to abnormal lab values were recorded in 1-4 patients for some lab tests per IV1b treatment group and none in the placebo group.

Table 7-10 Treatment-Emergent Shifts from Normal to Abnormal Labs in Phase 1 Studies

	Lab parameter	Placebo (n=5)	IV1b 200 mg (n=6)	IV1b 400 mg (n=12)	IV1b 800 mg (n=12)
Chemistry	ALT (SGPT)	0	0	1 (8%)	0
	Albumin	0	0	0	2 (17%)
	BUN	0	0	0	1 (8%)
	Chloride	0	0	0	2 (17%)
	Creatinine	0	0	1 (8%)	0
	Glucose	0	2 (33%)	3 (25%)	1 (8%)
	Lactate Dehydrogenase	0	0	1 (8%)	3 (25%)
	Potassium	0	0	1 (8%)	0
	Total Bilirubin	0	3 (50%)	2 (17%)	1 (8%)
Coagulation	Prothrombin Time	0	0	2 (17%)	0
Hematology	Basophils	0	1 (17%)	1 (8%)	1 (8%)
	Eosinophils	0	1 (17%)	1 (8%)	0
	Hematocrit	0	0	1 (8%)	0
	Hemoglobin	0	0	1 (8%)	0
	Lymphocytes	0	1 (17%)	4 (33%)	2 (17%)
	Monocytes	0	1 (17%)	0	0
	Neutrophils	0	0	1 (8%)	0
	Platelets	0	0	1 (8%)	0

Source: Tables 3.0-3, 3.0-4, and 3.0-5 on pages 51 to 56 of ISS.

Shifts in laboratory test values from normal to abnormal in Phase 3 studies are summarized in the table below. The lab shifts consisted of the types of laboratory abnormality commonly seen in patients with either end-stage

illness, or post-operative status, or malarial infections. There were no clear patterns in any of the parameters listed to suggest a dose response in reporting rates. Shifts in laboratory test values from abnormal at baseline to normal at the final observation were reported in 5-14% placebo patients, 5-52% of patients on IVIb 100 and 200 mg, 1-22% of patients on IVIb 400 mg, and 1-9% of patients on IVIb 800 mg.

Table 7-11 Treatment-Emergent Shifts from Normal to Abnormal Labs in Phase 3 Studies

	Lab parameter	Placebo (n=305-341)	IVIb <400 mg (N=54-60)	IVIb 400 mg (N=177-192)	IVIb 800 mg (N=258-297)	
Chemistry	ALT (SGPT)	42 (13%)	16 (28%)	22 (12%)	28 (10%)	
	AST (SGOT)	27 (8%)	9 (16%)	21 (12%)	19 (7%)	
	Albumin	126 (39%)	3 (5%)	43 (24%)	139 (50%)	
	BUN	92 (28%)	6 (10%)	42 (22%)	110 (38%)	
	Bicarbonate	14 (4%)	6 (10%)	11 (6%)	24 (8%)	
	Chloride	25 (7%)	10 (17%)	16 (8%)	28 (10%)	
	Creatinine	28 (8%)	7 (12%)	14 (7%)	29 (10%)	
	Glucose	85 (26%)	11 (19%)	42 (23%)	63 (22%)	
	Lactate Dehydrogenase	32 (10%)	8 (15%)	22 (12%)	30 (11%)	
	Potassium	49 (15%)	5 (8%)	18 (9%)	53 (18%)	
	Sodium	24 (7%)	8 (13%)	14 (7%)	17 (6%)	
	Total Bilirubin	9 (3%)	5 (9%)	6 (3%)	7 (3%)	
	Total Protein	131 (40%)	6 (10%)	75 (42%)	152 (55%)	
	Coagulation	Activated PTT	24 (7%)	10 (18%)	20 (11%)	20 (7%)
		Prothrombin Time:	37 (12%)	3 (5%)	25 (14%)	41 (16%)
	Hematology	Basophils	12 (4%)	1 (2%)	8 (4%)	8 (3%)
		Eosinophils	47(14%)	14 (24%)	49 (26%)	19 (7%)
Hematocrit		127 (37%)	11 (18%)	77 (40%)	166 (56%)	
Hemoglobin		136 (40%)	14 (23%)	68 (36%)	164 (55%)	
Lymphocytes		136 (41%)	2 (3%)	61 (33%)	121 (42%)	
Monocytes		44 (13%)	3 (5%)	35 (19%)	42 (14%)	
Neutrophils		92 (28%)	11 (19%)	66 (35%)	63 (22%)	
Platelets		25 (7%)	14 (23%)	12 (6%)	15 (5%)	
	WBC	71 (21%)	12 (20%)	36 (19%)	60 (20%)	

Source: Tables 3.0-6, 3.0-7, and 3.0-8 on pages 59 to 65 of ISS.

Abnormal laboratory test values either $\geq 3x$ of upper limit of normal range (ULN) or $\geq 1/3x$ of lower limit of normal range (LLN) in Phase 3 studies are summarized in the table below. There were no clear patterns in any of the parameters listed to suggest a dose response in reporting rates.

Table 7-12 Summary of Remarkable [$\geq 3x$ ULN or $\geq (1/3) x$ LLN] Abnormal Laboratory Tests in phase 3 Studies

		Placebo (N=345)	IV ibuprofen			
			<400 mg (N=61)	400 mg (N=195)	800 mg (N=304)	All dosage (N=560)
Chemistry	ALT (SGPT) $\geq 3x$ ULN	7/328 (2%)	1/59 (2%)	11/181 (6%)	7/281 (2%)	19/521 (4%)
	AST (SGOT) $\geq 3x$ ULN	10/328 (3%)	5/59 (8%)	12/181 (7%)	3/280 (1%)	20/520 (4%)
	Albumin $\geq (1/3)x$ LLN	1/328 (<1%)	4/58(7%)	1/181(<1%)	0	5/520(<1%)
	BUN $\geq 3x$ ULN	1/331 (<1%)	0	2/188 (1%)	0	2/534 (<1%)
	Creatinine $\geq 3x$ ULN	0	0	1/188 (<1%)	0	1/537 (<1%)
	Glucose $\geq 3x$ ULN	0	1/58 (2%)	1/188 (<1%)	1/287 (<1%)	3/533 (<1%)
	Lactate Dehydrogenase $\geq 3x$ ULN	5/333 (2%)	1/57 (2%)	4/186 (2%)	1/288 (<1%)	6/531 (1%)
	Total Bilirubin $\geq 3x$ ULN	1/328 (<1%)	1/59 (2%)	2/281 (1%)	2/181 (<1%)	5/521(<1%)
Hematology	Basophils $\geq 3x$ ULN	1/332 (<1%)	0/59	1/187 (<1%)	0	1/535 (<1%)
	Eosinophils $\geq 3x$ ULN	27/333 (8%)	2/59 (3%)	22/187 (12%)	2/290 (<1%)	26/536 (5%)
	Lymphocytes $\geq 3x$ ULN	0	0	1/188 (<1%)	0	1/537 (<1%)

	Lymphocytes \geq (1/3)x LLN	42/334 (13%)	19/59 (32%)	17/188 (9%)	21/290 (7%)	57/537 (11%)
	Neutrophils \geq (1/3)x LLN	3/334 (<1%)	0	0	1/290 (<1%)	1/537 (<1%)
	Platelets \geq 3x ULN	0	1/60 (2%)	0	0	1/548 (<1%)
	Platelets \geq (1/3)x LLN	6/339 (2%)	11/60 (18%)	9/191 (5%)	0	20/548 (4%)
	WBC \geq 3x ULN	2/338 (<1%)	3/60 (5%)	0	0	3/547 (<1%)

Source: Table 3.0-2 on pages 47 to 49 of ISS.

7.4.3 Vital Signs

The changes in vital signs from baseline had a lot of variations. For example within treatment differences for the IVIb 800 mg group were statistically significant with smaller p-values than the p-values for the statistically significant differences in vital signs between the placebo and IVIb 800 mg treatment groups (Source: Table 4.0-2 on pages 72 to 73). There were no clear patterns to suggest a dose response.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

Ibuprofen-related drug toxicities had been shown to be dose dependent in the studies of oral formulations (refer to the professional drug labeling for ibuprofen oral formulation).

7.5.2 Time Dependency for Adverse Findings

Time dependency for adverse findings could not be adequately assessed because of the short duration of exposure (mostly 4-8 doses or 1-2 days of exposure) to the IV treatments. Safety profile on long-term exposure to oral formulation of ibuprofen had been established (refer to the professional drug labeling for ibuprofen oral formulation).

7.5.3 Drug-Demographic Interactions (gender, race)

Analysis of drug-demographic interactions are not applicable because of the limited subpopulation size of the treatment groups divided by age, gender, or race for each of the three major study populations: post operative pain after major surgery, malaria, and critically/severely ill population (refer to the Review Section 6.7 for explanation).

7.5.4 Drug Disease Interactions

Refer to the professional drug labeling for ibuprofen oral formulation.

7.5.5 Drug-Drug Interactions

Refer to the professional drug labeling for ibuprofen oral formulation.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to the professional drug labeling for ibuprofen oral formulation.

7.6.2 Human Reproduction and Pregnancy Data

Refer to the professional drug labeling for ibuprofen oral formulation.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

(b) (4)

A pediatric plan consistent with the content of the Pediatric Written Request issued by the FDA was submitted by the Applicant on April 15, 2009. The proposed pediatric studies include pharmacokinetic study in hospitalized pediatric patients ages from birth to <16 years who are in need for IV treatment of fever, fever efficacy study in hospitalized pediatric patients aged <6 months who are in need for IV treatment of fever, and safety study in pediatric patients with fever or pain (if additional exposure is required). The Applicant has requested a deferral of the required pediatric assessments in the pediatric plan.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

There were no reports of drug overdose in the studies of IV ibuprofen. Ibuprofen is not known to have abuse potential and problems with withdrawal or rebound.

7.7 Additional Submission

There were 14 additional submissions dated from December 30, 2008 to April 22, 2009, all in response to the requests by the NDA reviewers for more information or for clarification.

8. POSTMARKETING EXPERIENCE

Ibuprofen IV injection has not been marketed and thus there were no post marketing data available.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Based on a brief review of the abstracts of the literature reports in the submission there were no additional efficacy and/or safety information on the use of IV ibuprofen other than findings from the clinical studies.

9.2 Labeling Recommendations

Labeling will be reviewed separately.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting planned for IV ibuprofen.

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/s/

Christina Fang
5/20/2009 12:20:52 PM
MEDICAL OFFICER

Ellen Fields
5/20/2009 12:35:39 PM
MEDICAL OFFICER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: May 18, 2009

TO: Kathleen Davies, Regulatory Project Manager
Christina Fang, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: #22-348

APPLICANT: Cumberland Pharmaceuticals

DRUG: Amelior Injection (Ibuprofen Injection)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: 1. Reduction of fever
2. Management of pain

CONSULTATION REQUEST DATE: January 23, 2009

DIVISION ACTION GOAL DATE: June 11, 2009

PDUFA DATE: June 11, 2009

I. BACKGROUND:

Cumberland Pharmaceuticals has submitted NDA 22-348, a 505(b)(2) application, for Amelior (ibuprofen) Injection for the indications of management of mild to severe pain and reduction of fever. Amelior is formulated as a sterile solution for injection and is administered intravenously. Currently there are no antipyretics that can be administered intravenously.

Clinical inspections were conducted in response to a routine audit request in support of NDA 22-348, to assess data integrity and human subject protection. Sites were selected on the basis of the number of enrollees. Investigator Henry Frazer was also selected because the results from his site had a larger treatment effect than the other study sites.

The protocols inspected include:

- A. Protocols #008a and 008b entitled "A Multi-Center, Randomized, Double-Blind, Placebo Controlled Trials of Ibuprofen injection (IVIb) for Treatment of Pain in Post-operative Adult Patients"
- B. Protocol 004 entitled "A Multi-Center, Randomized, Double-Blind, Parallel, Placebo-Controlled Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Adult Febrile Patients"

II. RESULTS (by Site):

Name and Location of Clinical Investigator (CI)	Protocol #: and # of Subjects:	Inspection Dates	Final Classification
Peter Morris, M.D. Wake Forest School of Medicine Baptist Medical Center Winston Salem, NC 27157	Protocol #004/ 30 subjects	March 16 to 18, 2009	NAI
John T. Promes, M.D. Orlando Regional Medical Center Orlando, FL 32806	Protocol #004/ 21 subjects	April 1 to 9, 2009	VAI
Henry Frazer, Pharm.D. Baptist Medical Center Montgomery, AL 36116	Protocol #008b/ 75 subjects	May 11 to 15, 2009	Pending (Preliminary classification NAI)
Lamar Snow, M.D. Mobile Infirmiry Medical Center 5 Mobile Infirmiry Circle Mobile, AL 36608	Protocol #008a/ 31 subjects Protocol #008b/ 39 subjects	April 27, to May 7, 2009	Pending (Preliminary classification OAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Peter Morris, M.D.
Wake Forest School of Medicine, Baptist Medical Center
Winston Salem, NC 27157
 - a. **What was inspected:** For Protocol #004, there were 30 subjects enrolled, and 30 subjects completed the study. Records for 15 subjects were reviewed during the inspection.
 - b. **General observations/commentary:** There was no under-reporting of adverse events. Efficacy endpoint data were verified. No regulatory violations were noted.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the pending application.

2. John T. Promes, M.D.
Orlando Regional Medical Center
Orlando, FL 32806
 - a. **What was inspected:** For Protocol #004, 21 subjects were randomized at the site and 19 subjects completed the study. An audit of 100% subjects' records including informed consent forms, source documents, and case report forms was conducted.
 - b. **General observations/commentary:** Inspection revealed that subject 5052 with the diagnosis of "closed head injury, facial laceration" was enrolled into the study in violation of protocol exclusion criterion "a history of severe head trauma."
An additional inspectional finding was that the DSMB discussed the need to exclude patients from this study because of literature suggesting that NSAIDs inhibit osteoblast proliferation and bone healing. Apparently, sometime after April 7, 2003, the sponsor advised against enrolling patients with fractures, particularly long bone or spinal fractures, under the exclusion criteria, "Be otherwise unsuitable for the study in the opinion of the investigator." The sponsor requested the sites to note exclusion of fractures in the screening log.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Henry Frazer, Pharm.D.
Baptist Medical Center
Montgomery, AL 36116

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol #008b, 82 were screened at the site, 75 subjects were randomized and 70 subjects completed the study. An audit of 20 subjects' records, including informed consent documents, source documents, and case report forms, was conducted. For the primary endpoint, reduction in the requirement for morphine use in the 24 hours following surgery measured by total morphine usage in the 24 hours compared to placebo (Normal Saline 0.9%), all 20 audited subjects' records were verified.
- b. **General observations/commentary:** There was no under-reporting of adverse events. Efficacy endpoint data were verified. No regulatory violations were noted.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the pending application.

4. Lamar Snow, M.D.
Mobile Infirmary Medical Center
5 Mobile Infirmary Circle, Mobile, AL 36608

Note: Observations noted for this site are based on review of the FDA 483 and communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol #008a, 31 subjects were randomized at the site and 30 subjects completed the study. An audit of 10 subjects' records, including informed consent documents, source documents, and case report forms, was conducted. For the primary endpoint, reduction in the requirement for morphine use in the 24 hours following surgery measured by total morphine usage in the 24 hours compared to placebo (Normal Saline 0.9%), all 31 randomized subjects' records were audited.

For Protocol #008b, 39 subjects were randomized at the site and all subjects completed the study. An audit of 10 subjects' records, including informed consent documents, source documents, and case report forms, was conducted.

For the primary endpoint, reduction in the requirement for morphine use in the 24 hours following surgery measured by total morphine usage in the 24 hours compared to placebo (Normal Saline 0.9%), all 39 randomized subjects' records were audited.

- b. **General observations/commentary:** The following regulatory violations were noted:
- i. Concerning the primary endpoint, morphine usage, discrepancies were noted for the following 4 subjects between the source documents and the data that are contained in the NDA data listings:
 - a. Protocol 008a, Subject 3255 had 28 mg of morphine administered according to the source documents, but the NDA listing states that 37 mg was administered.
 - b. Protocol 008b, Subject 7060 had 41.75 mg of morphine administered according to the source documents, but the NDA listing states that 20 mg was administered.
 - c. Protocol 008b, Subject 6057 had 43 mg of morphine administered according to the source documents, but the NDA listing states that 26 mg was administered.
 - d. Protocol 008b, Subject 8058 had 25 mg of morphine administered according to the source documents, but the NDA listing states that 40 mg was administered.
 - ii. Protocol 008a, Subject 1252 experienced an adverse event (AE), nausea and vomiting, that was not reported to the sponsor. All other AEs for the audited subjects were reported.
 - iii. Two of thirty subjects (Subject 2251 and Subject 4251) treated on protocol 008a were unblinded to study staff so that the medication administration records (MAR) for these subjects indicate the treatment assignment.
 - iv. The timings of the morphine doses for subjects 5056 and 8060 on protocol 008b appear to be altered in the copies of hospital records maintained at the study site compared with source documents maintained at the hospital. The protocol states, "If administered, morphine must be discontinued no later than 45 minutes prior to clinical trial material (CTM) administration. After the first dose of CTM is administered, the patient should not receive morphine again until self administration by PCA pump (or by staff at patient request)."
 - a. For subject 5056, the original hospital record notes two 5 mg morphine doses administered during surgery, but the study site copy of the anesthesia record was changed to note that a single entry of 10 mg of morphine was administered just prior to the surgery start time.
 - b. For subject 8060 the source indicates two 5 mg morphine doses, the first administered just prior to the 8am timeline and the second after the 8:30 timeline. The study site copy of the anesthesia record was changed to note that the second dose was administered just prior to the 8:45 timeline with the additional notation "08:35-CTM started by (b) (6) CRNA/ (b) (6) RN" These two subjects were not eligible for enrollment based on the original hospital record source documents.
 - v. Dr. Snow, the clinical investigator (CI) did not appear to have adequate oversight of the study.

- c. **Assessment of data integrity:** The reported morphine totals for the 4 subjects noted above could not be verified by the source documents, and one AE of nausea and vomiting was not reported to the sponsor. Given the inability to verify the primary endpoint data for the 4 subjects noted above, the review division may wish to consider excluding from analyses the efficacy data from these subjects. Data generated by this site for the other subjects appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of Dr. Snow and Dr. Promes found regulatory violations as noted above. The inspection of Dr. Morris did not find regulatory violations. The data from the Morris, Promes and Frazer sites appear acceptable in support of the proposed indication.

For the Snow site the significant findings concerning data integrity are that the morphine totals for the four subjects noted above could not be verified by the source documents, two subjects did not meet eligibility criteria based on source documents, and one AE of nausea and vomiting was not reported to the sponsor. Given the inability to verify the primary endpoint data for the four subjects noted above and the ineligibility of the two subjects based on timing of morphine administration relative to CTM administration, the review division may wish to consider excluding from analyses the efficacy data from these six subjects. Data generated by this site for the other subjects appear acceptable in support of the pending application.

The final classifications for the Frazer and Snow inspections are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Susan Leibenhaut, MD
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

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/s/

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