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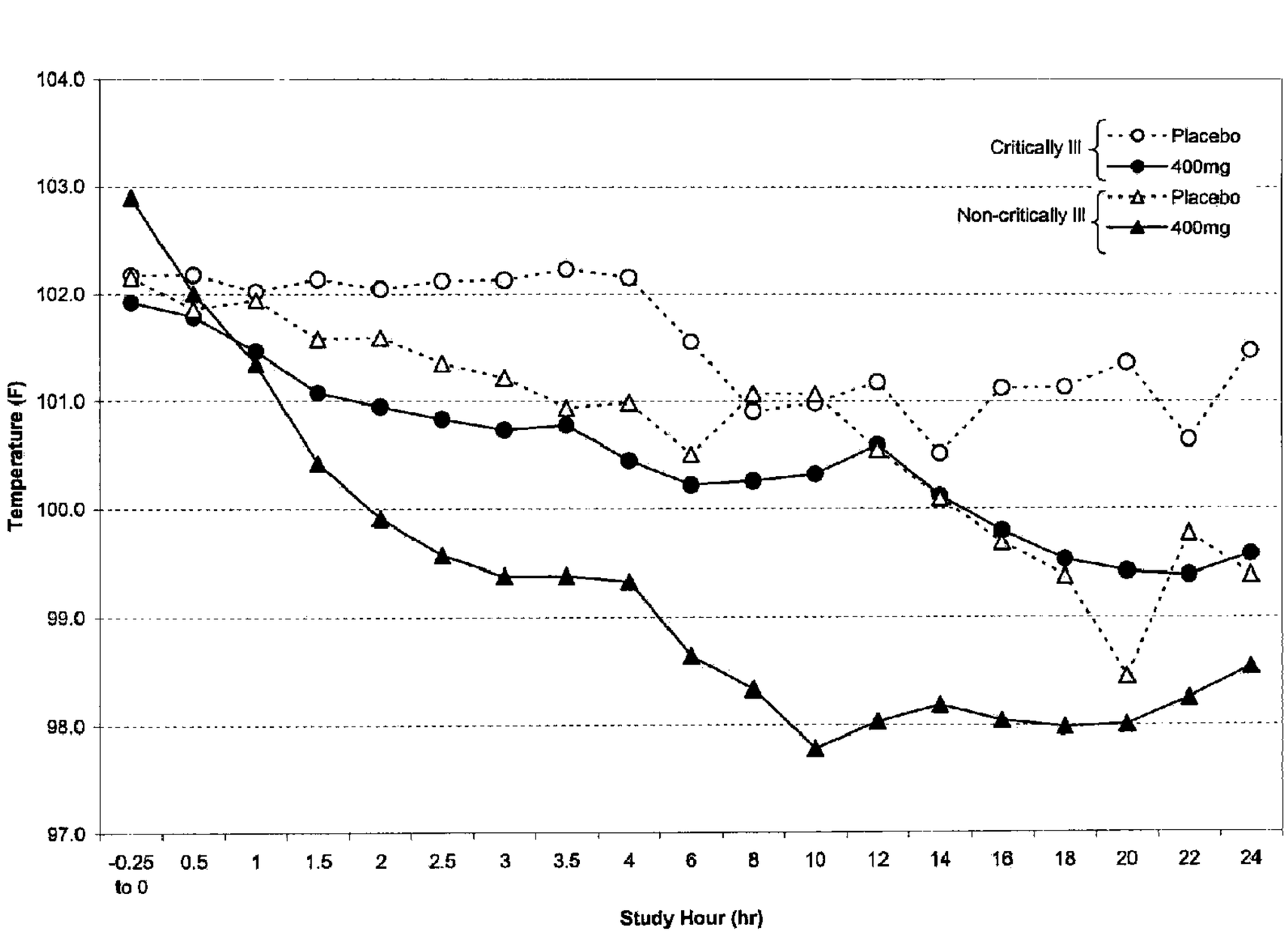
(54) Titre : TRAITEMENT DE PATIENTS GRAVEMENT ATTEINTS FAISANT APPEL A DE L'IBUPROFENE PAR VOIE INTRAVEINEUSE

(54) Title: TREATING CRITICALLY ILL PATIENTS WITH INTRAVENOUS IBUPROFEN

Figure 4



(57) Abrégé/Abstract:
Methods of treating at least one condition chosen from pain, inflammation, and fever in a critically ill patient in need thereof, comprising administering to the critically ill patient an intravenous pharmaceutical composition comprising ibuprofen using a first

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(13) A1

(57) Abrégé(suite)/Abstract(continued):
dosage regimen, wherein the first dosage regimen produces a first pharmacokinetic profile in critically ill patients that is about equivalent to a second pharmacokinetic profile produced by administration of the intravenous pharmaceutical composition using a second dosage regimen of ibuprofen to non-critically ill patients, wherein the at least one condition of the critically ill patient is thereby treated.

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Declarations under Rule 4.17:

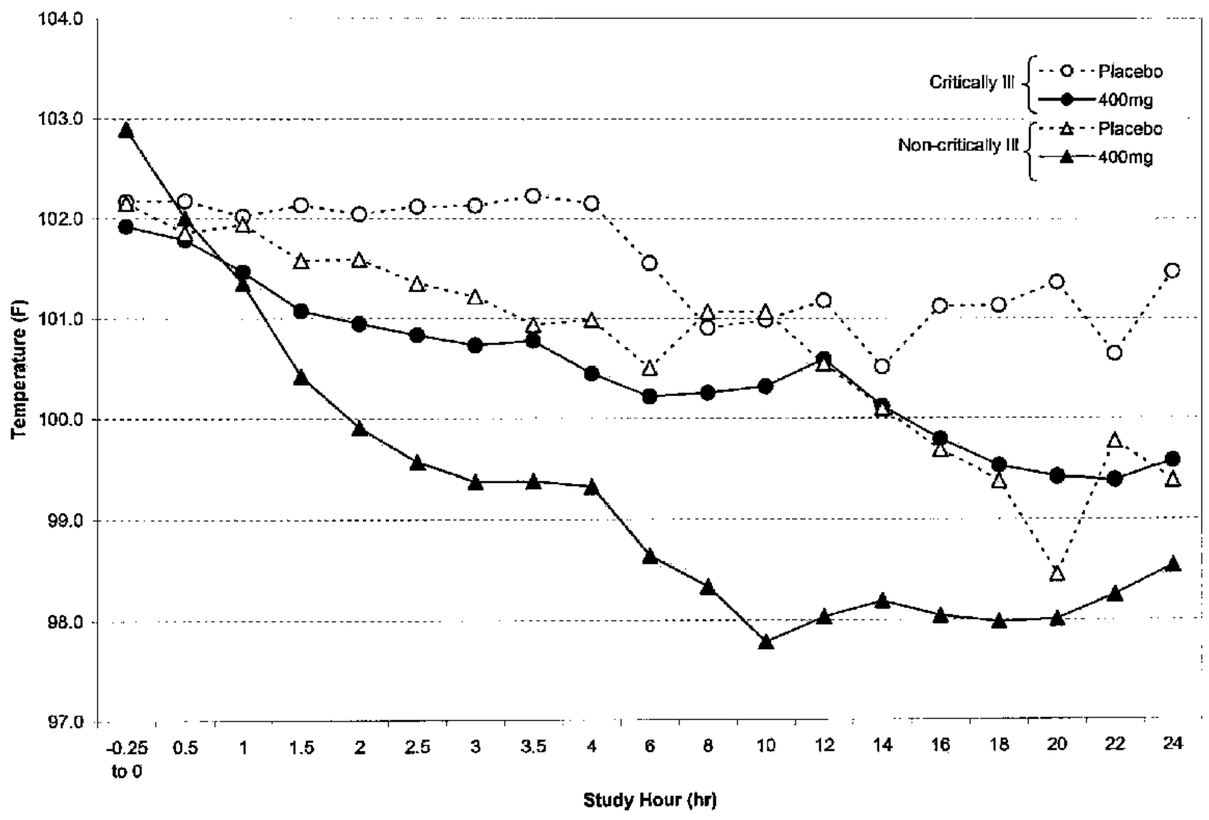
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) **Title**: TREATING CRITICALLY ILL PATIENTS WITH INTRAVENOUS IBUPROFEN

Figure 4



(57) **Abstract**: Methods of treating at least one condition chosen from pain, inflammation, and fever in a critically ill patient in need thereof, comprising administering to the critically ill patient an intravenous pharmaceutical composition comprising ibuprofen using a first dosage regimen, wherein the first dosage regimen produces a first pharmacokinetic profile in critically ill patients that is about equivalent to a second pharmacokinetic profile produced by administration of the intravenous pharmaceutical composition using a second dosage regimen of ibuprofen to non-critically ill patients, wherein the at least one condition of the critically ill patient is thereby treated.

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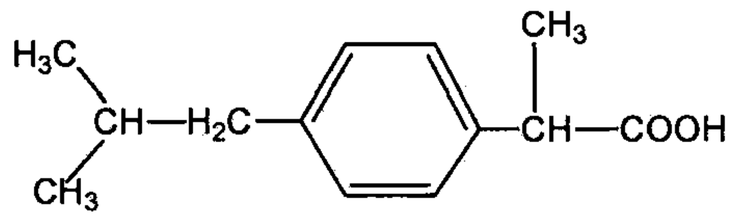
TREATING CRITICALLY ILL PATIENTS WITH INTRAVENOUS IBUPROFEN

This application claims priority to U.S. Provisional Patent Application No. 61/230,324, filed on July 31, 2009, the contents of which are incorporated herein by reference.

[001] Provided are methods of treating critically ill patients by administering an intravenous pharmaceutical composition comprising an effective amount of 2-(4-isobutylphenyl) propionic acid.

[002] 2-(4-isobutylphenyl) propionic acid, whose International Nonproprietary Name is ibuprofen, is a well-known anti-inflammatory drug having a molecular weight of 206.28 and the following chemical structure:



(Merck Index 12th ed., n4925, page 839). Originally patented in the 1960's, ibuprofen is now marketed generically, as well as under the tradenames of Motrin®, Advil®, and Nuprin® for the treatment of pain, inflammation, and fever. The U.S. Food and Drug Administration recently approved a new formulation of ibuprofen for intravenous administration to be marketed under the trade name Caldolor®.

[003] Ibuprofen is readily available as the racemic mixture ((RS)-Ibuprofen) of the two enantiomers, (R)-Ibuprofen and (S)-Ibuprofen. Even though the (S) enantiomer is the biologically active form, most preparations contain the racemic mixture since the (R) enantiomer is converted to the active (S) form in-vivo. For simplicity, hereinafter the term "ibuprofen" will be used to indicate any one of the (R) enantiomer, the (S) enantiomer, or the racemate.

[004] Although ibuprofen has many advantages over other analgesics such as aspirin and acetaminophen, it is very poorly soluble in water. Thus, certain dosage forms of ibuprofen, especially oral or injectable liquids, have been difficult to develop. Several U.S. patents have addressed this problem.

[005] For example, U.S. Pat. No. 4,309,421 appears to describe water-soluble complexes of ibuprofen and phospholipids suitable for parenteral administration. U.S. Pat. Nos. 4,859,704 and 4,861,797 appear to describe the synthesis of alkali metal salts of ibuprofen for preparing a liquid ibuprofen formulation.

[006] Other U.S. patents appear to address this problem by preparing an ibuprofen salt with a basic amino acid as the active pharmaceutical ingredient and then solubilizing the salt to produce a liquid dosage form.

[007] For example, U.S. Pat. No. 5,200,558 appears to describe enhanced analgesic effects of S (+) ibuprofen as salts of L and D amino acids, including arginine, in various dosage forms, including as an injectable solution. U.S. Pat. No. 4,279,926 appears to describe the use of basic amino acid salts of propionic acids for relieving pain and treating inflammatory conditions. Similarly, U.S. Pat. No. 5,463,117 appears to describe the preparation of salts of ibuprofen with basic amino acids. Finally, U.S. Pat. No. 6,005,005 appears to describe a liquid composition for oral use containing ibuprofen and arginine.

[008] U.S. Patent No. 6,727,286 B2 describes, among other things, a pharmaceutical composition comprising an aqueous solution of arginine and ibuprofen, wherein the molar ratio of arginine to ibuprofen is less than 1:1, as well as a method of making the same. That patent also provides a method of treating a condition chosen from pain, inflammation, fever, and/or other conditions alleviated by ibuprofen comprising administering a pharmaceutical composition comprising an aqueous solution of arginine and ibuprofen, wherein the molar ratio of arginine to ibuprofen is less than 1:1. The entire contents of U.S. Patent No. 6,727,286 B2 are hereby incorporated herein by reference.

[009] The U.S. Food and Drug Administration recently approved a new formulation of ibuprofen for intravenous administration to be marketed under the trade name Caldolor® by Cumberland Pharmaceuticals, Inc. Caldolor® contains the active ingredient ibuprofen. As described on the labeling for Caldolor®, "each 1 mL of solution contains 100 mg of ibuprofen in Water for Injection, USP. The product also contains 78 mg/mL arginine at a molar ratio of 0.92:1 arginine:ibuprofen. The solution pH is about 7.4." Caldolor® is sterile and is intended for intravenous administration only.

[010] Caldolor® possesses antiinflammatory, analgesic, and antipyretic activity. As such, Caldolor® is indicated in adults for the management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics. 400 mg to 800 mg of Caldolor® is administered intravenously every 6 hours as necessary to treat pain. Caldolor® is also indicated for the reduction of fever

in adults. 400 mg of Caldolor® is administered intravenously, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary to treat fever.

[011] Provided are methods of treating at least one condition chosen from pain, inflammation, and fever in a critically ill patient in need thereof. The methods include administering to the critically ill patient an intravenous pharmaceutical composition comprising ibuprofen using a first dosage regimen, wherein the first dosage regimen produces a first pharmacokinetic profile in critically ill patients that is about equivalent to a second pharmacokinetic profile produced by administration of the intravenous pharmaceutical composition using a second dosage regimen of ibuprofen to non-critically ill patients, wherein the at least one condition of the critically ill patient is thereby treated.

[012] In some embodiments the first dosage regimen includes administration of at least one dose of ibuprofen that is higher than any dose of ibuprofen administered in the second dosage regimen. In some embodiments the first dosage regimen comprises a dosing interval that is shorter than any dosing interval used in the second dosage regimen. In some embodiments the first pharmacokinetic profile produced by administration of the first dosage regimen of ibuprofen to critically ill patients includes an area under plasma concentration - time curve (AUC) over a period of time that is about equivalent to the AUC over the period of time of the second pharmacokinetic profile produced by administration of the second dosage regimen of ibuprofen to non-critically ill patients.

[013] In some embodiments the first dosage regimen includes administration of a dose of ibuprofen of greater than a dose administered to non-critically ill patients in a second dosage regimen, wherein the dose administered in the first dosage regimen is from 100 to 1600 mg. In some embodiments the dose administered in the first dosage regimen is selected from 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 800 mg, 1000 mg, 1200 mg, 1400 mg, 1600 mg, 2400 mg, and 3200 mg. In some embodiments the dose administered in the first dosage regimen is selected from 100 mg, 200 mg, 400 mg, and 800 mg.

[014] In some embodiments the first dosage regimen includes a dosing interval that is shorter than any dosing interval used in the second dosage regimen. In some embodiments the at least one condition is pain. In some embodiments the at least

one condition is inflammation. In some embodiments the at least one condition is fever.

[015] In some embodiments the critically ill patient is a patient receiving at least one form of treatment selected from treatment with a vasopressor and mechanical ventilation.

[016] In some embodiments the pharmaceutical composition is an aqueous solution of arginine and ibuprofen.

[017] In some embodiments the molar ratio of arginine to ibuprofen is selected from less than or equal to 1:1, less than or equal to 0.99:1, less than or equal to 0.98:1, less than or equal to 0.97:1, less than or equal to 0.96:1, less than or equal to 0.95:1, less than or equal to 0.94:1, less than or equal to 0.93:1, less than or equal to 0.92:1, less than or equal to 0.91:1, less than or equal to 0.90:1, less than or equal to 0.60:1. In some embodiments the pharmaceutical composition is Caldolor®.

[018] In some embodiments administering the first dosage regimen to critically ill patients reduces the at least one condition chosen from pain, inflammation, and fever to an about equivalent extent to the reduction of the at least one condition chosen from pain, inflammation, and fever achieved in non-critically ill patients to which the second dosage regimen is administered.

Brief Description of the Figures

[019] **Figure 1** shows mean ibuprofen plasma concentrations (hours 0-4) following administration of 100mg IVib in critically ill versus non-critically ill patients.

[020] **Figure 2** shows mean ibuprofen plasma concentrations (hours 0-4), following administration of 200 mg IVib in critically ill versus non-critically ill patients.

[021] **Figure 3** shows mean ibuprofen plasma concentrations (hours 0-4) following administration of 400 mg IVib in critically ill versus non-critically ill patients.

[022] **Figure 4** shows temperature over time by stratum, 400mg IVIb vs. placebo.

[023] Provided herein are methods of treating at least one condition chosen from pain, inflammation, and fever in a critically ill patient in need thereof.

[024] As used herein the term "treat," "treating" or "treatment" refers to the administration of ibuprofen to an individual who already manifests, has in the past manifested, and/or is at risk of manifesting at least one symptom of a disease or condition, that can be reduced or alleviated by administration of ibuprofen. Examples of such diseases and conditions include pain, inflammation, and fever.

[025] In some embodiments a "critically ill" patient is a patient receiving at least one of vasopressor support and mechanical ventilation. As used herein a patient receiving "vasopressor support" refers to a patient unable to maintain a sufficient blood pressure who is consequently being treated with a vassopressor to raise the patient's bloodpressure. Examples of vasopressor support medications include Norepinephrine (marketed for example under the brand name Levophed®).

[026] Certain methods described herein comprise administering to the critically ill patient an intravenous pharmaceutical composition comprising ibuprofen. Intravenous pharmaceutical compositions of ibuprofen include any formulation suitable for administration to a patient via any intravenous method, including a bolus. In some embodiments the rate of infusion is such that the dose is administered over a period of about 30 minutes. In some embodiments the rate of infusion is such that the dose is administered over a period of less than 30 minutes. In some embodiments the rate of infusion is such that the dose is administered over a period of greater than 30 minutes.

[027] In alternative embodiments of the treatment methods described herein a pharmaceutical formulation comprising ibuprofen is administered to a patient via an injection method. In such embodiments the pharmaceutical formulation of ibuprofen is a formulation suitable for administration to a patient via the injection method. Suitable injection methods include, in addition to intravenous injection, intraarterial infusion, intramuscular injection, transdermal injection, and subcutaneous injection.

[028] Suitable carriers for intravenous administration include physiological saline or phosphate buffered saline (PBS), and solutions containing solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[029] The formulation may include an aqueous vehicle. Aqueous vehicles include, by way of example and without limitation, Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include, by way of example and without limitation, fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must

be added to parenteral preparations packaged in multiple dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include, by way of example and without limitation, sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include, by way of example and without limitation, ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[030] Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, such as more than 1% w/w of ibuprofen.

[031] As used herein a "dosage regimen" refers to the protocol used to administer an intravenous pharmaceutical formulation comprising ibuprofen to a patient. In some embodiments the dosage regimen comprises a dose amount and dosing interval. In some embodiments the dosage regimen further comprises a dosing duration. As used herein "dosing duration" refers to the period of time over which a dose is administered. For example, if a volume of pharmaceutical composition comprising 400 mg of ibuprofen is administered over a dosing duration of 30 min and administration of a dose is initiated every 6 hours, then the dosage regimen is 400 mg, every six hours, administered over 30 minutes. In some embodiments the dosage duration is defined simply as 400 mg, every six hours.

[032] In some embodiments described herein a dosage regimen for critically ill patients is defined as one that produces a first pharmacokinetic profile in critically ill patients that is about equivalent to a second pharmacokinetic profile produced by administration of a second dosage regimen of ibuprofen to non-critically ill patients. As used herein, two pharmacokinetic profiles are "about equivalent" if they are defined by at least one parameter that is about equivalent between the two profiles. Non-limiting examples of such parameters include the area under plasma concentration over time curve (AUC) and the maximal plasma concentration reached following administration of a dose (Cmax).

[033] In some embodiments two pharmacokinetic parameters are about equivalent if the lower value is greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 96%, greater than 97%, greater than 98%, or greater than 99% of the higher value.

[034] The pharmacokinetic profiles of two dosage regimens are compared by determining the average pharmacokinetic profile in a population of patients receiving the first dosage regimen, determining the average pharmacokinetic profile in a population of patients receiving the second dosage regimen, and then comparing those two population dosage regimens.

[035] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[036] The following example represents specific embodiments of the foregoing discovery, and is not representative of the entire scope of the invention.

Example

[037] This study 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 vasopressor support and/or mechanical ventilation. Patients received intravenous ibuprofen (Caldolor®) at the indicated dosages.

[038] Analysis of the data sets assessing the efficacy of intravenous ibuprofen (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 Cmax and AUC for all doses of IVIb were significantly reduced in critically ill patients when compared to non-critically ill patients, while the pharmacokinetics remained first order in both patient populations. Table 1 presents the

summary pharmacokinetic parameters determined from the patients enrolled in the study, by IVIb dose level and stratum.

Table 1 Summary of Pharmacokinetic Parameters by IVIb Dose Level and Stratum

Treatment, Stratum		AUC_{0-4} (ug.h/mL)	$Cmax_{0-4}$ (ug/mL)	$Cmin_{dose1}$ (ug/mL)	$Tmin_{dose1}$ (h)	$Cmin_{dose6}$ (ug/mL)	$Tmin_{dose6}$ (h)	$T_{1/2}$ (h)	AUC_{0-4} /Dose
100 mg IVIb	Critically Ill n=14	16.10	8.23	2.19	4.0	2.3	25.7	2.42	161.01
	Non-critically Ill n=17	26.33	14.53	2.95	4.0	2.6	26.0	2.49	263.28
200 mg IVIb	Critically Ill n=12	19.62	11.46	2.29	3.8	1.9	26.0	2.56	98.07
	Non-critically Ill n=18	39.51	22.89	4.73	3.9	3.0	26.0	1.86	197.55
400 mg IVIb	Critically Ill n=14	45.94	25.70	4.69	3.9	5.0	26.0	2.32	114.84
	Non-critically Ill n=17	87.11	49.13	10.66	3.8	6.6	26.0	2.22	217.78

[039] Figures 1, 2 and 3 present the Cmax graphically for the treatment groups, by stratum.

[040] 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 the study. Figure 4 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 Cmax and AUC of IVIb which may limit the therapeutic effect.

[041] 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 2 presents the

percent (%) difference between the critically ill versus the non-critically ill stratums for the AUC_{0-4} and $Cmax_{0-4}$ pharmacokinetic parameters.

Table 2 Pharmacokinetic Parameters Differences in the 400 mg IVIb Dose Level and Stratum

Treatment, Stratum		**AUC_{0-4}** (ug.h/mL)	**$Cmax_{0-4}$** (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	39.51	22.89
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%*

[042] The values for the AUC and Cmax 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 for the patient being treated.

[043] In a prior study, in which pharmacokinetic samples were not obtained, Caldolor® dosing was up to 800 mg IV Ibuprofen every six hours. That dosage regimen resulted in a significant and sustained reduction in fever throughout the 48 hour dosing period. Since the majority of the patients in that trial would be considered as critically ill given the definition in the study reported in this Example, the results of that prior study support a dose up to 800 mg if required.

[044] It will be readily apparent to one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the methods and applications described herein are suitable and may be made without departing from the scope of the invention or any embodiment thereof. While the invention has been described in connection with certain embodiments, it is not intended to limit the invention to the

particular forms set forth, but on the contrary, it is intended to cover such alternatives, modifications and equivalents as may be included within the spirit and scope of the invention as defined by the following claims.

We claim:

1. A method of treating at least one condition chosen from pain, inflammation, and fever in a critically ill patient in need thereof, comprising administering to the critically ill patient an intravenous pharmaceutical composition comprising ibuprofen using a first dosage regimen, wherein the first dosage regimen produces a first pharmacokinetic profile in critically ill patients that is about equivalent to a second pharmacokinetic profile produced by administration of the intravenous pharmaceutical composition using a second dosage regimen of ibuprofen to non-critically ill patients, wherein the at least one condition of the critically ill patient is thereby treated.

2. The method of claim 1, wherein the first dosage regimen comprises administration of at least one dose of ibuprofen that is higher than any dose of ibuprofen administered in the second dosage regimen.

3. The method of claim 1, wherein the first dosage regimen comprises a dosing interval that is shorter than any dosing interval used in the second dosage regimen.

4. The method of claim 1, wherein the first pharmacokinetic profile produced by administration of the first dosage regimen of ibuprofen to critically ill patients comprises an area under plasma concentration - time curve (AUC) over a period of time that is about equivalent to the AUC over the period of time of the second pharmacokinetic profile produced by administration of the second dosage regimen of ibuprofen to non-critically ill patients.

5. The method of claim 1, wherein the first dosage regimen comprises administration of a dose of ibuprofen of greater than a dose administered to non-critically ill patients in the second dosage regimen, wherein the dose administered in the first dosage regimen is from 100 to 1600 mg.

6. The method of claim 5, wherein the dose of ibuprofen administered in the first dosage regimen is selected from 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 800 mg, 1000 mg, 1200 mg, 1400 mg, 1600 mg, 2400 mg, and 3200 mg.

7. The method of claim 6, wherein the dose of ibuprofen administered in the first dosage regimen is selected from 100 mg, 200 mg, 400 mg, and 800 mg.

8. The method of claim 1, wherein the first dosage regimen comprises a dosing interval that is shorter than any dosing interval used in the second dosage regimen.

9. The method of claim 8, wherein the dosing interval of the first dosing regimen is selected from dosing intervals of greater than 4 hours and greater than 6 hours.

10. The method of claim 1, wherein the at least one condition is pain.

11. The method of claim 1, wherein the at least one condition is inflammation.

12. The method of claim 1, wherein the at least one condition is fever.

13. The method of claim 1, wherein the critically ill patient is a patient receiving at least one of pressor support and mechanical ventilation.

14. The method of claim 1 wherein the pharmaceutical composition is an aqueous solution of arginine and ibuprofen.

15. The method of claim 14, wherein the molar ratio of arginine to ibuprofen is selected from less than or equal to 1:1, less than or equal to 0.99:1, less than or equal to 0.98:1, less than or equal to 0.97:1, less than or equal to 0.96:1, less than or equal to 0.95:1, less than or equal to 0.94:1, less than or equal to 0.93:1, less than or equal to 0.92:1, less than or equal to 0.91:1, less than or equal to 0.90:1, less than or equal to 0.60:1.

16. The method of claim 1, wherein administering the first dosage regimen to critically ill patients reduces the at least one condition chosen from pain, inflammation, and fever to an about equivalent extent to the reduction of the at least one condition chosen from pain, inflammation, and fever achieved in non-critically ill patients to which the second dosage regimen is administered.

Figure 1

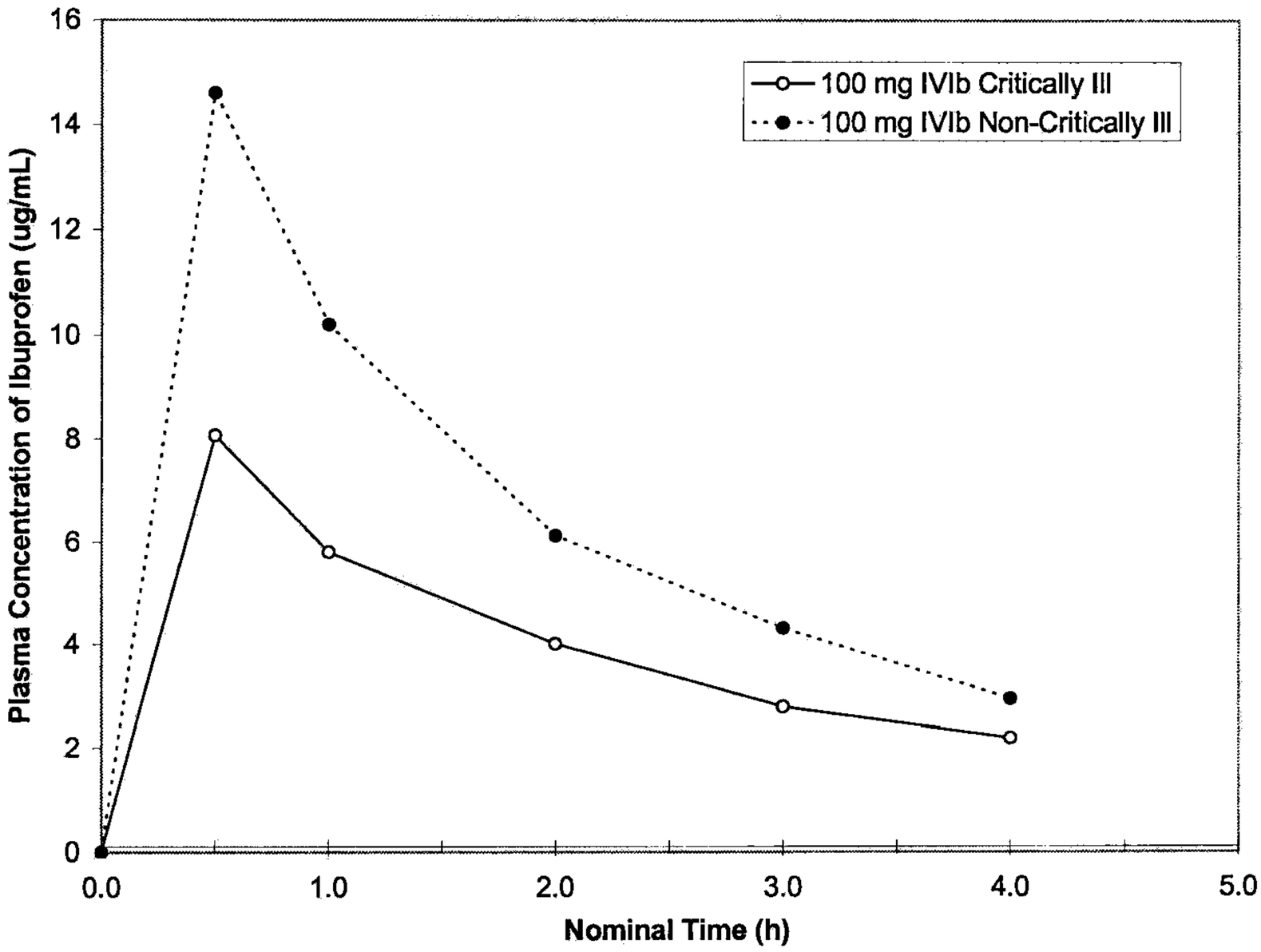

100 mg IVIb Critically Ill
100 mg IVIb Non-Critically Ill
Plasma Concentration of Ibuprofen (ug/mL)
Nominal Time (h)
0
2
4
6
8
10
12
14
16
0.0
1.0
2.0
3.0
4.0
5.0

Figure 2

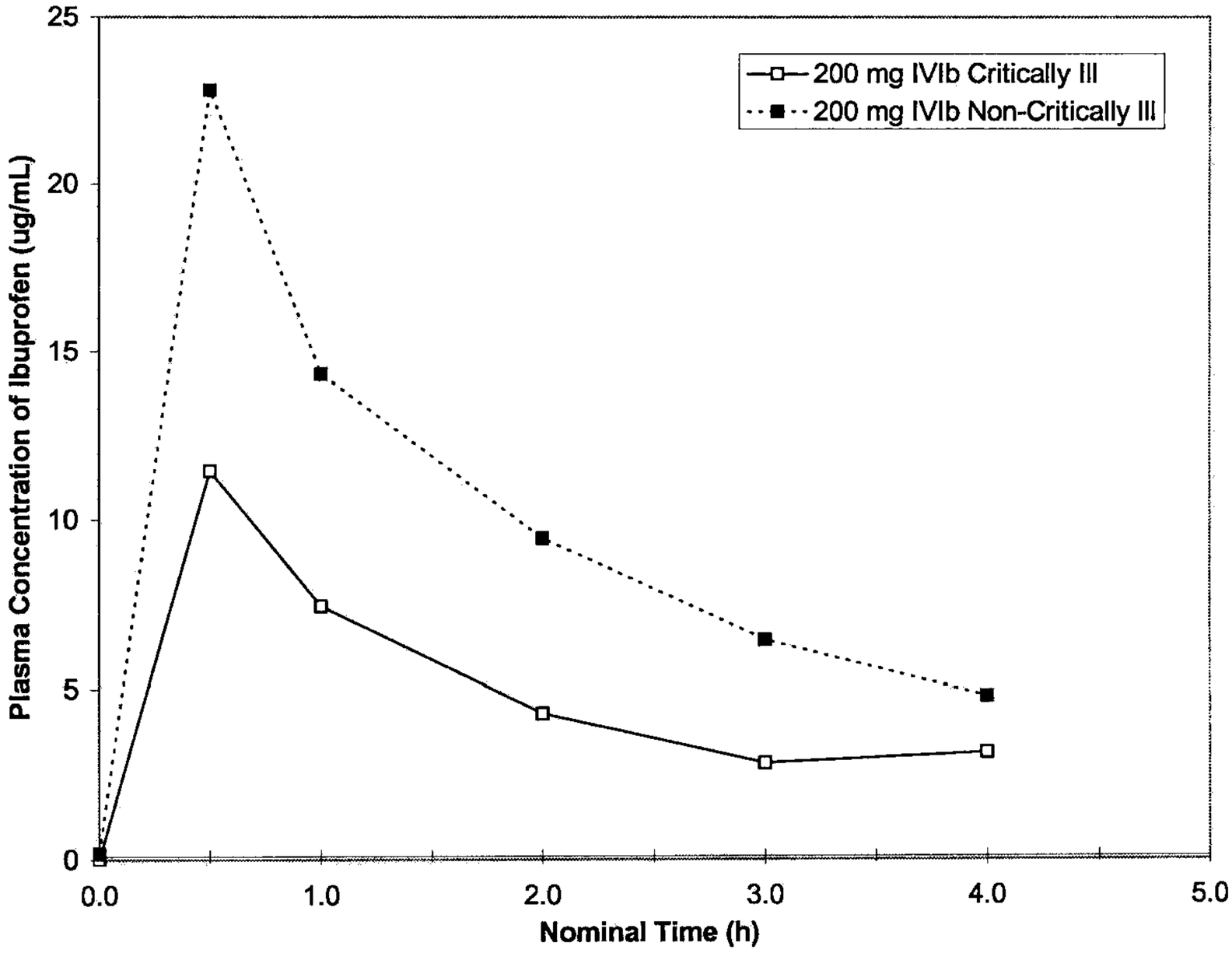

200 mg IVIb Critically Ill
200 mg IVIb Non-Critically Ill
Plasma Concentration of Ibuprofen (ug/mL)
0
5
10
15
20
25
0.0
1.0
2.0
3.0
4.0
5.0
Nominal Time (h)

Figure 3

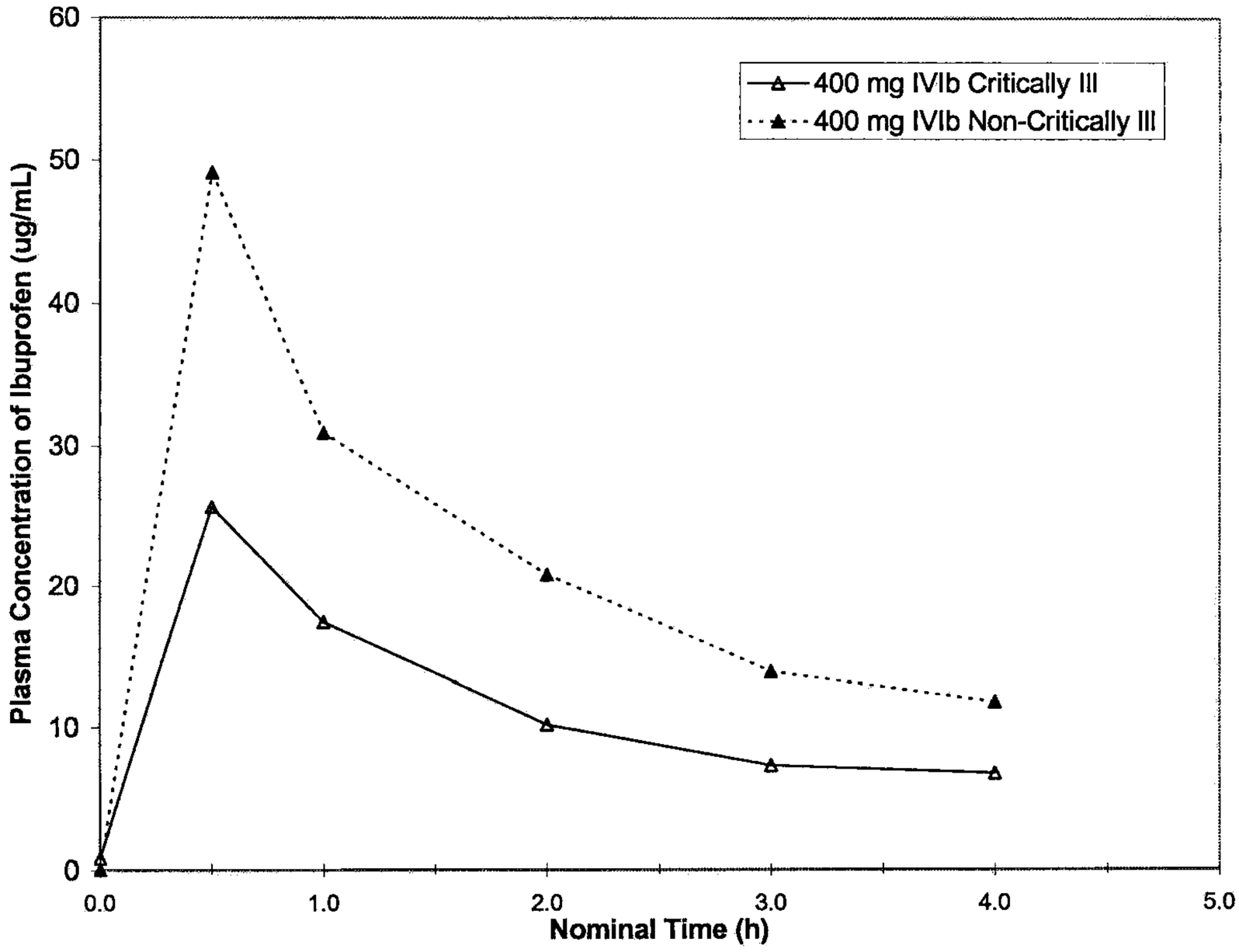

400 mg IVIb Critically Ill
400 mg IVIb Non-Critically Ill
Plasma Concentration of Ibuprofen (ug/mL)
0
10
20
30
40
50
60
0.0
1.0
2.0
3.0
4.0
5.0
Nominal Time (h)

Figure 4

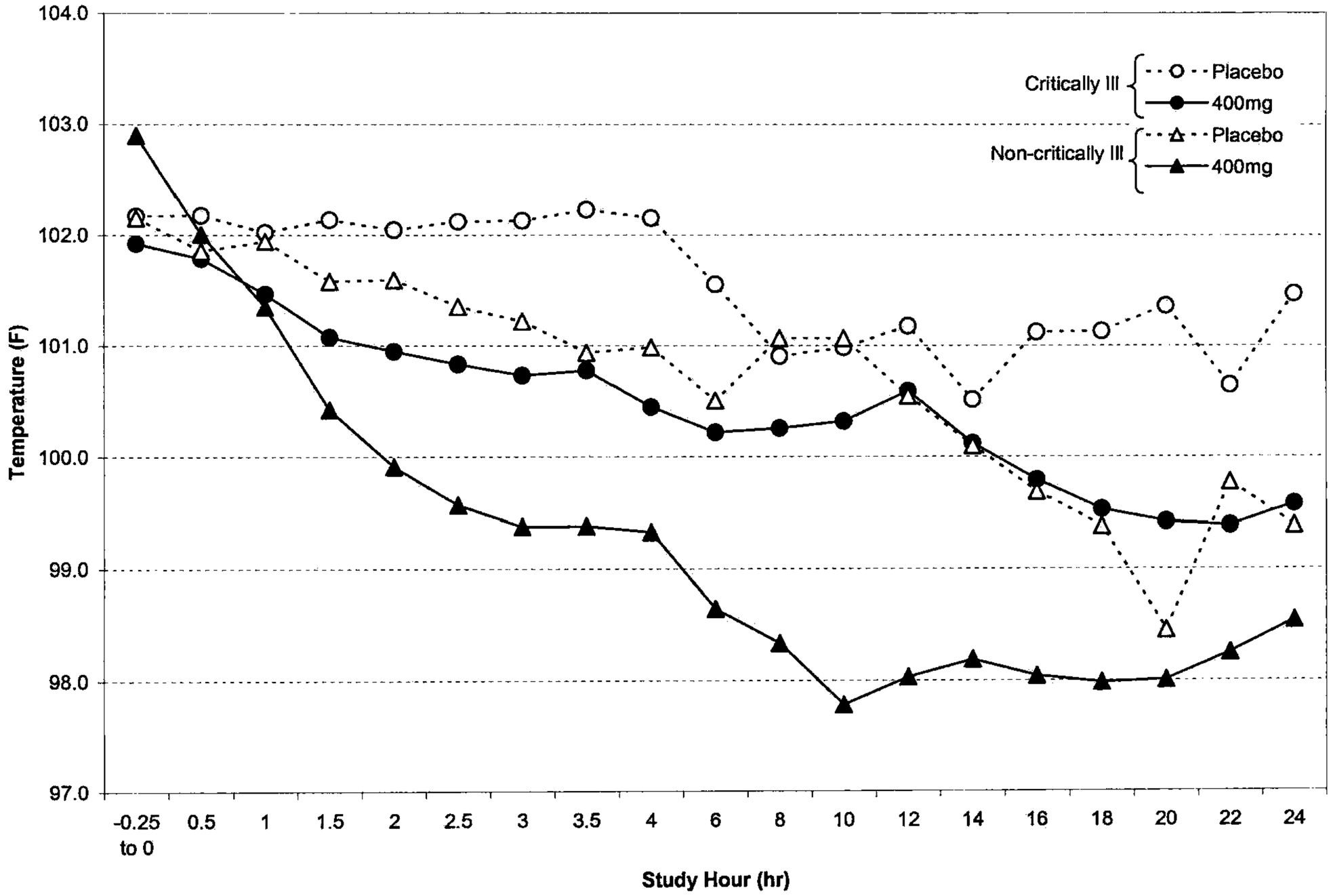
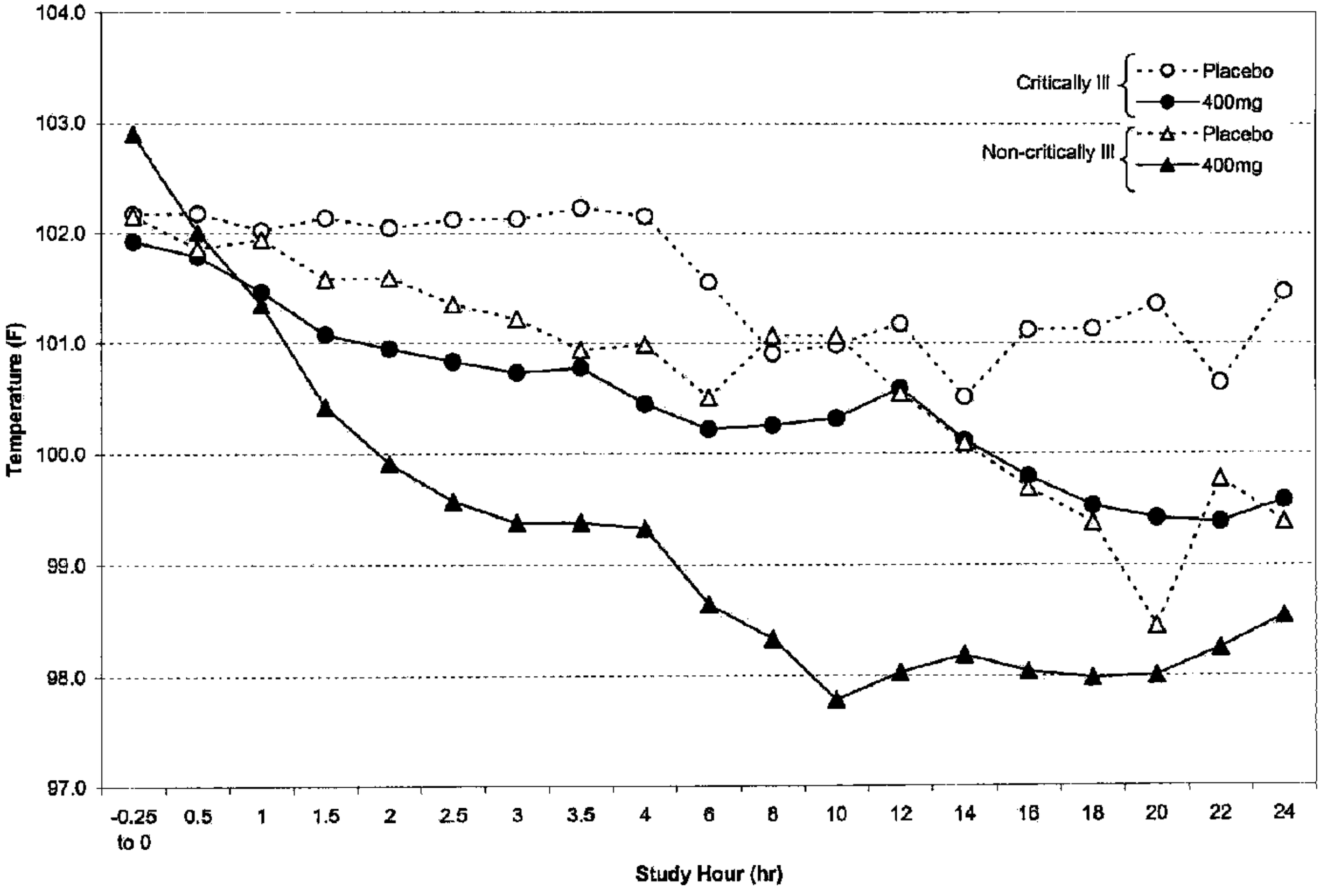

104.0
103.0
102.0
101.0
100.0
99.0
98.0
97.0
Temperature (F)
Critically Ill
Placebo
400mg
Non-critically Ill
Placebo
400mg
-0.25 to 0
0.5
1
1.5
2
2.5
3
3.5
4
6
8
10
12
14
16
18
20
22
24
Study Hour (hr)

Figure 4


104.0
103.0
102.0
101.0
100.0
99.0
98.0
97.0
Temperature (F)
Critically Ill
Placebo
400mg
Non-critically Ill
Placebo
400mg
-0.25 to 0
0.5
1
1.5
2
2.5
3
3.5
4
6
8
10
12
14
16
18
20
22
24
Study Hour (hr)