

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-348

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the NDA 22-349 submitted on 12/3/08. From OCP perspective, the information contained in the Application is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling.

1.2 Phase IV Commitments – Not applicable

1.3 Summary of CPB Findings

Cumberland Pharmaceuticals, Inc. has submitted ibuprofen intravenous injection (IVIb) for the indication of management of pain and reduction of fever in adult (b) (4) population. (b) (4)

A Pediatric Written Request will be issued to the Applicant. This NDA was

submitted under the Fast Track development program (granted on 7/15/08). References were made to three ibuprofen NDAs for this 505(b)(2) application: NDA 020-516, Children's Motrin (suspension; oral), NDA 020-402, Advil Liqui-Gels (capsule; oral), and NDA 017-463, Motrin (tablet; oral). In the current NDA, Advil Liqui-Gel was used as a reference.

In the current submission, the Applicant submitted one single dose relative bioavailability study (Study CPI-CL-001) and pharmacokinetic (PK) information from a Phase 3 study (Study CPI-CL-004 for fever indication). Only racemic ibuprofen was analyzed for PK analysis with a reverse phase HPLC system. It is well known that ibuprofen is a racemate, and, on average, 60% of R-ibuprofen is converted to S-ibuprofen, the active form, after oral administration ("pre-systemic gastrointestinal inversion"). As well, Hall et. al.* published a study which showed that there is also presence of inversion after intravenous ibuprofen administration in a similar manner as oral ibuprofen administration. It is speculated that higher S-ibuprofen concentrations led to greater inhibition of COX-1 (reduced thromboxane B2 concentrations) and greater inhibition of COX-2 (reduced prostaglandin E2 concentrations), resulting in reduction of pain and fever by prostanoids inhibition.

To-be-marketed formulation was used in all clinical trials. There is no concentration-response information submitted in this Application for IVIb. However, the Applicant conducted 2 Phase 3 studies per indication (see Clinical Review for additional details).

In Study CPI-CL-001, the Applicant compared 200, 400 and 800 mg of IVIb to equivalent doses of Advil Liqui-Gel. The results indicated that the observed ibuprofen exposure was similar (90% Confidence Interval (CI) calculation) when equivalent single doses of ibuprofen were administered either as IVIb or Advil Liqui-Gel over the dose range 200 to 800 mg, with one exception of Cmax following IVIb administration of a single 200 mg dose, which showed slightly lower Cmax than that of Advil Liqui-Gel Cmax (90% CI: 70.0 – 87.4). The observed ibuprofen Cmax and AUC IVIb exhibited a linear relationship from 200 to 800 mg. The observed T1/2 was approximately 2 – 2.5 h.

Dose	200mg (CPI-CL-001)		400mg (CPI-CL-001)		800mg (CPI-CL-001)	
	Advil Liqui-Gel	IVIb	Advil Liqui-Gel	IVIb	Advil Liqui-Gel	IVIb
No. of Patients	12	12	12	12	12	12
AUCinf (µg•h/mL) Mean (%CV)	69.862 (25.7%)	65.532 (21.5%)	110.887 (24.2%)	112.471 (29.2%)	218.817 (25.1%)	198.206 (20.0%)
Cmax (µg/mL) Mean (%CV)	24.697 (17.1%)	19.294 (16%)	42.939 (11.4)	39.217 (15.5%)	81.046 (23.2%)	72.640 (13.2%)
Tmax (h) Mean (%CV)	0.65 (25.9%)	1.13 (20.3%)	0.55 (25.6%)	1.05 (15.8%)	0.85 (60.4%)	1.00 (0)
T1/2 (h) Mean (%CV)	2.33 (9.6)	2.34 (12.4)	2.23 (19.5)	2.22 (20.1)	2.48 (15.6)	2.44 (12.9)

The 90% confidence intervals for the ratios of the geometric means:

	200 mg	400 mg	800 mg
C _{max}	78.2% (70.0 – 87.4%)	94.5% (84.3 – 105.9%)	91.1% (83.1 – 99.7%)
AUC 0-t	94.3% (84.2 – 105.6%)	100.3% (92.7 – 108.5%)	91.3% (86.9 – 96.1%)
AUC 0-inf	94.5% (84.3 – 105.9%)	100.6% (93.0 – 108.8%)	91.2% (86.5 – 96.2%)

Study CPI-CL-004 was a Phase 3 study for fever indication (patients who had temperatures of 101°F (38.3°C) or greater) where 100, 200 and 400 mg doses of IVIb were administered Q4h for 24 hours. In this study, blood samples were obtained from 0 – 4 and 20 – 26 h post IVIb administration. However, pharmacokinetic parameters were not presented for 20 – 26 h samples. The results indicated that the observed ibuprofen C_{max}0-4 and AUC0 - 4 exhibited a linear relationship from 100 mg to 400 mg. No PK parameters were presented for time-points 20-26 hours. However no dramatic differences in the parameters are expected after multiple dosing. This was confirmed when profiles from 0 - 4 h were compared with 20 - 26 h.

Dose	AUC0-4 (µg.h/mL)	C _{max} 0-4 (µg/mL)	T _{max} 0-4 (h)	T _{1/2} (h)
100 mg IVIb	22.33 ± 12.75	12.17 ± 6.78	0.5	2.47
200 mg IVIb	32.62 ± 17.39	18.94 ± 10.5	0.5	2.11
400 mg IVIb	70.64 ± 31.93	39.76 ± 17.75	0.5	2.26

With respect to ibuprofen exposure in healthy subjects and ill- patients, C_{max} and t_{1/2} were compared as an inter-study comparison. The observed C_{max} and t_{1/2} values were similar between healthy subjects and ill-patients. The observed AUC values were not compared due to lack of AUC values in ill-patients.

	200 mg		400 mg	
	Ill patients	Healthy subjects	Ill patients	Healthy subjects
C _{max} 0-4	18.9	19.3	39.8	42.9
T _{max} 0-4	0.5	1.13	0.5	0.55
T _{1/2}	2.11	2.34	2.26	2.22

Furthermore, the Applicant presented additional ibuprofen exposure analysis from Study CPI-CL-004 looking at ‘non-critically ill’ and ‘critically ill’ patients. The ‘critically-ill’ was defined as subjects who are hospitalized and require mechanical ventilation for respiratory failure, pressor support for hypotension, or both. The results indicated that ibuprofen PK parameters from ‘non-critically ill’ and ‘critically ill’ patients were somewhat different. The values for the AUC0-4 and C_{max}0-4 pharmacokinetic parameters for the critically ill patients were approximately 50% compared to the parameters for the non-critically ill patients.

Treatment, Stratum		AUC ₀₋₄ (µg.h/mL)	C _{max0-4} (µg/mL)	T _{max0-4} (h)	T _{half} (h)
100 mg IVIb	Critically Ill n=14	16.10	8.23	0.6	2.42
	Non-critically Ill n=17	26.33	14.53	0.5	2.49
200 mg IVIb	Critically Ill n=12	19.62	11.46	0.5	2.56
	Non-critically Ill n=18	39.51	22.89	0.5	1.86
400 mg IVIb	Critically Ill n=14	45.94	25.70	0.5	2.32
	Non-critically Ill n=17	87.11	49.13	0.5	2.22

The percent difference between the critically ill versus the non-critically ill groups for the AUC₀₋₄ and C_{max0-4} pharmacokinetic parameters:

Treatment, Stratum	AUC ₀₋₄ (µg h/mL)	C _{max0-4} (µg/mL)
100 mg IVIb Critically Ill / Non-critically Ill % Difference	61.2%	56.6%
200 mg IVIb Critically Ill / Non-critically Ill % Difference	49.6%	50.0%
400 mg IVIb Critically Ill / Non-critically Ill % Difference	52.7%	52.3%

However, these differences did not seem to have notable affect on the efficacy of the product in this population (see Clinical Review for additional details).

Overall, there are no concerns with this submission and information submitted within is acceptable.

*Hall, S.D., Rudy, A.C., Knight, P.M., and Brater, D.C., (1993) Lack of presystemic inversion of (R)- to (S)-ibuprofen in humans, *Clinical Pharmacology and Therapeutics*, 53, 393-400.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

The apparent rationale for the development of Ibuprofen Injection (IVIb) was to treat patients with (b) (4). Data available to the Applicant from preliminary investigations from placebo-controlled trials demonstrated reduced fever, heart rate, and lactic acidosis with intravenous ibuprofen in septic patients. Additionally, the studies also showed that intravenously administered ibuprofen was safe and well tolerated by patients unable to take oral medications. Therefore, the Applicant pursued a development of an intravenous ibuprofen formulation for those patients who cannot be treated with an oral dosage form.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Description and Composition of Drug Product

Ibuprofen Injection (IVIb) is a simple product containing ibuprofen and arginine as the main ingredients. It is a sterile injectable solution containing 100mg/mL of ibuprofen at a neutral pH of 7.0 to 8.0. Ingredients in the formulation meet or exceed current Pharmacopeial standards. The product is filled into (b) (4) (400mg) or (b) (4), (800mg) clear (b) (4) glass vials and sealed with (b) (4) stoppers and flip-off seals. The product is typically added to commercially available IV bags containing 5% dextrose or normal saline to avoid any potential for local irritation of administering undiluted drug. Table 1 provides formulation details.

Table 1 Composition of Ibuprofen Injection

Presentation		100 mg/mL.			
Strength		100 mg/mL			
Product Description		A clear, colorless to slightly yellow solution.			
	Ref.	Each mL contains	Each 4 mL contains	Each 8 mL contains	Function
Ibuprofen	USP	100 mg	400 mg	800 mg	Active Ingredient
Arginine	USP	78.0 mg	312 mg	624 mg	(b) (4)
WFI	USP	qs 1.0 mL	qs 4.0 mL	qs 8.0 mL	(b) (4)
(b) (4)					
Container Description		(b) (4) clear glass vial (400mg presentation)			
		(b) (4) clear glass vial (800mg presentation)			
Closure Description		(b) (4) closure			

2.1.3 What are the proposed therapeutic indication(s) and mechanism of action?

Currently, there are no intravenous medications approved in the United States for the treatment of fever in children or adults. Additionally, there are no intravenous ibuprofen formulations in the United States for the indications of treatment of fever and management of pain.

Ibuprofen Injection (IVIb) is indicated for the reduction of fever and management of pain in adult (b) (4) patients. Ibuprofen is a nonsteroidal anti-inflammatory drug

(NSAID). The oral formulation was first approved in the United States in 1974 and was afterward approved for nonprescription status in 1984. Ibuprofen was approved for use in the United States as an antipyretic in children in 1989, and soon after for over-the-counter (OTC) status in the mid-1990s.

The exact mechanism of action is not known for ibuprofen; however, it is believed to include inhibition of cyclooxygenase mediated prostaglandin formation. Ibuprofen inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activities and thereby synthesis of prostaglandins and thromboxanes.

2.1.4 What are the proposed dosage and route of administration?

The route of administration is via intravenous. The proposed dosage for pain and fever is as follows:

Mild to Severe Pain:

- Adults: 800 mg every 6 hours as necessary for relief of pain

Fever:

- Adults: 400 mg every 4 to 6 hours as necessary for relief of fever. (b) (4)
- 

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

The Applicant submitted data from seven clinical studies in support of this NDA for two indications, reduction of fever and management of pain. See Table 2 for a list of the trials.

Table 2 Clinical trials for IVib

Study	Full Title	N		Data Integrati on
(b) (4)	(b) (4)			
CPI-CL-001	A Phase I, Open-Label, Randomized, Single-Dose, Crossover, Pharmacokinetic, and Safety Study with Intravenous and Oral Ibuprofen in Healthy Subjects	36	PK & Safety	ISS
CPI-CL-003	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Crossover Study of the Safety and Tolerability of Ibuprofen Injection in Healthy Adult Subjects	12	Safety	ISS
CPI-CL-006*	A Single Center, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Ibuprofen Injection in Hospitalised Febrile Adult Patients	60	Pivotal: Fever	ISS/ISE
CPI-CL-004*	A Multicenter, Randomized, Double-blind, Parallel, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Adult Febrile Patients	120	Pivotal: Fever	ISS/ISE
CPI-CL-008A#	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection (IVib) for Treatment of Pain in Post-Operative Adult Patients	406	Pivotal: Pain	ISS/ISE
CPI-CL-008B#	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection (IVib) for Treatment of Pain in Post-Operative Adult Patients	319	Pivotal: Pain	ISS/ISE

With respect to clinical pharmacology, the Applicant submitted ibuprofen exposure information from Study CPI-CL-001 (pharmacokinetic and safety study) and Study CPI-CL-004 (pivotal fever study). Study CPI-CL-001 compared ibuprofen pharmacokinetic properties between oral and intravenous ibuprofen. Study CPI-CL-004 provided ibuprofen exposure information after multiple ibuprofen administration.

For fever, three studies were conducted; a study conducted under investigator IND (b) (4) Study CPI-CL-006 (hospitalized patients with malaria) and Study CPI-CL-004 (hospitalized adult patients with all-cause fever).

For pain, two studies were conducted, Study CPI-CL-008, Part A (hospitalized patients undergoing elective abdominal and orthopedic procedures) and Study CPI-CL-008, Part B (hospitalized patients undergoing elective abdominal hysterectomy procedures).

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Ibuprofen has been used for both fever and pain since the early 1970's. In the current submission, the Applicant measured body temperature and pain intensity for fever and pain indication for intravenous ibuprofen.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to II. F, Analytical Section; if no, describe the reasons)

Yes. See Analytical Section 2.6 for assay information.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

There is no concentration-response information submitted in this Application for IVIb. However, the Applicant conducted 2 Phase 3 studies per indication. In this section, the findings from the Phase 3 studies are briefly presented. The reader is referred to the Clinical Review for additional details.

Fever indication:

Study	Full Title	N		Data Integration
CPI-CL-006*	A Single Center, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Ibuprofen Injection in Hospitalised Febrile Adult Patients	60	Pivotal: Fever	ISS/ISE
CPI-CL-004*	A Multicenter, Randomized, Double-blind, Parallel, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Adult Febrile Patients	120	Pivotal: Fever	ISS/ISE

Study CPI-CL-004 was a multicenter, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of ibuprofen injection in adult febrile patients. Patients (120 patients (88 men, 32 women)) who had temperatures of 101°F or greater were randomized to receive IVIb at 100 mg, 200 mg, 400 mg or placebo, administered every 4 hours for 24 hours of treatment. For statistical analyses, randomization of patients was stratified based upon severity of illness (critically ill vs. non-critically ill).

The Applicant stated that all IVIb dose levels resulted in a statistically significant reduction in the number of patients with a temperature <101°F after 4 hours, compared to placebo. The results also showed dose-response trend which the 400mg dose showing the greatest response. The number of people achieving a reduction in fever (<101°F after 4 hours) were:

- Placebo: 9 of 28 patients;
- 100 mg IVIb: 20 of 31 patients (p=0.0138, vs. placebo);
- 200 mg IVIb: 22 of 30 patients (p=0.0018, vs. placebo); and
- 400 mg IVIb: 24 of 31 patients (p=0.0005, vs. placebo).

At 24 hours, the mean temperature decrease from baseline was:

Placebo: $2.07^{\circ}\text{F} + 2.37^{\circ}\text{F}$;

100 mg IVIb: $3.07^{\circ}\text{F} + 1.95^{\circ}\text{F}$, mean difference vs. placebo: 1.00°F (-4.77 to 6.75 95% CI);

200 mg IVIb: $3.12^{\circ}\text{F} + 1.88^{\circ}\text{F}$, mean difference vs. Placebo: 1.05°F (-1.40 to 10.21 95% CI);

400 mg IVIb: $3.45^{\circ}\text{F} + 2.02^{\circ}\text{F}$, mean difference vs. placebo: 1.38°F (-4.39 to 7.13 95% CI).

Additional analysis looking at non-critically ill vs. critically ill patients, Figure 1 compares the effect of placebo and a 400 mg dose of IVIb on body temperature in non-critically and critically ill hospitalized patients. The data implied that critically ill patients appear to have lower Cmax and AUC of IVIb, which appears to somewhat reduce the therapeutic effect, i.e., the decrease in temperature in for the critically ill patients were less due to the lower ibuprofen exposure.

The Applicant stated that the decrease over time in the placebo group was due to the patients enrolled in the study that were suffering from malaria and receiving concomitant anti-malarial drugs, which the concomitant anti-malarial drugs were treating the cause of the fever (Figure 2).

Figure 1 Temperature over time by stratum, 400mg IVIb vs. placebo, study CPI-CL-004

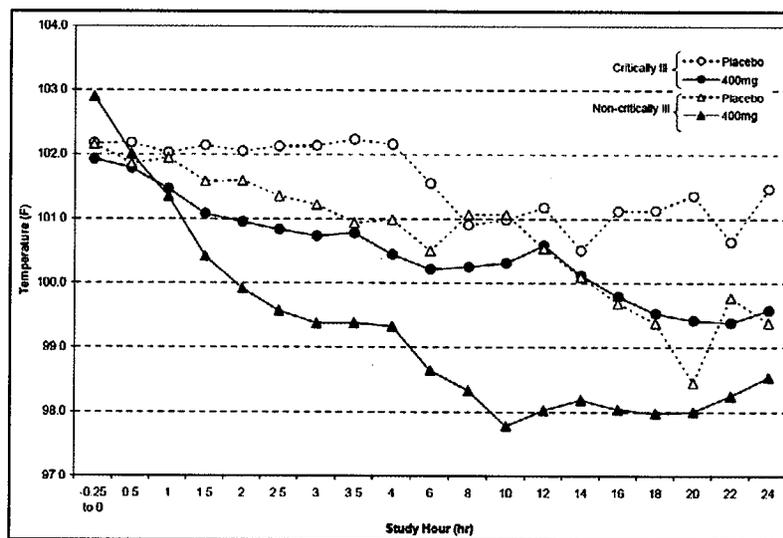
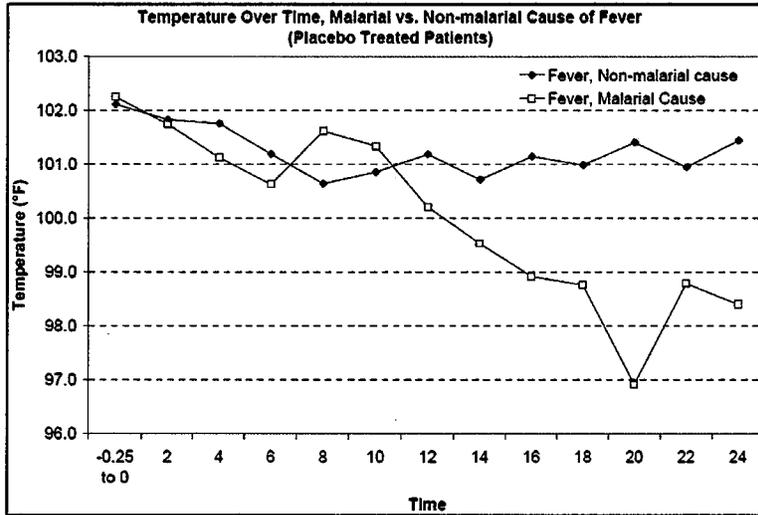


Figure 2 Placebo Temperature Response in Malaria vs. Non-malarial Patients (Study CPI-CL-004)



Study CPI-CL-006 was a single center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ibuprofen injection in hospitalized febrile adult patients. Patients (60 patients (48 men, 12 women)) with uncomplicated *P. falciparum* malaria having temperatures >100.4°F were randomized to IVIb 400 mg or placebo, administered every 6 hours for 72 hours of treatment. The primary endpoint was the reduction of fever within the first 24 hours of treatment, measured as the area above the temperature 98.6°F (37.0°C) vs. time curve (AUC-T°). There was a statistically significant reduction in AUC-T° for IVIb compared with placebo measured over 0-4 hours (p=0.0008), 0-24 hours (p=0.0019), and 0-72 hours (p=0.0303).

Pain indication:

Study	Full Title	N		Data Integration
CPI-CL-008A#	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection (IVIb) for Treatment of Pain in Post-Operative Adult Patients	406	Pivotal: Pain	ISS/ISE
CPI-CL-008B#	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection (IVIb) for Treatment of Pain in Post-Operative Adult Patients	319	Pivotal: Pain	ISS/ISE

Study CPI-CL-008, Part A was a multi-center, randomized, double-blind, placebo-controlled trial of ibuprofen injection (ivib) for treatment of pain in post-operative adult patients. This trial was designed to determine if IVIb can reduce the need for morphine, a 'morphine sparing-effect.' Patients (406 patients (87 men, 319 women)) who had undergone an elective abdominal or orthopedic surgery were randomized to IVIb 400 mg, IVIb 800 mg, or placebo, administered every 6 hours. Treatment ranged from 1 to 17 doses.

The results showed that, compared to placebo, there was a reduction in the use of morphine through 24 hours in patients receiving 800 mg IVIb ($p=0.030$). In patients receiving 400 mg IVIb, the treatment effect was not statistically significant ($p=0.458$). The Applicant reported that in the 342 efficacy evaluable patients, there was a 26% reduction in median morphine consumption in patients receiving 800 mg IVIb. In addition to the morphine sparing-effect, compared to placebo, patients receiving 800 mg IVIb experienced a greater reduction in pain as measured by the Visual Analog Scale (VAS) area under the curve for the first 24 hours after surgery ($p<0.001$). The incidence of nausea and diarrhea was also significantly less in the IVIb treated patients.

CPI-CL-008, Part B was a multi-center, randomized, double-blind, placebo-controlled trial of ibuprofen injection (ivib) for treatment of pain in post-operative adult patients. Part B was also designed to determine if IVIb can reduce the need for morphine, a 'morphine sparing-effect.'

Patients (319 female patients) who had undergone an elective abdominal hysterectomy surgery were randomized to IVIb 800 mg or placebo, administered every 6 hours. Treatment ranged from 1 to 12 doses. Compared to placebo, there was a reduction in the use of morphine through 24 hours in patients receiving 800 mg IVIb ($p<0.001$). There was a 21% reduction in median morphine consumption in patients receiving 800 mg IVIb (calculated from 287 efficacy evaluable patients). As with Par A, in addition to the morphine sparing-effect, patients receiving 800 mg IVIb experienced a greater reduction in pain as measured by the VAS area under the curve for the first 24 hours after surgery ($p<0.009$). Time to ambulation was also significantly shorter in the IVIb treated patients ($p=0.009$ compared to placebo).

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

Table 3 provides a summary of the number of patients who received intravenous ibuprofen in the four pivotal studies. Patients enrolled in study CPI-CL-004 received doses less than 400 mg IVIb. Patients enrolled in the pivotal pain studies, CPI-CL-008A and CPI-CL-008B, received 800 mg IVIb doses. Severity of illness and presence of malaria in the two pivotal fever studies is also included in the table.

Table 3 Number of Patients by Treatment Group in All Placebo and IVIb Patients in Pivotal Studies

Study	Placebo (N=345)	IVIb			Overall (N=560)
		< 400 mg (N=61)	400 mg (N=195)	800 mg (N=304)	
CPI-CL-004 (Fever)					
Critically Ill / No Malaria	13 (4%)	26 (43%)	14 (7%)	0 (0%)	40 (7%)
Non-critically Ill / No Malaria	5 (1%)	15 (25%)	7 (4%)	0 (0%)	22 (4%)
Critically Ill / Malaria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-critically Ill / Malaria	10 (3%)	20 (33%)	10 (5%)	0 (0%)	30 (5%)
Total CPI-CL-004	28 (8%)	61 (100%)	31 (16%)	NA	92 (16%)
CPI-CL-006, All Malaria (Fever)	30 (9%)	NA	30 (15%)	NA	30 (5%)
CPI-CL-008A (Pain)	134 (39%)	NA	134 (69%)	138 (45%)	272 (49%)
CPI-CL-008B (Pain)	153 (44%)	NA	NA	166 (55%)	166 (30%)

Drug exposure is presented in Table 4.

Table 4 Exposure to Study Drug IVIb Patients in Pivotal Studies, Duration of Study Drug

	IVIb			
	< 400 mg (N=61)	400 mg (N=195)	800 mg (N=304)	Overall (N=560)
Duration of Study Drug (days)				
N	61	195	304	560
Mean (SD)	2 (0.7)	2 (0.2)	2 (0.5)	2 (0.7)
Median	2	2	2	2
Min	1	1	1	1
Max	2	4	5	5
Total Cumulative Dose (mg)				
N	61	195	304	560
Mean (SD)	879 (327.2)	2661 (1194.6)	4211 (1491.3)	3308 (1716.2)
Median	600	2400	4000	4000
Min	100	400	800	100
Max	1200	5200	13600	13,600

Analysis of Adverse Events: Pivotal Studies

The number and percentage of all pivotal patients who reported Treatment-Emergent Adverse Events (TEAEs) were comparable between IVIb and placebo treatment groups. The number and percentage of all pivotal patients who reported TEAEs was also similar between IVIb treatment groups. In pivotal studies, there was no significant difference in the number of TEAEs reported between patients in the placebo and IVIb 400 mg and 800 mg treatment groups. TEAEs in the placebo and IVIb treatment groups are summarized below in Table 5 for all pivotal patients and by severity.

Table 5 Number of Patients experiencing TEAEs in Pivotal Studies

Patient group/subgroup	Placebo	IV Ib			
		< 400 mg	400 mg	800 mg	Overall
All Patients: Any TEAE	295 (86%)	52 (85%)	155 (79%)	260 (86%)	467 (83%)
Mild	173 (50%)	23 (38%)	94 (48%)	146 (48%)	263 (47%)
Moderate	102 (30%)	18 (30%)	45 (23%)	100 (33%)	163 (29%)
Severe	20 (6%)	11 (18%)	16 (8%)	14 (5%)	41 (7%)
N	345	61	195	304	560
p-value vs placebo			0.092	>0.999	
All Patients: Any Non-Serious TEAE	293 (85%)	49 (80%)	155 (79%)	260 (86%)	464 (83%)
N	345	61	195	304	560

Common Adverse Events: Pivotal Studies

The Applicant stated that the patient populations for the two indications were different. The patients enrolled in the two fever studies (N=180) were comprised of 100 malaria patients (patients were **defined as ‘non-critically ill’**). Of the remaining 80 fever patients, the source of fever was of varied etiologies (but not due to malaria) and the patients were stratified to critically ill (66%) and non-critically ill (34%).

The patients enrolled in the two pain studies were not previously hospitalized prior to admission. They were elective surgical procedure patients. As part of the pain studies’ design, all patients were eligible to receive morphine to manage pain. Many of the events experienced in the pain studies were consistent with those typically expected from patient’s undergoing surgery with anesthesia and morphine analgesia (i.e. nausea, vomiting, constipation, etc).

Overall there was no significant difference in the number and percentage of all pivotal patients who reported TEAEs, and was comparable between IV Ib and placebo treatment groups.

Indication: Fever

One study was conducted in a combination of critically ill or non-critically ill (USA) hospitalized febrile (all-cause fever) patients and the other was hospitalized febrile malaria patients (Asia). The Applicant stated that there are a high number of patients in both the IV Ib and placebo groups with baseline hematological laboratory values that fall outside of the reference range, predominantly hemoglobin, hematocrit and platelet counts, commonly expected in malaria patients. The decreased hemoglobin/hematocrit values are thought to be due to poor nutritional status of several of the patients prior to study enrollment. Many of the patients enrolled in the study had low baseline platelet counts, one of the clinical manifestations of falciparum malaria (Table 6).

Table 6 Number of Patients Experiencing Treatment-Emergent Adverse Events by System organ Classification and Preferred Term; Events that Occur in >3% of Patients; Fever Studies

System Organ Class Preferred Term	Placebo (N=58)	IV1b ≤ 400 mg (N=122)
Any Treatment-Emergent Event	37 (64%)	89 (73%)
Blood and lymphatic system disorders		
Anemia	4 (7%)	22 (18%)
Eosinophilia	7 (12%)	22 (18%)
Leukopenia	1 (2%)	4 (3%)
Lymphocytosis	2 (3%)	5 (4%)
Monocytosis	2 (3%)	2 (2%)
Neutropenia	2 (3%)	8 (7%)
Thrombocythemia	0	6 (5%)
Thrombocytopenia	2 (3%)	2 (2%)
Gastrointestinal disorders		
Abdominal pain	5 (9%)	8 (7%)
Diarrhea	3 (5%)	8 (7%)
Ileus	2 (3%)	2 (2%)
Nausea	3 (5%)	3 (2%)
Vomiting	2 (3%)	3 (2%)
General disorders and administration site conditions		
Multi-organ failure	1 (2%)	5 (4%)
Infections and infestations		
Bacteremia	0	4 (3%)
Pneumonia bacterial	0	6 (5%)
Investigations		
Blood lactate dehydrogenase increased	1 (2%)	6 (5%)
Metabolism and nutrition disorders		
Hypernatremia	0	5 (4%)
Hypoalbuminemia	1 (2%)	7 (6%)
Hypokalemia	5 (9%)	15 (12%)
Hypomagnesemia	1 (2%)	5 (4%)
Hypoproteinemia	2 (3%)	7 (6%)
Nervous system disorders		
Headache	0	4 (3%)
Vascular disorders		
Hypotension	1 (2%)	5 (4%)

Indication: Pain

The patients were from elective surgical procedures who received opioid, specifically morphine, analgesic. Many of the events experienced in the pain studies were consistent with those typically expected from patient's undergoing surgery with anesthesia and morphine analgesia. Table 7 presents TEAEs by system organ classification and preferred term; events that occur in >3% of patients from the pain studies.

Table 7 Treatment-Emergent Adverse Events by System organ Classification and Preferred Term; Events that Occur in >3% of Patients; Pain Studies

System Organ Class Preferred Term	Placebo (N=287)	IV1b	
		400 mg (N=134)	800 mg (N=304)
Any Treatment-Emergent Event	258 (90%)	118 (88%)	260 (86%)
Blood and lymphatic system disorders			
Anemia	6 (2%)	5 (4%)	7 (2%)
Gastrointestinal disorders			
Abdominal discomfort	0	4 (3%)*	2 (<1%)
Abdominal distension	10 (3%)	1 (<1%)	7 (2%)
Constipation	49 (17%)	23 (17%)	38 (13%)
Dyspepsia	2 (<1%)	6 (4%)*	4 (1%)
Flatulence	44 (15%)	10 (7%)*	49 (16%)
Nausea	179 (62%)	77 (57%)	161 (53%)*
Vomiting	50 (17%)	30 (22%)	46 (15%)
General disorders and administration site conditions			
edema peripheral	4 (1%)	1 (<1%)	9 (3%)
Pyrexia	32 (11%)	9 (7%)	16 (5%)*
Investigations			
Body temperature increased	8 (3%)	0	7 (2%)
Hemoglobin decreased	3 (1%)	4 (3%)	6 (2%)
Metabolism and nutrition disorders			
Hypokalemia	8 (3%)	5 (4%)	3 (<1%)
Nervous system disorders			
Dizziness	5 (2%)	8 (6%)*	13 (4%)
Headache	31 (11%)	12 (9%)	35 (12%)
Psychiatric disorders			
Insomnia	13 (5%)	4 (3%)	6 (2%)
Renal and urinary disorders			
Urinary retention	10 (3%)	7 (5%)	10 (3%)
Reproductive system and breast disorders			
Vaginal hemorrhage	16 (6%)	13 (10%)	13 (4%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (<1%)	4 (3%)*	2 (<1%)
Skin and subcutaneous tissue disorders			
Pruritus	47 (16%)	10 (7%)*	46 (15%)
Vascular disorders			
Hypertension	8 (3%)	1 (<1%)	4 (1%)
Wound hemorrhage	4 (1%)	4 (3%)	4 (1%)
*p<0.05			

2.2.4.3 Is the dose and dosing regimen consistent with the already approved drug product(s)?

The dose and dosing regimen are somewhat consistent with the already approved drug products, Advil Liqui-Gels and Motrin tablets. Ibuprofen is utilized in many different ailments, including pain, fever, menstrual cramps, arthritis, etc. with various doses. When under the care of a physician, the maximum dose of ibuprofen is 3.2 g daily. Otherwise, the maximum dose is 1.2 g daily. Currently, individuals should not use ibuprofen for more than 10 days for the treatment of pain or more than 3 days for the treatment of a fever unless directed by a physician. Children 6 months to 12 years of age usually are given 5-10 mg/kg of ibuprofen every 6-8 hours for the treatment of fever and pain. The maximum dose is 40 mg/kg daily.

As far as exposure is concerned, the Applicant compared the results from Study CPI-CL-001 to that of the Advil Liqui-Gel formulation (Table 8) and submitted in the Application. The ibuprofen exposure (C_{max} and AUC) appear to be similar between the intravenous ibuprofen and Motrin tablet.

Table 8 Pharmacokinetic parameter comparison of Adult Motrin tablet, Advil Liqui-Gel and ibuprofen intravenous infusion

Dose	200mg (2.8mg/kg) in Adults Motrin Insert#	Study CPI-CL-001					
		200mg IV		400mg IV		800mg IV	
Formulation	Suspension	Oral*	IV	Oral*	IV	Oral *	IV
No. of Patients	24	12	12	12	12	12	12
AUC _{0-t} (µg•h/mL)	-	67.982 (24.8%)	63.647 (20.7%)	108.255 (22%)	109.336 (26.4%)	212.117 (22.5%)	192.755 (18.5%)
AUC _{inf} (µg•h/mL) (CV%)	64 (27%)	69.862 (25.7%)	65.532 (21.5%)	110.887 (24.2%)	112.471 (29.2%)	218.817 (25.1%)	198.206 (20.0%)
C _{max} (µg/mL) (CV%)	19 (22%)	24.697 (17.1%)	19.294 (16%)	42.939 (11.4)	39.217 (15.5%)	81.046 (23.2%)	72.640 (13.2%)
T _{max} (h) (CV%)	0.79 (69%)	0.65 (25.9%)	1.13 (20.3%)	0.55 (25.6%)	1.05 (15.8%)	0.85 (60.4%)	1.00 (0)
Cl/F(mL/h/kg) (CV%)	45.6 (22%)	NR	NR	NR	NR	NR	NR
Elimination Rate Constant (hr ⁻¹) (CV%)	-	0.3003 (9.6%)	0.2998 (12.4)	0.3203 (17.3%)	0.3222 (17.9%)	0.2851 (14.8%)	0.2880 (12.8%)
T _{1/2} (CV%)	-	2.33 (9.6)	2.34 (12.4)	2.23 (19.5)	2.22 (20.1)	2.48 (15.6)	2.44 (12.9)

*Advil Liqui-Gel

#From Motrin tablet package insert

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

Study CPI-CL-001 was a single center, open-label, randomized, single dose, crossover study comparing IVIb to oral ibuprofen in healthy volunteers (36 subjects (24 men, 12 women)) with 7 day washout between administration. Doses were 200 mg, 400 mg and 800 mg of ibuprofen. The objectives of this study were to determine and compare ibuprofen exposure after intravenous and oral administration of ibuprofen at three different doses.

The results indicated that the observed ibuprofen exposure was similar when equivalent single doses of ibuprofen were administered either intravenously or orally over the dose range 200 to 800 mg, except for C_{max} following intravenous administration of a single 200 mg dose of ibuprofen, where this pharmacokinetic parameter was observed to be slightly lower than that observed following oral administration of an equivalent single dose. See Figure 3-5 for ibuprofen plasma profiles. See Table 9 and Table 10 for PK parameters and 90% CI calculations. No metabolites were assayed.

Figure 3 Mean plasma ibuprofen concentration profiles from intravenous administration

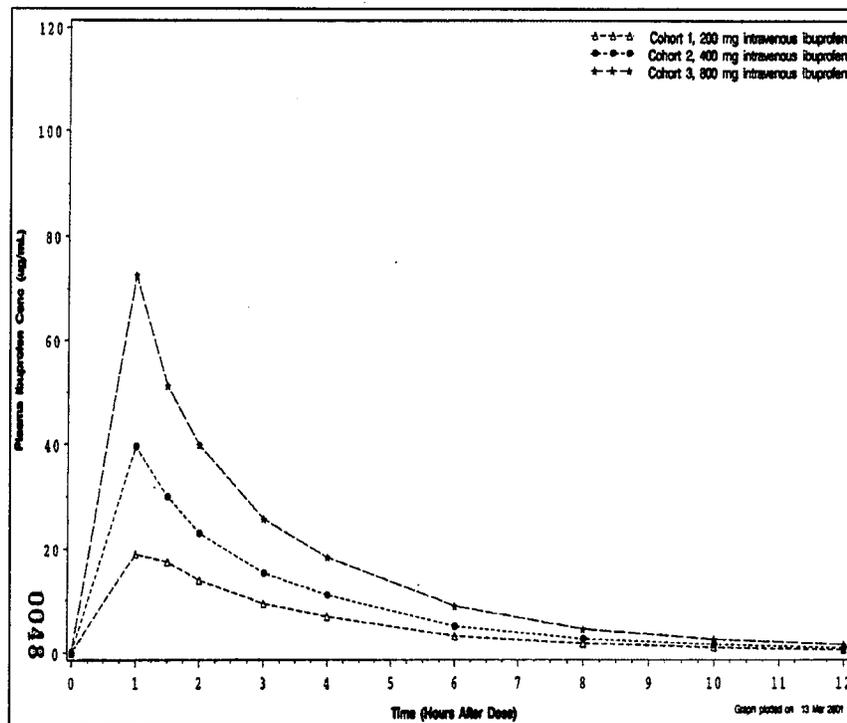


Figure 4 Mean plasma ibuprofen concentration profiles from oral administration (Advil Liqui-Gel reference)

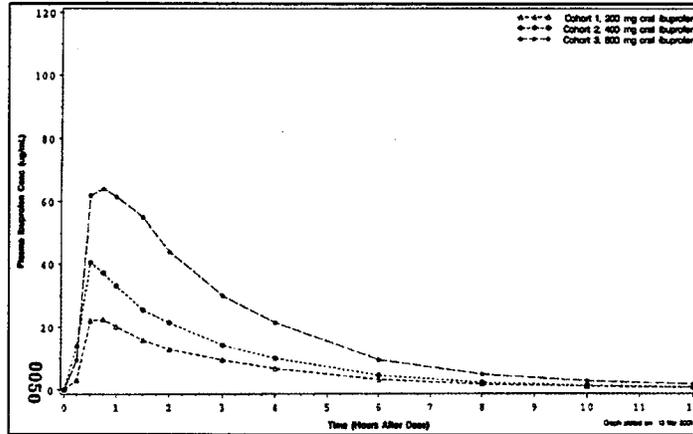


Figure 5 Plasma profiles of 200 mg from Advil Liqui-Gel and IV ibuprofen

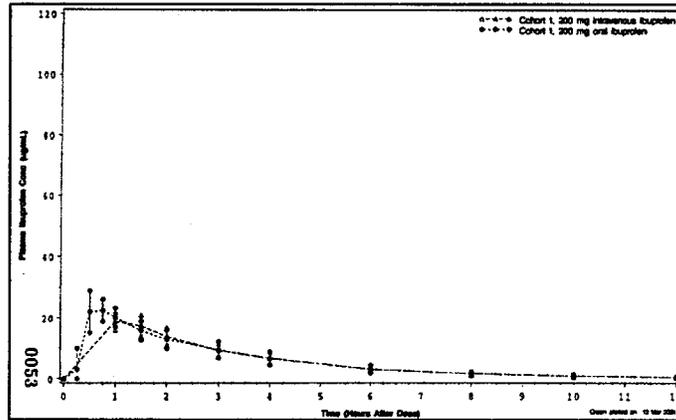


Figure 6 Plasma profiles of 400 mg from Advil Liqui-Gel IV ibuprofen

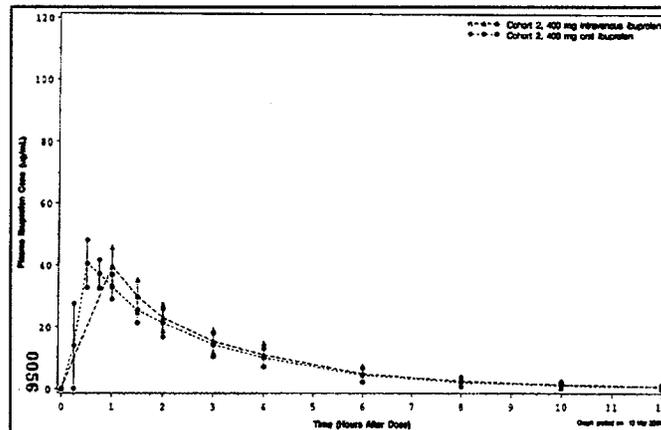


Figure 7 Plasma profiles of 800 mg from Advil Liqui-Gel IV ibuprofen

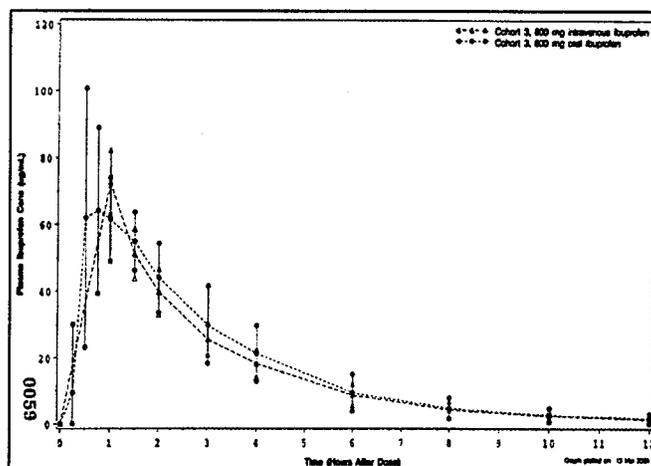


Table 9 PK parameters derived from plasma data for intravenous and oral ibuprofen Mean (CV%)

Dose	200mg (CPI-CL-001)		400mg (CPI-CL-001)		800mg (CPI-CL-001)	
	Oral	IV	Oral	IV	Oral	IV
No. of Patients	12	12	12	12	12	12
AUC _{0-t} (µg•h/mL)	67.982 (24.8%)	63.647 (20.7%)	108.255 (22%)	109.336 (26.4%)	212.117 (22.5%)	192.755 (18.5%)
AUC _{inf} (µg•h/mL)	69.862 (25.7%)	65.532 (21.5%)	110.887 (24.2%)	112.471 (29.2%)	218.817 (25.1%)	198.206 (20.0%)
C _{max} (µg/mL)	24.697 (17.1%)	19.294 (16%)	42.939 (11.4)	39.217 (15.5%)	81.046 (23.2%)	72.640 (13.2%)
T _{max} (h)	0.65 (25.9%)	1.13 (20.3%)	0.55 (25.6%)	1.05 (15.8%)	0.85 (60.4%)	1.00 (0)
Elimination Rate Constant (hr ⁻¹)	0.3003 (9.6%)	0.2998 (12.4)	0.3203 (17.3%)	0.3222 (17.9%)	0.2851 (14.8%)	0.2880 (12.8%)
T _{1/2} (h)	2.33 (9.6)	2.34 (12.4)	2.23 (19.5)	2.22 (20.1)	2.48 (15.6)	2.44 (12.9)

Table 10 The 90% confidence intervals for the ratios of the geometric means:

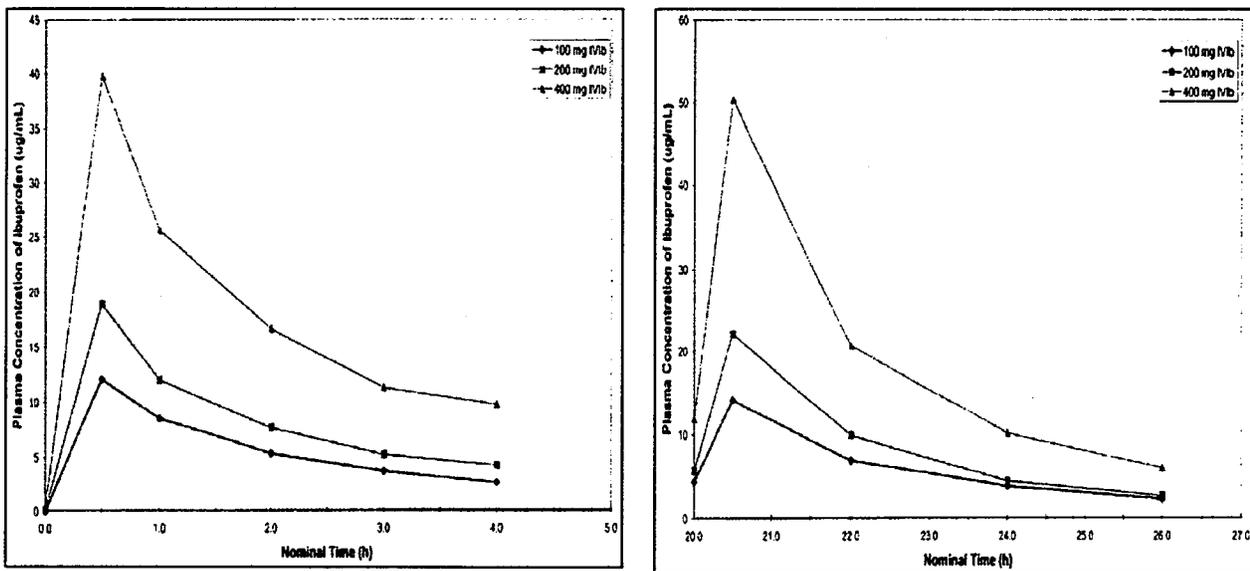
	200 mg	400 mg	800 mg
C _{max}	78.2% (70.0 – 87.4%)	94.5% (84.3 – 105.9%)	91.1% (83.1 – 99.7%)
AUC _{0-t}	94.3% (84.2 – 105.6%)	100.3% (92.7 – 108.5%)	91.3% (86.9 – 96.1%)
AUC _{0-inf}	94.5% (84.3 – 105.9%)	100.6% (93.0 – 108.8%)	91.2% (86.5 – 96.2%)

2.2.5.2 What are the multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

Study CPI-CL-004 was a multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and PK of ibuprofen injection in adult febrile patients (who had temperatures of 101°F (38.3°C) or greater; blood samples for PK analysis were obtained from the first 98 patients). Doses were 100 mg, 200 mg and 400 mg of ibuprofen or placebo, administered Q4h for 24 hours. For statistical analyses, patients were stratified based upon severity of illness, non-critically ill vs. critically ill (defined as subjects who are hospitalized and require mechanical ventilation for respiratory failure, pressor support for hypotension, or both). Blood sample collection (samples collected from the first 98 subjects enrolled in the study) for measurement of plasma ibuprofen concentration was performed at Hour 0, 0.5, 1, 2, 3, and 4 (before start of second infusion), and Hour 20 (immediately before start of last infusion), 20.5 (at the end of last infusion), 22, 24, and 26.

See Figure 8 for mean ibuprofen plasma concentrations from febrile patients). See Table 11 for PK parameters from the febrile patient for 0 – 4 hour time-points only; no 20 – 26 hour time-point PK parameters were presented. No metabolites were assayed.

Figure 8 Mean ibuprofen concentrations by treatment groups (hours 0 - 4 and 20 - 26):



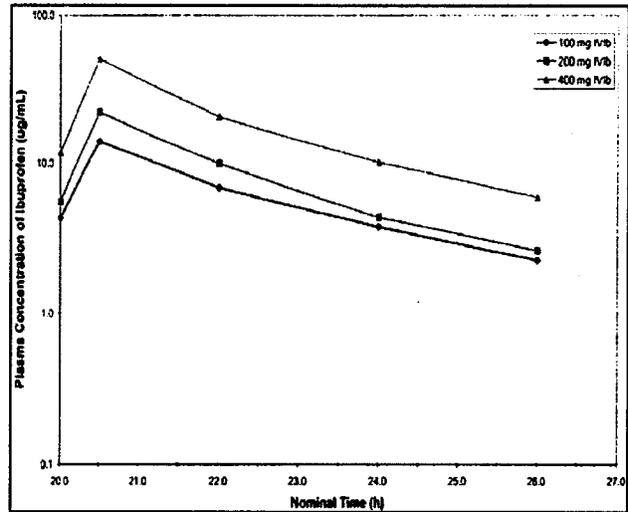
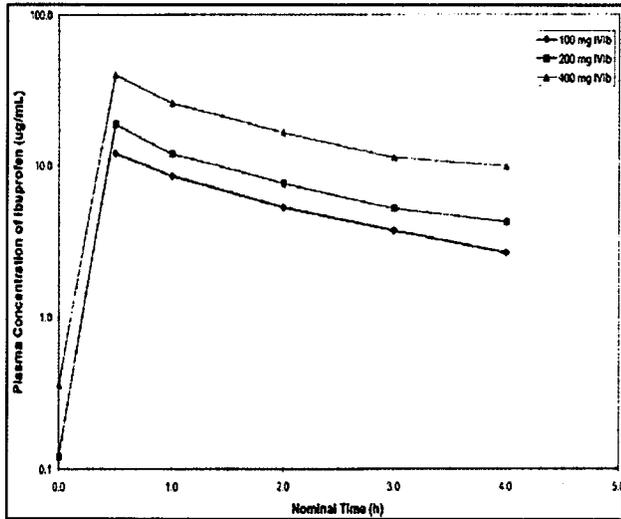
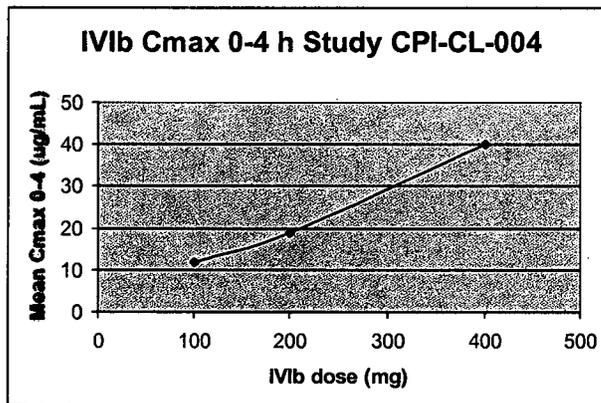
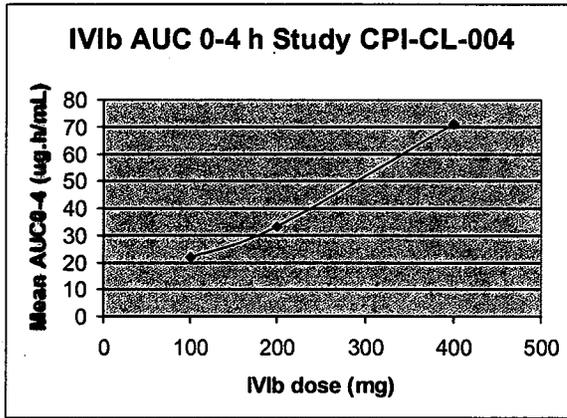


Table 11 Summary of PK Parameters by IVIb Dose Level for 0 -4 hour time points

Dose	AUC0-4 (µg. h/mL)	Cmax0-4 (µg/mL)	Tmax 0-4 (h)	Cmin dose1 (µg/mL)	Tmin dose1 (h)	Cmin dose6 (µg/mL)	Tmin dose6 (h)	T1/2 (h)
100 mg IVIb	22.33 ± 12.75	12.17 ± 6.78	0.5	2.65	4.0	2.5	25.9	2.47
200 mg IVIb	32.62 ± 17.39	18.94 ± 10.5	0.5	3.89	3.9	2.6	26.0	2.11
400 mg IVIb	70.64 ± 31.93	39.76 ± 17.75	0.5	8.27	3.8	6.0	26.0	2.26

The results indicated that the observed ibuprofen Cmax increased for 200 and 400 mg but the increase is not drastic. The AUC0-4 was approximately dose proportional for the 200 mg and 400 mg dose levels of IVIb. The dose normalized AUC0-4 was somewhat greater for the lower dose level of 100 mg IVIb than for the higher dose levels. No PK parameters were presented for time-points 20-26 hours. However no drastic differences in the parameters are expected.



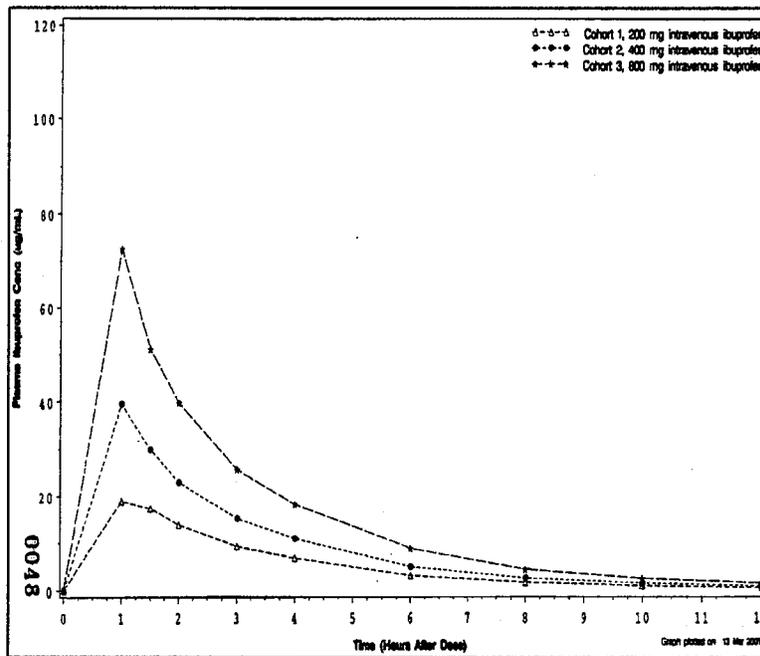


Additionally in Study CPI-CL-004 PK parameters from 'non-critically ill' vs. 'critically ill' patients were compared. This information is presented in the next section, 2.2.5.3.

2.2.5.3 How does the PK of the drug in healthy volunteers compare to that in patients?

Comparison (doses 200 and 400 mg) of the ibuprofen plasma concentration profiles (Compared PK parameters: Cmax, Tmax and T1/2; Table 12) appear to be similar.

Healthy volunteers ibuprofen plasma profile by doses (same as Figures 1):



Febrile patients mean ibuprofen concentrations by doses (hours 0-4) (same as Figure 7):

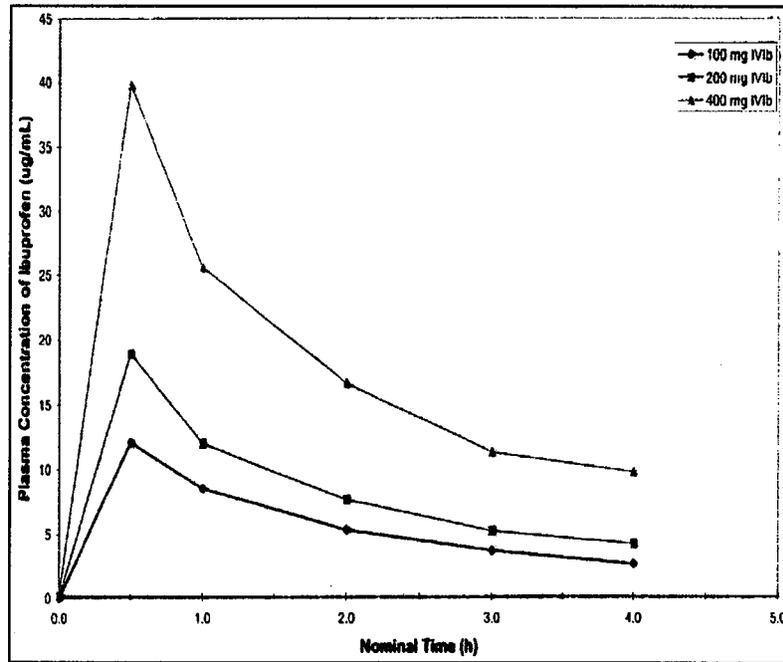


Table 12 PK parameter comparison of all ill-patients vs. healthy subjects

	200 mg		400 mg	
	Ill patients	Healthy subjects	Ill patients	Healthy subjects
Cmax 0-4	18.9	19.3	39.8	42.9
Tmax 0-4	0.5	1.13	0.5	0.55
T1/2	2.11	2.34	2.26	2.22

Additional analysis comparing ‘non-critically ill’ vs. ‘critically ill’ patients:

As stated above, Study CPI-CL-004 was a safety, efficacy and PK of ibuprofen injection in adult febrile patients (who had temperatures of 101°F (38.3°C) or greater). Doses were 100 mg, 200 mg and 400 mg of ibuprofen or placebo, administered Q4h for 24 hours. The ‘critically ill’ was defined as subjects who are hospitalized and require mechanical ventilation for respiratory failure, pressor support for hypotension, or both.

The results comparing ‘non-critically ill’ vs. ‘critically ill’ revealed a difference in PKs ibuprofen plasma profiles (Figure 9 – Figure 13). See Table 13 for PK parameters.

Figure 9 Mean ibuprofen concentrations (hours 0-4) by treatment group and randomization in critically ill vs. non-critically ill patients

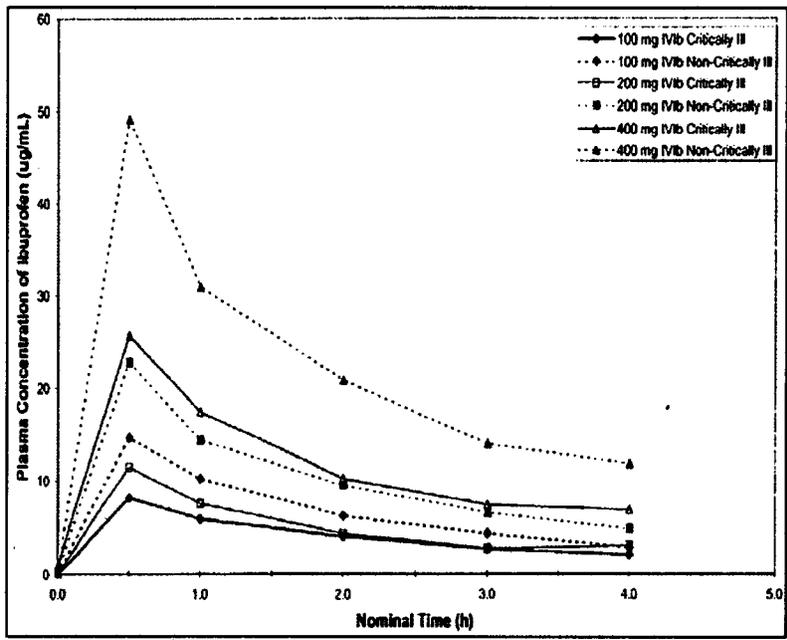


Figure 10 Mean ibuprofen concentrations (hours 20-26) by treatment group and randomization in critically ill vs. non-critically ill patients

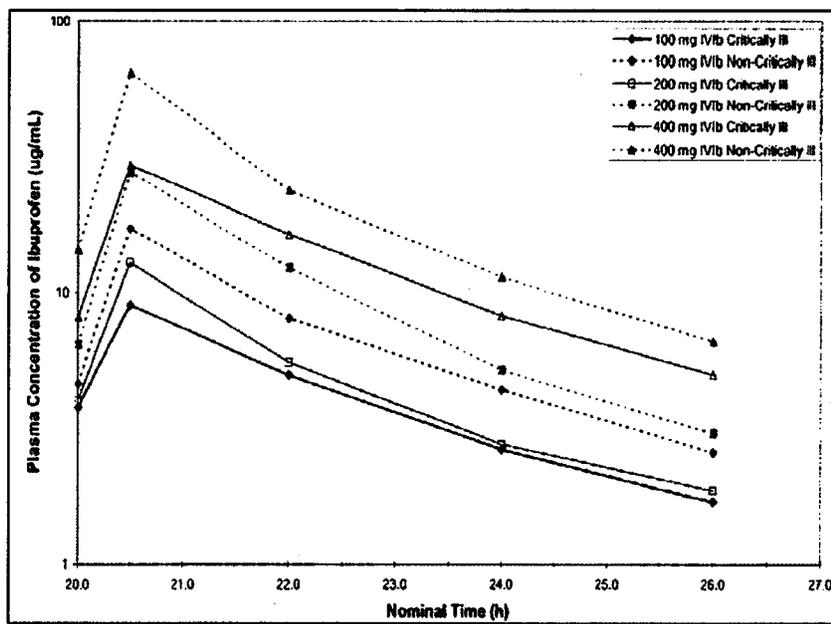


Figure 11 Mean ibuprofen concentrations (hours 0-4) from 100mg group from critically ill vs. non-critically ill patients

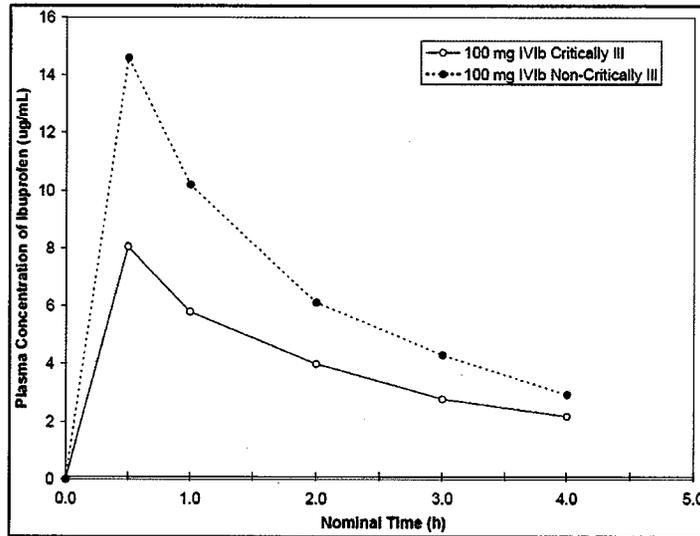


Figure 12 Mean ibuprofen concentrations (hours 0-4) from 200mg group, study CPI-CL-004

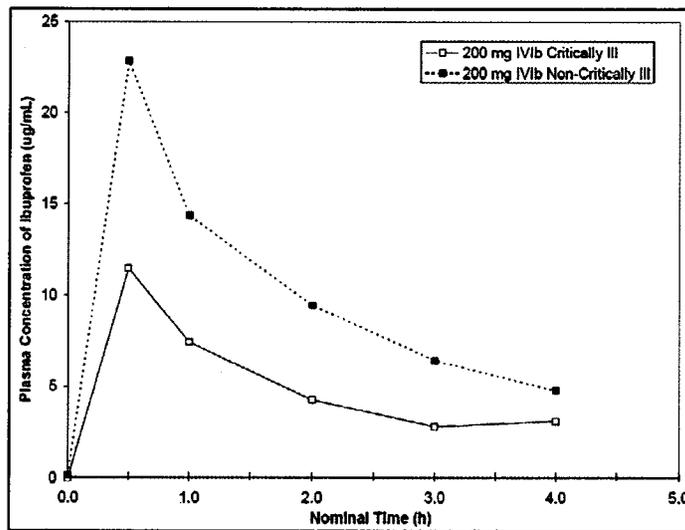


Figure 13 Mean ibuprofen concentrations (hours 0-4) from 400mg group, study CPI-CL-004

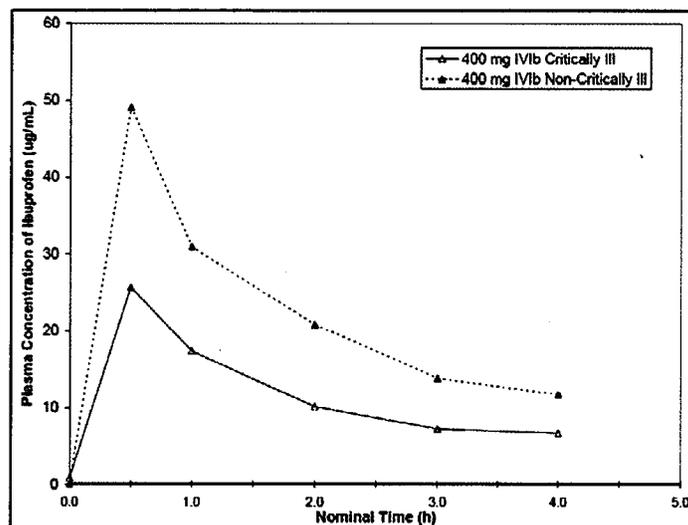


Table 13 Summary of PK parameters in critically ill vs. non-critically ill patients

Treatment, Stratum		AUC ₀₋₄ (µg.h/mL)	C _{max} ₀₋₄ (µg/mL)	T _{max} ₀₋₄ (h)	C _{min} ^{dose1} (µg/mL)	T _{min} ^{dose1} (h)	C _{min} ^{dose6} (µg/mL)	T _{min} ^{dose6} (h)	T _{half} (h)
100 mg IV Ib	Critically Ill n=14	16.10	8.23	0.6	2.19	4.0	2.3	25.7	2.42
	Non-critically Ill n=17	26.33	14.53	0.5	2.95	4.0	2.6	26.0	2.49
200 mg IV Ib	Critically Ill n=12	19.62	11.46	0.5	2.29	3.8	1.9	26.0	2.56
	Non-critically Ill n=18	39.51	22.89	0.5	4.73	3.9	3.0	26.0	1.86
400 mg IV Ib	Critically Ill n=14	45.94	25.70	0.5	4.69	3.9	5.0	26.0	2.32
	Non-critically Ill n=17	87.11	49.13	0.5	10.66	3.8	6.6	26.0	2.22

Table 14 below presents the percent difference between the critically ill versus the non-critically ill groups for the AUC₀₋₄ and C_{max0-4} pharmacokinetic parameters.

Table 14 Pharmacokinetic Parameters Differences in the 400 mg IVIb Dose Level and Stratum

Treatment, Stratum	AUC ₀₋₄ (µg.h/mL)	C _{max0-4} (µg/mL)
100 mg IVIb Critically Ill / Non-critically Ill % Difference	61.2%	56.6%
200 mg IVIb Critically Ill / Non-critically Ill % Difference	49.6%	50.0%
400 mg IVIb Critically Ill / Non-critically Ill % Difference	52.7%	52.3%

The values for the AUC and C_{max} pharmacokinetic parameters for the critically ill patients were approximately 50% compared to the parameters for the non-critically ill patients. However, these differences did not seem to have notable affect on the efficacy of the product in this population (see Clinical Review for additional details).

2.2.5.4 What is the known clinical pharmacology information of ibuprofen?

From Motrin tablet (N17463) Label (label approved on 9/10/07):

CLINICAL PHARMACOLOGY

MOTRIN tablets contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.

In clinical studies in patients with rheumatoid arthritis and osteoarthritis, MOTRIN tablets have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). MOTRIN tablets may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients when treated with MOTRIN tablets should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether MOTRIN tablets causes less peptic ulceration than aspirin, in one study involving 885 patients with rheumatoid arthritis treated for up to one year, there were no reports of gastric ulceration with MOTRIN tablets whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant $p < .001$).

Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin. Studies using ⁵¹Cr-tagged red cells indicate that fecal blood loss associated with MOTRIN tablets in doses up to 2400 mg daily did

not exceed the normal range, and was significantly less than that seen in aspirin-treated patients.

In clinical studies in patients with rheumatoid arthritis, MOTRIN tablets have been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity and to be associated with a statistically significant reduction of the milder gastrointestinal (see ADVERSE REACTIONS) and CNS side effects.

MOTRIN tablets may be used in combination with gold salts and/or corticosteroids. Controlled studies have demonstrated that MOTRIN tablets are a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea. In patients with primary dysmenorrhea, MOTRIN tablets have been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

The ibuprofen in MOTRIN tablets is rapidly absorbed. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs. time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of MOTRIN tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When MOTRIN tablets are administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food.

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when MOTRIN tablets were given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours. Studies have shown that following ingestion of the drug, 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[p-(2hydroxymethylpropyl) phenyl] propionic acid and metabolite B (37%), (+)-2-[p-(2carboxypropyl)phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

Additional known ibuprofen information from Clinical Pharmacology Online (Revision Date: 11/3/08):

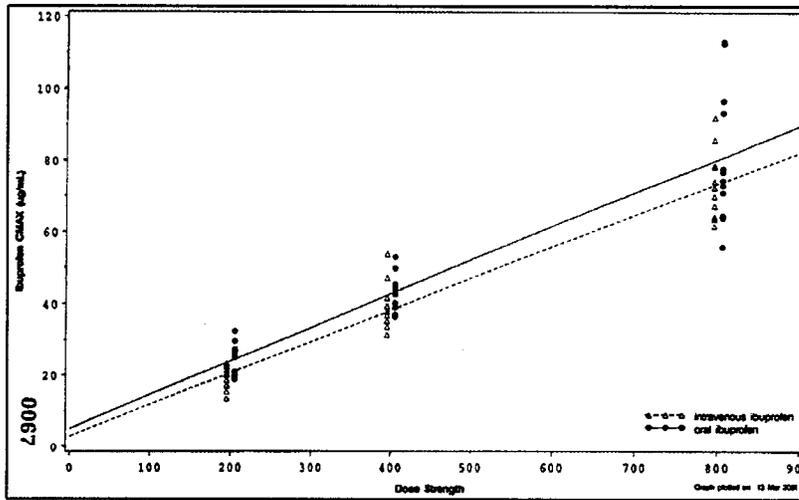
Ibuprofen is administered orally and is approximately 80% absorbed from the gut. The oral bioavailability of ibuprofen is similar between the different dosage forms, but the time to reach peak concentrations is roughly 120, 62, and 47 minutes after administration of tablets, chewable tablets, or suspension, respectively. With single doses up to 10 mg/kg, a dose response relationship exists in febrile children. There is also a correlation between the reduction of fever and drug concentration over time. In children, the antipyretic effect begins within 1 hour and **peaks within 2—4 hours. In treatment for inflammation, a few days to 2 weeks is generally required before a therapeutic response occurs. Ibuprofen is highly protein-bound (about 90—99%). Ibuprofen is a racemate, and, on average, 60% of R-ibuprofen is converted to S-ibuprofen. S-ibuprofen is metabolized via hepatic oxidation by cytochrome P450 2C9 to inactive metabolites. The cytochrome P450 enzyme 2C9 is polymorphic; CYP2C9(1) is the wild-type, and CYP2C9(2) and CYP2C9(3) are the most common variants. The variant CYP2C9(3) allele decreases enzyme activity to a greater extent than does CYP2C9(2), but clearance of racemic ibuprofen was reduced among all variant genotypes as compared with the wild-type (1/1). Higher S-ibuprofen concentrations led to greater inhibition of COX-1 (reduced thromboxane B2 concentrations) and greater inhibition of COX-2 (reduced prostaglandin E2 concentrations). Importantly, both thromboxane B2 and prostaglandin E2 concentrations were reduced the most among patients with the CYP2C9 genotypes (3/3), (1/3), (2/3), and (2/2). Plasma half-life of ibuprofen is between 2 and 4 hours. Ibuprofen is excreted in the urine: 50—60% as metabolites and approximately 10% as unchanged drug. Some biliary excretion may occur. Excretion is usually complete within 24 hours of oral administration. The elimination half-life of ibuprofen is significantly prolonged in patients with moderate to severe cirrhosis. Prospective studies of ibuprofen in patients with renal failure have not been conducted; however, dosage reduction is recommended in patients with chronic renal failure.**

2.2.5.5 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose linearity

The observed C_{max} and AUC exhibited a linear relationship as shown below (Figure 14).

Figure 14 Ibuprofen Cmax and AUC0-inf mean plot against dose strengths



AUC0-inf:

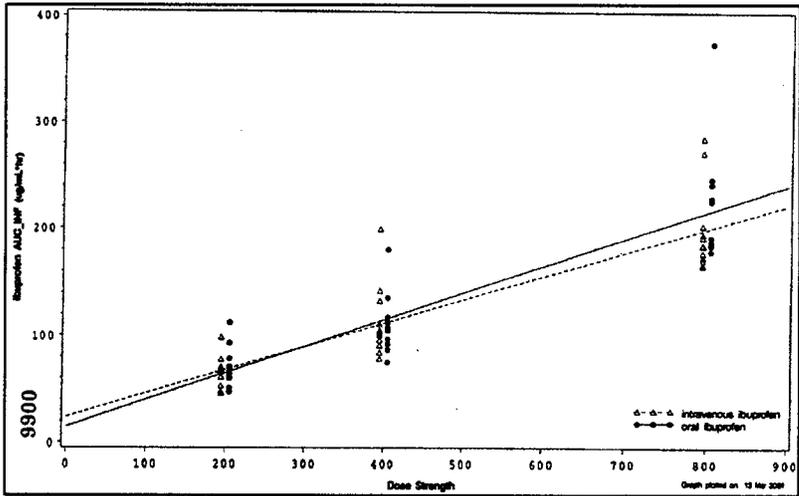


Table 15 Ibuprofen Cmax and AUC0-inf comparison between intravenous and oral administration

Dose	200mg		400mg		800mg	
	Oral	IV	Oral	IV	Oral	IV
AUCinf (µg·h/mL)	69.862 (25.7%)	65.532 (21.5%)	110.887 (24.2%)	112.471 (29.2%)	218.817 (25.1%)	198.206 (20.0%)
Cmax (µg/mL)	24.697 (17.1%)	19.294 (16%)	42.939 (11.4)	39.217 (15.5%)	81.046 (23.2%)	72.640 (13.2%)

Table 16 Mean x-fold calculation for 200 mg, 400 mg and 800 mg doses

Mean exposure x-fold calculation:

Dose	200mg		400mg - 2x dose		800mg – 4x dose	
Formulation	Oral	IV	Oral	IV	Oral	IV
AUCinf (µg•h/mL)	1	1	1.6x	1.7x	3.1x	3.0x
Cmax (µg/mL)	1	1	1.7x	2.0x	3.3x	3.8x

2.2.5.6 How do the PK parameters change with time following chronic dosing?

According to the multiple-dose study, see Section 2.2.5.2., the ibuprofen accumulation appears to be minimal.

2.2.5.7 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

From the single dose PK study the variability observed was less than 30%.

Ibuprofen Cmax and AUC0-inf comparison between intravenous and oral administration (Table 9):

Dose	200mg		400mg		800mg	
Formulation	Oral	IV	Oral	IV	Oral	IV
AUCinf (µg•h/mL)	69.862 (25.7%)	65.532 (21.5%)	110.887 (24.2%)	112.471 (29.2%)	218.817 (25.1%)	198.206 (20.0%)
Cmax (µg/mL)	24.697 (17.1%)	19.294 (16%)	42.939 (11.4)	39.217 (15.5%)	81.046 (23.2%)	72.640 (13.2%)

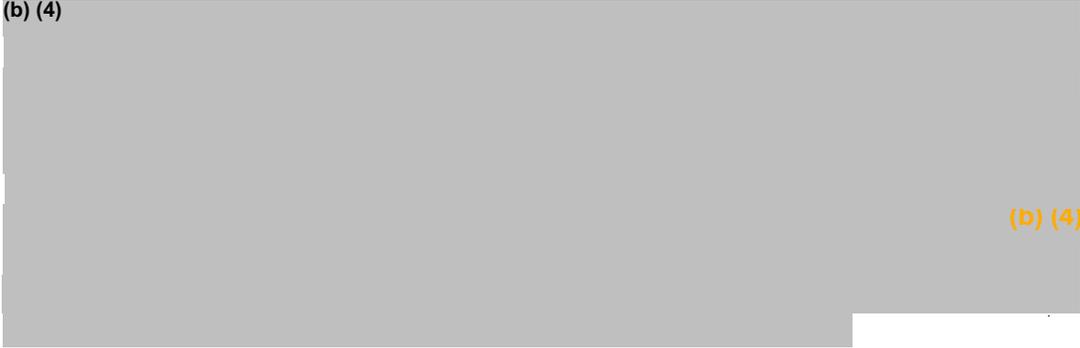
2.3 Intrinsic Factors

2.3.1.1 Elderly

The literature information suggested that the elimination half-life of ibuprofen is significantly prolonged in patients with moderate to severe cirrhosis. Regarding renal impairment, prospective studies of ibuprofen in patients with renal failure have not been conducted. Additionally, the literature information suggested that a dosage reduction is recommended in patients with chronic renal failure.

2.3.1.2 What is the status of pediatric studies and/or any pediatric plan for study?

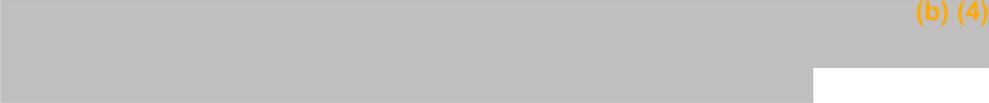
(b) (4)



(b) (4)



(b) (4)



(b) (4)

It is noted that there will be a Written Request for this product in the near future.

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

To-be-marketed formulation was used in all clinical trials.

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?



(b) (4)

This assay was developed and used for Study CPI-CL-001 in year 2001. The following Table 17 contains typical values observed for this assay.

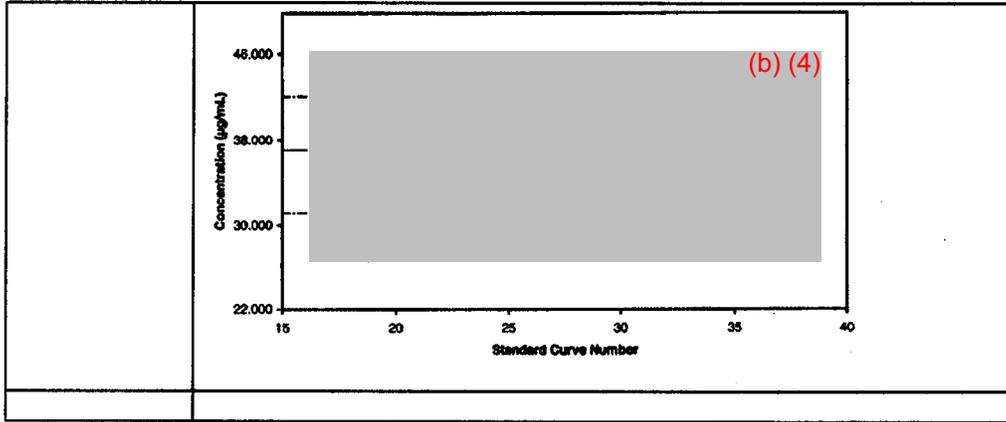
Table 17 Assay ALM I-005/1 information

Linearity	The calibration curve was linear in the range studied, 0.200 to 250 µg/mL. The mean coefficient of determination was 0.9955. The calculated concentrations using the 1/X ² weighting was used.			
Limit of quantitation	The limit of quantification was determined to be acceptable at 0.20 µg/mL.			
Accuracy & Precision	Intra-run:			
		QCL (0.600 Mg/mL)	QCM (20.0 Mg/mL)	QCH (200 Mg/mL)
	% Nominal	100.0	98.3	97.9
	CV	6.8	2.6	1.0
	Inter-run:			
		QCL (0.600 Mg/mL)	QCM (20.0 Mg/mL)	QCH (200 Mg/mL)
% Nominal	102.0	98.7	98.2	
CV	4.9	3.8	2.1	
Recovery	The values for recovery of ibuprofen at the low, medium and high levels were 87%, 88% and 93% respectively. The overall recovery was 89%. The CVs for the low, medium and high levels were 6.7%, 6.4% and 5.5% respectively.			
Stability	Stock Solutions: The fresh spiked working solution of ibuprofen was found to be stable for 28 days when stored at 4°C.			
	Ibuprofen in Plasma: Ibuprofen was shown to be stable in plasma for 5 days when stored in 5 mL polypropylene tubes at -20±10°C. =			
	Ibuprofen in Plasma after Freeze/Thaw Cycles: Ibuprofen was shown to be stable in plasma after three freeze/thaw cycles.			
	Ibuprofen in Plasma on Bench-Top: Ibuprofen was shown to be stable in plasma for up to 24 hours when kept on the bench at room temperature.			
	Ibuprofen in Final Extract: Ibuprofen and the internal standard (b) (4) were shown to be stable in the final extract for 5 days when stored at room temperature and at 4°C.			
	Fresh Spiked QC data: Data was acceptable from supporting fresh spike QC samples analyzed along with the long term plasma stability, freeze/thaw and the benchtop runs.			

It is noted that the ALM I-005/1 method was modified, ALM I-005/2, slightly and utilized for Study CPI-CL-004, a Phase 3 fever study. The new range was from 0.20 to 50 µg/mL and (b) (4) was added to samples in order to further stabilize the internal standard. ALM I-005/2 method also added a gradient wash and changes to the constitution of the mobile phases. ALM I-005/2 method was validated and the results indicated that method was applicable in assessing ibuprofen

concentration (*Addendum 3* to the Validation Report for ALM 1-005/1 (Technical Report Number C346/05). The typical values from the validation report are presented below.

Limit of quantitation:	The limit of quantification was determined to be acceptable at 0.20 µg/mL.																				
Linear Range:	The response of the assay was linear over the nominal concentration range of 0.200 µg/mL to 50.0 µg/mL during the analysis of study samples. The range of results for the accuracy of the Ibuprofen standards was 98 to 101% and the precision was 0.9 to 4.0%.																				
Inter-run Accuracy and Precision:	<p>The results of the analysis of ac samples from the 21 accepted analytical runs were:</p> <table border="1"> <thead> <tr> <th></th> <th>QCL (0.589 µg/mL)</th> <th>QCM (7.49 µg/mL)</th> <th>QCH (37.4 µg/mL)</th> </tr> </thead> <tbody> <tr> <td>MEAN</td> <td>0.591</td> <td>7.37</td> <td>37.0</td> </tr> <tr> <td>SD</td> <td>0.019</td> <td>0.425</td> <td>0.922</td> </tr> <tr> <td>% NOMINAL</td> <td>99</td> <td>99</td> <td>99</td> </tr> <tr> <td>CV (%)</td> <td>3</td> <td>6</td> <td>3</td> </tr> </tbody> </table>		QCL (0.589 µg/mL)	QCM (7.49 µg/mL)	QCH (37.4 µg/mL)	MEAN	0.591	7.37	37.0	SD	0.019	0.425	0.922	% NOMINAL	99	99	99	CV (%)	3	6	3
	QCL (0.589 µg/mL)	QCM (7.49 µg/mL)	QCH (37.4 µg/mL)																		
MEAN	0.591	7.37	37.0																		
SD	0.019	0.425	0.922																		
% NOMINAL	99	99	99																		
CV (%)	3	6	3																		
Stability	<p>Stability of the QC samples for the duration of the study was demonstrated as shown by the Quality Control Scatter Plots (Figures 7 to 9). The solid lines in the scatter plots represent the nominal concentrations of the QCs and the dotted lines represent the limits at ± 15% of the nominal concentration.</p>																				



Both methods are appropriately validated and there are no issues.

3 Detailed Labeling Recommendations

The proposed Labeling language is acceptable.

12 CLINICAL PHARMACOLOGY	Source
12.1 Mechanism of Action	
Amelior's mode of action, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.	1.14.3.2: Reference Listed Drug, NDA #017463: Motrin® Ibuprofen Tablets, Section: Clinical Pharmacology
(b) (4)	
(b) (4) that possesses anti-inflammatory, analgesic and antipyretic activity.	1.14.3.2: Reference Listed Drug, NDA #017463: Motrin® Ibuprofen Tablets, Section: Clinical Pharmacology 2
12.3 Pharmacokinetics	
Ibuprofen is a racemic mixture of [-]R- and [+]S-isomers. In vivo and in vitro studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. The pharmacokinetic parameters of Amelior determined in a study with volunteers are presented below.	5.3.7.1 CPI-CL-001 CSR, section 8.3.1

Pharmacokinetic parameters of Amelior		
	400 mg Amelior Mean (CV%)	800 mg Amelior Mean (CV%)
No. of Patients	12	12
AUC (µg.h/mL)	109.3 ^(b) _(A) (26.4)	192. ^(b) _(A) (18.5)
Cmax (µg/mL)	39.2 ^(b) _(A) (15.5)	72.6 ^(b) _(A) (13.2)
KEL (1/h)	0.32 ^(b) _(A) (17.9)	0.2 ^(b) _(A) (12.8)
T _{1/2} (h)	2.22 (20.1)	2.44 (12.9)

AUC = Area-under-the-curve
Cmax = Peak plasma concentration
CV = Coefficient of Variation
KEL = First-order elimination rate constant
T_{1/2} = Elimination half-life

Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 µg/mL). Protein binding is saturable, and at concentrations >20 µg/mL binding is nonlinear. Based on oral dosing data there is an age- or fever-related change in volume of distribution for ibuprofen. (b) (4)

5.4 Reference: NDA #017463: Motrin® Ibuprofen Suspension, Section: Clinical Pharmacology

4 Appendices

(b) (4)

4.2 Individual Study Review

4.2.1 Study CPI-CL-001

Title: A Phase I, Open-Label, Randomized, Single-Dose, Crossover, Pharmacokinetic and Safety Study with Intravenous and Oral Ibuprofen in Healthy Subjects

Name of Sponsor/Company: Cumberland Pharmaceutical Inc.

Name of Finished Product: Amelior®

Name of Active Ingredients: Ibuprofen					
Title of Study: CPI-CL-001: A Phase I, Open-Label, Randomized, Single-Dose, Crossover, Pharmacokinetic and Safety Study with Intravenous and Oral Ibuprofen in Healthy Subjects.					
Investigators: Alan Moskwa, M.B.B.S.					
Study center: [REDACTED]					(b) (4)
Publication (reference): Not Applicable					
Study Period: Date of first enrollment: 23 Jan 2001 Date of last completed: 21 Feb 2001				Phase of Development: I	
Objectives: • To determine C _{MAX} , AUC, and AUC _{INF} of intravenously and orally administered ibuprofen at three different doses; • To compare the pharmacokinetic profiles of intravenous and oral ibuprofen; and, • To compare the safety and tolerability of single intravenous and oral doses of ibuprofen by assessing adverse experiences, physical examinations, clinical chemistries, and haematology.					
Methodology: Single-center, open-label, single-dose, randomized, crossover study					
Measurements/ Treatments	Periods *				
	Screening Period (Days -14 to 1)	Baseline Period 1 (Days -1 to 1)	Treatment Period 1 (Day 1)	Baseline Period 2 (Days 7 to 8)	Treatment Period 2 (Day 8)
Inclusion/Exclusion	X				
Informed Consent	X				
Complete Medical History	X				
Physical Examination	X				X [†]
Vital Signs	X	X	X [†]	X	X [†]
Concomitant Medication	X	X		X	
βHCG (females only)	X	X		X	
Urine Drug Screen	X				
HIV Test	X				
Hepatitis B Antigen Test	X				
Electrocardiogram	X				
Hematology	X				X [†]
Clinical Chemistry	X				X [†]
CTM Administration			X		X
Blood Sample Collection for ibuprofen Concentration [‡]			X		X
AE Monitoring			X		X
<p>* Cohort 2 began after Cohort 1 completed Treatment Period 2. Cohort 3 began after Cohort 2 completed Treatment Period 2. Days 2 to 7 were washout days outside the clinic.</p> <p>† Taken prior to discharge.</p> <p>‡ For subjects who received IVIB, blood samples for ibuprofen concentrations were collected before dosing, at the end of the 60-minute infusion, and at 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the beginning of infusion. For subjects who received oral ibuprofen, blood samples for ibuprofen concentrations were collected before dosing and at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after oral administration.</p>					
Number of patients: Planned: 36 participants Analyzed: 36 participants					

Diagnosis and main criteria for inclusion:

- healthy volunteers, males or females, aged 18 to 65 years, inclusive, at the time of enrollment;
- if female and were of nonchildbearing potential; or if a female of childbearing potential, had a negative pregnancy test at Screening and agreed to practice an acceptable form of birth control;
- if female, were nonlactating;
- able and willing to abstain from caffeine containing beverages (e.g., coffee, soda, or tea) and caffeine-containing food (e.g. chocolate) for approximately 24 hours prior to and until 8 hours after CTM administration;
- within 80% to 120% of ideal body weight (IBW);
- had negative human immunodeficiency virus (HIV) and hepatitis B antigen test results; and,
- able to understand the requirements of the study; had provided written informed consent; and agreed to abide by the study restrictions and to return for the required assessments.

Test product, dose and mode of administration, batch number:

Ibuprofen Injection, 100mg/ml given intravenously as a single dose as follows:

Cohort 1: 200mg given via syringe pump over a 60 minute interval

Cohort 2: 400mg given via syringe pump or 400mg in 500ml normal saline given via an infusion pump over a 60 minute interval.

Cohort 3: 800mg given in 24ml normal saline given via a syringe pump or 800mg in 600ml normal saline given via an infusion pump over a 60 minute interval.

Batch Number: K03942

Duration of treatment: Each subject received each of the two treatments on separate occasions, separated by a 7 day washout period. Each cohort was randomized to: Sequence A received Ibuprofen administered intravenously followed by orally (6 subjects); and , Sequence B received Ibuprofen administered orally followed by intravenously (6 subjects).

Cohort	Dose Level (mg)	Period	Subjects	Method of Intravenous Dose Administration
1	200	1	01, 03, 05, 07, 10, 12	2 mL IVIB (100 mg/mL) via a syringe pump over a 60-minute interval
		2	02, 04, 06, 08, 09, 11	2 mL IVIB (100 mg/mL) via a syringe pump over a 60-minute interval
2	400	1	14, 15, 17	4 mL IVIB (100 mg/mL) via a syringe pump over a 60-minute interval
			20, 23, 24	4 mL IVIB (100 mg/mL) in 500 mL normal saline via an infusion pump over a 60-minute interval
		2	13, 16, 18, 19, 21, 22	4 mL IVIB (100 mg/mL) in 500 mL normal saline via an infusion pump over a 60-minute interval
3	800	1	26, 28, 30	8 mL IVIB (100 mg/mL) in 24 mL normal saline via a syringe pump over a 60-minute interval
			32, 34, 35	8 mL IVIB (100 mg/mL) in 600 mL normal saline via an infusion pump over a 60-minute interval
		2	25, 27, 29, 31, 33, 36	8 mL IVIB (100 mg/mL) in 600 mL normal saline via an infusion pump over a 60-minute interval

Cohort	Dose Level (mg)	Period	Subjects	Oral Dose Administration
1	200	1	02, 04, 06, 08, 09, 11	1 x 200 mg Liqui-gel capsule
		2	01, 03, 05, 07, 10, 12	1 x 200 mg Liqui-gel capsule
2	400	1	13, 16, 18, 19, 21, 22	2 x 200 mg Liqui-gel capsules
		2	14, 15, 17, 20, 23, 24	2 x 200 mg Liqui-gel capsules
3	800	1	25, 27, 29, 31, 33, 36	4 x 200 mg Liqui-gel capsules
		2	26, 28, 30, 32, 34, 35	4 x 200 mg Liqui-gel capsules

Reference therapy, dose and mode of administration, batch number:

Advil® Liqui-gel Capsules, 200mg/capsule was given per os, given with 240ml of room temperature water as a single dose as follows: Cohort 1: 200mg; Cohort 2: 400mg; Cohort 3: 800mg
Batch Number: 3001219

Criteria for evaluation: Pharmacokinetics: The concentration of ibuprofen was determined in all samples of plasma, from all subjects using a validated HPLC assay method. Safety: The safety of ibuprofen was assessed by monitoring of adverse events, vital signs, and clinical chemistry and hematological parameters in blood. The safety and tolerability of ascending intravenous doses of ibuprofen was assessed progressively by thorough review of both clinical laboratory and medical evaluation data.

Statistical Methods:

Safety: Descriptive statistical methods were used to summarize key safety data. The general strategy of the safety analysis was to examine the data summaries for any trends amongst the dose levels. No formal hypothesis testing was performed.

Pharmacokinetic: For all subjects, the mean, standard deviation and CV% of plasma concentrations was calculated in each treatment group. In addition, for each treatment group the mean and standard deviation was calculated for pharmacokinetic parameters for all subjects within each cohort. A comparison of the pharmacokinetics of intravenous and oral ibuprofen was made by applying a parametric (normal-theory) general linear model to each of the calculated pharmacokinetic parameters and observations using SAS® (Version 8.1) GLM Procedure. In addition, the logarithmic transformations (using natural logarithms) of AUC, AUC_INF and CMAX were analyzed with the same model. The analysis of variance (ANOVA) model included the effects of treatment, subject, period and sequence. The treatments were compared using an average bioequivalence approach based on the two one-sided tests procedure to determine whether the average values for the pharmacokinetic parameters determined after administration of intravenous ibuprofen and oral ibuprofen were comparable. With a 5% level of significance, this involved constructing 90% confidence intervals for the ratios of the intravenous and oral ibuprofen geometric means for each pharmacokinetic parameter of interest within each cohort.

The 90% confidence intervals for the ratios of the geometric means were obtained from the antilogs of the lower and upper bounds of the 90% confidence intervals for the difference in the means of the log-transformed data. Mean ratio values, intrasubject and intersubject variability (CV%) values, were provided for log-transformed values.

The linearity of ibuprofen pharmacokinetics after intravenous and oral ibuprofen was assessed for each of the pharmacokinetic parameters CMAX, AUC and AUC_INF. Regression models of best fit were selected using PROC REG in SAS® (Version 8.1), with a selection criterion of choosing the model which minimises Mallows' C(p).

Blood sample collection: For IVIB - predosing, at the end of the 60-minute infusion, and at 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the beginning of infusion; . For oral formulation – predosing, at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after oral administration.

The plasma was separated from red blood cells by centrifugation (2390 x g, 10 minutes, 4°C) as soon as possible after collection and promptly frozen at -20°C (± 5°C) until analysis according to the laboratory's standard operating procedure. The concentration of ibuprofen was determined in the plasma from all subjects using a validated HPLC assay. The assay which was sensitive, and specific, had a lower limit of quantification of 0.2 µg/mL and was linear over the nominal concentration range of 0.2 µg/mL to 250 µg/mL. The analytical procedures were conducted in compliance with CMAX Standard Operating Procedures, the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) and the Food and Drug Administration (FDA) GLP Procedures.

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS: Statistical analyses to compare the treatments were performed on the plasma concentration data and pharmacokinetic parameters from the 36 subjects who completed the study. When comparing the pharmacokinetics of intravenously administered ibuprofen with orally administered ibuprofen, the following results were obtained:

- 200, 400 and 800 mg dose level the mean ratios of the LSMEANS (with 90% confidence intervals, and p-values) for the log-transformed parameters LCMAX, LAUC and LAUC_INF:

The 90% confidence intervals for the ratios of the geometric means:

	200 mg	400 mg	800 mg
Cmax	78.2% (70.0 – 87.4%), p = 0.0024	94.5% (84.3 – 105.9%), p = 0.3888	91.1% (83.1 – 99.7%), p = 0.0920
AUC 0-t	94.3% (84.2 – 105.6%), p = 0.3663	100.3% (92.7 – 108.5%), p = 0.9485	91.3% (86.9 – 96.1%), p = 0.0085
AUC 0-inf	94.5% (84.3 – 105.9%), p = 0.3888	100.6% (93.0 – 108.8%), p = 0.8975	91.2% (86.5 – 96.2%), p = 0.0101

When assessing the linearity of ibuprofen pharmacokinetics after intravenous and oral administration, the following results were obtained:

- For both intravenously and orally administered ibuprofen, AUC, AUC_INF and CMAX increased in an approximately linear manner with dose.
- For oral ibuprofen, AUC, AUC_INF and CMAX were shown to be directly proportional to dose administered.
- For intravenous ibuprofen CMAX was shown to be directly proportional to dose administered.
- For both intravenously and orally administered ibuprofen, KEL was constant over the dose range studied.

SAFETY RESULTS: With the exception of one severe adverse event, deemed to be unrelated to the study drug, all adverse events reported during the conduct of this study were considered to be of mild or moderate severity. No serious adverse events were reported. There was an observable trend between treatment groups with respect to the incidence of certain adverse events when intravenous ibuprofen was administered. Irritation, pain and bruising at the site of infusion occurred in a number

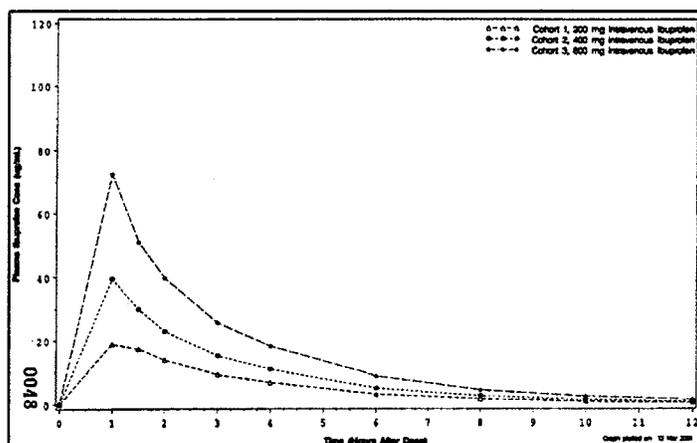
of subjects when intravenous ibuprofen was administered (one subject in Cohort 1, seven subjects in Cohort 2, and six subjects in Cohort 3). There was an observable trend with respect to decreasing creatinine clearance (GFR) levels following both oral and intravenous administration. Apart from the injection site related adverse events from intravenous ibuprofen infusion and the decrease in GFR levels related to either intravenous or oral ibuprofen, there was no dose dependency for the incidence rate for all of the other reported adverse events. All vital sign measurements taken during the study observation period were deemed to be acceptable (no significant abnormalities) by the Principal Investigator and/or Medical Officer. There were no clinically significant observable trends in measurements obtained from baseline to the end of the study. There were no clinically significant changes in physical findings from Screening to the end of Treatment Period 2.

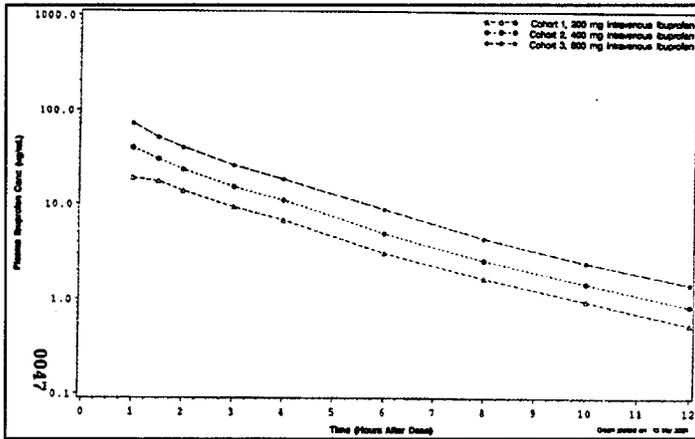
CONCLUSION: Apart from the injection site related adverse events from intravenous infusion and the decrease in GFR levels related to either intravenous or oral ibuprofen, there were no clinically significant safety-related concerns following administration of single doses of intravenous or oral ibuprofen in the dose range 200 mg to 800 mg. The pharmacokinetic parameters were observed to be similar when equivalent single doses of ibuprofen were administered either intravenously or orally over the dose range 200 to 800 mg, except for CMAX following intravenous administration of a single 200 mg dose of ibuprofen, where this pharmacokinetic parameter was observed to be considerably lower than that observed following oral administration of an equivalent single dose.

Date of the Report: 30 Mar 2001

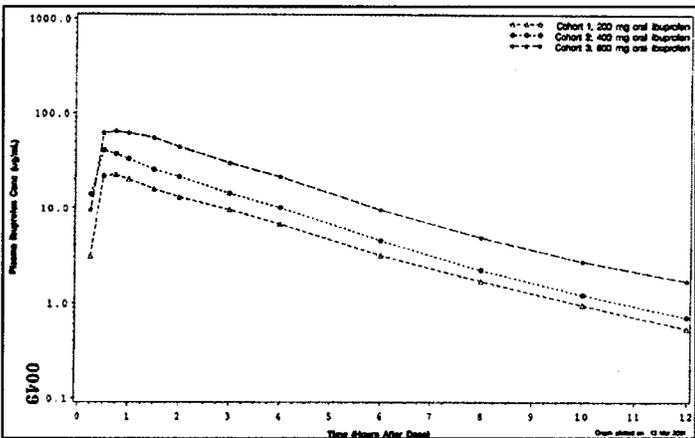
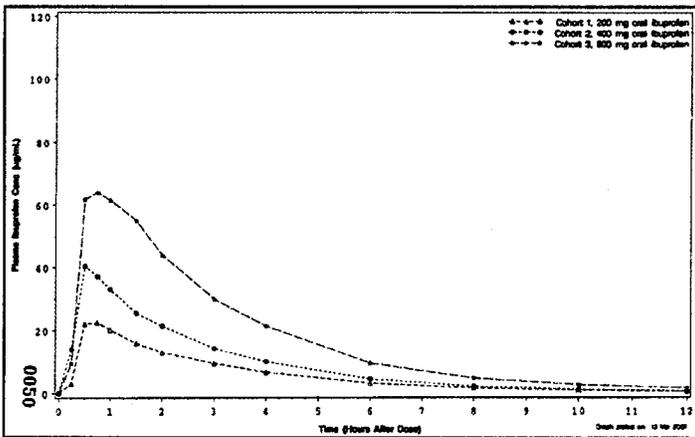
Results:

Mean plasma ibuprofen concentration profiles from intravenous administration (treatment)

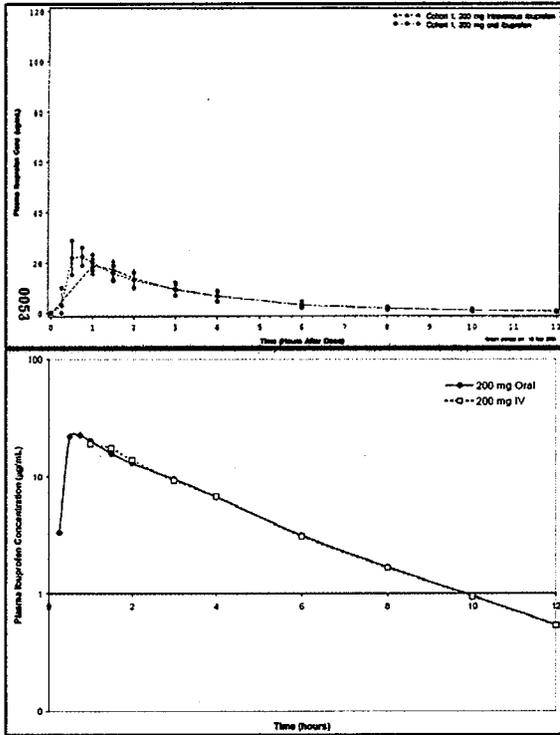




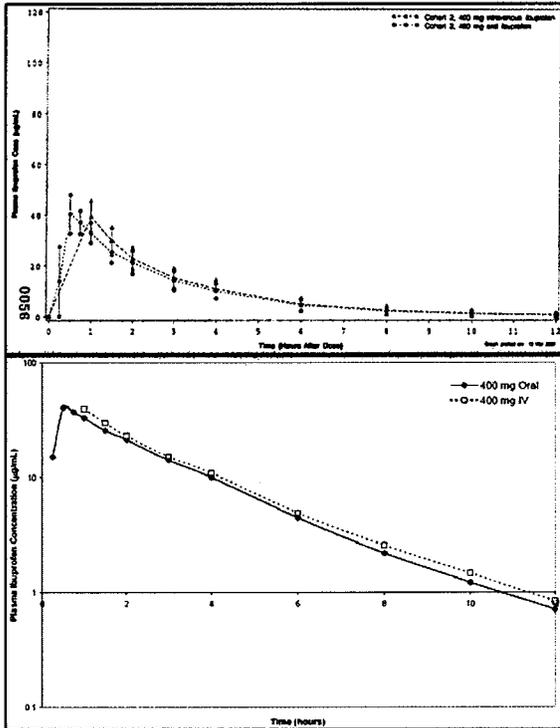
Mean plasma ibuprofen concentration profiles from oral administration (reference)



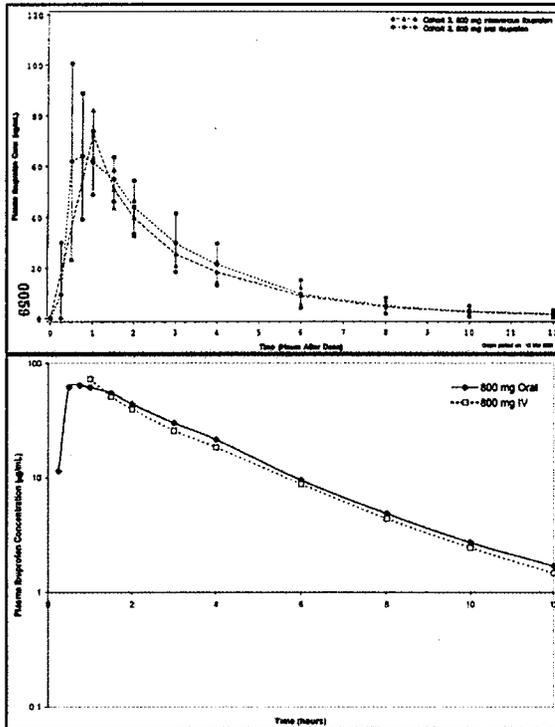
Pharmacokinetics of 200 mg Oral and IV ibuprofen



Pharmacokinetics of 400 mg Oral and IV ibuprofen



Pharmacokinetics of 800 mg Oral and IV ibuprofen



PK parameters derived from plasma data for intravenous and oral ibuprofen Mean (CV%)

Dose	200mg (CPI-CL-001)		400mg (CPI-CL-001)		800mg (CPI-CL-001)	
	Oral	IV	Oral	IV	Oral	IV
No. of Patients	12	12	12	12	12	12
AUC _{0-t} (µg·h/mL)	67.982 (24.8%)	63.647 (20.7%)	108.255 (22%)	109.336 (26.4%)	212.117 (22.5%)	192.755 (18.5%)
AUC _{inf} (µg·h/mL)	69.862 (25.7%)	65.532 (21.5%)	110.887 (24.2%)	112.471 (29.2%)	218.817 (25.1%)	198.206 (20.0%)
C _{max} (µg/mL)	24.697 (17.1%)	19.294 (16%)	42.939 (11.4)	39.217 (15.5%)	81.046 (23.2%)	72.640 (13.2%)
T _{max} (h)	0.65 (25.9%)	1.13 (20.3%)	0.55 (25.6%)	1.05 (15.8%)	0.85 (60.4%)	1.00 (0)
Elimination Rate Constant (hr ⁻¹)	0.3003 (9.6%)	0.2998 (12.4)	0.3203 (17.3%)	0.3222 (17.9%)	0.2851 (14.8%)	0.2880 (12.8%)
T _{1/2}	2.33 (9.6)	2.34 (12.4)	2.23 (19.5)	2.22 (20.1)	2.48 (15.6)	2.44 (12.9)

Least Squares Means and 90% Confidence Intervals of Ibuprofen Pharmacokinetic Parameters IVIB = 200mg Intravenous Ibuprofen; Oral = 200mg Oral Ibuprofen N=12

Parameter	Treatment L.S. Means		LS Mean Ratio (IVIB/Oral) %	90% Confidence Intervals for LS Mean Ratio %		P-value from ANOVA	Power (%)	Intra Subject CV%	Inter Subject CV%
	IVIB	Oral							
AUC	63.647	67.982	93.6%	83.1%	104.1%	0.2959	87.67	.	.
LAUC	4.134	4.193						.	.
gLAUC	62.440	66.236	94.3%	84.2%	105.6%	0.3663	89.65	15.3	14.2
AUC_INF	65.532	69.862	93.8%	83.2%	104.4%	0.3134	87.07	.	.
LAUC_INF	4.162	4.219						.	.
gLAUC_INF	64.211	67.968	94.5%	84.3%	105.9%	0.3888	88.97	15.5	15.0
C _{MAX}	19.294	24.697	78.1%	68.1%	88.1%	0.0026	90.44	.	.
LC _{MAX}	2.947	3.193						.	.
gLC _{MAX}	19.052	24.364	78.2%	70.0%	87.4%	0.0024	90.73	15.0	5.7
T _{MAX}	1.13	0.65	174.5%	151.8%	197.1%	0.0001	27.30	.	.
KEL	0.2998	0.3003	99.8%	94.6%	105.1%	0.9529	99.96	.	.
THALF	2.34	2.33	100.7%	95.5%	106.0%	0.8072	99.95	.	.

Mean values for Treatments IVIB and Oral are the least squares means (LSMEANS) from the ANOVA

Parameters with the L prefix are log-transformed parameters

Parameters with the gL prefix are geometric least squares means derived by back-transforming

least squares means of log-transformed parameters

Power = power (%) to detect 20% differences between treatments (α=0.05)

. = value not calculated

Least Squares Means and 90% Confidence Intervals of Ibuprofen Pharmacokinetic Parameters IVIB =400mg Intravenous Ibuprofen; Oral =400mg Oral Ibuprofen N=12

Parameter	Treatment L.S. Means		LS Mean Ratio (IVIB/Oral) %	90% Confidence Intervals for LS Mean Ratio %		P-value from ANOVA	Power (%)	Intra Subject CV%	Inter Subject CV%
	IVIB	Oral							
AUC	109.336	108.255	101.0%	93.2%	108.8%	0.8200	98.28	.	.
LAUC	4.667	4.664						.	.
gLAUC	106.382	106.078	100.3%	92.7%	108.5%	0.9485	99.24	10.6	20.5
AUC_INF	112.471	110.887	101.4%	93.5%	109.3%	0.7503	97.98	.	.
LAUC_INF	4.691	4.685						.	.
gLAUC_INF	108.919	108.298	100.6%	93.0%	108.8%	0.8975	99.24	10.6	22.4
C _{MAX}	39.217	42.939	91.3%	83.0%	99.7%	0.0900	96.91	.	.
LC _{MAX}	3.659	3.754						.	.
gLC _{MAX}	38.821	42.690	90.9%	83.8%	98.7%	0.0625	98.88	11.1	7.9
T _{MAX}	1.05	0.55	190.1%	167.6%	212.6%	0.0000	27.57	.	.
KEL	0.3222	0.3203	100.6%	97.0%	104.2%	0.7672	99.99	.	.
THALF	2.22	2.23	99.6%	96.0%	103.2%	0.8390	99.99	.	.

Mean values for Treatments IVIS and Oral are the least squares means (LSMEANS) from the ANOVA

Parameters with the L prefix are log-transformed parameters

Parameters with the gL prefix are geometric least squares means derived by back-transforming least squares means of log-transformed parameters

Power = power (%) to detect 20% differences between treatments (α=0.05)

. = value not calculated

Least Squares Means and 90% Confidence Intervals of Ibuprofen Pharmacokinetic Parameters IVIB = 800mg Intravenous Ibuprofen; Oral = 800mg Oral Ibuprofen N=12

Parameter	Treatment L.S. Means		LS Mean Ratio (IVIB(Oral) %)	90% Confidence Intervals for LS Mean Ratio %		P-value from ANOVA	Power (%)	Intra Subject CV%	Inter Subject CV%
	IVIB	Oral							
AUC	192.755	212.117	90.9%	84.2%	97.5%	0.0320	99.55	.	.
LAUC	5.248	5.338							
gLAUC	190.121	208.149	91.3%	86.9%	96.1%	0.0085	99.99	6.8	16.1
AUC_INF	198.206	218.817	90.6%	83.5%	97.7%	0.0371	99.17	.	.
LAUC_INF	5.273	5.365							
gLAUC_INF	195.091	213.857	91.2%	86.5%	96.2%	0.0101	99.99	7.1	17.6
C _{MAX}	72.640	81.046	89.6%	80.0%	99.3%	0.0804	92.07	.	.
LC _{MAX}	4.278	4.371							
gLC _{MAX}	72.085	79.159	91.1%	83.1%	99.7%	0.0920	97.43	12.3	13.7
T _{MAX}	1.00	0.85	117.1%	84.2%	150.0%	0.3691	14.31	.	.
K _{EL}	0.2880	0.2851	101.0%	94.1%	108.0%	0.7956	99.31	.	.
THALF	2.44	2.48	98.4%	92.2%	104.6%	0.6468	99.77	.	.

Mean values for Treatments IVIB and Oral are the least squares means (LSMEANS) from the ANOVA

Parameters with the L prefix are log-transformed parameters

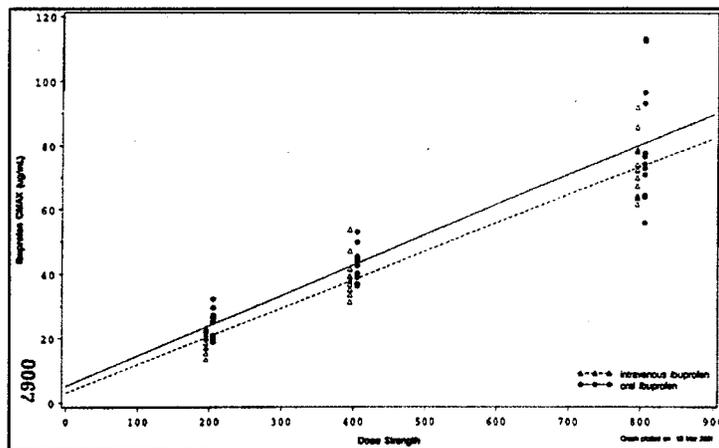
Parameters with the gL prefix are geometric least squares means derived by back-transforming least squares means of log-transformed parameters

Power = power (%) to detect 20% differences between treatments (α=0.05)

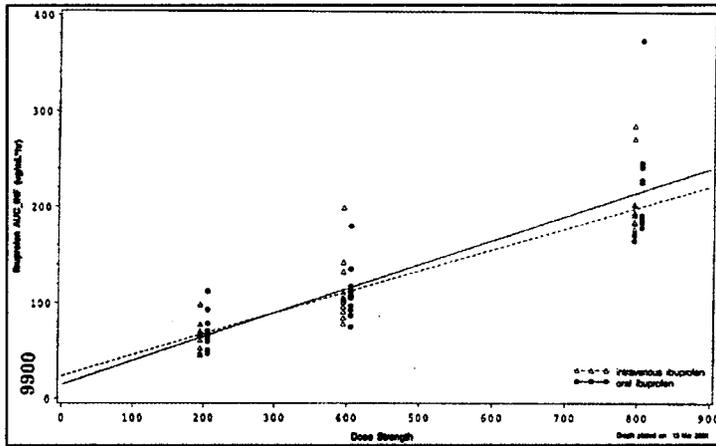
. = value not calculated

Dose linearity

C_{max}:



AUC0-inf:



4.2.2 Study CPI-CL-004

Title: A multicenter, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of ibuprofen injection in adult febrile patients

Investigators: (b) (4)	
[Redacted]	
Publication (reference): Not Applicable	
Study Period: Date of first enrollment: 11 Jun 2002 Date of last completed: 8 Aug 2005	Phase of Development: III

<p>Objectives:</p> <ul style="list-style-type: none"> • To evaluate the efficacy of 400 mg IVIb on reducing fever greater than or equal to 101.0°F (38.3°C), determined by the percentage of subjects with temperature less than 101.0°F (38.3°C) at 4 hours after administration of a single dose, as compared with the efficacy of parallel placebo treatment. • To evaluate the efficacy of 100 mg and 200 mg IVIb on reducing fever greater than or equal to 101.0°F (38.3°C), determined by the percentage of subjects with temperature less than 101.0°F (38.3°C) at 4 hours after administration of a single dose of IVIb, as compared with the efficacy of parallel placebo treatment; • To evaluate the efficacy of three dose levels of IVIb by assessing the percentage of treatment failures (subjects whose temperature is greater than or equal to 103.0°F [39.4°C] after a minimum of 2 hours after a dose of CTM) during the first 24 hours of treatment, as compared with the efficacy of parallel placebo treatment; • To evaluate the efficacy of three dose levels of IVIb by assessing the time to afebrility (the first time at which a patient's temperature is less than 101.0°F [38.3°C]) during the first 24 hours of treatment, as compared with the efficacy of parallel placebo treatment; • To evaluate the safety and tolerability of repeated intravenous doses of IVIb by assessing treatment-emergent AEs, as compared with the safety of parallel placebo treatment. • To determine the pharmacokinetic profile of three dose levels of IVIb.
Methodology: Multi-center, randomized, double-blind, parallel, placebo-controlled study
Number of patients: Planned: 120 participants Analyzed: 120 participants
<p>Diagnosis and main criteria for inclusion: To be eligible for this study, the patient must have met all of the following criteria:</p> <ul style="list-style-type: none"> • Be hospitalized. • Have 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 preferred method of temperature measurement was core. If a non-core route was used, temperature measurement should have been verified by an additional route of measurement; the route of temperature measurement used immediately before randomization should be used immediately before dosing and for all temperature measurements during the Treatment Period.) • Have adequate intravenous access. • Have the ability to understand the requirements of the study, been willing to provide written informed consent (as evidenced by signature on an informed consent document approved by an Institutional Review Board [IRB]), and have agreed to abide by the study restrictions and to return for the required assessments (If the patient was incapacitated, informed consent was to be sought from a legally acceptable representative.) <p>Randomized subjects were to be febrile within 15 minutes prior to first dose of CTM. This was to be confirmed and recorded as a separate assessment in the case report form. If the randomized patient no longer met fever inclusion criteria, they were not to be administered CTM. No additional follow-up was required for these subjects. However, if the patient redeveloped fever meeting inclusion criteria, CTM could then be administered. Baseline assessments were required to be repeated if outside the defined baseline time window.</p>
Test product, dose and mode of administration, batch number: Intravenous ibuprofen: 100, 200 or 400 mg, intravenous. Batch Number: L1019420
Duration of treatment: 6 doses, one dose every 4 hours
Reference therapy, dose and mode of administration, batch number: Normal Saline, 100 ml, intravenous.

Criteria for evaluation:

Efficacy: To evaluate the effectiveness of IV Ibuprofen in the reduction of fever compared with the effectiveness of parallel placebo treatment

Safety: To evaluate the safety and tolerability of repeated intravenous doses of IVIb by assessing treatment-emergent AEs, as compared with the safety of parallel placebo treatment.

CONCLUSION: At 4 hours, in the ITT population, 24 of 31 (77%) of subjects in the 400 mg IVIb group, compared to 9 of 28 (32%) of the Placebo group had a temperature less than 101.0°F (or 38.3°C), $p=0.0005$ (CMH test adjusted by center), also clearly demonstrating the efficacy of the 400 mg dose of IVIb on reducing fever and meeting the primary endpoint.

Further, doses of 100mg and 200 mg were also found to be statistically significant in reducing fever at the 4 hour primary endpoint.

There were no statistically significant differences between treatment groups compared with placebo in terms of adverse event occurrence (limited to events occurring in at least 3 subjects) except for bacteraemia where the incidence was 13% in the 100mg treatment group ($n=4$) vs. 0% in the placebo group ($p=0.045$). There were no statistically significant differences in the occurrence of serious adverse events or deaths in any treatment group when compared with placebo.

There were no statistically significant differences between treatment groups with regards to the requirements for transfusion, actual or percent change from baseline for any of the laboratory values monitored during the study. There were no subjects who experienced bleeding complications and no subjects experienced renal complications that were thought to be related to CTM administration.

In this multi-center study comparing IVIb to placebo, 120 patients (88 men, 32 women) who had temperatures of 101°F (38.3°C) or greater were randomized to IVIb at 100 mg, 200 mg, and 400 mg or placebo, administered every 4 hours for 24 hours of treatment. For statistical analyses, randomization of patients was stratified based upon severity of illness (critically ill vs. non-critically ill).

All IVIb dose levels resulted in a statistically significant reduction in the number of patients with a temperature $<101^\circ\text{F}$ after 4 hours, compared to placebo. The number of people achieving a reduction in fever ($<101^\circ\text{F}$ after 4 hours) were:

Placebo: 9 of 28 patients;

100 mg IVIb: 20 of 31 patients ($p=0.0138$, vs. placebo);

200 mg IVIb: 22 of 30 patients ($p=0.0018$, vs. placebo); and

400 mg IVIb: 24 of 31 patients ($p=0.0005$, vs. placebo).

DRUG CONCENTRATION MEASUREMENTS

Blood samples for pharmacokinetic analysis were obtained from the first 98 subjects enrolled in the study. Blood sample collection for measurement of plasma ibuprofen concentration was performed at Hour 0 (immediately before start of first infusion), Hour 0.5 (at the end of first infusion), Hour 1, Hour 2, Hour 3, Hour 4 (before start of second infusion); Hour 20 (immediately before start of last infusion), Hour 20.5 (at the end of last infusion), Hour 22, Hour 24, and Hour 26 (Samples collected from the first 98 subjects enrolled in the study). The plasma samples were shipped from the Clinical Centers to the sponsor, on dry ice, and were stored at approximately -20° to -70°C until batched and shipped to (b) (4) for analysis. The analytical method used for the determination of ibuprofen concentrations in plasma samples was (b) (4) - Determination of Ibuprofen in Human Plasma by HPLC. The method extracted Ibuprofen and (b) (4) (Internal Standard) from plasma using

liquid/liquid extraction. The compounds were separated by HPLC on a C18 reverse phase column, and the eluates monitored by an UV-Vis detector set at (b) (4). The extracts were assayed against a calibration curve. The method range was from 0.20 to 50 µg/mL.

PK analysis:

The following pharmacokinetic parameters were determined for each patient:

- **AUC₀₋₄**, area under the concentration-time curve for Dose 1 (over the interval from Hour 0 to Hour 4), calculated by using the linear-log trapezoidal rule: linear trapezoidal rule up to time to maximum concentration, and then log trapezoidal rule for the remainder of the curve to Hour 4;
- **C_{max}dose1**, the maximum concentration of drug after the first dose (over the interval from Hour 0 to Hour 4), and **T_{max}dose1**, the time to maximum concentration of drug after the first dose (over the interval from Hour 0 to Hour 4);
- **C_{min}dose1**, the minimum concentration of drug after the first dose (over the interval from Hour 0 to Hour 4), and **T_{min}dose1** the time to minimum concentration of drug after the first dose (over the interval from Hour 0 to Hour 4);
- **C_{min}dose6**, the minimum concentration of drug after the sixth dose (over the interval from Hour 20 to Hour 26), and **T_{min}dose6**, the time to minimum concentration of drug after the sixth dose (over the interval from Hour 20 to Hour 26).

Results:

1. Placebo control ibuprofen levels

a. Plasma samples were collected at baseline and specific post-dosing times during the study from a subset of subjects (n=98) to measure the pharmacokinetics of ibuprofen. Of the 97 subjects with baseline samples available, 6 subjects were positive for very low levels of ibuprofen at baseline (minimum of 0.220 and maximum of 8.54 ug/mL).

These levels are thought to have been so low that the potential for effects on temperature were insignificant. There was not a significant difference between the treatment groups. Mean ibuprofen levels at baseline were: 100 mg IVlb 0.00; 200mg IVlb 0.121; 400 mg IVlb 0.360; and Placebo 0.055 (n=97). For perspective, even in the 100 mg IVlb group, the lowest CTM dose, mean ibuprofen levels following a single dose at 30 minutes were 12.042. *There are no indications that the 6 subjects with low levels of ibuprofen at baseline received ibuprofen in the 4 hours prior to dosing with CTM.*

All samples collected from subjects receiving IVlb at the 200 mg and 400 mg dose levels were assayed as having measurable plasma concentrations of ibuprofen at all time points for pharmacokinetic analysis following dosing in the first and sixth dose intervals. For the 100 mg IVlb dose level, one patient (5053) had plasma concentrations of ibuprofen below the lower limit of quantitation at Hour 4.

Five subjects randomized to placebo treatment had very low but measurable concentrations of ibuprofen during the dosing period. Three of the subjects (2003, 2051, and 6003) had similar very low levels of ibuprofen throughout the sampling period

making sampling error unlikely. For one patient (8016), Hour 0.5 was the only time point with measurable concentrations of ibuprofen.

Appendix 16.2.5.3: Concomitant Medications table showed that Patients 2003, 2051 and 6003 did not take any ibuprofen-related products.

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Appendix 16.2.5.3
Concomitant Medications

Protocol No. CPI-CL-084

Drug Name	Indication	Essential	Start Date	Stop Date	Outcome		
Placebo 2051	Critically III	Pepcid IV	Gastrointestinal prophylaxis	No	21/Jul/2002	NA	Yes
Placebo 2051	Critically III	Potassium IV	Hypokalemia	No	21/Jul/2002	NA	Yes
Placebo 2051	Critically III	Enoxaparin	Deep vein thrombosis prophylaxis	No	24/Jul/2002	NA	Yes
Placebo 2051	Critically III	Parlorel	Suspected neuroleptic malignant syndrome	No	24/Jul/2002	25/Jul/2002	No
Placebo 2051	Critically III	Furosemide	Volume overload with rhabdomyolysis	No	24/Jul/2002	24/Jul/2002	No
Placebo 2051	Critically III	Epoetin	Anemia	No	24/Jul/2002	24/Jul/2002	No
Placebo 2051	Critically III	Combivent	Pneumonia	No	25/Jul/2002	NA	Yes
Placebo 2051	Critically III	Ativan (Lorazepam)	Sedation protocol	No	25/Jul/2002	NA	Yes
Placebo 2051	Critically III	Fentanyl	Sedation protocol	No	25/Jul/2002	NA	Yes
Placebo 2051	Critically III	Clonidine	Hypertension	No	25/Jul/2002	NA	Yes
Placebo 2051	Critically III	Succinylcholine	Intubation procedure	No	25/Jul/2002	25/Jul/2002	No
Placebo 2051	Critically III	Levofloxacin	Pneumonia	No	26/Jul/2002	NA	Yes
Placebo 2051	Critically III	Acetaminophen	Fever	No	28/Jul/2002	28/Jul/2002	No
Placebo 2051	Critically III	Albuterol (Salbutamol)	Pneumonia	No	29/Jul/2002	NA	Yes
Placebo 2051	Critically III	Ipratropium	Pneumonia	No	29/Jul/2002	NA	Yes
Placebo 2051	Critically III	Oxymetazoline	Sinusitis	No	30/Jul/2002	NA	Yes
Placebo 2051	Critically III	Methylprednisolone	Pneumonia	No	30/Jul/2002	31/Jul/2002	No
Placebo 2051	Critically III	Proclamine	Nutrition support	No	31/Jul/2002	31/Jul/2002	No
Placebo 6003	Critically III	Pepcid (Famotidine)	Gastroenteritis	No	29/Sep/2003	NA	Yes
Placebo 6003	Critically III	Bactrim	Abdominal abscesses	No	29/Sep/2003	NA	Yes
Placebo 6003	Critically III	Flagyl (Metronidazole)	Abdominal abscesses	No	29/Sep/2003	NA	Yes
Placebo 6003	Critically III	Vancocin	Abdominal abscesses	No	29/Sep/2003	NA	Yes
Placebo 6003	Critically III	Ceftriaxone	Abdominal abscesses	No	30/Sep/2003	30/Sep/2003	No
Placebo 6003	Critically III	Zithromax	Abdominal abscesses	No	30/Sep/2003	05/Oct/2003	No
Placebo 6003	Critically III	Morphine	Pain	No	30/Sep/2003	NA	Yes
Placebo 6003	Critically III	Versed (midazolam)	Abdominal abscesses	No	30/Sep/2003	30/Sep/2003	No
Placebo 6003	Critically III	Ativan (Lorazepam)	Abdominal abscesses	No	30/Sep/2003	30/Sep/2003	No
Placebo 6003	Critically III	Benadryl	Pruritis	Yes	30/Sep/2003	01/Oct/2003	No
Placebo 6003	Critically III	Fentanyl	Agitation	No	30/Sep/2003	01/Oct/2003	No
Placebo 6003	Critically III	Maxipime (Cefepime)	HRV infection	No	30/Sep/2003	NA	Yes
Placebo 6003	Critically III	Haldol	Sedation/agitation	No	01/Oct/2003	NA	Yes
Placebo 6003	Critically III	Diprivan	Agitation	No	01/Oct/2003	03/Oct/2003	No
Placebo 6003	Critically III	Potassium Chloride	Hypokalemia	No	05/Oct/2003	05/Oct/2003	No
Placebo 2003	Non-Critically III	Ipratropium	Bronchitis	No	15/Jun/2002	10/Jul/2002	No
Placebo 2003	Non-Critically III	Sulfamethox	Peritonitis	No	17/Jun/2002	10/Jul/2002	No
Placebo 2003	Non-Critically III	Casanthranol / Docusate	To prevent constipation	No	01/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Dalteparin sodium	Antithrombotic prophylaxis	No	01/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Fluconazole	Peritonitis	No	01/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Fosinopril	Hypertension	No	01/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Levothyroxine	Hypothyroidism	No	01/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Promethazine	Nausea	No	01/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Piperacillin	Peritonitis	No	01/Jul/2002	NA	No
Placebo 2003	Non-Critically III	Clonidine	Hypertension	No	03/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Clonidine	Hypertension	No	03/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Famotidine	Gastro intestinal prophylaxis	No	06/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Diffucan	Peritonitis	No	06/Jul/2002	NA	No
Placebo 2003	Non-Critically III	Albuterol (Salbutamol)	Bronchitis	No	08/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	HCTZ / Triamterene	Hypertension	No	09/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Vancocin	Peritonitis	No	09/Jul/2002	15/Jul/2002	No
Placebo 2003	Non-Critically III	Imipenem/cilastatin	Peritonitis	No	10/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Lidocaine 1%	Local anesthetic	No	10/Jul/2002	10/Jul/2002	No
Placebo 2003	Non-Critically III	Darvocet	Pain from gout	No	11/Jul/2002	12/Jul/2002	No
Placebo 2003	Non-Critically III	Methylprednisolone	Gout	No	11/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Prednisone	Gout	No	12/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Colchicine	Gout	No	13/Jul/2002	NA	Yes
Placebo 2003	Non-Critically III	Prednisone	Gout	No	13/Jul/2002	13/Jul/2002	No
Placebo 8016	Non-Critically III	Artesunate	Antimalaria	No	22/Oct/2002	26/Oct/2002	No
Placebo 8016	Non-Critically III	Alum milk	Abdominal pain	Yes	23/Oct/2002	25/Oct/2002	No
Placebo 8016	Non-Critically III	Primaquine	Antimalaria	No	27/Oct/2002	NA	Yes

The other patient (4057) had measurable concentrations of ibuprofen throughout the first dose interval (Hour 0 to Hour 4), but was discontinued after the fourth dose, and no

samples were collected in the sixth dose interval so it is not known if the patient's levels would have remained throughout the period.

Placebo	4057	Critically ill	Etiomidate	Intubation	No	05/Mar/2003	05/Mar/2003	No
Placebo	4057	Critically ill	Midazolam	Sedation	No	05/Mar/2003	09/Mar/2003	No
Placebo	4057	Critically ill	Phenytoin	Questionable seizure	No	05/Mar/2003	06/Mar/2003	No
Placebo	4057	Critically ill	Calcium chloride	Hypokalemia	No	05/Mar/2003	08/Mar/2003	No
Placebo	4057	Critically ill	Ceftriaxone	Aspiration	No	05/Mar/2003	11/Mar/2003	No
Placebo	4057	Critically ill	Vancomycin	Meningitis, aspiration pneumonia	No	05/Mar/2003	11/Mar/2003	No
Placebo	4057	Critically ill	Magnesium sulfate	Vitamin supplement	No	06/Mar/2003	08/Mar/2003	No
Placebo	4057	Critically ill	Thiamine	Vitamin supplement	No	06/Mar/2003	08/Mar/2003	No
Placebo	4057	Critically ill	Folic acid	Vitamin supplement	No	06/Mar/2003	08/Mar/2003	No
Placebo	4057	Critically ill	Multivitamins	Vitamin supplement	No	06/Mar/2003	08/Mar/2003	No
Placebo	4057	Critically ill	Furosemide	Myoglobinuria	No	06/Mar/2003	09/Mar/2003	No
Placebo	4057	Critically ill	Lactulose	Elevated ammonia	No	06/Mar/2003	10/Mar/2003	No
Placebo	4057	Critically ill	Lorazepam	Sedation	No	06/Mar/2003	07/Mar/2003	No
Placebo	4057	Critically ill	Acetaminophen	Fever	No	06/Mar/2003	06/Mar/2003	No
Placebo	4057	Critically ill	Acyclovir	Prophylaxis - possible meningitis	No	06/Mar/2003	09/Mar/2003	No
Placebo	4057	Critically ill	Carbamazepine	Seizure	No	06/Mar/2003	NA	Yes
Placebo	4057	Critically ill	Carbidopa-levodopa	Neuroleptic malignant syndrome	No	06/Mar/2003	06/Mar/2003	No
Placebo	4057	Critically ill	Cisatracurium besylate	Chemical paralysis	No	06/Mar/2003	09/Mar/2003	No
Placebo	4057	Critically ill	Dantrolene	Neuroleptic malignant syndrome	No	06/Mar/2003	06/Mar/2003	No
Placebo	4057	Critically ill	Sodium bicarbonate	Metabolic acidosis	No	06/Mar/2003	06/Mar/2003	No
Placebo	4057	Critically ill	Vitamin K	Thrombocytopenia	Yes	06/Mar/2003	07/Mar/2003	No
Placebo	4057	Critically ill	Potassium chloride	Hypokalemia	Yes	06/Mar/2003	11/Mar/2003	No
Placebo	4057	Critically ill	Potassium phosphate	Hypokalemia	Yes	06/Mar/2003	09/Mar/2003	No
Placebo	4057	Critically ill	Ranitidine	Gastritis prophylaxis	No	06/Mar/2003	07/Mar/2003	No
Placebo	4057	Critically ill	Lansoprazole	Gastritis prophylaxis	No	07/Mar/2003	NA	Yes
Placebo	4057	Critically ill	Magnesium sulfate	Hypomagnesemia	Yes	07/Mar/2003	10/Mar/2003	No
Placebo	4057	Critically ill	Calcium gluconate	Hypokalemia	No	07/Mar/2003	11/Mar/2003	No
Placebo	4057	Critically ill	Neutra-phos	Hypokalemia	Yes	07/Mar/2003	11/Mar/2003	No
Placebo	4057	Critically ill	Acetaminophen	Fever	No	09/Mar/2003	09/Mar/2003	No
Placebo	4057	Critically ill	Propofol	Sedation	No	10/Mar/2003	10/Mar/2003	No

It's unclear why these patients had measurable levels but since they were very low, they do not have an impact on the study.

By protocol, the use of antipyretic medications (NSAIOs, acetaminophen, aspirin) and other medications (corticosteroids) that were thought to affect temperature were excluded within the 4 hours prior to receipt of the first dose of CTM and throughout the initial 24 hour treatment period. In addition, medications such as corticosteroids and NSAIDs were excluded for the first 120 hours of study to allow for evaluation of adverse effects of IV1b compared to Placebo. Ten subjects received excluded concomitant medications (three subjects received two excluded medications). Only 4 subjects received excluded medications during the 24 hour treatment period: 2 subject received Tylenol and 2 received corticosteroids. During the post treatment phase but prior to 120 hours, 1 subject received Darvocet at study hour 26, 4 subjects received corticosteroids, 3 subjects received ibuprofen and 2 subjects received Tylenol. The protocol deviations were dealt with through excluding subjects from the EEP analyses at 4 and 24 hours for the primary and secondary assessments of temperature. In addition, the use of antipyretic procedures, such as the use of cold packs, tepid baths, etc. were restricted during the 24 hour treatment period. There were 9 subjects who received antipyretic procedures such as cold packs or tepid water baths. The subjects were to have been discontinued upon initiation of antipyretic procedures; however, in error, they were not discontinued and are included in both safety and efficacy analyses. The subjects were not excluded from analyses since there were so few instances and they were distributed among each of the treatment groups and such treatments are rarely effective in reducing temperature to normal.

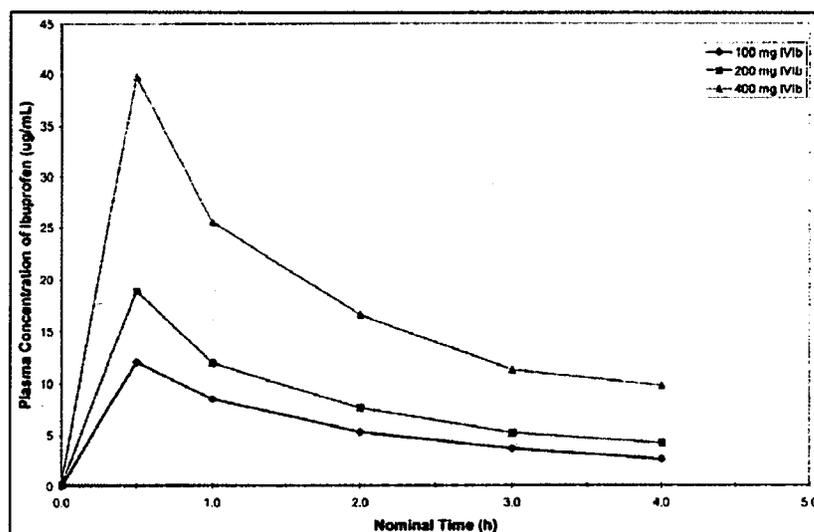
2. A value of half LOQ was used as the estimate of the concentration at Hour 4 in using the log trapezoidal rule to calculate AUG for the first dose interval for patient 5053.

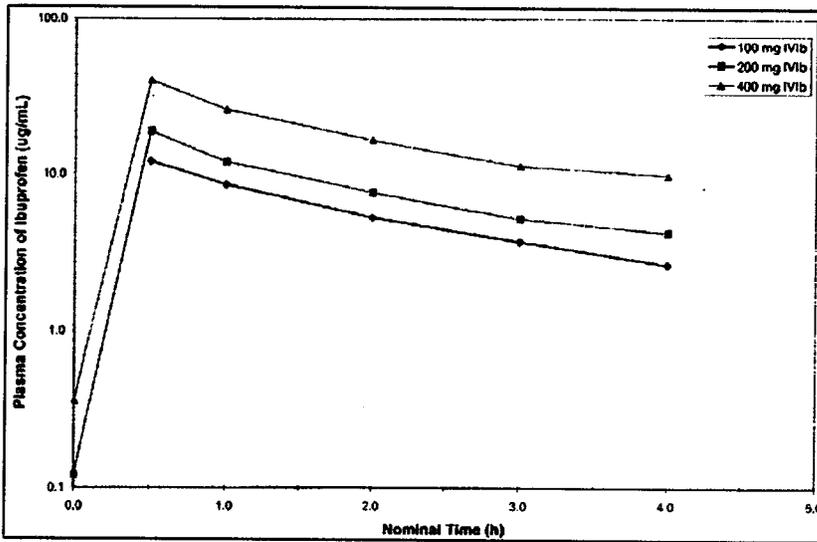
3. The rate of terminal elimination of plasma ibuprofen was not calculated for subjects 4059, 5053, and 5059, who had concentrations below quantitation at Hour 24 and Hour 26 (following the sixth dose). These three patients received the 100mg dose of GTM.

4. The time to maximum concentration following the first dose was at Hour 0.5 for all subjects receiving 400 mg IVIb and for most subjects receiving 100 mg IVIb and 200 mg IVIb, with a few subjects at the lower dose levels achieving maximum plasma concentration at Hour 1

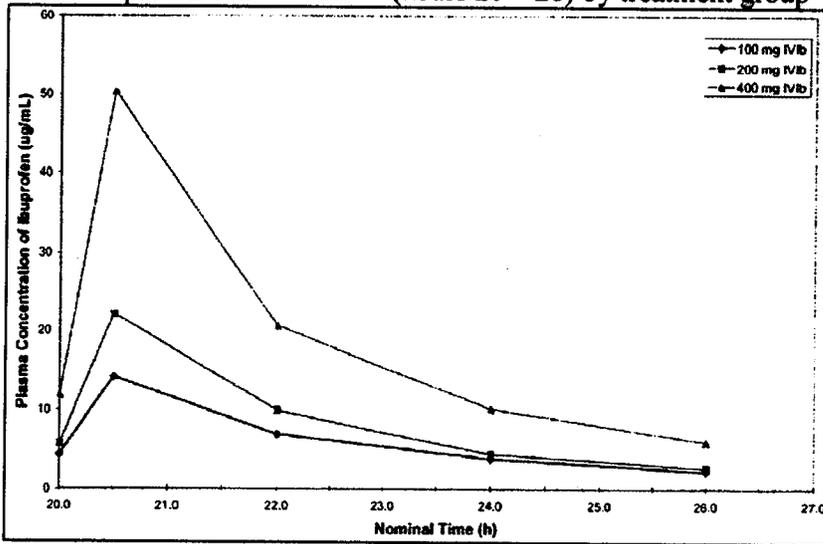
5. Figures

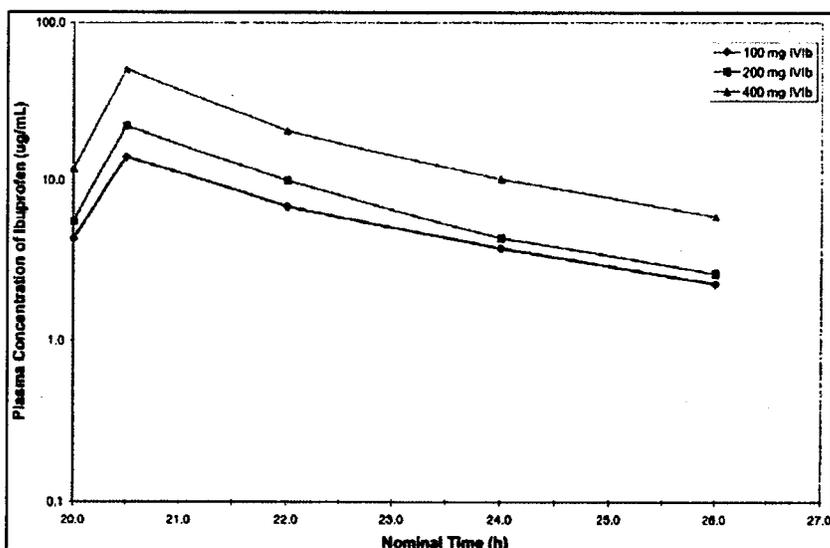
Mean ibuprofen concentrations (hours 0-4) by treatment group:





Mean ibuprofen concentrations (hours 20 – 26) by treatment group





6. Parameter table

Summary of Pharmacokinetic Parameters by IVIb Dose Level

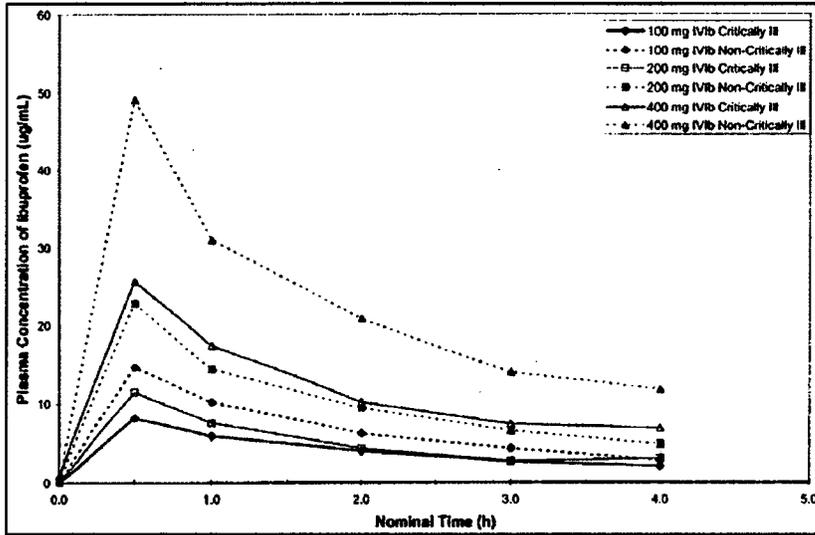
Dose	AUC ₀₋₄ (ug.h/mL)	C _{max} ₀₋₄ (ug/mL)	T _{max} ₀₋₄ (h)	C _{min} _{dose1} (ug/mL)	T _{min} _{dose1} (h)	C _{min} _{dose6} (ug/mL)	T _{min} _{dose6} (h)	T _{half} (h)
100 mg IVIb	22.33 ± 12.75	12.17 ± 6.78	0.5	2.65	4.0	2.5	25.9	2.47
200 mg IVIb	32.62 ± 17.39	18.94 ± 10.5	0.5	3.89	3.9	2.6	26.0	2.11
400 mg IVIb	70.64 ± 31.93	39.76 ± 17.75	0.5	8.27	3.8	6.0	26.0	2.26

The AUC₀₋₄ was approximately dose proportional for the 200 mg and 400 mg dose levels of IVIb. The dose normalized AUC₀₋₄ was somewhat greater for the lower dose level of 100 mg IVIb than for the higher dose levels.

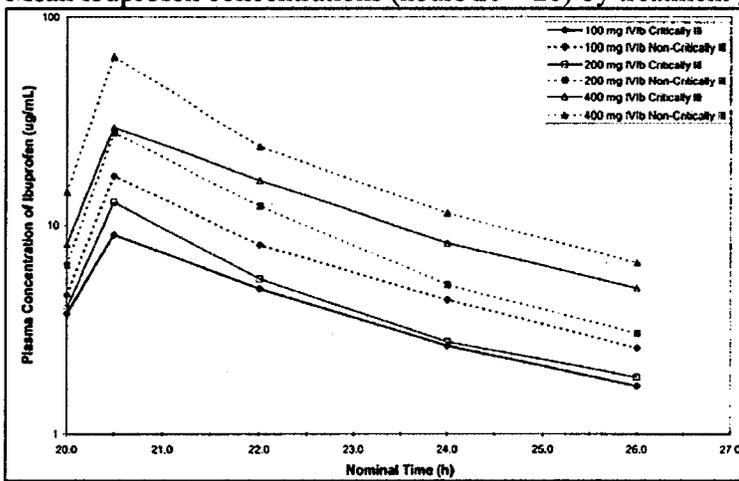
7. Additional PK analysis:

CPI-CL-004 was conducted in hospitalized patients who were stratified by severity of illness (critically ill vs. non-critically ill). Critically ill patients were defined as receiving pressor support and/or mechanical ventilation. Analysis of the data sets assessing the efficacy of IVIb for the treatment of fever in non-critically ill and critically ill hospitalized patients revealed a difference in pharmacokinetics and treatment effect on reduction in temperature. The C_{max} and AUC for all doses of IVIb are significantly reduced in critically ill patients when compared to non-critically ill patients, while the pharmacokinetics remained first order in both patient populations.

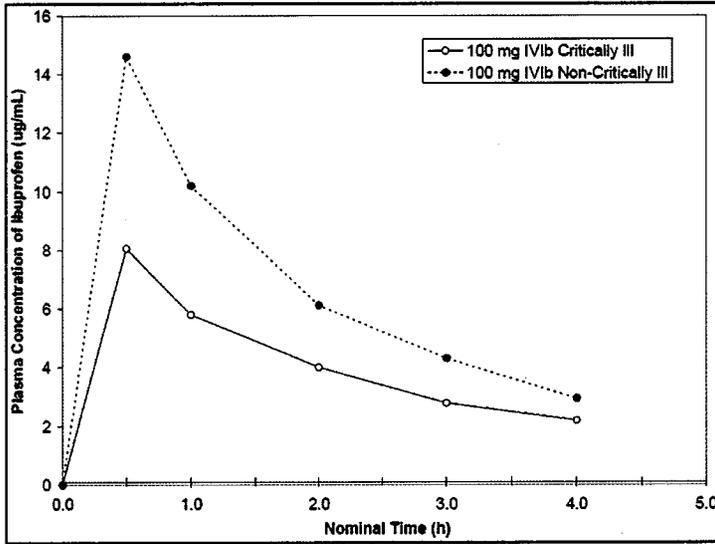
Mean ibuprofen concentrations (hours 0-4) by treatment group and randomization



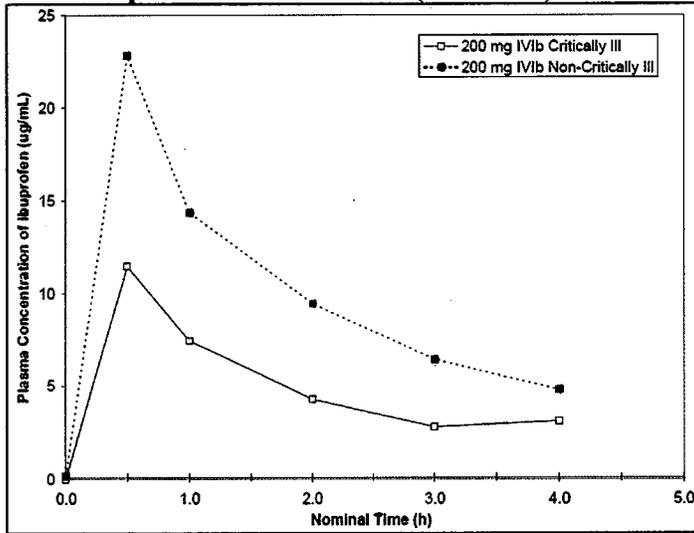
Mean ibuprofen concentrations (hours 20 – 26) by treatment group and randomization



Mean ibuprofen concentrations (hours 0-4) from 100mg group, study CPI-CL-004



Mean ibuprofen concentrations (hours 0-4) from 200mg group, study CPI-CL-004



Mean ibuprofen concentrations (hours 0-4) from 400mg group, study CPI-CL-004

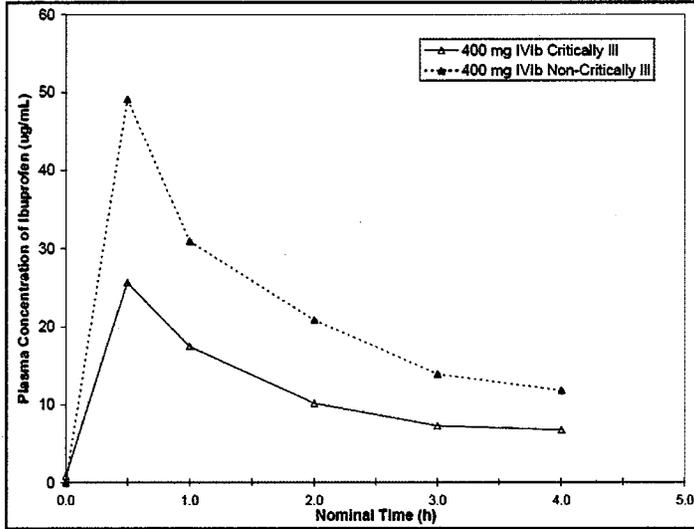


Table below presents the summary pharmacokinetic parameters from the patients enrolled in CPI-CL-004, by IVIb dose level and stratum.

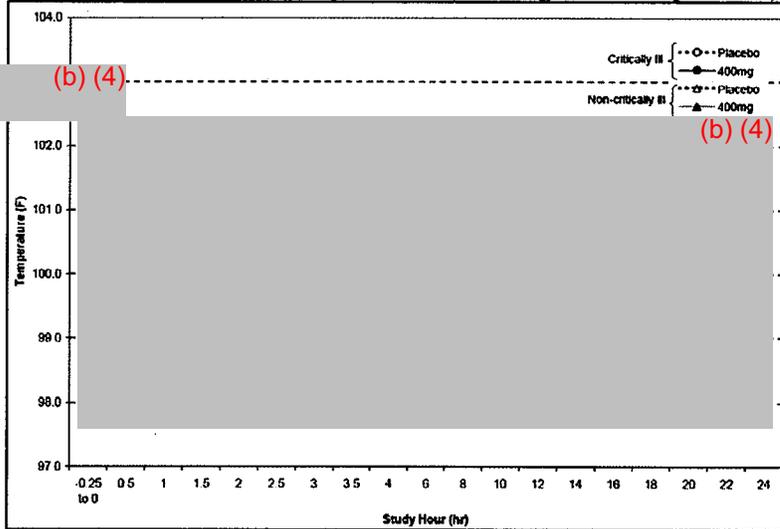
Summary of Pharmacokinetic Parameters by IVIb Dose Level and Stratum

Treatment, Stratum		AUC ₀₋₄ (ug.h/mL)	C _{max} ₀₋₄ (ug/mL)	T _{max} ₀₋₄ (h)	C _{min} _{dose1} (ug/mL)	T _{min} _{dose1} (h)	C _{min} _{dose6} (ug/mL)	T _{min} _{dose6} (h)	T _{half} (h)
100 mg IVIb	Critically Ill n=14	16.10	8.23	0.6	2.19	4.0	2.3	25.7	2.42
	Non-critically Ill n=17	26.33	14.53	0.5	2.95	4.0	2.6	26.0	2.49
200 mg IVIb	Critically Ill n=12	19.62	11.46	0.5	2.29	3.8	1.9	26.0	2.56
	Non-critically Ill n=18	39.51	22.89	0.5	4.73	3.9	3.0	26.0	1.86
400 mg IVIb	Critically Ill n=14	45.94	25.70	0.5	4.69	3.9	5.0	26.0	2.32
	Non-critically Ill n=17	87.11	49.13	0.5	10.66	3.8	6.6	26.0	2.22

8. Exposure-response analysis:

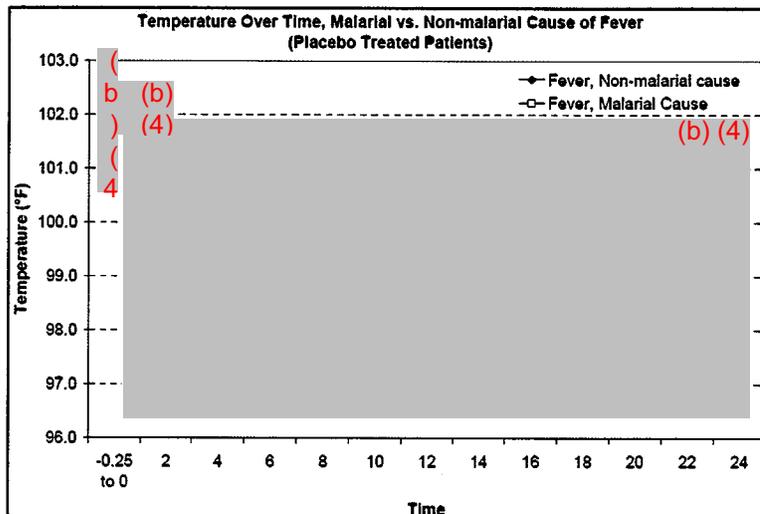
The efficacy of IVIb for the treatment of fever in the non-critically and critically ill patients was examined to better understand the clinical relevance of the pharmacokinetic difference presented in study CPI-CL-004. Figure below compares the effect of placebo and a 400 mg dose of IVIb on body temperature in non-critically and critically ill hospitalized patients. These data suggest that severity of illness appears to lower C_{max} and AUC of IVIb which appears to somewhat diminish the therapeutic effect.

Temperature over time by stratum, 400mg IVIb vs. placebo, study CPI-CL-004



The decrease over time in the placebo group is attributed to the patients enrolled in the study that were suffering from malaria and receiving concomitant anti-malarial drugs (thereby treating the cause of the fever), as displayed in figure below.

Placebo Temperature Response in Malaria vs. Non-malarial Patients (Study CPI-CL-004)



While 400 mg is proposed as the effective dose for the indication of reduction of fever, a dose adjustment up to 800 mg for the treatment of fever may be warranted if the reduction in fever at a lower dose is not adequate. Table below presents the percent difference between the critically ill versus the non-critically ill groups for the AUC₀₋₄ and C_{max}₀₋₄ pharmacokinetic parameters.

Pharmacokinetic Parameters Differences in the 400 mg IVIb Dose Level and Stratum

Treatment, Stratum	AUC ₀₋₄ (ug.h/mL)	C _{max} ₀₋₄ (ug/mL)
100 mg IVIb		
Critically Ill	16.10	8.23
Non-critically Ill	26.33	14.53
Critically Ill / Non-critically Ill % Difference	61.2%	56.6%
200 mg IVIb		
Critically Ill	19.62	11.46
Non-critically Ill	39.510	22.893
Critically Ill / Non-critically Ill % Difference	49.6%	50.0%
400 mg IVIb		
Critically Ill	45.94	25.70
Non-critically Ill	87.11	49.13
Critically Ill / Non-critically Ill % Difference	52.7%	52.3%

The values for the AUC and C_{max} pharmacokinetic parameters for the critically ill patients were approximately 50% compared to the parameters for the non-critically ill patients. This difference suggests that the dose may need to be increased from 400 mg up to 800 mg for treatment of fever, depending upon the severity of illness. While pharmacokinetic samples were not obtained in the study conducted under IND (b) (4) (b) (4) study), dosing in this study was 10mg/kg, up to 800 mg IV ibuprofen every six hours for a 48 hour duration. Based on the critically ill classification in study CPI-CL-004, the majority of patients in the (b) (4) study would have been defined as critically ill.

Therefore the efficacy observed at the 800mg dose in the (b) (4) study supports both the safety and efficacy of an 800mg dose every 6 hours in critically ill patients if they do not obtain an adequate temperature reduction with a 400mg dose.

9. Data tables: Appendix 14.3.5.5

Plasma ibuprofen Concentration (ug/mL)	Treatment								Total Number of Samples
	N	100 mg IVib	N	200 mg IVib	N	400 mg IVib	N	Placebo	
Nominal Time (h)									
0.0	24	0.000	26	0.121	25	0.360	22	0.055	97
0.5	24	12.042	26	18.877	25	39.758	23	0.071	98
1.0	24	8.481	26	11.955	25	25.551	23	0.073	98
2.0	23	5.298	25	7.600	25	16.594	23	0.058	96
3.0	22	3.689	26	5.195	25	11.268	22	0.066	95
4.0	23	2.651	26	4.222	25	9.786	22	0.067	96
20.0	23	4.304	24	5.601	23	11.856	19	0.043	89
20.5	22	14.140	25	22.153	23	50.349	19	0.044	89
22.0	22	6.895	26	9.893	23	20.627	19	0.046	90
24.0	22	3.744	26	4.344	23	10.097	19	0.043	90
26.0	22	2.244	26	2.619	23	5.956	19	0.047	90

Plasma ibuprofen Concentration (ug/mL)	Treatment											
	Nominal Time (h)	100 mg IVib				200 mg IVib				400 mg IVib		
		N	100 mg IVib Critically III	N	100 mg IVib Non-Critically III	N	200 mg IVib Critically III	N	200 mg IVib Non-Critically III	N	400 mg IVib Critically III	N
0.0	9	0.000	15	0.000	9	0.000	17	0.185	10	0.854	15	0.030
0.5	9	8.064	15	14.600	9	11.455	17	22.806	10	25.701	15	49.128
1.0	9	5.806	15	10.201	9	7.447	17	14.342	10	17.452	15	30.951
2.0	9	4.010	15	6.126	9	4.297	17	9.457	10	10.208	15	20.851
3.0	9	2.788	15	4.312	9	2.824	17	6.450	10	7.304	15	13.910
4.0	9	2.193	15	2.945	9	3.132	17	4.798	10	6.762	15	11.802
20.0	9	3.752	15	4.619	9	3.991	17	6.406	10	8.061	15	14.296
20.5	9	8.954	15	17.104	9	12.782	17	27.424	10	29.200	15	63.944
22.0	9	4.958	15	8.002	9	5.523	17	12.206	10	16.268	15	23.430
24.0	9	2.622	15	4.386	9	2.745	17	5.191	10	8.170	15	11.336
26.0	9	1.692	15	2.559	9	1.869	17	3.017	10	4.989	15	6.577

Treatment		AUC ₀₋₄ (ug.h/mL)	Cmax ₀₋₄ (ug/mL)	Tmax ₀₋₄ (h)	Cmin _{dosed1} (ug/mL)	Tmin _{dosed1} (h)	Cmin _{dosed6} (ug/mL)	Tmin _{dosed6} (h)	Thalf (h)	AUC ₀₋₄ /Dose
100 mg IV/b	N	23	24	24	23	23	20	20	20	23
	Mean	22.326	12.167	0.5	2.651	4.0	2.5	25.9	2.47	223.26
	Stdev	12.748	6.779	0.1	1.890	0.0	1.5	0.4	1.15	127.48
	Min	3.760	3.679	0.5	0.000	4.0	0.3	24.0	0.19	37.60
	Max	50.307	24.667	1.0	8.180	4.0	5.7	26.0	4.90	503.07
200 mg IV/b	N	26	26	26	26	26	26	26	25	26
	Mean	32.623	18.934	0.5	3.888	3.9	2.6	26.0	2.11	163.12
	Stdev	17.387	10.498	0.1	2.671	0.3	2.8	0.0	1.05	86.93
	Min	9.367	7.788	0.5	0.542	3.0	0.3	26.0	1.23	46.83
	Max	70.212	49.913	1.0	10.895	4.0	13.7	26.0	5.11	351.06
400 mg IV/b	N	25	25	25	25	25	23	23	23	25
	Mean	70.643	39.758	0.5	8.270	3.8	6.0	26.0	2.26	176.61
	Stdev	31.925	17.751	0.0	5.070	0.4	4.9	0.0	0.95	79.81
	Min	25.753	16.664	0.5	0.850	3.0	1.7	26.0	1.48	64.38
	Max	141.771	72.257	0.5	22.294	4.0	23.8	26.0	5.54	354.43

Treatment, Stratum		AUC ₀₋₄ (ug.h/mL)	Cmax ₀₋₄ (ug/mL)	Tmax ₀₋₄ (h)	Cmin _{dosed1} (ug/mL)	Tmin _{dosed1} (h)	Cmin _{dosed6} (ug/mL)	Tmin _{dosed6} (h)	Thalf (h)	AUC ₀₋₄ /Dose	
100 mg IV/b	Critically III	N	9	9	9	9	9	6	6	6	9
		Mean	16.101	8.230	0.6	2.193	4.0	2.3	25.7	2.42	161.01
		Stdev	14.638	6.348	0.2	2.888	0.0	1.8	0.8	1.49	146.38
		Min	3.760	3.679	0.5	0.000	4.0	0.4	24.0	0.19	37.60
		Max	50.307	23.839	1.0	8.180	4.0	4.7	26.0	4.79	503.07
	Non-critically III	N	14	15	15	14	14	14	14	14	14
		Mean	26.328	14.530	0.5	2.945	4.0	2.6	26.0	2.49	263.28
		Stdev	9.954	6.043	0.1	1.166	0.0	1.4	0.0	1.04	99.54
		Min	7.197	5.234	0.5	0.508	4.0	0.3	26.0	1.31	71.97
		Max	42.139	24.667	1.0	4.416	4.0	5.7	26.0	4.90	421.39
200 mg IV/b	Critically III	N	9	9	9	9	9	9	9	9	9
		Mean	19.615	11.455	0.5	2.293	3.8	1.9	26.0	2.56	98.07
		Stdev	7.014	2.760	0.0	1.697	0.4	2.1	0.0	1.57	35.07
		Min	9.806	7.885	0.5	0.556	3.0	0.3	26.0	1.26	49.03
		Max	30.987	16.390	0.5	5.393	4.0	6.4	26.0	5.11	154.93
	Non-critically III	N	17	17	17	17	17	17	17	16	17
		Mean	39.510	22.893	0.5	4.732	3.9	3.0	26.0	1.86	197.55
		Stdev	17.383	10.968	0.1	2.743	0.2	3.2	0.0	0.53	86.92
		Min	9.367	7.788	0.5	0.542	3.0	0.3	26.0	1.23	46.83
		Max	70.212	49.913	1.0	10.895	4.0	13.7	26.0	3.36	351.06
400 mg IV/b	Critically III	N	10	10	10	10	9	9	9	9	10
		Mean	45.937	25.701	0.5	4.689	3.9	5.0	26.0	2.32	114.84
		Stdev	16.195	8.313	0.0	2.936	0.3	4.3	0.0	0.84	40.49
		Min	25.753	16.664	0.5	0.850	3.0	2.0	26.0	1.53	64.38
		Max	80.147	42.542	0.5	10.453	4.0	12.7	26.0	4.01	200.37
	Non-critically III	N	15	15	15	15	15	14	14	14	15
		Mean	87.113	49.128	0.5	10.657	3.8	6.6	26.0	2.22	217.78
		Stdev	29.188	16.141	0.0	4.822	0.4	5.4	0.0	1.05	72.97
		Min	37.351	20.310	0.5	3.677	3.0	1.7	26.0	1.48	93.38
		Max	141.771	72.257	0.5	22.294	4.0	23.8	26.0	5.54	354.43

Note: Patients time-points vs. plasma ibuprofen concentrations information: Study report cpicl004.pdf pages 1129-1154 (Appendix 16.2.5.1 of the study report). It is noted that there were some placebo patients, e.g., #2003 ('non-critically ill' patient) and 2051 ('critically ill' patient), who had measurable ibuprofen concentrations at 200 – 400 ng/mL (see below); they were from (b) (4) clinical center.

Treatment	Site/In No.	Sample No.	Sampling Time (h)	Date Observed	Time Obtained	Plasma Ibuprofen Concentration (µg/mL)	Hemolysed?	Time Spun	Time Frozen	# Plasma Tubes 3 (mL)	Sample Drawn from:	Comments
Placebo	2003	1	0.0	(b) (4)	14:45	0.322		16:30	16:55	3	Separate IV Line	
Placebo	2003	2	0.5	(b) (4)	15:47	0.287		16:30	16:55	4	Separate IV Line	
Placebo	2003	3	1.0	(b) (4)	16:16	0.335		16:30	16:54	4	Separate IV Line	
Placebo	2003	4	2.0	(b) (4)	17:25	0.234		16:50	20:15	4	Separate IV Line	
Placebo	2003	5	3.0	(b) (4)	18:20	0.291		19:50	20:15	4	Separate IV Line	
Placebo	2003	6	4.0	(b) (4)	19:25	0.277		19:50	20:15	4	Separate IV Line	
Placebo	2003	7	20.0	(b) (4)	10:20	0.281		11:23	11:38	3	CTM IV Line	Peripherally inserted central catheter line double lumen CTM infused site
Placebo	2003	8	20.5	(b) (4)	11:00	0.297		11:23	11:30	3	CTM IV Line	Peripherally inserted central catheter line
Placebo	2003	9	22.0	(b) (4)	13:11	0.288		15:50	16:03	3	CTM IV Line	Peripherally inserted central catheter
Placebo	2003	10	24.0	(b) (4)	15:22	0.272		15:32	16:03	3	CTM IV Line	Peripherally inserted central catheter
Placebo	2003	11	26.0	(b) (4)	17:20	0.391		17:29	17:29	3	CTM IV Line	Peripherally inserted central catheter
Placebo	2007	1	0.0	(b) (4)	ND	NS		ND	ND	ND	ND	Sample not collected
Placebo	2007	2	0.5	(b) (4)	11:48	0.000		16:33	16:44	3	Separate IV Line	Central line right subclavian medial port dedicated
Placebo	2007	3	1.0	(b) (4)	12:10	0.000		15:33	15:44	3	Separate IV Line	Central line right subclavian medial port dedicated
Placebo	2007	4	2.0	(b) (4)	13:14	0.000		15:33	15:44	3	Separate IV Line	
Placebo	2007	5	3.0	(b) (4)	14:10	0.000		15:33	15:44	3	Separate IV Line	
Placebo	2007	6	4.0	(b) (4)	15:03	0.000		15:33	15:44	3	Separate IV Line	
Placebo	2007	7	20.0	(b) (4)	06:50	0.000		11:15	11:32	3	Separate IV Line	
Placebo	2007	8	20.5	(b) (4)	07:29	0.000		11:15	11:32	3	Separate IV Line	
Placebo	2007	9	22.0	(b) (4)	08:55	0.000		11:15	11:32	3	Separate IV Line	
Placebo	2007	10	24.0	(b) (4)	11:03	0.000		11:15	11:32	3	Separate IV Line	
Placebo	2007	11	26.0	(b) (4)	12:47	0.000		12:50	13:05	3	Separate IV Line	
Placebo	2051	1	0.0	(b) (4)	16:03	0.220		20:14	20:39	4	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	2	0.5	(b) (4)	18:41	0.389		20:14	20:39	3	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	3	1.0	(b) (4)	19:12	0.381		20:14	20:39	3	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	4	2.0	(b) (4)	20:06	0.318		20:14	20:39	4	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	5	3.0	(b) (4)	21:04	0.312		22:24	22:45	4	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	6	4.0	(b) (4)	22:06	0.296		22:24	22:45	4	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	7	20.0	(b) (4)	14:00	0.257		16:16	16:38	4	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	8	20.5	(b) (4)	14:40	0.249		16:16	16:38	3	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	9	22.0	(b) (4)	16:02	0.282		16:16	16:38	3	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	10	24.0	(b) (4)	18:00	0.246		20:00	20:12	3	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc
Placebo	2051	11	26.0	(b) (4)	19:52	0.236		20:00	20:12	3	Separate IV Line	Double lumen peripherally inserted central catheter flushed + wasted 5cc

Key: NS = No Sample

July-2006

Treatment	Rand'n No.	Centre	Randomization	AUC ₀₋₄ (µg.h/mL)	Cmax ₀₋₄ (µg/mL)	Tmax ₀₋₄ (h)	Cmin _{0:05:01} (µg/mL)	Tmin _{0:05:01} (h)	Cmin _{0:05:05} (µg/mL)	Tmin _{0:05:05} (h)	Thalf (h)
Placebo	2051	(b) (4)	Critically III	1.3	0.4	0.5	0.3	4.0	0.2	26.0	15.6
Placebo	3054	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	3055	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	4053	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	4057	(b) (4)	Critically III	3.1	0.9	4.0	0.7	0.0	NA	NA	NA
Placebo	4062	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	5051	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	5055	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	5061	(b) (4)	Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	6003	(b) (4)	Critically III	0.1	0.2	1.0	0.0	0.5	0.3	26.0	17.5
Placebo	2003	(b) (4)	Non-Critically III	1.2	0.3	1.0	0.3	4.0	0.3	24.0	UNK
Placebo	2007	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8005	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8003	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8009	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8009	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8016	(b) (4)	Non-Critically III	0.1	0.2	0.5	0.0	NA	0.0	NA	NA
Placebo	8020	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8022	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8026	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8032	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8034	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA
Placebo	8039	(b) (4)	Non-Critically III	0.0	0.0	NA	0.0	NA	0.0	NA	NA

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Appendix 16.1.7.1
Randomization Scheme

Run# No.	Treatment	Clinical Center	Stratum												
1001	400 mg IV/b	(b)	Non-Critically III	4067	Placebo	(b)	Critically III	5063	400 mg IV/b	(b)	Critically III	8023	400 mg IV/b	(b)	Non-Critically III
1002	200 mg IV/b	(4)	Non-Critically III	4068	400 mg IV/b	(4)	Critically III	5064	200 mg IV/b	(4)	Critically III	8024	100 mg IV/b	(4)	Non-Critically III
2001	100 mg IV/b	(b)	Non-Critically III	4069	200 mg IV/b	(b)	Critically III	6001	100 mg IV/b	(b)	Non-Critically III	8025	100 mg IV/b	(b)	Non-Critically III
2002	400 mg IV/b	(4)	Non-Critically III	4070	100 mg IV/b	(4)	Critically III	6002	200 mg IV/b	(4)	Non-Critically III	8026	Placebo	(4)	Non-Critically III
2003	Placebo	(b)	Non-Critically III	4071	400 mg IV/b	(b)	Critically III	6003	Placebo	(b)	Critically III	8027	200 mg IV/b	(b)	Non-Critically III
2005	100 mg IV/b	(4)	Non-Critically III	4072	100 mg IV/b	(4)	Critically III	6004	400 mg IV/b	(4)	Non-Critically III	8028	400 mg IV/b	(4)	Non-Critically III
2006	200 mg IV/b	(b)	Non-Critically III	4073	Placebo	(b)	Non-Critically III	6005	Placebo	(b)	Non-Critically III	8029	200 mg IV/b	(b)	Non-Critically III
2007	Placebo	(4)	Non-Critically III	4074	200 mg IV/b	(4)	Critically III	6006	200 mg IV/b	(4)	Non-Critically III	8030	400 mg IV/b	(4)	Non-Critically III
2051	Placebo	(b)	Critically III	4075	200 mg IV/b	(b)	Non-Critically III	6007	100 mg IV/b	(b)	Non-Critically III	8031	100 mg IV/b	(b)	Non-Critically III
3051	400 mg IV/b	(4)	Critically III	4076	100 mg IV/b	(4)	Critically III	6008	400 mg IV/b	(4)	Non-Critically III	8032	Placebo	(4)	Non-Critically III
3052	100 mg IV/b	(b)	Critically III	4077	400 mg IV/b	(b)	Critically III	6051	400 mg IV/b	(b)	Non-Critically III	8033	200 mg IV/b	(b)	Non-Critically III
3053	200 mg IV/b	(4)	Critically III	4078	Placebo	(4)	Critically III	8001	100 mg IV/b	(4)	Non-Critically III	8034	Placebo	(4)	Non-Critically III
3054	Placebo	(b)	Critically III	4079	400 mg IV/b	(b)	Critically III	8002	400 mg IV/b	(b)	Non-Critically III	8035	400 mg IV/b	(b)	Non-Critically III
3055	Placebo	(4)	Critically III	4080	100 mg IV/b	(4)	Critically III	8003	Placebo	(4)	Non-Critically III	8036	100 mg IV/b	(4)	Non-Critically III
3056	100 mg IV/b	(b)	Critically III	5001	400 mg IV/b	(b)	Non-Critically III	8004	200 mg IV/b	(b)	Non-Critically III	8037	400 mg IV/b	(b)	Non-Critically III
3058	400 mg IV/b	(4)	Critically III	5002	200 mg IV/b	(4)	Non-Critically III	8005	200 mg IV/b	(4)	Non-Critically III	8038	100 mg IV/b	(4)	Non-Critically III
3058	200 mg IV/b	(b)	Critically III	5003	100 mg IV/b	(b)	Non-Critically III	8006	400 mg IV/b	(b)	Non-Critically III	8039	Placebo	(b)	Non-Critically III
4051	400 mg IV/b	(4)	Critically III	5004	Placebo	(4)	Non-Critically III	8007	100 mg IV/b	(4)	Non-Critically III	8040	200 mg IV/b	(4)	Non-Critically III
4052	200 mg IV/b	(b)	Critically III	5005	100 mg IV/b	(b)	Non-Critically III	8008	Placebo	(b)	Non-Critically III	9001	100 mg IV/b	(b)	Non-Critically III
4053	Placebo	(4)	Critically III	5006	400 mg IV/b	(4)	Non-Critically III	8009	Placebo	(4)	Non-Critically III	9002	200 mg IV/b	(4)	Non-Critically III
4054	100 mg IV/b	(b)	Critically III	5007	200 mg IV/b	(b)	Non-Critically III	8010	200 mg IV/b	(b)	Non-Critically III	11051	100 mg IV/b	(b)	Critically III
4055	100 mg IV/b	(4)	Critically III	5051	Placebo	(4)	Critically III	8011	100 mg IV/b	(4)	Non-Critically III				
4056	400 mg IV/b	(b)	Critically III	5052	400 mg IV/b	(b)	Critically III	8012	400 mg IV/b	(b)	Non-Critically III				
4057	Placebo	(4)	Critically III	5053	100 mg IV/b	(4)	Critically III	8013	100 mg IV/b	(4)	Non-Critically III				
4058	200 mg IV/b	(b)	Critically III	5054	200 mg IV/b	(b)	Critically III	8014	200 mg IV/b	(b)	Non-Critically III				
4059	100 mg IV/b	(4)	Critically III	5055	Placebo	(4)	Critically III	8015	400 mg IV/b	(4)	Non-Critically III				
4060	400 mg IV/b	(b)	Critically III	5056	200 mg IV/b	(b)	Critically III	8016	Placebo	(b)	Non-Critically III				
4061	200 mg IV/b	(4)	Critically III	5057	400 mg IV/b	(4)	Critically III	8017	100 mg IV/b	(4)	Non-Critically III				
4062	Placebo	(b)	Critically III	5058	100 mg IV/b	(b)	Critically III	8018	400 mg IV/b	(b)	Non-Critically III				
4063	400 mg IV/b	(4)	Critically III	5059	100 mg IV/b	(4)	Critically III	8019	200 mg IV/b	(4)	Non-Critically III				
4064	200 mg IV/b	(b)	Non-Critically III	5060	400 mg IV/b	(b)	Critically III	8020	Placebo	(b)	Non-Critically III				
4065	100 mg IV/b	(4)	Critically III	5061	Placebo	(4)	Critically III	8021	200 mg IV/b	(4)	Non-Critically III				
4066	Placebo	(b)	Critically III	5062	200 mg IV/b	(b)	Critically III	8022	Placebo	(b)	Non-Critically III				

July-2006

Analytical Report for Study CPI-CL-004:

Protocol Number: CM1901

Analytical site: [REDACTED]

(b) (4)

4.2.3 Analytical Assay

4.2.3.1 ALM I-005/1 Method

Analytical Method, ALM I-005/1, Summary:

HPLC Operating Conditions	Mobile Phase Flow Rate	1.0 mL/min
	Run Time	21 + 5 minutes
	Injection Volume	15 + 5 µL
	UV-VIS Detector Wavelength	225 nm
Mobile Phase A = 78% Methanol in 10 mM Sodium Phosphate pH 2.6 Buffer		
Mobile Phase B = 60% Acetonitrile in 10 mM Sodium Phosphate pH 2.6 Buffer		

Prior to plasma sample analysis standard/calibration curves for ibuprofen and (b) (4) were produced by measuring the amount of ibuprofen and (b) (4) present in a series of dilutions of a solution containing a known amount of ibuprofen or (b) (4) respectively. Quality control samples of ibuprofen at low, medium, and high concentrations were also prepared and measured alongside plasma samples to monitor and maintain the quality of the method.

Assay performance information

Specificity	Ten blank plasma batches were assayed and all were found to pass the blank plasma criteria for interference at the retention times of ibuprofen and (b) (4). Stock solutions of lignocaine, caffeine, acetylsalicylic acid, paracetamol and nicotine were injected onto the HPLC system and showed no peaks that would interfere with ibuprofen or (b) (4).																																																																																																																													
Linearity	<p>The calibration curve was linear in the range studied, 0.200 Mg/mL to 250 Mg/mL. The mean coefficient of determination was 0.9955. The calculated concentrations using the 1/X² weighting more closely described the actual concentrations of Ibuprofen and therefore this weighting option was selected.</p> <table border="1" data-bbox="480 831 1243 1251"> <thead> <tr> <th rowspan="2">Analytical Run No.</th> <th colspan="8">CONCENTRATION (µg/mL)</th> </tr> <tr> <th>STD 1 (0.200)</th> <th>STD 2 (0.400)</th> <th>STD 3 (2.00)</th> <th>STD 4 (5.00)</th> <th>STD 5 (10.0)</th> <th>STD 6 (50.0)</th> <th>STD 7 (125)</th> <th>STD 8 (250)</th> </tr> </thead> <tbody> <tr> <td>VAL-1</td> <td>a</td> <td>0.400</td> <td>1.989</td> <td>5.149</td> <td>9.956</td> <td>50.798</td> <td>125.362</td> <td>240.662</td> </tr> <tr> <td>VAL-2</td> <td>0.205</td> <td>0.376</td> <td>2.062</td> <td>5.125</td> <td>10.112</td> <td>50.327</td> <td>125.976</td> <td>238.243</td> </tr> <tr> <td>VAL-3</td> <td>0.195</td> <td>0.416</td> <td>2.127</td> <td>4.788</td> <td>10.120</td> <td>50.360</td> <td>125.758</td> <td>234.510</td> </tr> <tr> <td>VAL-4</td> <td>0.201</td> <td>0.396</td> <td>1.968</td> <td>5.175</td> <td>10.381</td> <td>51.223</td> <td>124.729</td> <td>231.573</td> </tr> <tr> <td>VAL-5</td> <td>0.199</td> <td>0.403</td> <td>1.990</td> <td>5.114</td> <td>10.258</td> <td>51.553</td> <td>125.441</td> <td>229.938</td> </tr> <tr> <td>VAL-6</td> <td>0.196</td> <td>0.415</td> <td>2.064</td> <td>5.070</td> <td>10.098</td> <td>51.109</td> <td>123.739</td> <td>229.483</td> </tr> <tr> <td>VAL-7</td> <td>0.195</td> <td>0.424</td> <td>1.929</td> <td>4.808</td> <td>9.996</td> <td>49.426</td> <td>129.065</td> <td>254.398</td> </tr> <tr> <td>VAL-8</td> <td>0.197</td> <td>0.411</td> <td>2.032</td> <td>4.971</td> <td>9.969</td> <td>50.729</td> <td>126.165</td> <td>239.088</td> </tr> <tr> <td>Mean</td> <td>0.198</td> <td>0.405</td> <td>2.020</td> <td>5.025</td> <td>10.111</td> <td>50.691</td> <td>125.779</td> <td>237.237</td> </tr> <tr> <td>SD</td> <td>0.004</td> <td>0.015</td> <td>0.063</td> <td>0.153</td> <td>0.147</td> <td>0.661</td> <td>1.537</td> <td>8.138</td> </tr> <tr> <td>% Nominal</td> <td>99.0</td> <td>101.3</td> <td>101.0</td> <td>100.5</td> <td>101.1</td> <td>101.4</td> <td>100.6</td> <td>94.9</td> </tr> <tr> <td>CV</td> <td>2.0</td> <td>3.7</td> <td>3.1</td> <td>3.0</td> <td>1.5</td> <td>1.3</td> <td>1.2</td> <td>3.4</td> </tr> </tbody> </table> <p>a – below an elevated LOQ</p>	Analytical Run No.	CONCENTRATION (µg/mL)								STD 1 (0.200)	STD 2 (0.400)	STD 3 (2.00)	STD 4 (5.00)	STD 5 (10.0)	STD 6 (50.0)	STD 7 (125)	STD 8 (250)	VAL-1	a	0.400	1.989	5.149	9.956	50.798	125.362	240.662	VAL-2	0.205	0.376	2.062	5.125	10.112	50.327	125.976	238.243	VAL-3	0.195	0.416	2.127	4.788	10.120	50.360	125.758	234.510	VAL-4	0.201	0.396	1.968	5.175	10.381	51.223	124.729	231.573	VAL-5	0.199	0.403	1.990	5.114	10.258	51.553	125.441	229.938	VAL-6	0.196	0.415	2.064	5.070	10.098	51.109	123.739	229.483	VAL-7	0.195	0.424	1.929	4.808	9.996	49.426	129.065	254.398	VAL-8	0.197	0.411	2.032	4.971	9.969	50.729	126.165	239.088	Mean	0.198	0.405	2.020	5.025	10.111	50.691	125.779	237.237	SD	0.004	0.015	0.063	0.153	0.147	0.661	1.537	8.138	% Nominal	99.0	101.3	101.0	100.5	101.1	101.4	100.6	94.9	CV	2.0	3.7	3.1	3.0	1.5	1.3	1.2	3.4
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Sensitivity	<p>The limit of quantification was determined to be acceptable at 0.200 Mg/mL after evaluation of the intra-run data and inter-run data compiled from seven runs.</p> <table border="1" data-bbox="472 1402 1149 1507"> <thead> <tr> <th></th> <th>Intra-run</th> <th>Inter-run (n=7)</th> </tr> </thead> <tbody> <tr> <td>% Nominal</td> <td>101.5</td> <td>99.0</td> </tr> <tr> <td>CV</td> <td>4.4</td> <td>9.1</td> </tr> </tbody> </table> <p>Intra-run:</p>		Intra-run	Inter-run (n=7)	% Nominal	101.5	99.0	CV	4.4	9.1																																																																																																																				
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Replicate Number	QCLOQ (0.200 µg/mL)	
	Conc.	% Diff
1	0.199	-0.5
2	0.195	-2.5
3	0.211	5.5
4	0.198	-1.0
5	0.217	8.5
6	0.196	-2.0
Mean	0.203	
SD	0.009	
% Nominal	101.5	
CV	4.4	

Limits: % Nominal between 80% and 120% of the actual concentration
CV ≤ 20%

Inter-run:

Analytical Run No.	QCLOQ (0.200 µg/mL)	
	Conc.	% Diff
VAL-2	0.185	-7.5
	0.180	-10.0
	0.179	-10.5
VAL-3	0.188	-6.0
	0.199	-0.5
VAL-4	0.194	-3.0
	0.202	1.0
VAL-5	0.225	12.5
	0.213	6.5
VAL-6	0.199	-0.5
	0.195	-2.5
VAL-7	0.211	5.5
	0.198	-1.0
VAL-8	0.238	19.0
	0.191	-4.5
VAL-9	0.210	5.0
	0.227	13.5
VAL-10	0.197	-1.5
	0.174	-13.0
VAL-11	a	-
	0.164	-18.0
Mean	0.198	
SD	0.018	
% Nominal	99.0	
CV	9.1	

a – sample lost in processing

Limits: % Nominal between 80% and 120% of the actual concentration
CV ≤ 20%

Accuracy & Precision

Intra-run

	QCL (0.600) Mg/mL)	QCM (20.0) Mg/mL)	QCH (200) Mg/mL)
% Nominal	100.0	98.3	97.9
CV	6.8	2.6	1.0

Analytical Run No: VAL-1

Replicate No.	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Conc.	% Diff	Conc.	% Diff	Conc.	% Diff
1	0.609	1.5	19.798	-1.0	192.656	-3.7
2	0.589	-1.8	19.956	-0.2	196.095	-2.0
3	0.671	11.8	20.432	2.2	198.839	-0.6
4	0.557	-7.2	19.032	-4.8	195.146	-2.4
5	0.609	1.5	19.248	-3.8	196.689	-1.7
6	0.566	-5.7	19.546	-2.3	195.792	-2.1
Mean	0.600		19.669		195.869	
SD	0.041		0.506		2.020	
% Nominal	100.0		98.3		97.9	
CV	6.8		2.6		1.0	

Limits: % Nominal between 85% and 115% of the actual concentration
CV ≤ 15%

Inter-run

	QCL (0.600) Mg/mL	QCM (20.0) Mg/mL	QCH (200) Mg/mL
% Nominal	102.0	98.7	98.2
CV	4.9	3.8	2.1

Analytical Run No.	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Conc.	% Diff	Conc.	% Diff	Conc.	% Diff
VAL-1	0.609	1.5	19.798	-1.0	192.656	-3.7
	0.589	-1.8	19.956	-0.2	196.095	-2.0
	0.671	11.8	20.432	2.2	198.839	-0.6
VAL-2	0.618	3.0	20.236	1.2	202.017	1.0
	0.604	0.7	21.016	5.1	196.815	-1.6
	0.583	-2.8	20.086	0.4	200.191	0.1
VAL-3	0.609	1.5	18.352	-8.2	196.765	-1.6
	0.609	1.5	19.645	-1.8	195.964	-2.0
	0.575	-4.2	18.928	-5.4	198.582	-0.7
VAL-4	0.638	6.3	20.744	3.7	203.230	1.6
	0.636	6.0	21.277	6.4	199.950	0.0
	0.655	9.2	20.297	1.5	196.087	-2.0
VAL-5	0.642	7.0	18.962	-5.2	193.163	-3.4
	0.580	-3.3	19.361	-3.2	197.380	-1.3
	0.586	-2.3	19.384	-3.1	189.481	-5.3
VAL-6	0.594	-1.0	20.318	1.6	195.062	-2.5
	0.611	1.8	19.815	-0.9	195.270	-2.4
	0.653	8.8	20.243	1.2	194.410	-2.8
VAL-7	0.570	-5.0	19.374	-3.1	196.040	-2.0
	0.621	3.5	18.376	-8.1	195.196	-2.4
	0.618	3.0	19.545	-2.3	193.184	-3.4
VAL-8	0.597	-0.5	19.245	-3.8	187.842	-6.1
	0.556	-7.3	19.182	-4.1	194.160	-2.9
	0.655	9.2	19.352	-3.2	205.820	2.9
Mean	0.612		19.747		196.425	
SD	0.030		0.752		4.042	
% Nominal	102.0		98.7		98.2	
CV	4.9		3.8		2.1	

Limits: % Nominal between 85% and 115% of the actual concentration
CV ≤ 15%

Recovery

The values for recovery of ibuprofen at the low, medium and high levels were 87%, 88% and 93% respectively. The overall recovery was 89%. The CVs for the low, medium and high levels were 6.7%, 6.4% and 5.5% respectively.

Replicate No.	Peak height Unextracted	Peak height Extracted	Dilution Factor	Recovery (%)
QCL				
1	742	617	1.000	79.92
2	750	698	1.000	90.41
3	743	678	1.000	87.82
4	807	726	1.000	94.04
5	801	616	1.000	79.79
6	790	687	1.000	88.99
Mean	772	670		86.83
SD	30	45		5.8
CV	3.9	6.7		6.7
QCM				
1	24450	24221	1.000	95.81
2	24523	20461	1.000	80.93
3	24507	22029	1.000	87.14
4	26009	21915	1.000	86.69
5	26078	21405	1.000	84.67
6	26120	23689	1.000	93.70
Mean	25281	22287		88.16
SD	864	1418		5.6
CV	3.4	6.4		6.4
QCH				
1	235117	222685	1.000	92.04
2	235489	217375	1.000	89.84
3	235300	247280	1.000	102.21
4	248312	226522	1.000	93.63
5	248742	222882	1.000	92.12
6	248709	210562	1.000	87.03
Mean	241945	224551		92.81
SD	7279	12441		5.1
CV	3.0	5.5		5.5
OVERALL RECOVERY (%)				89.27

$$\text{Recovery \%} = \frac{\text{Peak Height Extracted}}{\text{Mean Peak Height Unextracted}} \times \frac{\text{Dilution Factor}}{1} \times \frac{100}{1}$$

Stability

Stock Solutions: The fresh spiked working solution of ibuprofen was found to be stable for 28 days when stored at 4°C.

Storage DAYS	QCL (0.600 µg/mL)			QCM (20.0 µg/mL)			QCH (200 µg/mL)		
	PHR Fresh	PHR Stored	% Diff PHR	PHR Fresh	PHR Stored	% Diff PHR	PHR Fresh	PHR Stored	% Diff PHR
	28	0.0092	0.0092		0.3004	0.3067		2.9353	2.9347
	0.0092	0.0091		0.3008	0.3064		2.9375	2.9356	
	0.0092	0.0091		0.3008	0.3064		2.9384	2.9346	
	0.0092	0.0092		0.3008	0.3067		2.9371	2.9364	
	0.0092	0.0092		0.3009	0.3066		2.9398	2.9375	
	0.0092	0.0092		0.3009	0.3068		2.9360	2.9374	
Mean	0.0092	0.0092	-1%	0.3008	0.3068	2%	2.9373	2.9360	0%

$$\% \text{ Diff PHR} = \frac{\text{Mean PHR Stored} - \text{Mean PHR Fresh}}{\text{Mean PHR Fresh}} \times \frac{100}{1}$$

Limit: % Difference of mean peak height ratio of Stored Vs Fresh ≤5%

Ibuprofen in Plasma: Ibuprofen was shown to be stable in plasma for 5 days when stored in 5 mL polypropylene tubes at -20±10°C.

Storage DAYS	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability
5	0.570		19.374		196.040	
	0.621		18.376		195.196	
	0.618		19.545		193.184	
Mean	0.603	0.5	19.098	-4.5	194.807	-2.6

$$\% \text{ Diff Stability} = \frac{\text{Mean Measured Conc (Day X)} - \text{Actual Conc}}{\text{Actual Conc}} \times \frac{100}{1}$$

Limit: % difference at each time point for QCL, QCM, QCH ≤20%

Ibuprofen in Plasma after Freeze/Thaw Cycles: Ibuprofen was shown to be stable in plasma after three freeze/thaw cycles.

Freeze/Thaw Cycle	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff	Measured Conc.	% Diff	Measured Conc.	% Diff
1	0.570		19.374		196.040	
	0.621		18.376		195.196	
	0.618		19.545		193.184	
Mean	0.603	0.5	19.098	-4.5	194.807	-2.6
2	0.581		19.576		194.521	
	0.595		18.893		193.484	
	0.608		19.382		195.314	
Mean	0.595	-0.8	19.284	-3.6	194.440	-2.8
3	0.584		18.755		197.563	
	0.597		19.094		190.821	
	0.609		19.622		200.943	
Mean	0.597	-0.5	19.157	-4.2	196.376	-1.8

$$\% \text{ Diff} = \frac{\text{Mean Measured Conc (F/T Cycle X)} - \text{Actual Conc}}{\text{Actual Conc}} \times \frac{100}{1}$$

Limit: % Diff of the mean measured concentration ≤20% of the actual concentration.

Ibuprofen in Plasma on Bench-Top: Ibuprofen was shown to be stable in plasma for up to 24 hours when kept on the bench at room temperature.

On Bench (Hours)	QCL (0.603 µg/mL)*		QCM (19.236 µg/mL)*		QCH (193.341 µg/mL)*	
	Measured Conc.	% Diff	Measured Conc.	% Diff	Measured Conc.	% Diff
0	0.642		18.962		193.163	
	0.580		19.361		197.380	
	0.586		19.384		189.481	
Mean	0.603	0.0	19.236	0.0	193.341	0.0
4	0.618		20.293		192.133	
	0.600		20.369		194.755	
	0.605		19.627		192.693	
Mean	0.608	0.8	20.096	4.5	193.194	-0.1
24	0.591		19.418		192.856	
	0.576		19.765		201.733	
	0.601		20.087		189.510	
Mean	0.589	-2.3	19.757	2.7	194.700	0.7

* NOTE – Concentrations are the mean measured concentration at Time 0

$$\% \text{ Diff Benchtop Plasma Stability} = \frac{\text{Mean Measured Conc (x hour)} - \text{Mean Measured Conc (0 hour)}}{\text{Mean Measured Conc (0 hour)}} \times \frac{100}{1}$$

Limit: % Diff of the mean measured conc. ≤20% of mean measured conc. at time 0.

Ibuprofen in Final Extract: Ibuprofen and the internal standard (b) (4) were shown to be stable in the final extract for 5 days when stored at room temperature and at 4°C.

Room temperature:

Time Extract Stored (Days)	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff	Measured Conc.	% Diff	Measured Conc.	% Diff
3	0.575		18.462		182.539	
	0.552		18.248		185.257	
	0.568		17.944		186.880	
Mean	0.565	-5.8	18.225	-8.9	184.892	-7.6
5	0.580		20.108		190.170	
	0.601		19.044		192.849	
	0.592		20.075		197.017	
Mean	0.591	-1.5	19.742	-1.3	193.345	-3.3

$$\% \text{ Diff Extract Stability} = \frac{\text{Mean Measured Conc (Time X)} - \text{Actual Conc}}{\text{Actual Conc}} \times \frac{100}{1}$$

Limit: % difference at each time point for QCL, QCM, QCH ≤20%

4°C:

Time Extract Stored (Days)	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff	Measured Conc.	% Diff	Measured Conc.	% Diff
3	0.707		17.801		183.047	
	0.572		18.216		187.254	
	0.567		18.057		187.816	
Mean	0.615	2.5	18.025	-9.9	186.039	-7.0
5	0.623		18.997		191.811	
	0.583		18.655		199.940	
	0.575		19.598		196.821	
Mean	0.594	-1.0	19.083	-4.6	196.191	-1.9

$$\% \text{ Diff Extract Stability} = \frac{\text{Mean Measured Conc (Time X)} - \text{Actual Conc}}{\text{Actual Conc}} \times \frac{100}{1}$$

Limit: % difference at each time point for QCL, QCM, QCH ≤20%

Fresh Spiked QC data: Data was acceptable from supporting fresh spike QC samples analyzed along with the long term plasma stability, freeze/thaw and the benchtop runs.

Fresh Spiked QC data:

Analytical Run No.	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Conc.	% Diff	Conc.	% Diff	Conc.	% Diff
VAL-5	0.603	0.5	20.087	0.4	189.395	-5.3
	0.599	-0.2	21.283	6.4	194.722	-2.6
	0.588	-2.0	20.661	3.3	192.000	-4.0
VAL-7	0.617	2.8	19.166	-4.2	198.161	-0.9
	0.606	1.0	20.412	2.1	200.432	0.2
	0.621	3.5	18.874	-5.6	201.081	0.5
Mean	0.606		20.081		195.965	
SD	0.012		0.915		4.720	
% Nominal	101.0		100.4		98.0	
CV	2.0		4.6		2.4	

Limits: % Nominal between 85% and 115% of the actual concentration
CV ≤ 15%

Addendum 1: Study Report C114/01 - Validation Report for ALM I-005/1

Stock solution stability and long term plasma stability was tested for ALM I-005/1 method and reported in this addendum. Results from the stock solution stability and long term plasma stability were acceptable.

Stability of Ibuprofen Working Solution:

Storage DAYS	QCL (0.600 µg/mL)			QCM (20.0 µg/mL)			QCH (200 µg/mL)		
	PHR Fresh	PHR Stored	% Diff PHR	PHR Fresh	PHR Stored	% Diff PHR	PHR Fresh	PHR Stored	% Diff PHR
52	0.0091	0.0089		0.2940	0.3004		2.8249	2.9059	
	0.0091	0.0089		0.2948	0.3001		2.8243	2.9071	
	0.0091	0.0090		0.2948	0.3002		2.8277	2.9093	
	0.0091	0.0089		0.2947	0.3004		2.8305	2.9112	
	0.0091	0.0090		0.2948	0.2995		2.8331	2.9557	
	0.0091	0.0090		0.2938	0.3008		2.8292	2.9067	
Mean	0.0091	0.0089	-2%	0.2945	0.3002	2%	2.8283	2.9160	3%

$$\% \text{ Diff PHR} = \frac{\text{Mean PHR Stored} - \text{Mean PHR Fresh}}{\text{Mean PHR Fresh}} \times 100$$

Limit: % Difference of mean peak height ratio of Stored vs Fresh ≤ 5%

Stability of Internal Standard (b) (4) Working Solution:

Storage	IS (500 µg/mL)		
	PHR Fresh	PHR Stored	% Diff PHR
50	3.3477	3.3697	
	3.3487	3.3372	
	3.3502	3.3626	
	3.3490	3.3728	
	3.3289	3.3683	
	3.3226	3.3051	
Mean	3.3412	3.3526	0%

$$\% \text{ Diff PHR} = \frac{\text{Mean PHR Stored} - \text{Mean PHR Fresh}}{\text{Mean PHR Fresh}} \times \frac{100}{1}$$

Limit: % Difference of mean peak height ratio of Stored Vs Fresh ≤5%

Stability of Ibuprofen in Plasma stored at -20 ± 10°C:

Storage	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability
54	0.589		19.738		191.274	
	0.585		19.561		191.500	
	0.593		19.498		190.211	
Mean	0.589	-1.8	19.599	-2.0	190.995	-4.5

$$\% \text{ Diff Stability} = \frac{\text{Mean Measured Conc (Day X)} - \text{Actual Conc}}{\text{Actual Conc}} \times \frac{100}{1}$$

Limit: % difference at each time point for QCL, QCM, QCH ≤20%

Supporting Fresh Spiked QC Data:

Analytical Run No.	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Conc.	% Diff	Conc.	% Diff	Conc.	% Diff
VAL-10	0.618	3.0	21.063	5.3	199.971	0.0
	0.612	2.0	20.249	1.2	194.782	-2.6
	0.609	1.5	19.823	-0.9	187.798	-6.1
Mean	0.613		20.378		194.184	
SD	0.005		0.630		6.109	
% Nominal	102.2		101.9		97.1	
CV	0.8		3.1		3.1	

Limits: % Nominal between 85% and 115% of the actual concentration,
CV ≤ 15%

Addendum 2: Study Report C208/03 - Validation Report for ALM I-005/1

Long term plasma stability was tested and is reported in this addendum for ALM I-005/1 method.

Ibuprofen was shown to be stable in plasma in all three QC samples, low, medium and high ibuprofen concentrations, for 505 days when stored in 5 mL polypropylene tubes – 20 ± 10°C.

Table 3: Linearity - Summary of Calibration Curve Sample Concentrations

Analytical Run No.	CONCENTRATION (µg/mL)							
	STD 1 (0.201)	STD 2 (0.401)	STD 3 (2.01)	STD 4 (5.02)	STD 5 (10.0)	STD 6 (50.2)	STD 7 (125)	STD 8 (251)
PT-1		0.397	2.09	4.99	10.3	50.8	123	238
% Nominal		99.0	104.0	99.4	103.0	101.2	98.4	94.8

*STD 1 omitted due to aberrant response factor.

Table 4: Long Term Stability of Ibuprofen in Plasma stored at -20±10°C
Analytical Run No: CM1901 AR#PT-1

	QCL (0.601 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability
QC FRESH SPIKED	0.582		20.502		195.264	
	0.618		19.355		192.826	
	0.643		19.348		192.357	
Mean	0.614	2.2	19.7	-1.3	193	-3.3
Storage DAYS	QCL (0.600 µg/mL)		QCM (20.0 µg/mL)		QCH (200 µg/mL)	
	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability
505	0.645		20.476		196.753	
	0.630		20.263		199.307	
	0.604		20.398		190.892	
Mean	0.626	4.3	20.4	1.9	196	-2.2

$$\% \text{ Diff Stability} = \frac{\text{Mean Measured Conc (Day X)} - \text{Actual Conc}}{\text{Actual Conc}} \times 100$$

Limit: % difference at each time point for QCL, QCM, QCH ≤15%

4.2.3.2 ALM I-005/2 Method

Specificity:

Representative chromatograms of extracted blank plasma, extracted blank plasma spiked with Internal Standard, lowest and highest extracted standards, extracted pre-dose subject sample showed that the analytical method was specific for ibuprofen measurement.

Linear Range:

The response of the assay was linear over the nominal concentration range of 0.200 µg/mL to 50.0 µg/mL during the analysis of study samples. The range of results for the

accuracy of the Ibuprofen standards was 98 to 101% and the precision was 0.9 to 4.0% (below table).

Concentration (µg/mL) Batch # 01								
Analytical Run #	STD 1 (0.202)	STD 2 (0.403)	STD 3 (2.01)	STD 4 (5.04)	STD 5 (10.1)	STD 6 (20.2)	STD 7 (40.3)	STD 8 (80.4)
AR#17	0.203	a	1.955	4.869	10.412	19.943	41.290	51.374
AR#18	0.210	0.373	1.958	4.879	11.066	19.879	41.042	50.331
AR#19	0.201	0.409	2.003	4.899	10.227	20.747	41.159	50.807
AR#20	0.197	0.421	2.009	5.088	10.440	19.860	39.032	49.816
AR#21	0.201	0.405	2.024	5.103	9.829	20.357	40.491	50.282
AR#22	0.204	0.400	1.945	4.944	10.205	20.394	41.868	50.282
AR#23	0.198	0.420	2.000	4.997	10.173	20.311	39.810	50.209
AR#24	0.201	0.407	2.035	4.877	9.891	20.554	41.308	50.232
AR#25	0.203	0.398	2.012	5.230	9.885	19.742	41.110	50.237
AR#26	0.199	0.411	2.100	4.964	9.988	a	39.488	a
AR#27	0.201	0.407	2.084	4.906	9.697	a	41.019	51.059
AR#28	0.203	0.399	2.016	4.832	10.432	a	40.806	50.469
MEAN	0.202	0.405	2.01	4.95	10.2	20.2	40.7	50.4
SD	0.003	0.013	0.047	0.141	0.374	0.352	0.841	0.494
% NOMINAL	100	101	100	98	101	100	101	100
% CV	2	3	2	3	4	2	2	1

Concentration (µg/mL) Batch # 03								
Analytical Run #	STD 1 (0.201)	STD 2 (0.402)	STD 3 (2.01)	STD 4 (5.02)	STD 5 (10.0)	STD 6 (20.1)	STD 7 (40.2)	STD 8 (80.2)
AR#29	0.201	b	2.000	4.834	9.950	20.288	41.101	50.843
AR#30	0.205	0.387	1.976	4.963	10.055	19.752	41.716	51.178
AR#31	0.200	0.403	2.083	4.962	9.764	c	40.137	50.073
AR#33	0.198	0.416	1.939	5.168	9.856	20.471	40.326	49.151
AR#34	0.204	0.389	1.990	5.303	10.197	19.673	39.363	49.860
AR#35	0.198	0.413	2.030	5.097	10.037	19.761	39.464	49.879
AR#36	0.205	0.389	2.000	4.833	10.112	20.698	41.435	49.478
AR#37	0.194	0.432	1.930	5.010	9.860	20.633	39.900	49.845
AR#38	0.202	0.398	1.919	5.207	10.149	20.908	39.242	49.145
MEAN	0.201	0.403	1.99	5.04	10.0	20.3	40.3	49.9
SD	0.004	0.016	0.052	0.163	0.149	0.485	0.919	0.694
% NOMINAL	100	100	99	100	100	101	100	99
% CV	2	4	3	3	2	2	2	1

a - omitted due to aberrant response factor
c - omitted due to processing error

b - omitted due to poor chromatography

Sensitivity:

The limit of quantification was defined as the lowest calibrator in the standard curve (nominal concentration 0.200 µg/mL). The percentage of the mean measured concentration to the nominal concentration of the LOQ was 100% with a CV of 2% (above table).

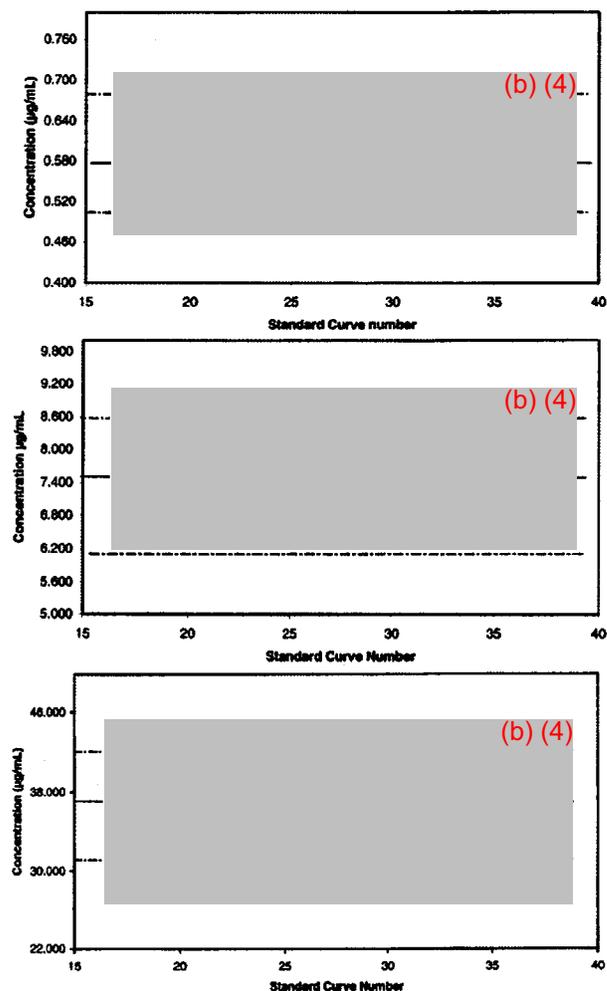
Inter-run Accuracy and Precision:

The results of the analysis of ac samples from the 21 accepted analytical runs were:

	QCL (0.599 µg/mL)	QCM (7.49 µg/mL)	QCH (37.4 µg/mL)
MEAN	0.591	7.37	37.0
SD	0.019	0.425	0.922
% NOMINAL	99	98	99
CV (%)	3	6	3

Stability:

Stability of the QC samples for the duration of the study was demonstrated as shown by the Quality Control Scatter Plots (Figures 7 to 9). The solid lines in the scatter plots represent the nominal concentrations of the QCs and the dotted lines represent the limits at $\pm 15\%$ of the nominal concentration.



The sample storage time from the first date of dosing to the last date of sample analysis was 1178 days (24th Sep 2002 to 15th Dec 2005). Plasma stability at -20°C has been reported in Addendum 3 (Technical Report Number C346/05) to the Technical Report C098/01, Validation Report for ALM 1-005/2 (Refer to Appendix II) as 1022 days.

Addendum Study Report C346/05 - Validation Report for ALM I-005/2

(Note: this section is labeled as Addendum 3 in the validation report ALM I-005/1)

The original assay method, when applied to subject samples, was found to give undesirable internal standard response variability and was therefore re-developed and re-issued as ALM I-005/2. The current validation was performed to validate the changes made to ALM I-005/1 including the addition of a (b) (4),

(b) (4) to the HPLC and lowering of the upper LOQ to a more appropriate level. The typical results from the ALM I-005/2 method is presented below:

Standard curve linearity:

Table 3: Linearity - Summary of Calibration Curve Sample Concentrations - Analytical Run No. 1

Analytical Run No.	CONCENTRATION (µg/mL)							
	STD 1 (0.202)	STD 2 (0.403)	STD 3 (2.02)	STD 4 (5.04)	STD 5 (10.1)	STD 6 (20.2)	STD 7 (40.3)	STD 8 (50.4)
1	0.202	*	2.015	4.949	10.162	20.231	40.795	*
% Nominal	100	-	100	98	101	100	101	-

*STD 2 and 8 omitted due to processing error

Table 4: Linearity - Summary of Calibration Curve Sample Concentrations - Analytical Run No. 2

Analytical Run No.	CONCENTRATION (µg/mL)							
	STD 1 (0.201)	STD 2 (0.402)	STD 3 (2.01)	STD 4 (5.02)	STD 5 (10.0)	STD 6 (20.1)	STD 7 (40.2)	STD 8 (50.2)
2	0.202	0.398	1.919	5.207	10.149	20.908	39.242	49.145
% Nominal	100	99	95	104	101	104	98	98

Accuracy and precision – intra run:

Replicate No.	QCL (0.599 µg/mL)		QCM (7.49 µg/mL)		QCH (37.4 µg/mL)	
	Conc.	% Diff	Conc.	% Diff	Conc.	% Diff
1	0.600	0.2	a	-	a	-
2	0.598	-0.2	7.444	-0.6	39.721	6.2
3	a	-	7.402	-1.2	a	-
4	0.575	-4.0	a	-	37.455	0.1
5	0.591	-1.3	7.384	-1.4	37.304	-0.3
6	a	-	7.512	0.3	37.770	1.0
Mean	0.591		7.44		38.1	
SD	0.011		0.057		1.123	
CV	2		1		3	
% Nominal	99		99		102	

a = omitted due to sample processing error

Limits: % Nominal between 85% and 115% of the actual concentration
CV ≤ 15%

Limit of quantitation:

Replicate Number	QCLOQ (0.200 µg/mL)	
	Conc.	% Diff
1	0.205	2.5
2	0.197	-1.5
3	0.198	-1.0
4	0.199	-0.5
5	0.201	0.5
6	a	-
Mean	0.200	
SD	0.003	
% Nominal	100	
CV	2	

a = omitted due to sample processing error

Limits: % Nominal between 80% and 120% of the actual concentration
CV ≤ 20%

Long-term stability of ibuprofen in plasma stored at $-20 \pm 10^\circ \text{C}$:

Storage DAYS	QCL (0.599 µg/mL)		QCM (7.49 µg/mL)		QCH (37.4 µg/mL)	
	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability
92	0.564		7.062		34.776	
	0.617		7.045		36.972	
	0.563		6.946		34.226	
Mean	0.581	-3.0	7.018	-6.3	36.325	-5.5
Storage DAYS	QCL (0.602 µg/mL)		QCM (20.1 µg/mL)		QCH (201 µg/mL)	
	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability	Measured Conc.	% Diff Stability
1022	0.639		18.347		a	
	0.683		19.860		a	
	0.670		19.110		a	
Mean	0.684	10.3	19.108	-4.9	-	-

a = omitted, over calibration curve range

Limit: % difference at each time point for QCL, QCM, QCH ≤ 15%

4.3 Consult Review (including Pharmacometric Reviews) - Not applicable

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form General Information About the Submission

	Information		Information	
NDA Number	22-349	Brand Name	TBD	
OCPB Division (I, II, III)	II	Generic Name	Intravenous ibuprofen	
Medical Division	HFD-170	Drug Class	NSAIDs	
OCPB Reviewer	David Lee	Indication(s)	Fever/Pain	
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Solution	
		Dosing Regimen	Single dose	
Date of Submission	12/3/08	Route of Administration	Intravenous	
Estimated Due Date of OCPB Review	-	Sponsor	Cumberland	
Medical Division Due Date		Priority Classification	3P	
PDUFA Due Date	6/11/09			
Clin. Pharm. and Biopharm. Information				
	"X" included if filing at	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	x			
Isozyme characterization:	x			
Blood/plasma ratio:	x			
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				Deferral
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 1:				
Phase 2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		

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this page is the manifestation of the electronic signature.**

/s/

David Lee
5/4/2009 04:15:37 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
5/11/2009 07:53:57 AM
BIOPHARMACEUTICS