CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-903

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Abraham Karkowsky, M.D., Ph.D. Team-Leader, Division of Cardiovascular and Renal Products, HFD-110

SUBJECT: Approval of ibuprofen L-Lysine (NeoProfen ™; Farmacon-IL, LLC, sponsor) - Amendment

TO: Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products, HFD-110

I am amending my review which I filed on 1 March 2006. This memo incorporates information that was submitted by Farmacon –IL, LLC, and that I received after filing the initial review. The conclusions of the original review remain unaltered.

This submission contains the case report forms of those infants whose endpoint was reached by the category reflecting an assessment by the treating neonatologist that these premature infants had a hemodynamically significant ductus. This endpoint accounted for the largest fraction of infants requiring rescue and who achieved the study endpoint. Of the patients who required rescue, there were 14 NeoProfen and 25 placebo patients who met this criterion for rescue. In this submission, case report forms were available for 11 NeoProfen and 23 placebo patients in.

In order to obtain a better understanding of the status of the infant I looked at the following pages within the CRF.

- Physical exam sheet to assess cardiovascular status at the time rescue was considered.
- Rescue sheet, to see if additional symptoms were described.
- The echocardiogram performed at the time of rescue.

With respect to symptoms described either on the reason for contemplation of rescue or during the physical exam at the time rescue was contemplated, approximately 2/3 of the subjects 34 assessed CRFs had some descriptions. Unfortunately, the CRF would often describe the exam as "PDA" without a further description of what signs were observed.

The rescue echocardiogram page was evaluated to assess whether the impression of the neonatologist was consistent with a significant patent ductus arteriosus. Any ductus

classified as medium or large, any ductus greater than 2 mm on the ECHO report sheet I considered as strong evidence that the ductus was likely sufficiently symptomatic to warrant treatment. Smaller ductus size, or just a description of whether there was a patent ductus and whether there was shunting was clear evidence that the ductus was open but less convincing that the ductus was producing symptoms. Of those who I had data for two placebo patients and one NeoProfen patient did not have suggestive or convincing evidence that the ductus was large, medium or significant.

In summary, this submission allows supports the conclusion that NeoProfen patients required less frequent rescue due to a functionally significant PDA.

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/s/

Abraham Karkowsky
3/8/2006 11:23:54 AM
MEDICAL OFFICER

Amendment to original review

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
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FROM: Abraham Karkowsky, M.D., Ph.D. Team-Leader, Division of Cardiovascular and Renal Products, HFD-110

SUBJECT: Approval of ibuprofen L-Lysine (NeoProfen ™; Farmacon-IL, LLC, sponsor)

TO: Dr. Norman Stockbridge, Director, Division of cardiovascular and Renal Products, HFD-110

This memo supports the approval recommendation for NeoProfen at a regimen of 10 mg/kg first dose, followed at 24 and 48 hours by doses of 5 mg/kg. Its use should be limited to close symptomatic patent ductus arteriosus (PDA), in premature infants of < [redacted] weeks gestational age with birth weight of between 500 to [redacted] grams. Approval is based on a prospective, randomized, clinical trial in which NeoProfen, at the above regimen was administered as a prophylaxis to premature infants with ECHO evidence of a PDA but who were asymptomatic at the time of enrollment. There is convincing evidence that the use of NeoProfen facilitates closure of the ductus. There is also suggestive evidence that the closure is associated with a decrease in signs associated with a hemodynamically significant shunting.

There is insufficient information as to long-term outcomes after NeoProfen treatment to recommend its use as a prophylactic treatment for severely premature neonates. There is no indication that mortality, irreversible morbidity or the hospital course of the premature infants was altered by the prophylactic use of NeoProfen. Given the uncertainty of the long-term risk and benefit, the use of NeoProfen as a prophylactic treatment exposes a large number of premature infants, perhaps unnecessarily to the risks attendant to its use. It is more prudent to limit NeoProfen's use to the treatment of symptomatic premature neonates.

Labeling recommendations were edited by the reviewers and Drs. Stockbridge, Unger and Targum. The edited labeling is included in the briefing package.

The following reviews were consulted in the course of constructing this memo.

- Medical Officer Review by Maryann Gordon, M.D., dated 20 January 2006.
- Biostatistics review by Steven Bai, Ph.D., dated 12 December 2005.
- Pharmacology Review by C.A. Resnick, Ph.D., dated 24 February 2006.
- Biopharmaceutic review by Elena V. Mishina, Ph.D., dated 25 January 2006.

- Chemistry Review by Raj Misra, Ph.D. (with contributions by Monica Cooper, Ph.D.), dated 3 February 2006; review by Monica D, Cooper, Ph.D., dated 23 February 2006.
- Product Quality Microbiology Review by Robert J. Mello, Ph.D., dated 14 February 2006.
- Proprietary Trade name review by Tina M. Tezky, dated 20 September 2005; minutes of an internal meeting, dated 6 January 2006.
- Clinical Inspection by Sharon K. Gershon, Pharm.D., dated 1 February 2006.
- DDMAC memorandum From Lance McLeroy and Iris Masucci, dated 11 January 2006.

Reliability of the data:

Three sites in the one pivotal clinical trial were audited. The three sites were Blair Cox, M.D./Charles R Rosenfeld, M.D., Dallas Texas; Paul Wozniak, M.D., San Diego CA; Bart Van Overmeire, M.D., Ph.D., Edgegem, Belgium. These sites enrolled 25, 21 and 25 infants, respectively. No site was issued a form 483. Dr. Overmeire's site was involved in the two supportive databases.

The establishment inspection report for both the drug substance [redacted] and the drug product [redacted] were acceptable.

With respect to financial disclosures, one investigator [redacted] who was one of the investigators of the [redacted] studies [redacted] disclosed proprietary interest in the product tested. The [redacted] studies were either completed [redacted] or nearly completed / [redacted] when Farmacon obtained the rights to the information of the study. The [redacted] studies were sponsored by [redacted] . The financial arrangement for the [redacted] studies was made independent of the results of these studies. With respect to the contribution to the [redacted] study, [redacted] was audited and no violations were observed.

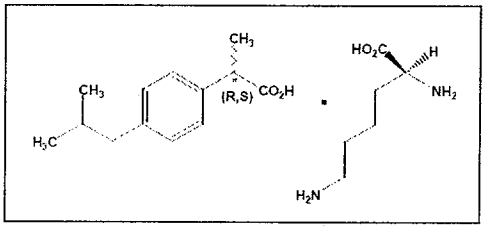
In summary, there seems to be no impediment to accepting the data from the [redacted] studies as accurate.

Chemistry/Microbiology:

The structure of the product is shown in Figure 1. The product is a salt of ± ibuprofen and L-lysine in a 1:1 ratio. It is supplied as a carton containing three vials; each vial containing 2 ml of a 10 mg/ml solution of ibuprofen (20 mg ibuprofen, 34.18 mg of the ibuprofen-lysine salt). Each vial contains excess of drug for the treatment for the largest infant (1000grams) with the first dose (10 mg/kg), which would require a dose needed 10 mg.

Figure 1: Structure, name, formula and other data for ibuprofen L-lysine

Chemical Name:
1) L-Lysine, mono[α-methyl-4-(2-methylpropyl)benzeneacetate]
2) Benzeneacetic acid, α-methyl-4-(2-methylpropyl)-, L-lysine (1:1)



Molecular Formula: $C_{19}H_{32}N_2O_4$
MW = 352.48
CAS = 57469-77-9

Dr. Cooper's review recommends approval of the current formulation. The deficiencies noted in Dr. Misra's review and transmitted to Farmacon-IL, LLC in letters dated 11 August 2005 and 5 December 2005 have been adequately addressed.

- Dr. Cooper recommended a retest date of [redacted] ; for the drug substance when it is stored at controlled room temperature.
- An expiration date of 24 months for the drug product when stored at controlled room temperature (20-25^0 with excursions to 15-30^0) and protected from light.

The microbiologist recommended approval. The drug substance, ibuprofen L-lysine is formulated in water for injection, pH adjusted [redacted] The drug is then [redacted]

Chemistry and microbiology specifications and controls appear adequate for approval.

Pharmacology:

The ductus arteriosus is a conduit connecting the pulmonary artery with the descending aorta. *In utero* the ductus functions to shunt placenta-derived relatively low tension oxygenated blood around the lungs. Its closure in full-term infants occurs rapidly after birth with final closure approaching 100% by 96 hours. Persistence of the patent ductus arteriosus is associated with prematurity, respiratory distress syndrome, increased fluid administration, and asphyxia.

There is a clear association both with post-natal oxygenation as well as with inhibition of prostaglandins in provoking closure of the ductus. In utero, ductus arteriosus tone is maintained by prostaglandins, predominantly PGE2 and to a much lesser extent PGI2. Prostaglandin receptors sensitive to PGE exist as four subtypes EP1, EP2, EP3 and EP4. There

appears to be interspecies differences in the specific receptors moderating ductus patency[1]. Closure of the ductus, in those who it did not close spontaneously could be mediated by removal of the PGE2 and PGI2 signals that keeps the ductus open.

In humans, the administration of NSAIDs in late pregnancy provokes premature closure of the ductus and may lead to neonatal demise. PGE1 (Alprostadil) is currently approved for the palliative care of neonates with congenital cardiac disease who are dependent on the persistence of the PDA to maintain oxygenation. Indomethacin, a prostaglandin synthetase inhibitor is currently approved for the closure of hemodynamically significant ductus arteriosus in small premature infants, who are unresponsive to standard therapy. All the above suggest a pivotal role of prostaglandins in the persistent patency of the ductus.

Ibuprofen is currently approved as an anti-inflammatory agent. Ibuprofen's mode of action is not completely understood, but it may be related to its ability to inhibit, in human blood, cyclo-oxygenase activity of the enzyme prostaglandin endoperoxide synthetase 1 and 2 and thereby inhibit generation of prostaglandins. The S-isomer of ibuprofen is approximately 17 times more potent than the R-isomer in inhibiting cyclo-ogygenase (COX)-1 and greater than 100 fold more selective in inhibiting COX-2 activity[2]. It would seem likely, therefore, in premature infants, ibuprofen would be useful, by inhibiting prostaglandin synthesis, in closing a patent ductus arteriosus.

With respect to the ability of ibuprofen to alter prostaglandin generation in premature neonates at the doses used in this study, there did not appear to be any effects on the concentrations of any of several prostaglandin species. Approximately 33 and 35 neonates treated with ibuprofen and placebo, respectively, had blood drawn for the assay of prostaglandin levels (see table 1). The timing of the measurements was baseline, one hour post-first dose and one hour after the third dose. There did not demonstrate any effect of ibuprofen on any of several prostaglandin or thromboxane B2 levels, either compared to baseline measurements or to corresponding placebo values.

Table 1:Prostaglandin and thromboxane levels (in pg/ml)before and after doses of ibuprofen in premature neonates

Treatment group	6-ketoPGF1 alpha	PGE2 levels x2	PGF2 alpha	TXB2 Levels x 2
Ibuprofen				
Prior to dose 1				
N	31	30	31	31
Mean ± SE	8286 ± 1426	3862 ± 773	1450 ± 202	2260 ± 279
Median (Min-max)	5101 (813-28413)	1671 (168- 14199)	1096 (181- 4965)	1851 (672-8325)
One hour post dose 1				
N	32	32	32	32
Mean ± SE	8883 ± 1858	3922 ± 733	1478 ±212	2411 ± 313
Median (Min-max)	3971 (232- 43642)	1926 (107-13999)	1074 (213-4683)	2052 (101-7467)
One hour post dose 3				
N	33	33	33	33
Mean ± SE	7577 ± 1302	3729 ± 571	1255 ± 182	1814 ± 199
Median (Min-max)	3884 (198-33084)	2754 (187-12450)	778 (145-3803)	1538 (305-4393)

[1] Smith GCS, "The Pharmacology of the Ductus Arteriosus" ; Pharmacology Reviews 1998; 50, 35-58.
[2] Neupert W, Brugger R, Euchenhofer C, Brune K, Geisslinger G; " Effects of ibuprofen enantiomers and its coenzyme A thioesters in Human Prostaglandin endoperoxide Synthetases" Br J Pharmacol 1997; 122, 487-492

Placebo				
Prior to dose 1				
N	37	37	37	37
Mean ± SE	9413 ± 1108	3666 ± 607	2458 ± 331	19468 ± 9498
Median (Min-max)	7131 (900-19686)	2336 (243-15455)	1777 (344-9582)	3559 (425-33704)
One hour post dose 1				
N	37	37	37	37
Mean ± SE	9731 ± 1245	3561 ± 583	2280 ± 319	19037 ± 9542
Median (Min-max)	7292(278-27121)	2223 (233-14398)	1834 (296-9098)	2582 (528-337487)
One hour post dose 3				
N	34	34	34	34
Mean ± SE	8145 ± 1263	4262 ± 678	2158 ± 328	13287 ± 4529
Median (Min-max)	5330 (737-29208)	2599 (221-16328)	1466 (378-8949)	2433 (531-114369)

Information relevant to the safety of the l-lysine salt component of ibuprofen is derived from a 13-week toxicity study in which L-lysine was fed to rats at concentrations of 5% of their diet. There were apparently no adverse effects.

With respect to the safety of multiple intravenous injections (14 days) of ibuprofen L-lysine in animal neonates, a single study in neonatal beagle dogs the study was terminated early (day 8) because of deaths in the majority of dogs. The major lesions seen on pathologic examination were related to the injection sites. In addition renal nephrosis and emboli in the pulmonary vessels were reported. Some of the deaths were attributed by the pathologist to sepsis. The lowest of the two doses in this study was 80 mg/kg//day, equivalent to approximately 5.5 times the doses proposed for humans. Given the current, as well as published experience in human neonates of the use of ibuprofen, the relevance of the neonatal beagle study is unclear.

Biopharmaceutic:

In adults, after oral administration, plasma ibuprofen appears to decline in a biphasic manner with plasma half-life of 2-4 hours for the racemate. Ibuprofen is metabolized by oxidation by the CYP 2C9 to form two inactive metabolites. These metabolites as well as their glucuronides are subsequently excreted in the urine, accounting for 50-60% of the oral dose. Less than 10% of the drug is excreted in the urine unchanged. The remainder of the drug is eliminated in the feces as metabolites and unabsorbed drug. As noted above there are differences in the COX-inhibition of the R- and S- isomers of ibuprofen. In adults there is slow and incomplete conversion of the less active R-isomer to the more active S-isomer.

Neonates and particularly premature neonates have immature systems needed for metabolizing and excreting drugs. Consequently, extrapolating the kinetic and dynamic effects from adults is unlikely to be accurate.

Dr. Mishina's review notes, only minimal kinetic data was collected during this development program. Four blood samples were collected from 56 ibuprofen-treated neonates for measurement of ibuprofen concentrations. The assay was not a stereo-selective assay and the results reflect pooled R- and S- ibuprofen concentrations. The timing of the kinetic measurements was 1 hour after the first dose, prior to the second dose (at 24 hours), prior to the

second dose (48 hours) and 72 hours after the last dose (120 hours). None of these measurements capture peak concentrations of ibuprofen (immediately post end of the 15 minute infusion). None of the metabolites of ibuprofen were measured. Urine was not analyzed for metabolites. Concentrations of racemic ibuprofen at 1, 24, 48 and 120 hours were 35 ± 9.0, 25 ± 7.5; 28 ± 14, 13 12 ug/ml, respectively.

Published data[3] (see Figure 2), of the kinetics of ibuprofen in similarly-aged neonates and with the same regimen as proposed for approval, captured measurements of ibuprofen made closer to the end of the intravenous infusion. In this publication, measurements included 0.5 and 1 hour after the end of the infusion. The average Cmax was 43.5 ± 11.2 (mean ± SD).

Figure 2 Ibuprofen concentrations from reference 3.

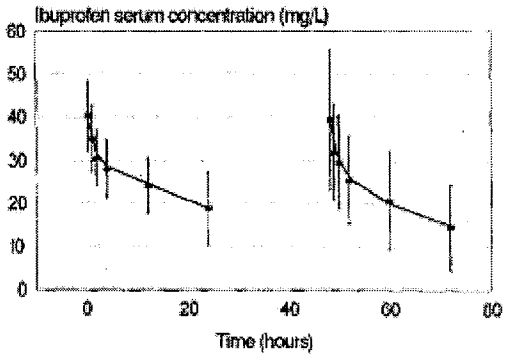


Fig 1. Ibuprofen plasma concentration versus time (mean ± standard deviation [SD]) after first and third doses.

Clinical:

The approval of ibuprofen for the treatment of hemodynamically significant patent ductus arteriosus is derived primarily from one prospective, placebo-controlled, multicenter study (#FCR-00-01/CB88). Two additional studies # CB88A and CB88B are supportive in nature. The two supportive studies were not performed under an IND and no prospective protocol was submitted to the FDA. The data obtained from these studies were retrospectively re-analyzed to support this application. CRFs were recreated and filled out in retrospect. Only pivotal data were source verified.

Efficacy:

Study FCR-00-01/CB88 was a randomized, placebo-controlled study of premature infants with assessed gestational age between 25 and 30 weeks, who weigh between 500 and 1000 g at the time of birth. They were to be less than 72 hours old and have an asymptomatic PDA at the time of enrollment. The definition of asymptomatic PDA includes the absence of three of the following five signs of suggestive of a hemodynamically significant ductus. Alternatively, if the

[3] Overmeire BV, Touw D, Schepens PJC, Kearns GL, Van den Anken JN; " Ibuprofen pharmacokinetics in Preterm Infants with Patent Ductus Arteriosus; Clin Pharamcol Therapeutics, 2001, 70; 4: 336-343.

neonatologist considered the degree of shunting significant, the PDA was considered as significant.

- Bounding pulses
- Hyperdynamic precordium
- Pulmonary edema
- Increased cardiac silhouette
- Systolic murmur

Or

- In view of the neonatologist is deemed to have a hemodynamically significant ductus.

Subjects were excluded for among other reasons:

- Major congenital or chromosomal abnormalities or the expectation that survival would be less than 48 hours.
- Confounding medical conditions such as shock (requiring vasopressors to maintain MAP); renal failure or oliguria; low platelet count (< 75,000 mm^3); bleeding diathesis (oozing form puncture wounds)
- Either maternal exposure within 72 hours of birth or exposure of the neonate within 24 hours of birth to NSAIDs.

The primary metric of efficacy was the need for rescue therapy to treat infants who develop a hemodynamically significant PDA as judged by the above-listed criteria. The protocol stipulates that a repeat Echocardiogram be performed prior to rescue.

Only a single dose regimen was studied. The regimen consisted of a 10 mg/kg infusion over 15 minutes of drug (NeoProfen) or placebo (NaCl) followed at approximately 24 and 48 hours with a 5 mg/kg infusion over 15 minutes.

The final evaluation of the subjects was at 36-weeks assessed gestational age, transfer from hospital, discharge or death.

The study enrolled 136 subjects, 68 to the NeoProfen and 68 to placebo. The baseline demographic data suggest the two groups were balanced. The gestational age, birth weight, maternal characteristics and delivery room history were similar.

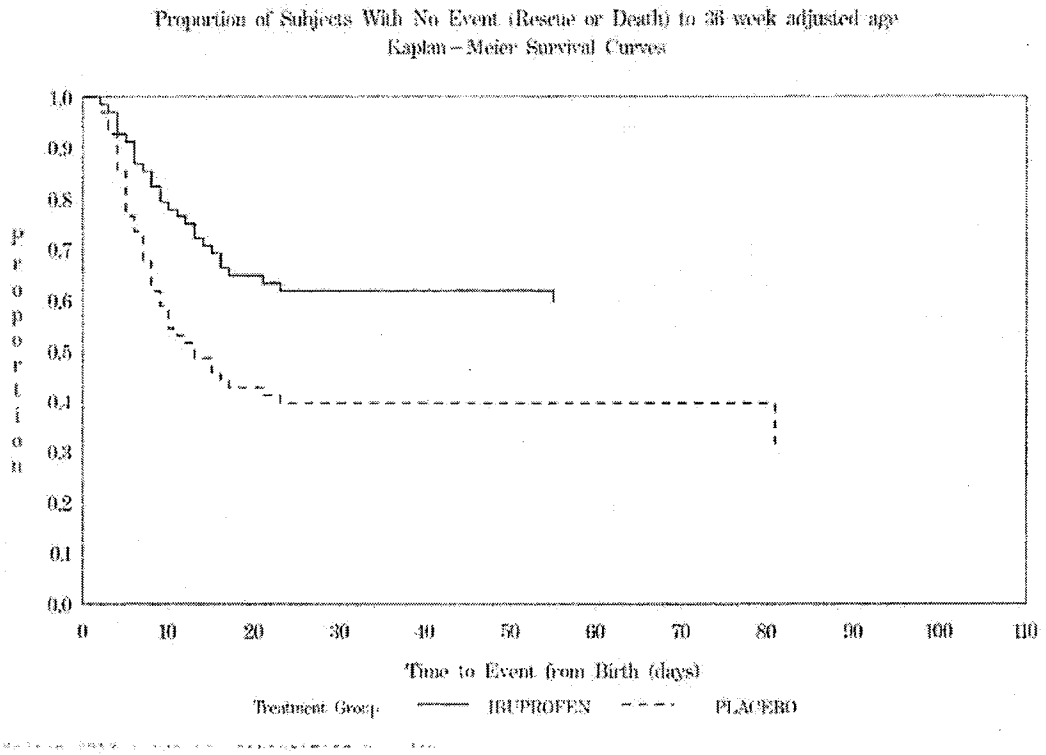
Table 2 Demographic of those enrolled into study FRC-00-01/CB88

Variable	NeoProfen (N=68)	Placebo (N=68)
Gestational age mean ± SD	26.1 ± 1.3	26.2 ± 1.4
< 27 weeks	51 (75%)	49 (72%)
27-28 weeks	14 (21%)	15 (22%)
29-31 weeks	3 (4%)	4 (6%)
Birth weight (g); mean ± SD	799 ± 129	797 ± 133
Gender male/ female n/n (% female)	32/36 (53%)	37/31 (46%)
Race Caucasian/Hispanic/Black /Other	23/21/17/7	18/28/18/4
1 minute /5 minute Apgar score; mean ± SD	4.3 ± 2.6/6.7 ± 2.1	4.4 ± 2.4/ 6.7 ± 1.9
Maternal age (years); mean ± SD	28 ± 6.6	28 ± 6.6

Received prenatal steroids yes (%)	51 (75%)	48 975%)
Type of delivery (vaginal/C-section)(%)	28 (42%)/ 40 (60%)	21 (31%)/ 47 (69%)
N % requiring resuscitation in the delivery room	68 (100%)	(93%)
Age at randomization (days)	1.5	1.4
PDA confirmed by Echo	68 (100%)	68 (100%)
Evidence of ductal shunting	Yes (98%)	Yes (100%)

A graph of the time-course for patients, who had events through 14 days, and throughout the observation period are shown below. The time course shows early separation of the curves by day 5 or 6; with nearly all events occurring by day 21 (See Figure 3).

Figure 3: Endpoints in study FRC-00-01/CB88, during the 14-day pivotal period and throughout the rest of the observation period.



With respect to the signs that necessitated rescue therapy (see Table 3), the results were largely driven by the assessment of the neonatologist, who deemed the shunting significant. Approximately 30% of those patients who were contemplated for rescue did not subsequently receive rescue therapy. Of those patients contemplated for rescue, 80% had significant shunting.

With respect to the rescue therapy, approximately 47% of those in the ibuprofen (8/17) and 27% (9/33) subject in the placebo group eventually required surgical ligation of the ductus.

Table 3 Outcome of patients in study FRC-00-01/CB88, including results of ECHO exams

	Ibuprofen (n=68)	Placebo (N=68)	p-value
# who required rescue/died or dropped out (primary metric)	21 (31%)	36 (53%)	
Required rescue	17 (25%)	33 (49%)	0.0028^
Died before day 14 without rescue	4 (6%)	3 (4%)	
Dropped out prior to day 14	0 (0%)	0 (0%)	
Characteristics of signs/ symptoms necessitating rescue**			
Bounding pulse	6 (9%)	12 (18%)	
Hyperdynamic precordium	2 (3%)	3 (4%)	
Pulmonary edema	3 (4%)	5 (7 %)	
Increased cardiac silhouette	1 (1%)	5 (7%)	
Systolic murmur	6 (9%)	15 (46%)	
Hemodynamically significant ductus per neonatologist***	14 (21%)	25 (37%)	
Day 14 characteristics of Ductus			
PDA confirmed by ECHO	Yes 10; no 45; missing 13	Yes 15; no 42, missing 11	
Evidence of ductal shunting	Yes 9; no 46; missing 13	Yes 14; no 43, missing 11	
Characteristics at time of contemplation of rescue			
PDA confirmed by ECHO	Yes 29; no 4	Yes 44; no 3	
Evidence of ductal shunting	Yes 27; no 7	Yes 43; no 4	
Nature of Rescue therapy: Any	17 (25%)	33 (49%)	
Indomethacin or ibuprofen	15	33	
Indomethacin	11	29	
Ibuprofen	4	4	
Surgical ligation	8*	9	

^Logistic regression model with factors as treatment and site.
**Required 3 of the five for consideration for rescue.
*** Sufficient by itself to consider rescue therapy.
* Two subjects were surgically ligated without prior medical rescue.

There did not appear to be any evidence that early ibuprofen treatment altered the general course of hospitalization of these preemies. The need for oxygen, for ventilation (Table 4), the risk of intracranial hemorrhage or development of intraventricular hemorrhage (table 5), necrotizing enterocolitis (Table 5) was not altered by early treatment. Long term follow up for neuro-developmental assessments (i.e., at approximately at 18 months) were not performed. Deaths during the entire observation period favored ibuprofen but the small difference is as likely as not being the play-of-chance.

Table 4: Status of respiratory support, study FRC-00-01/CB88.

	Require O_2				Intubated			
	NeoProfen		Placebo		NeoProfen		Placebo	
	Yes	Missing	Yes	Missing	Yes	Missing	Yes	Missing
Day 1	66 (97%)	0 (0%)	62 (91%)	0 (0%)	56 (82%)	0 (0%)	52 (77%)	0 (0%)
Day 4	61 (92%)	2 (3%)	56 (83%)	1 (2%)	42 (64%)	2 (3%)	41 (61%)	1 (2%)
Day 14	56 (89%)	5 (7%)	55 (87%)	6 (9%)	38 (60%)	5 (7%)	35 (56%)	6 (9%)

Table 5: Description of intracranial hemorrhage and necrotizing entercolitis, study FRC-00-01/CB88

	NeoProfen	Placebo
IVH through day 14	23/67 (34%)	22/67 (33%)
IVH Grade III-IV	11/67 (16%)	10/67 (15%)
IVH all study records	26/67 (39%)	25/67 (37%)
IVH Grade III-IV all study records	11/67 (16%)	10/67 (15%)
Necrotizing enterocolitis (NEC)	9 (14%)	9 (14%)
Pre-NEC	3 (4%)	4 (6%)
Definite	2 (3)	0 (0%)
Advanced	4 (6%)	5 (7%)

Dose-response:

There is no information in this submission concerning regimens other than the single regimen NeoProfen of a 10 mg/kg dose followed at 24 and 48 hours by 5 mg/kg dose intravenously, administered over 15 minute. This regimen was used in all studies. This regimen appears to be sufficiently effective and safe for approval.

Subgroup analyses:

There did not appear to be any differences in efficacy based on gender. Categorizing subjects based on birth weight < 750 grams and 751-1015 grams did not indicate a difference in benefit based on birth weight. Considering those < and ≥ 28 weeks the number requiring rescue also favored active treatment.

With respect to the effect of NeoProfen based on race, there were substantial effects in the black and Hispanic group, but little effect in Caucasians. The direction of effect in Caucasian infants, however, was not adverse (See Table 6).

Table 6: Outcome based on race study FRC-00-01/CB88

Demographic group	Ibuprofen-L-lysine	Placebo
Black (number requiring rescue /number enrolled) (%)	2/17 (12%)	8/18 (44%)
Hispanic (number requiring rescue /number enrolled) (%)	5/21 (24%)	17/28 (61%)
Caucasian (number requiring rescue /number enrolled) (%)	8/23 (35%)	7/18 (39%)
Other (number requiring rescue /number enrolled) (%)	2/7 (29%)	1/4 (25%)

Safety:

Deaths:

There were 10 deaths during the 14-day observation period, five in each treatment group. There were three additional ibuprofen deaths and 5 placebo deaths during the rest of the hospital observation period. The Tabular listing of the deaths is shown below. The causes of death in the two groups consist of events, which unfortunately, are common in the severely premature population. The causes of deaths include respiratory failure, sepsis or sepsis secondary to NEC and IVH.

Table 7: Cause of death study FRC-00-01/CB88

Pt ID/gender/ gestational age	Cause	Age (days)
Ibuprofen		
8901013/F/24	Proteus and Staphylococcus septicemia	55
8901033/F/26	Respiratory failure	3
8901034/F/26	Respiratory failure	22
9341032/F/25	Refractory PPHN, extreme prematurity, severe metabolic acidosis	8
9351032/M/26	Sepsis Pseudomonas, IVH grade III	8
9501019/F/23	Suspected sepsis, NEC with perforation , post mortem blood culture grew E faecalis and lung culture of yeast	35
9802021/M/26	IVH grade IV, elective extubation	6
9801012/F/23	IVH grade IV on right and Grade III on left, elective extubation	2
Placebo		
8901011/M/27	Pneumothorax	2
8901015/F/24	Neonatal sepsis	41
8901017/F/27	Pulmonary interstitial emphysema leading to intractable hypoxemia	13
8902048/F/27	Cardiac arrest, extreme acidosis	11
9001003/M/23	NEC with suspected sepsis	81
9401010/M/26	Perforated NEC	59
9412004/M/24	Perforated NEC	21
9551020/M/25	Neonatal sepsis, withdrawal of care per parent's request	24
9552084/M/26	Cardio-respiratory failure secondary to fungal septic shock	13
9551044/F/24	Severe IVH, redirected care, cardiorespiratory failure	5

Overall adverse events:

Dr. Ellis Unger (Deputy Director) recoded the large number of events based on re-categorizing the verbatim description. Each verbatim description could be classified under more than one term. For example, pulmonary hemorrhage would be classified under bleeding and respiratory. Below are listed those re-categorized events with at least three more events in the NeoProfen-treated group. None of the events would by themselves be considered as evidence for a drug-related adverse event. Events more frequent in the placebo group than the NeoProfen group by at least three subjects, e.g., metabolic acidosis 22 (32%) versus 17(25%) were not included in this table. Overall, there is insufficient numbers of subjects to either suggest that NeoProfen increases or decreases any set of adverse events.

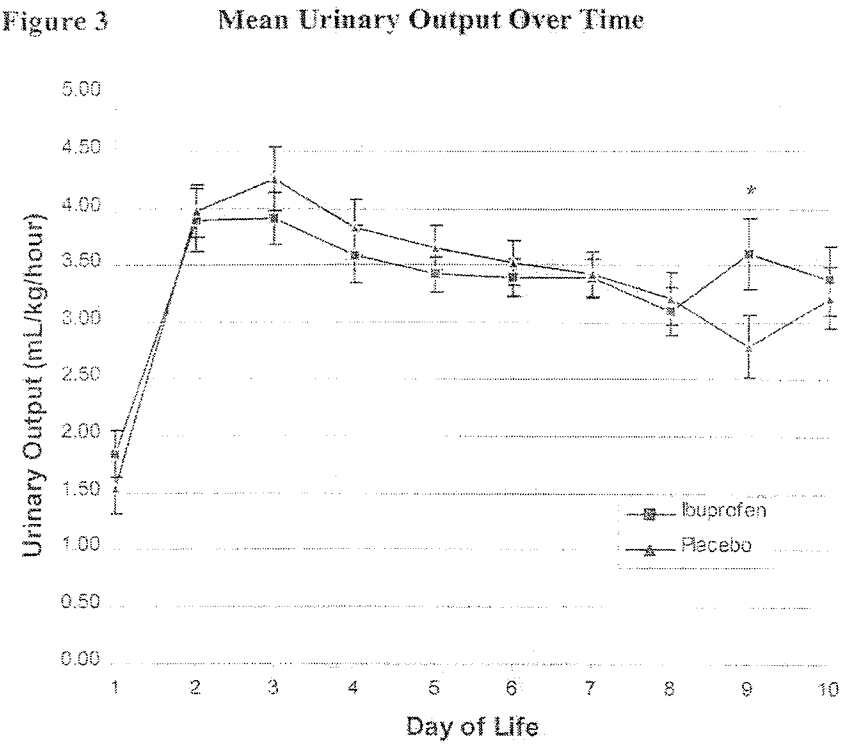
Table 8; Adverse events occurring during the observation period and up to 30-days after the use of drug in study FRC-00-01/CB88, with number at least 3 greater in the ibuprofen treated group.

Term	NeoProfen (N=68)	Placebo (N=68)
Apnea	25 (37%)	22 (32%)
Bleeding	24 (35%)	19 (29%)
Hyperbilirubinemia, icterus	23 (34%)	21 (31%)
Intraventricular hemorrhage	22 (32%)	18 (26%)
Anemia	22 (32%)	18 (26%)
Desaturation, hypoxia	16 (25%)	13 (19%)
Respiratory infection	13 (19%)	8 (12%)
Renal failure, insufficiency	13 (19%)	8 (12%)
Hyponatremia	13 (19%)	11 (16%)
Hypoglycemia	8 (12%)	4 (6%)
Skin lesion, irritation	7 (10%)	3 (4%)
Urinary tract infection	6 (9%)	2 (3%)
Adrenal insufficiency	5 (7%)	1 (1%)
Hypernatremia	5 (7%)	3 (4%)
Edema, fluid overload	4 (6%)	0 (0%)
Atelectasis	4 (6%)	2 (3%)
Respiratory failure	3 (4%)	0 (0%)
Conjunctivitis, eye infection	3 (4%)	1 (1%)
Heart murmur	3 (4%)	1 (1%)
Vomiting	3 (4%)	1 (1%)
Intestinal perforation	3 (2%)	0 (0%)
Patent ductus arteriosus	3 (4%)	0 (0%)

Effects on Urine output:

Compared to placebo (Figure 4), there was a small decrease in urinary output in the ibuprofen group on days 2-6 of life (probably day 1-4 of treatment), with a compensatory increase in urine output on day 9 (day 8 of treatment). Adverse events classified as renal insufficiency were more frequent among ibuprofen treated infants. This category captures renal insufficiency, oliguria, anuria, elevated BUN, elevated creatinine or renal failure.

Figure 4: Urine output study FRC-00-01/CB88



Study CB88A

This was a randomized, multicenter, but open-labeled study comparing indomethacin to ibuprofen in premature infants with ECHO-documented PDAs, with respiratory distress syndrome and who were between 37 to 84 hours old. Those premature infants not randomized, received no treatment. The doses of ibuprofen were the same as used in study FCR-00-01/CB88. The dose of Indomethacin was 0.2 mg/kg body weight at 12 hour intervals (for three doses). There were 73 infants in each of the ibuprofen and Indomethacin groups.

With respect to safety, there were seven ibuprofen, and six indomethacin patients who died by day 17. The specifics are shown below:

Table 9: Specifics of death study CB88A

Pt ID/Gender/GA weeks)	Reason	Age (day) of onset
Ibuprofen		
#29/M/27	Pneumothorax day 6, pulmonary hypertension, heart failure, thrombocytopenia sepsis	27
#95/F/26	Grade III-IV IVH, bradycardia, poor saturation	2
#203/M/ 26	IVH , Candida culture	15
#207/F/29	Sepsis, taken off ventilator	29
#216/M/28	Pneumothorax, Candida infection, NEC	15
#302/M/26	IVH, oxygen desaturation	3
#512/M/29	IVH progressed from day 1 to Grade IV on day 5	6
Indomethacin		
#3/F/25	Sepsis, rapid deterioration	11

#5/F/26	IVH grade III, NEC	3
#56/M/27	Respiratory deterioration/ IVH, intervention discontinued	5
#208/F/Not stated	Hyperglycemia, hypertension, Candida infection, poor urinary output, cholestasis	17
#210/F/26	Surgical ligation on study day 2, hypotension, bleeding, metabolic acidosis low urine output, IVH grade II	4
#501/M/28	Bilateral IVH evolved to grades II and III	2

Serious adverse events in the ibuprofen and indomethacin treated groups are shown in Tables 10 and 11.

Table 10: Serious adverse events study CB88A

Term	Ibuprofen	Indomethacin
Sepsis neonatal	36 (49%)	30 (41%)
Intraventricular hemorrhage	8 (11%)	5 (7%)
Hydrocephalus	3 (4%)	0 (0%)
Respiratory distress syndrome	3 (4%)	1 (1%)
NEC	2 93%)	2 (3%)
Catheter sepsis	2 (3%)	0 (0%)
Pneumonia	2 (2%)	2(2%)
Pneumothorax	2 (3%)	2 (3%)
Periventricular leukomalacia	1 (1%)	1 (1 %)
Candida infection	1 (1%)	3 (4%)
Mu8lti-organ failure	0 (0%)	2 (3%)

Table 11: Selected adverse events study CB88A

Event	Ibuprofen (n=73)	Indomethacin (n=73)
NEC diagnosed at follow up	10 (14%)	11 (15%)
Advanced NEC	1 (1%)	2 (3%)
Bronchopulmonary dysplasia-Need for O_2 at 28 days	44 (60%)	35 (48%)
IVH		
IVH all grades all records	20 (27%)	20 (26%)
IVH grade III-IV all records	9(12%)	5 (7%)

CB88B

This study was a randomized, double-blind, placebo-controlled, multicenter study, conducted outside of the IND. No protocol was submitted and the data was retrospectively captured and transcribed to ad hoc CRFs. Those enrolled were preterm infants < 30 weeks assessed gestational age, and less than 6 hours of age. No assessment of baseline PDA status was made. Infants were assigned to ibuprofen with the same regimen as used in other studies, or placebo.

There were 433 infants randomized to either ibuprofen (n=215) or placebo (n=218). The mean birth weight in the ibuprofen and placebo groups was 1047 and 1065 grams, respectively.

There were 35 reported deaths 14 in the ibuprofen group and 21 in the placebo group during the 14-day observation period. Overall, there were 47 deaths; 22 in the ibuprofen group and 25 in the placebo group. There was no strong signal suggesting either a benefit or harm of ibuprofen. The specifics of the cause of death are shown below:

Table 12: Deaths study CB88B

Patient ID/Gender/GA	Event	Day of death
Ibuprofen		
#12/F/27	Respiratory failure	3
#49/M/27	Persistent hypoxemia, respiratory acidosis, cardiac failure, pulmonary interstitial emphysema	3
#50/F/29	IVH grade IV, coagulation problems	4
#51/F/29	IVH Grade IV, coagulation problems	5
# 72/F/27	Cardio-respiratory failure	54
#110/F/29	Sepsis	6
#214/M26	Grade III-IV IVH, stopped therapy	1
# 216/F/29	IVH, septic shock	7
# 313/F/24	Sepsis	55
#316/M/29	IVH grade III	25
#325/F/24	Respiratory failure	32
#343/F/24	Respiratory failure	57
#438/M/27	Sepsis, multiple organ failure	32
#465/M/24	Kidney insufficiency	18
#466/M/24	IVH Grade IV	2
#501/M/24	Sepsis with Candida albicans	24
#508/M/29	Grade III IVH, respiratory failure	8
#614/F/25	Sepsis, Grade III-IV IVH	38
# 615/M/27	IVH Grade IV	4
# 627/M/30	Kidney insufficiency, injection site extravasations	31
#703/M/25	Cardiac failure	40
#736/M/25	IVH Grade IV	2
Placebo		
#27/M/26	Cardio-respiratory arrest	2
#30/F/26	Cardio-respiratory arrest	2
#40/M/27	E. coli sepsis, cardio-respiratory arrest, possible IVH	4
#44/M/26	Hypoxemia	0
#58/M/28	Metabolic acidosis, E. coli sepsis	1
#61/M/29	IVH Grade IV	3
# 88/M/28	Respiratory insufficiency	9
# 95/M/27	Cardiovascular failure	26
#99/M/27	IVH	2
#201/F/25	IVH and intra-parenchymal hemorrhage	6
#206/M/25	IVH Grade IV, care discontinued	2
#211/M/26	IVH Grade II-IV, hypovolemic shock, care discontinued	1
#218/M/26	Peri-operative complications	58
#225/F/28	Septic shock and ICH	4
#301/F/27	Respiratory failure	8
#322/F/25	Respiratory and circulatory failure	1
#331/M/25	Respiratory insufficiency	22
#405/F/27	Septic shock	41
#406/F/29	Enterobacter sepsis	59
#431/F/25	Respiratory failure and pneumothorax	13
#616/F/27	IVH Grade IV	4
#651/F/26	Multiple organ failure	16
#667/M/27	IVH Grade IV	5
#728/M/26	Cardiac failure	2
#746/F/28	IVH grade IV, leukomalacia	57

The number of infants with serious adverse was slightly greater in the placebo group than in the treated group. The sponsor's tabulation of the results is shown below. I've also included information from other outcomes of concern.

Table 13: Serious adverse events study CB88B

Term	Ibuprofen	Placebo
Intestinal perforation	11 (5%)	4 (2%)
Neonatal infection	6 (3%)	1 (< 1%)
Neonatal sepsis	29 (14%)	51 (23%)
IVH	15 (7%)	17 (8%)
ANY IVH (serious and non-serious)	65 (30%)	69 (32%)
Grade III-IV	15 (8%)	18 (8%)
leucomalacia	47 (22%)	38 (18%)
RDS	10 (5%)	11 (5%)
Catheter sepsis	7 (3%)	8 (4%)
NEC	4 (2%)	11 (5%)
Meconium ileus	3 (1%)	5 (2%)
Thrombocytopenia	2 (1%)	6 (2%)

There were 8 ibuprofen subjects who discontinued for evidence of low urine output or indications of renal failure (not included as serious adverse events).

In summary, the retrospective nature of the assessment of adverse events diminishes the reliability of the results. Nevertheless, the results of this and the other post-hoc assessed studies are sufficiently similar for a reasonable description of NeoProfen's safety.

DMETS:

DMETS expressed concern for the potential of medication errors related to the look-alike similarities between NeoProfen, the proposed Trade name, and Naprosyn and Naproxyn when transcribed. Since, however, NeoProfen would be available only as a clear intravenous formulation, whereas the liquid forms of Naprosyn and Naproxyn are suspensions. The likelihood of inadvertently administering a suspension for intravenous use was considered by the Division and Office to be remote. Farmacon-IL was notified that the trade name NeoProfen was acceptable.

DDMAC:

DDMAC's comments related to the proposed labeling were considered in the process of the Division's editing of the label.

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/s/

Abraham Karkowsky
3/1/2006 04:51:23 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type: NDA

Submission Number: 21,903

Submission Code: N-000

Letter Date: 8/30/05

Stamp Date: 9/02/05

PDUFA Goal Date 3/01/06

Reviewer Name: Maryann Gordon, MD

Review Completion Date: 01/20/06

Established Name: Ibuprofen Lysinate Injection

(Proposed) Trade Name: TBD

Therapeutic Class: Nonsteroidal anti-inflammatory agent

Applicant: Farmacon-IL, LLC

Priority Designation: P

Formulation: Injection

Indication: Patent ductus arteriosus

Intended Population: Premature, low birth weight infants

1. Executive summary

One pivotal study and two supportive[1] studies have demonstrated ibuprofen L-lysine (hereafter referred to as ibuprofen) to be effective in closing asymptomatic as well as symptomatic patent ductus arteriosus (PDA) in premature infants. Similar to indomethacin, the only drug currently approved for the treatment of symptomatic PDA, ibuprofen induces oliguria with concomitant increases in BUN and serum creatinine. This effect on the kidney appears to be transient. Minor anemia is also associated with the use of ibuprofen. The relationship between the use of ibuprofen in premature infants and the occurrence of intraventricular hemorrhage remains unknown. Overall, there are no convincing data showing the benefit of using ibuprofen prior to the development of symptomatic PDA.

Efficacy

One study (and supporting data) convincingly showed that the prophylactic use of ibuprofen in premature infants is effective in decreasing the need to treat these infants for symptomatic patent ductus arteriosus (PDA). Although not as well studied (one supportive study), ibuprofen also was shown to be effective in the treatment of symptomatic PDA, the indication preferred by this reviewer.

Safety

There is no indication from either of the three studies or meta-analyses that ibuprofen increases the mortality rate in premature infants. Controlled studies and the literature showed less urine output with concomitant fluid retention and increases in BUN and serum creatinine in infants randomized to ibuprofen compared to those randomized to placebo. These abnormalities appear to resolve by one week after the last dose. Necrotizing enterocolitis, intestinal perforation, and respiratory failure were the most commonly reported serious adverse events (2.9% placebo-subtracted). The placebo subtracted incidence rate for grade III/IV intraventricular hemorrhage was 1.5%[2].

Adverse events described as "significant but not serious" included anemia (10.3% placebo-subtracted), sepsis (8.8% placebo-subtracted), and pneumonia (5.8% placebo-subtracted), sepsis (3.8% placebo-subtracted), and hypernatremia (4.5% placebo subtracted). The reporting rate for hypotension in one of the supporting studies was high (9.4% placebo-subtracted), but this was not confirmed by other studies and questions were raised about the blinded status of the individual who transcribed the case record forms.

Questions about an adverse effect of ibuprofen on the premature lung, particularly its role in promoting pulmonary hypertension in very young infants (<6 hours from birth), have been raised in the literature[3]. There is little evidence of pulmonary complications hypertension in this NDA data base.

Formulation: The trial conducted in the U.S. used ibuprofen L-lysine; the formulation used in Europe (including that used in the supportive studies) is ibuprofen d,l-lysine. [redacted]

The sponsor had been advised to characterize the pharmacologic activity, if any, of the lysine component of the formulation.

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[1] Studies were not conducted under the IND, studies were not always blinded, primary endpoints were changed, case record forms were created retrospectively and were completed in an unblinded fashion.

[2] Based on revised information

[3] Gournay V, Savagner C, Thiriez G, Kuster A, Roze JC. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002;359:1486-7

Recommendation: approval for the use of ibuprofen for the closure of [redacted] patent ductus arteriosus in premature infants weighing between 500 and [redacted] kg, inclusive, up to [redacted] weeks gestational age. [redacted]

Deficiencies [redacted] : long term (one year or longer) outcome data evaluating long term mortality as well as growth and development in infants who received ibuprofen because of a symptomatic PDA. Dose response studies are recommended but may not be possible with limited sample sizes.

Conclusions about the superiority or inferiority of ibuprofen in safety and efficacy compared to indomethacin are not possible [redacted] Long term outcome data regarding the kidney as well as other organs such as the brain are unknown and should be pursued by the sponsor. Considering the adverse events associated with ibuprofen, the lack of long term outcome data, the high spontaneous closure rates, the lack of obvious harm when treatment is delayed until the onset of symptoms, and the satisfactory results with closing symptomatic PDA with treatment, prophylactic use is not recommended.

Four month safety update: Study FTP-03-01 (treatment protocol) was an open-label, uncontrolled trial in infants weighing between 500 and 1750 g with a hemodynamically significant PDA, and unresponsive to 12 hours of the usual medical management. This treatment protocol permitted investigators who were not part of the clinical development program to treat premature infants with ibuprofen lysine IV. Data for 16 infants who participated in this study were considered in the initial NDA. There were 25 additional infants enrolled into the protocol since the cut off date for the NDA. Of the 25 infants not described previously, 6 died after enrolling in the ibuprofen-lysine IV treatment protocol. One infant died from respiratory failure, two infants died from severe bronchopulmonary dysplasia, one died from necrotizing enterocolitis, one died from septic shock, and one died from multi-system organ failure. This information does not alter the overall conclusions of the NDA review.

Introduction

Patent ductus arteriosus (PDA) is a common complication for premature infants, thought to occur in 40-80% of low birth weight premature infants. Not all of these infants become symptomatic. One report[4] stated that out of 3779 very low birth weight infants, 28% required treatment for PDA. Those who do become symptomatic can develop congestive heart failure and are considered to be at an increased risk of developing chronic long disease, intraventricular hemorrhage, necrotizing enterocolitis. Indomethacin is the only drug currently approved for closure of a hemodynamically significant PDA when usual medical treatment (fluid restriction, diuretics, digitalis, respiratory support, etc.) is ineffective. Surgical ligation is used when indomethacin fails to close the ductus. Information about the studies used to approve the use of indomethacin is briefly discussed below.

Indocin® IV

In double blind, placebo controlled studies with indomethacin IV (Indocin® IV) with 460 preterm infants, those randomized to indomethacin did not have significantly higher rates of spontaneous intraventricular hemorrhage, major gastrointestinal bleeding, retrolental fibroplasia or pneumothorax. Events that were higher in the indomethacin group compared to placebo included significant reduction in urine output (accompanied by elevations of BUN, serum creatinine, reductions in glomerular filtration rate and

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[4] Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, et al. Variations in practice and outcomes in the Canadian NICU Network 1996-1997. Pediatrics 2000;106:1070-9.

creatinine clearance and weight gain) as well as electrolyte imbalance including hyponatremia, elevated serum potassium, and weight gain. The infants who received indomethacin also had a higher incidence of bleeding.

Cochrane reviews (ibuprofen)
There are two meta-analyses by the Cochrane review, one examining the use of ibuprofen as treatment[5] and one examining the use of ibuprofen in prevention[6]. Summaries from both reviews are presented here.

Ibuprofen studies for NDA review
Three completed controlled studies (FCR-00-011CB88, CB88A, and CB88B) and one ongoing uncontrolled study (FTP-03-01) are included in the review.

Cochrane reviews

Ibuprofen for treatment of PDA
"Eleven studies including 620 patients compared the effectiveness of ibuprofen to indomethacin for the closure of a PDA. There was no statistically significant heterogeneity of treatment effect for any of the outcomes. For the primary outcome (failure of ductal closure), there was no statistically significant difference between ibuprofen and indomethacin groups [typical RR 0.96 (95% CI 0.74, 1.25)]. There were no statistically significant differences in mortality, surgical duct ligation, duration of ventilator support, IVH [intraventricular hemorrhage], PVL [periventricular leukomalacia], NEC [necrotizing enterocolitis], time to full enteral feeds, ROP [retinopathy of prematurity], sepsis, duration of hospital stay or gastrointestinal bleed. For many of these outcomes the sample size was small and the estimates imprecise. The incidence of decreased urine output (< 1 cc/kg/hr) was lower in the ibuprofen group as compared to the indomethacin group [NNT 9 (95% CI 5-14)]. This was the only statistically significant clinical finding favoring ibuprofen. Chronic lung disorder defined as oxygen requirement at 28 days post-natally was statistically significantly more likely to occur in the ibuprofen group [typical RR 1.37 (95% CI 1.01, 1.86); NNH 7 (95% CI 3 - 100)]. There was a similar trend for CLD at 36 weeks corrected gestational age."

The reviewers' concluded:
"We found no statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing the PDA. Ibuprofen reduces the risk of oliguria. However, ibuprofen may increase the risk for chronic lung disease, and pulmonary hypertension has been observed in three infants after prophylactic use of ibuprofen. Based on currently available information ibuprofen does not appear to confer a net benefit over indomethacin for the treatment of a PDA. We conclude that indomethacin should remain the drug of choice for the treatment of a PDA. The most urgent research question to be answered is whether ibuprofen compared to

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[5] Ohlsson A, Walia, R, Shah S, "Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants" published as a Cochrane review in The Cochrane Library, Issue 1, 2005.

[6] Shah S, Ohlsson A, "Ibuprofen for the prevention of patent ductus arteriosus in preterm/or low birth weight infants" published as a Cochrane review in The Cochrane Library, Issue 4, 2005.

indomethacin confers an improved rate of intact survival (survival without impairment) at 18 months corrected age."

Ibuprofen for prevention of PDA
"Four trials (n = 623) were included in the review. There was a statistically significant decrease in the incidence of PDA on day three in the ibuprofen group [typical RR 0.36 (95% CI 0.26, 0.49); typical RD -0.29 (95% CI -0.37, -0.21); NNT 3 (95% CI 3, 5); 3 trials, n=488]. There was a significant increase in the serum creatinine levels in the ibuprofen group [WMD 0.11 mg/dl (95% CI 0.06, 0.17); 2 trials, n=438]. There were no statistically significant differences in mortality, grade 3 or 4 IVH, chronic lung disease (CLD) at 28 days or 36 weeks, need for surgical closure of PDA, NEC, GI hemorrhage, time to reach full feeds and urine output. One trial[7] reported on three infants in the ibuprofen group who developed pulmonary hypertension responsive to nitric oxide treatment."

The reviewers' concluded:
"Prophylactic use of ibuprofen reduces the incidence of PDA. However, further trials, which address potential adverse effects including pulmonary hypertension, are needed. Such trials should include long term neuro-developmental outcomes. Trials comparing the effectiveness of prophylactic use of indomethacin versus ibuprofen may be warranted with particular reference to IVH, need for surgical ligation and neuro-developmental outcome."

Summary of efficacy
Conclusions
Premature infants with an asymptomatic PDA randomized to ibuprofen early after birth were significantly more likely to not require rescue therapy to close a PDA that became symptomatic compared to those randomized to placebo (study FCR-00-01/CB88 with support from CB88B). There is evidence to support [redacted]

(open label study CB88A).

There is no evidence that doses/dosing intervals other than 10 mg/kg followed by 2 doses of 5 mg/kg each, after 25 and 48 hrs are not as effective and safer. There are no studies evaluating dose response/dosing intervals.

Completed controlled, randomized study summaries
There are three studies in this category. One study is pivotal (conducted under IND); the other two studies were based on re-analyses of the primary endpoint from journal articles[8]. There are numerous other published articles discussing studies, not conducted under an IND, with the use of ibuprofen either as [redacted] These studies were not submitted as part of the NDA.

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[7]Gournay V, Savagner C, Thiriez G, Kuster A, Roze JC. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002;359:1486-7.

[8] [redacted] sent trained nurses to Belgium to source verify the original data and then transferred these data to new CRFs developed by [redacted] They noted they have exclusive rights to all original data and CRFs of the European studies. Dr. Gordon expressed concern that although the source verification was likely done in a thorough manner, it nevertheless was being done on trials that were unblinded and thus could further compromise the integrity of the data. Meeting minutes 4-28-04

All three submitted studies used a single dose of ibuprofen lysine IV: 10 mg/kg followed by 2 doses of 5 mg/kg each, after 25 and 48 hrs. All had the primary endpoint for the NDA of the proportion of infants who were rescued (i.e., received indomethacin IV, ibuprofen IV (European sites only), and/or underwent surgical ligation), died, or dropped out on or prior to study day 14 because of a symptomatic PDA. The evidence of a symptomatic PDA required a positive ECHO and 3 of the following: bounding pulse, hyperdynamic precordium, pulmonary edema, increased cardiac silhouette, systolic murmur, or, in view of the neonatologist, there was a hemo-dynamically significant ductus. The three studies are shown in detail in the table below.

study ID	countries involved	control group	no. of subjects randomized/ duration of study	prophylaxis or treatment
FCR-00-01/CB88 (pivotal)	US and Belgium	placebo	136/14 days	prophylaxis
CB88A (journal article)	Belgium	no treatment+	210/14 days	treatment ^
CB88B (journal article)	Belgium	placebo	433/28 days	prophylaxis

+a randomized indomethacin group was also included in the study
^ i.e., had a diagnosis of respiratory distress syndrome.

Follow up outcome were collected at 36 weeks adjusted gestational age

Study FCR-00-01/CB88 was a double-blind, placebo-controlled, randomized, multicenter study evaluating a three-day treatment course with ibuprofen IV or placebo given to very low birth weight infants (500 to 1000 g) with non-symptomatic PDA at less than 72 hours of life. The study was conducted under the US IND.

Study CB88A was a randomized, prospective, active-controlled multicenter study that enrolled preterm infants (gestational age < 33 weeks) with respiratory distress syndrome (RDS) and an echocardiographically confirmed PDA. The re-analysis included data from three groups of preterm infants: no treatment, indomethacin IV, ibuprofen lysine IV. The no treatment group consisted of non randomized infants who did not receive any active treatment per parental request. The data from the no treatment group were not included in the original publication.

Study CB88B was a double-blind, placebo-controlled, randomized, multicenter study in asymptomatic infants of ≤ 30 weeks' gestational age. Primary safety endpoints were the percentage of infants with intraventricular hemorrhage (IVH) and the percentage of infants with periventricular leukomalacia (PVL). Infants received either three doses of ibuprofen IV or three doses of placebo. Although the primary objective of this study was to evaluate the safety of ibuprofen IV in the prevention of PDA, the reanalysis evaluated the proportion of infants who were rescued, died, or dropped out on or prior to Study Day 14.

Ongoing, open label, uncontrolled study
There is one ongoing study with one open investigational site.

study ID/type of subject	countries involved	control	no. of subjects

		group/dose used	enrolled/efficacy
FTP-03-01/low birth weight with hemodynamically significant PDA		none/10 mg/kg followed by two doses of 5 mg/kg given 24 hand 48 hrs later.	16/8 had closed ductus after first ibuprofen course, and 8 required further rescue treatment

Study FTP-03-0l (treatment protocol) is an ongoing, open-label, uncontrolled safety trial in infants weighing between 500 and 1750 g with a hemodynamically significant PDA, unresponsive to 12 hours of the usual medical management. Infants receive three doses of ibuprofen IV. If this therapy fails to induce ductal closure and the ductus is judged to be hemodynamically significant, the same treatment could be repeated, the infant could be treated with indomethacin IV, or undergo surgical ligation. The incidence of adverse events, serious or life threatening conditions, or death, especially of those known to be related to the use of investigational drug in infants such as renal failures, metabolic disturbances, gastrointestinal, hepatic, and hematological abnormalities are to be reported. Closure or non-closure of the PDA was also reported. This study is not discussed further in this efficacy review.

Results

The primary efficacy endpoint was the proportion of infants who received rescue treatment for PDA, died, or dropped out on or prior to study day 14. The results for all controlled studies are shown below by clinical trial.

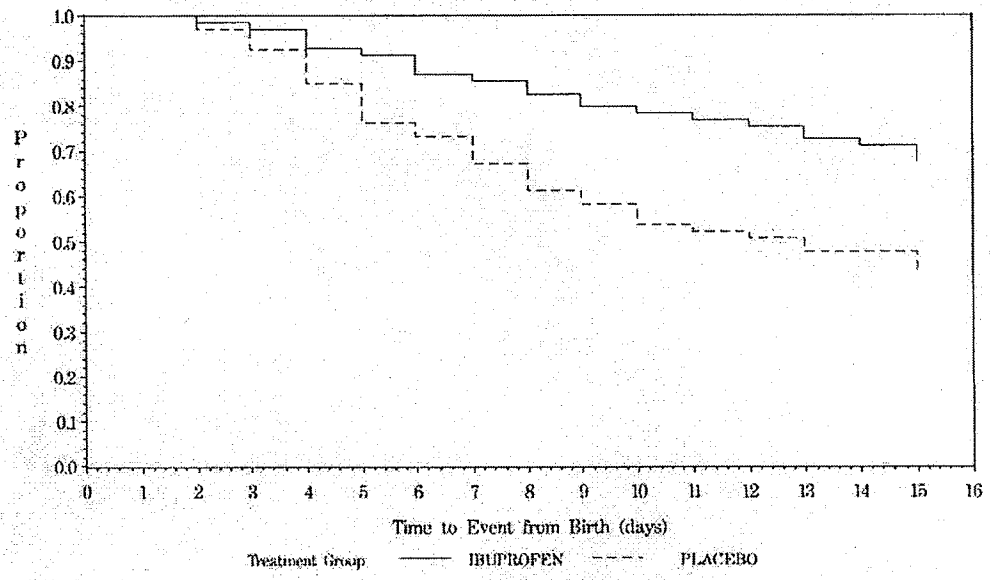
No. and (percent) rescued, died, or dropped out

study	ibuprofen	indo-methacin	placebo or no Rx	odds ratio estimate (95% CI)	p-value
FCR-00-01/CB88	21 (30.4)	NA	36 (53.7)	0.329 (0.157, 0.689)	0.0032+
CB88A++	25 (34.2)	24 (32.9)	32 (50.0)		0.0131^
CB88B	31 (14.4)	NA	68 (31.2)		<0.0001

+ibuprofen vs. placebo (logistic regression)
++study was treatment of symptomatic PDA
^ibuprofen vs. placebo

The figure below shows the proportion of infants not needing rescue, death or dropout through day 14 for the pivotal study FCR-00-01/CB88.

Figure 1 **Proportion of Infants With No Event (Rescue, Death, or Dropout) on or Prior to Study Day 14 (Study FCR-00-01/CB88)**



Note: Median Study Day 1 age is approximately one day. Curves ending at proportion > 0 show the remaining percentage of infants censored. Infants were censored on Study Day 14.
Log-rank p-value is 0.0033.
Cross-reference: Section 10.3, Figure 1

The number and percent of subjects requiring rescue treatment are shown below by study.

No. and (percent) of subjects rescued

study	ibuprofen	indo-methacin	Placebo or no Rx
FCR-00-01/CB88	17 (24.6)	NA	21 (30.9)
CB88A	19 (26.0)	15 (20.5)	25 (39.1)
CB88B	12 (5.6)+	NA	46 (21.1)

+denominator is 214

In all three studies, fewer subjects who received ibuprofen required rescue therapy compared to subjects who received placebo or no treatment.

Blood concentration

The mean average ibuprofen concentrations were 24.8 ug/mL and 25.2 ug/mL for subjects who did and those who did not receive rescue therapy, died or dropped out, respectively.

Subpopulations

The percentages of infants who were rescued, died, or dropped out by gender for the pivotal study are shown below.

No. and (percent) of subjects

Gender	Ibuprofen n = 69	Placebo n = 67
Male	24.2 (8/33)	52.8 (19/36)
Female	36.1 (13/36)	54.8 (17/31)

Subjects, regardless of gender, were less likely to require rescue therapy, or to die or to drop out of study if they had been randomized to ibuprofen.

The proportion of infants who were rescued, or died, or dropped out always lower in the group randomized to ibuprofen compared to placebo independent of birth weight, gestational age, delivery type, and requirement for high frequency oscillatory ventilation.

Dose/dosing interval
Studies evaluating various doses and dosing intervals of ibuprofen were not submitted as part of the NDA.

Summary of safety
Conclusions
There is no indication from either of the three studies or the meta-analyses that ibuprofen increases the mortality rate. All three studies, and the literature, showed less urine output with concomitant fluid retention and increases in BUN and serum creatinine in infants randomized to ibuprofen compared to those randomized to placebo (FCR-00-01/CB88 and CB88B) or no treatment (CB88A). These abnormalities appear to resolve by one week after the last dose and there is no evidence of long lasting harm. While one study (CB88A) indicated that renal impairment may be greater with indomethacin compared to ibuprofen, a confirmatory study would be necessary for one to have confidence in this conclusion.

Serious adverse events in pivotal study FCR-00-01/CB88 that were reported more often by ibuprofen subjects include grade III/IV intraventricular hemorrhage (incidence rate of 4.4% placebo-subtracted), necrotizing enterocolitis, intestinal perforation, and respiratory failure (each with an incidence rate of 2.9% placebo-subtracted). In the study CB88A, reporting of serious intraventricular hemorrhage was higher in the ibuprofen group (11%) compared to indomethacin (6.8%) and no treatment (7.8%). Reporting of nonserious (grade I/II) intraventricular hemorrhage in study FCR-00-01/CB88 was higher in the ibuprofen group (3.0% placebo-subtracted). Neither meta-analyses nor CB88B found a higher incidence of serious intraventricular hemorrhage with ibuprofen. Of the other serious events stated above, only intestinal perforation is higher in the ibuprofen group compared to placebo in study CB88B (3.3% placebo-subtracted).

Adverse events described as "significant but not serious" and reported in study FCR-00-01/CB88 with a high incidence rate include anemia (10.3% placebo-subtracted) confirmed by lower mean hemoglobin /hematocrit study day 4 in the ibuprofen group compared to placebo, sepsis (8.8% placebo-subtracted), and pneumonia (5.8% placebo-subtracted). Sepsis was reported in study CB88B (3.8% placebo-subtracted). Hypernatremia was also reported more often in the ibuprofen group (4.5% placebo subtracted). The reporting rate for hypotension in study CB88B was high (9.4% placebo-subtracted), but this was not confirmed by other studies and questions were raised about the blinded status of the individual who transcribed the case record forms for the two supporting studies.

Study summaries
Study FCR-00-01/CB88 was designed to determine whether prophylactic treatment with ibuprofen lysine IV would reduce the need for rescue therapy (indomethacin or surgical ligation) for a symptomatic PDA

when given to new-born very low birth weight infants with a non-symptomatic PDA. In this double-blind, placebo-controlled, randomized, multicenter study, ibuprofen lysine IV or placebo was administered intravenously to 136 premature infants < 30 weeks' gestational age who weighed between 500 and 1000 g and exhibited a non-symptomatic PDA with ECHO-documented evidence of ductal shunting. Infants in the ibuprofen lysine IV group received a three-day dosing regimen: an initial dose of 10 mg/kg followed by two doses of 5 mg/kg each, after 24 and 48 hours. Infants in the placebo group received a three-day dosing regimen with the same volume: an initial dose of 1.0 mL/kg followed by two doses of 0.5 mL/kg each, after 24 and 48 hours. The study drugs were infused continuously over a period of 10 to 15 minutes.

Safety summary
Mean urine output was lower for days of life one through five for the ibuprofen group (292 mL) compared to the placebo group (302 mL). By day 6, the mean outputs were equivalent. Mean BUN and serum creatinine values were also higher in the ibuprofen group although these elevations also were temporary.

Other safety findings:
-the numbers of deaths reported up to study day 14 were identical for the 2 treatment groups (5 deaths per group);
-the incidence rates[9], placebo subtracted, for ibuprofen subjects reporting IVH either as grade I/II or grade III/IV were 1.5% and 0%, respectively;
-the incidence rate, placebo subtracted, for ibuprofen subjects reporting necrotizing enterocolitis (reported as a serious adverse event) was 2.9%;
-the reporting rates, placebo subtracted, for pulmonary hemorrhage and pulmonary hypertension -4.4% and 1.4%;
-the incidence rate, placebo subtracted, for anemia was 10.3%;
-the incidence rate, placebo subtracted, for sepsis was 8.8%.

Serious adverse events reported by at least 2 ibuprofen subjects and reported more often by ibuprofen subjects compared to placebo subjects are shown below.

No. and (percent) of subjects

	Ibuprofen Lysine IV (N=68)	Placebo (N =68)	placebo subtracted
Number of subjects with ≥1 serious adverse event	29 (42.6)	31(45.6)	-3.0
Intraventricular hemorrhage neonatal+	10 (14.7)	7 (10.3)	4.4
Necrotizing enterocolitis neonatal	7 (10.3)	5 (7.4)	2.9
Intestinal perforation	2 (2.9)	0 (0.0)	2.9
Respiratory failure	2 (2.9)	0 (0.0)	2.9

+grade III/IV

Adverse events that were designated as significant but not serious and had a placebo subtracted reporting rate of 3% or greater are shown below.

No. and (percent) of subjects

	Ibuprofen (n=68)	Placebo (n=68)	placebo subtracted %
Number of subjects with at least	60 (88.2)	63 (92.6)	

[9] numbers based on revised data.

one adverse event			-4.4
Preferred Term			
Anemia neonatal^	21 (30.9)	14 (20.6)	10.3
Sepsis neonatal	21 (30.9)	15 (22.1)	8.8
Neonatal pneumonia	9 (13.2)	5 (7.4)	5.8
Hypernatremia	5 (7.4)	2 (2.9)	4.5
Hypoglycemia neonatal	7 (10.3)	4 (5.9)	4.4
Urinary tract infection neonatal	6 (8.8)	3 (4.4)	4.4
Intraventricular hemorrhage neonatal grades I/II	11 (16.2)	9 (13.2)	3.0

^the incidence rates for blood transfusions were 3% less in the ibuprofen group compared to placebo. Changes in hematocrit and hemoglobin are shown below.

Mean baseline and change from baseline (SD) for hematocrit and hemoglobin

Parameter (unit)	Evaluation	Mean	
		Ibuprofen n=69	Placebo n =67
Hematocrit (%)			
	Baseline	42.5 (6.3)	42.3 (7.0)
	Change to Worst	-0.9 (3.8)	0.6 (4.2)
	Change to Last	-6.5 (6.3)	-3.9 (8.1)
Hemoglobin (g/dL)			
	Baseline	14.2 (2.1)	14.1 (2.4)
	Change to Worst	-0.1 (1.0)	0.4 (1.6)
	Change to Last	-1.9 (2.1)	- 1.1 (2.7)

Changes in hematocrit/hemoglobin indicate that the use of ibuprofen could cause a minor anemia.

Study CB88A was a randomized, open label, prospective, active-controlled multicenter study that enrolled preterm infants (gestational age < 33 weeks) with respiratory distress syndrome (RDS) and a PDA confirmed by echocardiogram. Study CB88A report is the reanalysis of data from the original publication with creation of case record forms used to collect data for the study report and inclusion of data from a third group (a "no treatment" group) that was not randomized. There were 146 infants randomly assigned to receive three doses of either indomethacin IV (0.2 mg/kg of body weight, given at 12-hour intervals) or ibuprofen lysine IV (first dose of 10 mg/kg, followed at 24-hour intervals by two doses of 5 mg/kg each), starting on the second or third day of life. The medications were infused over a period of 10-15 minutes. There were 64 infants who were in the "no treatment" group. The primary efficacy endpoint for the reanalysis was the proportion of infants who were rescued on or prior to Study Day 14. Safety was provided for the 14-day study period as well as up to 36 weeks gestational age.

Safety summary

Compared to the no treatment group, subjects who received ibuprofen showed a decrease in urine output and a rise in BUN and creatinine. By day of life 14, the values for the 2 active treatment groups became similar, indicating that any drug-induced adverse effects on the kidney are most likely short-lived. There is an indication that there is less fluid accumulation with lower increases in BUN and serum creatinine in the ibuprofen group compared to indomethacin. Any definitive conclusions regarding long term renal effects and the use of ibuprofen compared to indomethacin would need a confirmatory study.

Mean hematology parameters were lower for both ibuprofen and indomethacin subjects compared to the no treatment group for days of life 1, 4, and 8. The anemia reported with the use of indomethacin and ibuprofen appears to be of little consequence.

The numbers of subjects who died either during to study (through day 14) or after study day 14 are shown below.

	ibuprofen n=73	indomethacin n=73	no treatment n=64
died on or before study day 14	4 (5)	4 (5)	2 (3)
died after study day 14	3 (4)	2 (3)	2 (3)

The deaths rates are similar across treatment groups.

Compared to indomethacin, the incidence rates were higher in the ibuprofen groups for several reported events (sepsis, IVH, and hydrocephalus).

Table 13 Common Treatment-Emergent Serious Adverse Events

	Ibuprofen (N=73) n (%)	Indomethacin (N=73) n (%)	No Treatment (N=64) n (%)
Number of subjects with ≥1 serious adverse event	36 (49.3)	30 (41.1)	22 (34.4)
Preferred Term			
Sepsis neonatal	16 (21.9)	11 (15.1)	15 (23.4)
Intraventricular haemorrhage neonatal	8 (11.0)	5 (6.8)	5 (7.8)
Hydrocephalus	3 (4.1)	0 (0.0)	2 (3.1)
Neonatal respiratory distress syndrome	3 (4.1)	1 (1.4)	2 (3.1)
Necrotising enterocolitis neonatal	2 (2.7)	2 (2.7)	1 (1.6)
Catheter sepsis	2 (2.7)	0 (0.0)	0 (0.0)
Neonatal pneumonia	2 (2.7)	2 (2.7)	1 (1.6)
Pneumothorax	2 (2.7)	2 (2.7)	3 (4.7)
Periventricular leukomalacia	1 (1.4)	1 (1.4)	2 (3.1)
Neonatal Candida infection	1 (1.4)	3 (4.1)	0 (0.0)
Neonatal multi-organ failure	0 (0.0)	2 (2.7)	0 (0.0)

Includes preferred terms with an incidence of ≥2.0% in any treatment group. Presentation is in the order of decreasing incidence in the ibuprofen treatment group.
Cross-reference: Appendix Table 1004

Serious adverse events including pulmonary hemorrhage, pulmonary hypertension, necrotizing enterocolitis, and bronchopulmonary dysplasia were similar for the active treatment groups. The reporting of IVH throughout the trial is shown below.

No. and (percent) of subjects

	ibuprofen % (n/N)	indomethacin % (n/N)	no treatment % (n/N)
IVH though study day 14	25 (18/72)	26 (17/66)	17 (10/59)
IVH grade III/IV though study day 14	13 (9/72)	8 (5/66)	7 (4/59)
IVH all study records+	27 (20/73)	29 (20/68)	21 (13/61)

IVH grade III/IV all study records+	12 (9/73)	7 (5/68)	7 (4/61)
IVH diagnosed at follow up	12 (16.4)	7 (9.6)	10 (15.6)

+Through day of life 102

There was more IVH diagnosed at follow up in the ibuprofen group (16.4%) compare to the indomethacin group (9.6%).

Study CB88B was a double-blind, placebo-controlled, randomized, multicenter trial in infants of ≤ 30 weeks' gestational age. The study was conducted in Belgium and not under an IND. The original objective was to evaluate safety of ibuprofen in premature infants with particular emphasis on the occurrence of IVH and periventricular leukomalacia (PVL). Study CB88A report is the reanalysis of data from the original publication with retrospective creation of case record forms used to collect data for the study report. The primary endpoint for the reanalysis was the proportion of infants who required rescue therapy (indomethacin or surgical ligation) for a symptomatic PDA on or prior to Study day 14. Safety was provided for the 14-day study period as well as up to 36 weeks gestational age.

Four hundred thirty-three infants (215 randomized to ibuprofen and 218 randomized to placebo) received either three doses of ibuprofen lysine IV (initial loading dose of 10 mg/kg within the first six hours of life, followed by two doses of 5 mg/kg after 24 hours and 48 hours) or three doses of placebo (initial dose of 1 mL/kg, followed by 0.5 mL/kg after 24 hours and 48 hours).

Safety summary

Urine output was significantly less for the ibuprofen group compared to placebo study days 1-2. By day 4, urine output was similar for the two groups. Mean BUN and serum creatinine values were higher in the ibuprofen group on study day 3. The differences disappeared over a short time period, although mean creatinine was still higher on day 7 in the ibuprofen group compared to placebo.

Mean (SD) creatinine (mg/dl)

day 1		day 3		day 7	
ibuprofen	placebo	ibuprofen	placebo	ibuprofen	placebo
0.81 (0.33)	0.78 (0.18)	1.16 (0.26)	1.02 (0.22)	0.91 (0.23)	0.86 (0.22)

mean (SD) creatinine (mg/dl)

day 1		day 3		day 7	
ibuprofen	placebo	ibuprofen	placebo	ibuprofen	placebo
0.81 (0.33)	0.78 (0.18)	1.16 (0.26)	1.02 (0.22)	0.91 (0.23)	0.86 (0.22)

Table 15

By day 7, creatinine values were similar between the treatment groups.

There were 11 reported deaths in the ibuprofen group and 18 in the placebo group on or before study day 14. Between study days 14 and 28, there were 3 deaths reported for each treatment group.

Serious adverse events reported more often by the ibuprofen group compared to placebo were intestinal perforation and neonatal infection (placebo subtracted incidence rates of 3.3% and 2.3%, respectively).

The treatment groups have similar reporting rates of IVH regardless of grade (30.2% and 31.7% for ibuprofen and placebo, respectively, for all grades combined).

The incidence rate for subjects with any NEC diagnosed was 11.2% for the ibuprofen group[10] compared to 11.5% for the placebo group[11].

The reporting of leukomalacia was slightly higher in the ibuprofen group (22%) compared to placebo (17.6%). This is probably a chance finding.

The placebo subtracted incidence rate for significant but not serious adverse events was the highest for hypotension/neonatal hypotension (9.4%), followed by urine output decreased/ oliguria (4.6%), neonatal jaundice (4.3%), and sepsis (3.8%). This is the first and only indication that hypotension is being reported at a high rate in the ibuprofen group. Jaundice is also a surprise.

Study FTP-03-01 (treatment protocol) was an open-label, uncontrolled safety trial in infants weighing between 500 and 1750 g with a hemodynamically significant PDA, unresponsive to 12 hours of the usual medical management. Infants received three doses of ibuprofen lysine IV (initial dose of 10 mg/kg, followed by two doses of 5 mg/kg after 24 hours and 48 hours).

A total of 16 subjects had been enrolled at the time of NDA preparation. There were 2 reported deaths: one death resulted from pulmonary interstitial emphysema at day of life 15 and one death from fungal sepsis, bowel perforation and respiratory failure at day of life 12. Reported serious adverse events are shown in the table below.

No. and (percent) of subjects

	Ibuprofen n=16
Number of infants with ≥ 1 treatment-emergent serious adverse event	11(68.8)
Event	
Retinopathy of prematurity[12]	7 (43.8)
Intraventricular hemorrhage[13]	6 (37.5)
Death	2 (12.5)
Necrotising enterocolitis neonatal	1 (6.3)
Renal failure	1 (6.3)

Retinopathy of prematurity is the most commonly reported serious event followed by IVH. There is no control group, making any conclusions difficult.

Drug interactions

The following concomitant drugs had a higher than expected placebo subtracted rate for selected significant but nonserious adverse events in study FCR-00-01/CB88.

-Aminoglycosides and anemia: placebo subtracted rate was 13.8% (10/56 used ibuprofen and aminoglycoside; 2/49 used placebo and aminoglycoside).

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[10] Missing 44 subjects

[11] missing 56 subjects

[12] compared to 11% ≥ stage 3 ROP reported in Lee (2000)

[13] compared to 10% ≥ grade 3 IVH reported in Lee (2000)

-Cephalosporins and sepsis: placebo subtracted rate was 15.9% (7/21 used ibuprofen and cephalosporin; 4/23 used placebo and cephalosporin).
-sodium bicarbonate and anemia: placebo subtracted rate was 13.1% (18/48 used ibuprofen and sodium bicarbonate; 11/445 used placebo and sodium bicarbonate).
-sodium bicarbonate and sepsis: placebo subtracted rate was 15.5% (16/48 used ibuprofen and sodium bicarbonate; 8/45 used placebo and sodium bicarbonate).
-Lasix and anemia: placebo subtracted rate was 14.4% (16/26 used ibuprofen and Lasix; 4/17 used placebo and lasix).
-dopamine/dobutamine and sepsis: placebo subtracted rate was 17.2% (7/24 used ibuprofen and dopamine/dobutamine; 3/25 used placebo and dopamine/dobutamine).
-dopamine/dobutamine and apnea: placebo subtracted rate was 13.0 % (6/24 used ibuprofen and dopamine/dobutamine; 3/25 used placebo and dopamine/dobutamine).
-penicillin/aminopenicillin and anemia: placebo subtracted rate was 24.4 % (14/39 used ibuprofen and penicillin/aminopenicillin; 3/26 used placebo and penicillin/aminopenicillin).
-penicillin/aminopenicillin and metabolic acidosis: placebo subtracted rate was 14.1 % (10/39 used ibuprofen and penicillin/aminopenicillin; 3/26 used placebo and penicillin/aminopenicillin).
-penicillin/aminopenicillin and hyponatremia: placebo subtracted rate was 19.3 % (9/39 used ibuprofen and penicillin/aminopenicillin; 1/26 used placebo and penicillin/aminopenicillin).
-penicillin/aminopenicillin and hyperbilirubinemia: placebo subtracted rate was 14.1 % (7/39 used ibuprofen and penicillin/aminopenicillin; 1/26 used placebo and penicillin/aminopenicillin).

It is difficult to draw any conclusions about the interactions of a particular medication and ibuprofen based on data from the small sample size.

Birth weight
Infant between 750g or less were more likely to have anemia if they received ibuprofen (8.7%). Infants over 751 g were more likely to have sepsis if they received ibuprofen (10.1%).

Gender
Female infants were more likely to have anemia if they received ibuprofen (17.2%).

Withdrawal effects
This has not been investigated during this development program.

INDIVIDUAL STUDY REVIEWS

FCR-00-01/CB88 Clinical Study Review

This was a double-blind, placebo-controlled, randomized, multicenter study designed to evaluate the effect of ibuprofen lysine IV compared to placebo on the closure of non-symptomatic patent ductus arteriosus (PDA) in premature infants weighing between 500 and 1000 kg, inclusive, and less than 72 hours old. The study was conducted in the USA (10 sites) and Belgium (1 site).

Subjects were randomized centrally to either ibuprofen lysine IV (first dose of 10 mg/kg, followed by two doses of 5 mg/kg given 24 hours apart) or placebo IV. Drug administration took place over 3 days. Stratification was based on weight (500 to 750 kg and 751 kg to 1000 kg). A total of 136 subjects were randomized.

Inclusion criteria

premature newborn infants of either gender admitted to the neonatal intensive care unit of each of the participating hospitals and

1. had a birth weight of 500 to 1000 grams, up to 30 weeks gestational age;
2. had a non-symptomatic PDA with evidence of ductal shunting documented by ECHO;
3. were less than 72 hours of age at the time of randomization;
4. if an infant was one of a multiple birth, he/she was one of the two oldest infants who met the eligibility criteria;
5. the consent form signed by parent.

Exclusion criteria

1. Major congenital malformations and/or chromosomal anomalies;
2. Proven, severe congenital bacterial infection;
3. Maternal antenatal NSAID exposure < 72 hours prior to delivery;
4. Treatment with pharmacological replacement steroid therapy at anytime since birth;
5. Unremitting shock requiring very high doses of vasopressors (i.e., inability to maintain mean arterial blood pressure appropriate for gestational age + 2 standard deviations using volume and maximal vasopressor therapy as defined by the individual institution);
6. Renal failure or oliguria defined as urine flow rate < 0.5 mL/kg/hr in the eight hours prior to randomization (anuria was acceptable if infant was in first 24 hours of life);
7. Platelet count < 75,000/mm3;
8. Clinical bleeding tendency (i.e., oozing from puncture sites);
9. Expected survival less than 48 hours in the opinion of the attending neonatologist;
10. Participation in other clinical intervention trials. Exceptions had to be approved;
11. Symptomatic PDA as documented by three of the following five criteria: bounding pulse, hyperdynamic precordium, pulmonary edema, increased cardiac silhouette, systolic murmur. Or, in view of the neonatologist, was deemed to have a hemodynamically significant ductus.
12. Exposure to NSAIDs at any time since birth.

Study plan

The primary efficacy parameter was the need for rescue therapy (indomethacin or surgery) to treat a symptomatic PDA through study day 14. A symptomatic PDA was defined as documentation of three of the following five criteria: bounding pulse, hyperdynamic precordium, pulmonary edema, increased cardiac silhouette, systolic murmur, or had a hemodynamically significant ductus as determined by a neonatologist.

Other study evaluations included clinical laboratory tests, fluid intake and output, echocardiograms, physical assessment, weight and vital signs, cerebral ultrasound measurement of IVH, respiratory function, NEC, occurrence of severe pulmonary hemorrhage, and presence of pulmonary hypertension.

Follow-up outcomes were collected at 36 weeks adjusted gestational age ±7 days, at the time of discharge or transfer from facility, or at the time of death. Additional data collected included occurrence of retinopathy of prematurity (ROP), occurrence of bronchopulmonary dysplasia (BPD), and diagnosis of peri-ventricular leukomalacia (PVL). Adverse events were collected through 30 days after the last dose of study drug.

Disallowed medication:
-maternal antenatal NSAID received <72 hours prior to delivery;
-pharmacological replacement steroid therapy
-NSAID except study drug.

A data and safety monitoring committee reviewed data (groups were identified as A and B) at various points of subject completion. Efficacy outcome was not split into groups A and B.

Results
Subjects were randomized between July, 2002 and September, 2004.

Disposition of subjects
The numbers of subjects randomized by drug group are shown below.

Number of subjects

	ibuprofen	placebo
randomized	68	68
received wrong study drug	1	0
did not receive all 3 doses of study drug	5	7
died on or before day 14	5	5
premature study discontinuation except death	3	6
followed to study day 14	62	63

A total of 136 subjects were randomized, 68 to ibuprofen and 68 to placebo. One subject in both groups did not receive the study drug to which he was randomized. These two subjects were prematurely discontinued after receiving 2 doses of study drug because the randomization numbers did not match the syringe numbers. There were 13 subjects (5 ibuprofen and 7 placebo) who did not receive all 3 doses of study drug and 124 subjects who did. There were 5 ibuprofen and 5 placebo deaths up to study day 14.

A total of 119 subjects completed the study and 17 subjects (7 ibuprofen and 10 placebo) who prematurely discontinued including deaths. The reasons for the discontinuations are shown in the table below.

No. and (percent) of subjects

	Ibuprofen Lysine IV	Placebo
Intent-to-treat population, n	68	68
Completed the study	61	58
Prematurely discontinued the study (total)	7 (10.3)	10 (14.7)
Reason for discontinuation		
Adverse event	1 (1.5)	0 (0.0)
Removed by physician	1 (1.5)	4 (5.9)

Infant expired	4 (5.9)b	4 (5.9)c
Other	1 (1.5)	2 (2.9)

b A fifth infant (Subject 9502035) also died during the 14-day study period, but primary reason for premature discontinuation was 'removed by physician' (treatment with Indocin was planned).
c A fifth infant (Subject 8902048) also died during the 14-day study period, but primary reason for premature discontinuation was 'removed by physician' (IVH Grade 2).

The most common reason for not completing the study was death which occurred equally in both groups.

Demographics
Subject characteristics at baseline are shown below by treatment group.

Demographic and Baseline Characteristics

Variable	Ibuprofen (N=68)	Placebo (N=68)
Mean age (days)	1.5	1.4
Birth weight (g)		
Mean (SD)	798.5 (128.74)	797.3 (132.80)
Minimum, Maximum	537.0, 1005.0	530.0, 1015.0
Gestational age category (wks)		
<27,n(%)	51 (75.0)	49 (72.1)
27-28, n (%)	14 (20.6)	15 (22.1)
29-31,n(%)	3 (4.4)	4 (5.9)
Mean (SD)	26.1 (1.30)	26.2 (1.42)
Minimum, Maximum	23.0,30.3	23.4,30.0
Gender, n (%)		
Male	32 (47.1)	37 (54.4)
Female	36 (52.9)	31 (45.6)
Race, n (%)		
Caucasian	23 (33.8)	18 (26.5)
Hispanic	21 (30.9)	28(41.2)
Black	17 (25.0)	18 (26.5)
Other	6 (8.8)	2 (2.9)
Asian or Pacific Islander	1 (1.5)	2 (2.9)
1 Minute Apgar Score	(n-67)	(n-67)
Mean (SD)	4.3 (2.6)	4.4 (2.4)
Minimum, Maximum	0.0,9.0	0.0,9.0
5 Minute Apgar Score	(n-67)	(n=68)
Mean (SD)	6.7 (2.1)	6.7 (1.9)
Minimum, Maximum	1.0, 10.0	0.0,9.0
Maternal age (years)		
Mean (SD)	28.0 (6.6)	27.8 (6.6)
Minimum, Maximum	16.0,42.0	16.0,42.0
Received Prenatal Steroids, n (%)		
Yes	51 (75.0)	48 (70.6)
No	16 (23.5)	20 (29.4)
Not Available	1 (1.5)	0 (0.0)
One of Multiple Birth, n (%)		
Yes	14 (20.6)	19 (27.9)
No	54 (79.4)	49 (72.1)

Resuscitated in Delivery Room, n (%)		
Yes	68 (100.0)	63 (92.6)
No	0 (0.0)	4 (5.9)
Not Available	0 (0.0)	1 (1.5)
Type of Delivery, n (%)		
Vaginal	28(41.2)	21 (30.9)
C-section	40 (58.8)	47 (69.1)

SD=standard deviation

Mean birth weight was about 800 g, majority of subjects had a gestational age less than 27 weeks, approximately half were male, about one third were white, mean 1 and 5 minute Apgar were 4 and nearly 7, mean maternal age was 28 years, most subjects were not one of multiple births, nearly all had been resuscitated in the delivery room, and the majority had been born by C-section. The groups were reasonably well balanced considering the relatively small sample size.

Primary efficacy endpoint

The number and percent of subjects requiring rescue therapy (medical and/or surgical) are shown in the table below by treatment groups. There are also results including those who died or dropped out prior to study day 14 in addition to those requiring rescue.

No. and (percent) of subjects

	Ibuprofen (n=68)	Placebo (n=68)	p-values
Rescued through Study Day 14	17 (25.0)	33 (48.5)	0.0029a 0.0013b
Total rescued, died, or dropped out on or prior to Study Day 14	21 (30.9)	36 (52.9)	0.0052a 0.0014b

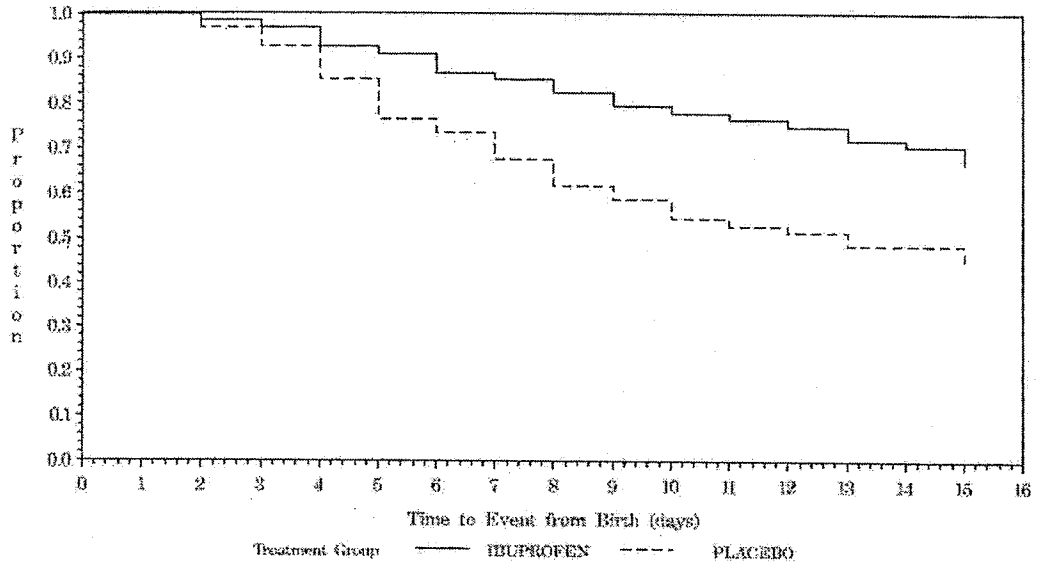
a Chi-square test based on logistic regression controlling for site.

b Logistic regression with factors for treatment group, site, birth weight group (500-750 g, 751-1015 g), gestational age (< 28, >28 weeks), sex, use or non-use of high frequency oscillatory ventilation, and maximum weight loss during the first seven days of life.

The incidence rate of subjects randomized to ibuprofen who required rescue therapy at or before day 14 was significantly different from than the rate of subjects randomized to placebo (25% and 48.5%, respectively). In addition, the incidence rate for subjects randomized to ibuprofen who required rescue therapy, died, or dropped out on or before day 14 was significantly less than the rate for the subjects randomized to placebo (30.9% and 52.9%, respectively).

Kaplan-Meier survival analysis for the proportion of infants with no need for rescue therapy, did not die, or did not drop out of the study through day 14 is shown below.

Figure 2 **Proportion of Infants With No Event (Rescue, Death, or Dropout) on or Prior to Study Day 14**



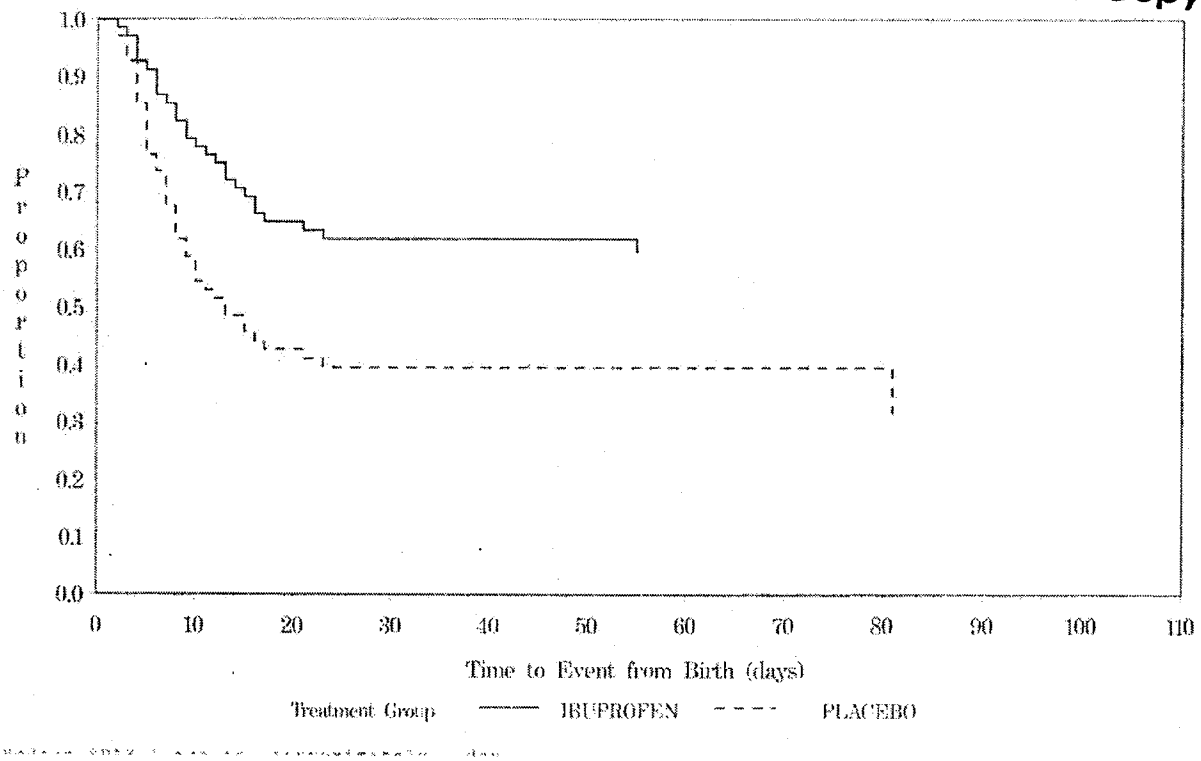
Note: Median Study Day 1 age is approximately one day. Curves ending at proportion > 0 show the remaining percentage of infants censored.
Log-rank p-value is 0.0056.

The curves for ibuprofen and placebo begin to separate, in favor of ibuprofen, most obviously by day 4.

Follow up information was obtained in 96% of all study patients (65 ibuprofen subjects and 65 placebo subjects). The Kaplan-Meier survival analysis for all rescues and deaths to 36 weeks gestational age is shown below.

Appears This Way
On Original

Figure 3
Proportion of Subjects With No Event (Rescue or Death) to 36 week adjusted age
Kaplan – Meier Survival Curves



There was a large treatment difference between ibuprofen and placebo for the proportion of infants needing rescue therapy and deaths up to 36 weeks gestational age.

Needing rescue therapy

Mean ages at start of first rescue therapy were 8.7 and 6.9 days for the ibuprofen and placebo groups, respectively.

The numbers of subjects who received drug and/or surgery as rescue therapy through study day 14 are shown below.

No. and percent (%) of subjects

	Ibuprofen n=68	Placebo n=68
received any rescue treatment	17 (25.0)	33 (48.5)
Indomethacin or Ibuprofen	15	33
Indomethacin	11	29
Ibuprofen	4	4
Surgical ligation	8[a]	9

a Two subjects were surgically ligated without prior medical rescue.

There were almost twice as many placebo subjects who needed rescue therapy (48.5%) within the 14 day study period compared to ibuprofen subjects (25.0%). Of the subjects who received rescue therapy, 17

underwent surgical ligation (8 ibuprofen and 9 placebo). All but 2 of the 17 subjects received medical rescue therapy (indomethacin and/or ibuprofen) prior to undergoing surgical ligation.

The signs of symptomatic PDA reported for the subjects who required rescue treatment through day 14 are shown below.

Number and (percent) of subjects

Symptom	Ibuprofen n=17	Placebo n=33
Bounding pulse	6 (35.3)	12 (36.4)
Hyperdynamic precordium	2 (11.8)	3 (9.1)
Pulmonary edema	3 (17.6)	5 (15.2)
Increased cardiac silhouette	1 (5.9)	5 (15.2)
Systolic murmur	6 (35.3)	15 (45.5)
Hemodynamically significant ductus per neonatologist	14 (82.4)	25 (75.8)

The signs of a symptomatic PDA were similar for both treatment groups.

The percents of subjects with no evidence of ductal shunting as determined by last ECHO obtained on day of life 9-19 were similar for the treatment groups (76.7% and 70.5% for ibuprofen and placebo, respectively).

Respiratory status

The incidence rates of those subjects who required oxygen and/or were intubated are shown below by treatment group.

No. and (percent) of subjects

	ibuprofen n=68		placebo n=68	
requiring oxygen?	Yes	missing	Yes	missing
day 1	66 (97.1)	0	62 (91.2)	0
day 4	61 (92.4)	2	56 (83.6)	1
day 14	56 (88.9)	5	55 (87.3)	6
intubated today?				
day 1	56 (82.4)	0	52 (76.5)	0
day 4	42 (63.6)	2	41 (61.2)	1
day 14	38 (60.3)	5	35 (55.6)	6

Table 9

There were small differences, probably inconsequential, between groups regarding the need for oxygen and/or intubation through day 14.

Results of echocardiogram

Echocardiograms were obtained at 1) < 72 hours of age, 2) study day 14, and 3) contemplating rescue. The study day 14 echo was not required if the subject's PDA had been closed by surgical ligation. The data obtained at these evaluations included

-was the PDA confirmed by echocardiogram?,

-was there evidence of ductal shunting?

-what was ductal size at the narrowest diameter.

No. of subjects

	ibuprofen n=68	placebo n=68
<72 hours of age		
PDA confirmed by echo	yes: 68, no: 0	yes: 68, no: 0
evidence of ductal shunting	yes: 67, no: 1	yes: 67, no: 1
mean ductal diameter (mm)	2.1 (n=33)	2.2 (n=29)
study day 14		
No. closed by surgery	8	9
PDA confirmed by echo	yes: 10, no: 45, missing: 13	yes: 15, no: 42 missing: 11
evidence of ductal shunting	yes: 9, no: 46, missing: 13	yes: 14, no: 43, missing: 11
mean ductal diameter (mm)	0.5 (n=12)	0.7 (n=14)
no. who underwent surgical ligation by day 14	8	9
no. who needed rescue medication by day 14	15	33
no. who discontinued by day 14 including deaths	8	11
contemplating rescue		
PDA confirmed by echo	yes: 29, no: 5	yes: 44, no: 3
evidence of ductal shunting	yes: 27, no: 7	yes: 43, no: 4
mean ductal diameter (mm)	2.6 (n=10)	2.9 (n=10)

Table 13 from study report

Safety

The mean ages at first dose of study drug were similar for the treatment groups (1.5 and 1.4 days for ibuprofen and placebo, respectively). The mean number of days on study drug was 12.7 for ibuprofen subjects and 12.8 days for placebo subjects.

Serious safety

Deaths

The reported deaths occurring during and after the 14 day study period are shown below by treatment group.

No. and (%) of subjects

	died during 14 day study period	died after 14 day study period	total deaths
Ibuprofen n=68	5 (7.4)	3 (4.4)	8 (11.8)
Placebo n=68	5 (7.4)	5 (7.4)	10 (14.7)

Appendix table 25

There were 10 deaths (5 ibuprofen and 5 placebo) reported during and an additional 8 deaths (3 ibuprofen and 5 placebo) reported after the 14-day study period.

The 18 reported deaths are shown in the table below.

Deaths

Subject #/Gender	Preferred Term[a]	Days to Onset/ Time to Death[b]	Cause of Death	Age at Death (days)	Gestational Age (weeks) at Birth
Ibuprofen					
89010 13/Female	Sepsis neonatal	14/54	Septicemia caused by Proteus Staphylococcus	55	25.4
8901 033/Female	Respiratory failure	0/1	Respiratory failure	3	26.0
8901 034/Female	Respiratory failure	9/19	Respiratory failure	22	26.3
9351 032/Female	Neonatal respiratory distress syndrome	4/7	Refractory PPHN, extreme prematurity, severe metabolic acidosis	8	25.4
9502035/ Male	Sepsis neonatal	3/7	Sepsis-Pseudomonas; IVH grade III	8	26.0
9501019/ Female	Necrotizing enterocolitis neonatal	3/34	Suspected sepsis; NEC with perforation; results of post-mortem with blood culture of *E. faecalis* and lung culture of yeast	35	23.0
9802021/ Male	Intraventricular hemorrhage neonatal	5/5	Elective extubation	6	25.7
9801012/ Female	Intraventricular hemorrhage neonatal	1/1	Extubation secondary to IVH Grade IV on the right and Grade III on the left	2	23.4
Placebo					
8901011/ Male	Pneumothorax	III	Pneumothorax	2	26.9
8901015/ Female	Sepsis neonatal	17/40	Untreatable infection	41	24.4
8901017/ Female	Hypoventilation neonatal	11/12	Pulmonary interstitial emphysema leading	13	27.4

			to refractory hypoxemia		
8902048/ Female	Sepsis neonatal	9/10	Cardiac arrest with extreme acidosis	11	27.0
9001 003/Male	no reported SAE	NA/81	NEC with suspected sepsis	81	23.4
94010 10/Male	no reported SAE	NA/58	Perforated NEC	59	26.0
9412004/ Male	Necrotizing enterocolitis neonatal	19/19	Perforated NEC	21	24.3
9551 020/Male	Sepsis neonatal	12/21	Withdrawal of care per parents' request	24	25.0
9552084 /Male	Fungal sepsis	10/12	Cardiorespiratory failure secondary to fungal septic shock	13	26.0
9551 044/Female	Thrombocyto-penia Intraventricular hemorrhage neonatal	3/3 -1/3	Re-directed care; extreme prematurity; severe IVH; cardiorespiratory failure	5	24.0

NA = Not applicable, SAE: serious adverse-event; PPHN = persistent pulmonary hypertension

a Adverse event with outcome of death.

b Days elapsed since first dose of study drug.

The reasons given for the 8 ibuprofen deaths included 2 cases of sepsis, 3 cases of respiratory failure/distress syndrome, 2 cases of intraventricular hemorrhage, and 1 case of necrotizing enterocolitis/sepsis.

The reasons given for the 10 placebo deaths included 4 cases of sepsis/suspected sepsis, 3 cases of perforated necrotizing enterocolitis/sepsis, 1 pneumothorax, 1 pulmonary interstitial emphysema, and 1 extreme prematurity/intraventricular hemorrhage.

The mean ages at deaths for all subjects who died were 17.4 days and 27 days for ibuprofen and placebo, respectively (table 25 form 28). The causes of death were similar across treatment groups. There were slightly higher mortality rates in the placebo group when all reports of death are included.

Treatment-Emergent Serious Adverse Events

SAEs reported by at least 2% of subjects in either treatment group are shown below.

No. and (percent) of subjects

	Ibuprofen Lysine IV (N=68)	Placebo (N =68)	placebo subtracted
Number of subjects with ≥1 serious adverse event	29 (42.6)	31(45.6)	-3.0
Intraventricular hemorrhage neonatal+	10 (14.7)	7 (10.3)	4.4
Necrotizing enterocolitis neonatal	7 (10.3)	5 (7.4)	2.9
Intestinal perforation	2 (2.9)	0 (0.0)	2.9
Respiratory failure	2 (2.9)	0 (0.0)	2.9
Sepsis neonatal	9 (13.2)	11 (16.2)	-3.0
Patent ductus arteriosus	3 (4.4)	6 (8.8)	-4.4
Adrenal insufficiency	2 (2.9)	1 (1.5)	1.4
Thrombocytopenia	1 (1.5)	2 (2.9)	-1.4
Neonatal respiratory distress syndrome	1 (1.5)	2 (2.9)	-1.4
Pneumothorax	1 (1.5)	2 (2.9)	-1.4
Pulmonary hemorrhage	0 (0.0)	2 (2.9)	-2.9

+only grades III and IV were reported as serious adverse events. Grades I and II were reported as significant but not serious adverse events.

The serious events reported more often by ibuprofen subjects include (grade III and IV) intraventricular hemorrhage (placebo subtracted rate of 4.4%), necrotizing enterocolitis, intestinal perforation, and respiratory failure (placebo-subtracted rate of 2.9% each).

The serious events including intraventricular hemorrhage, necrotizing enterocolitis, pulmonary hemorrhage, and pulmonary hypertension are discussed below.

Intraventricular hemorrhage (IVH)
IVH was identified by cerebral ultrasound and graded from I to IV.

The number and percent of subjects with reported IVH are shown below by degree of severity and treatment group.

No and (percent) of subjects

		(highest) IVH grade			
	any+	I	II	III	IV
ibuprofen n=66	20 (30.3)	4 (6.1)	8 (12.1)	6 (9.1)	2 (3.0)
placebo n=67	22 (32.8)	4 (6.0)	8 (11.9)	7 (10.4)	3 (4.5)

+through study day 14
Table 14

The incidence rates for subjects with any IVH were similar for the treatment groups (34.3% and 32.8% for ibuprofen and placebo, respectively) through study day 14. The rates by severity were also similar.

The sponsor sent a revised table incorporating corrections into the following table.

Number and (percent) of subjects

	Ibuprofen Lysine (n=68)	Placebo (n=68)
IVH through Study Day 14	34.3 (23/67)	32.8 (22/67)
IVH Grade 3-4 through Study Day 14	16.4 (11/67)	14.9 (10/67)
IVH - all study records	38.8 (26/67)	37.3 (25/67)
IVH Grade 3-4 - all study records	16.4 (11/67)	14.9 (10/67)

The incidence rates are similar across treatment groups and grades of IVH.

Necrotizing enterocolitis (NEC)
NEC was grouped by stages:
-Pre-NEC: suspect or stage I suggestive clinical signs but X-ray non-diagnostic
-Definite: stage II pneumatosis intestinalis either mildly ill or moderately ill (acidosis, thrombocytopenia or ascites).
-Advanced: stage III critical with impending or proven perforation.

The reports of NEC by treatment group are shown below.

No. and (percent) of subjects

	ibuprofen n=65	placebo n=65
any stage	9 (13.8)	9 (13.8)
pre-NEC	3	4
Definite	2	0
Advanced	4	5

Table 11

The incidence rates for reports of NEC were similar for both treatment groups for all stages combined as well as for individual stages.

Pulmonary hemorrhage, pulmonary hypertension
The reporting rates for these adverse events are shown below.

No. and (percent) of subjects

	Ibuprofen (n=68)	Placebo (n=68)
pulmonary hemorrhage	1 (1.5)	4 (5.9)
pulmonary hypertension	2 (2.9)	1 (1.5)

There is little difference between treatment groups regarding reporting rates of pulmonary hemorrhage or hypertension.

Others adverse events
Adverse events that were described as significant but not serious and reported by at least 5% of subjects in a treatment group are shown below.

No. and (percent) of subjects

	Ibuprofen	Placebo	placebo subtracted

	(n=68)	(n=68)	%
Number of subjects with at least 1 adverse event	60 (88.2)	63 (92.6)	-4.4
Preferred Term			
Anemia neonatal	21 (30.9)	14 (20.6)	10.3
Sepsis neonatal	21 (30.9)	15 (22.1)	8.8
Neonatal pneumonia	9 (13.2)	5 (7.4)	5.8
Hypernatremia	5 (7.4)	2 (2.9)	4.5
Hypoglycemia neonatal	7 (10.3)	4 (5.9)	4.4
Urinary tract infection neonatal	6 (8.8)	3 (4.4)	4.4
Intraventricular hemorrhage neonatal grades I/II	11 (16.2)	9 (13.2)	3.0
Hypocalcaemia	7 (10.3)	5 (7.4)	2.9
Blood urea increased	6 (8.8)	4 (5.9)	2.9
Hyperbilirubinemia neonatal	11 (16.2)	10 (14.7)	1.5
Oxygen saturation decreased	4 (5.9)	3 (4.4)	1.5
Respiratory failure	4 (5.9)	3 (4.4)	1.5
Neonatal apneic attack	19 (27.9)	18 (26.5)	1.4
Neonatal hyponatremia	12 (17.6)	11 (16.2)	1.4
Metabolic acidosis	13 (19.1)	16 (23.5)	-4.4
Hyperglycemia	11 (16.2)	12(17.6)	-1.4
Feeding problem in newborn	7 (10.3)	8 (11.8)	-1.5
Neonatal hypotension	7 (10.3)	9 (13.2)	-2.9
Thrombocytopenia neonatal	4 (5.9)	5 (7.4)	-1.5
Abdominal distension	4 (5.9)	6 (8.8)	-2.9
Medical device complication	4 (5.9)	6 (8.8)	-2.9
Jaundice neonatal	4 (5.9)	5 (7.4)	-1.5
Lung disorder	4 (5.9)	5 (7.4)	-1.5
Neonatal respiratory distress syndrome	3 (4.4)	9 (13.2)	-8.8
Blood glucose increased	2 (2.9)	5 (7.4)	-4.5
Fecal occult blood positive	2 (2.9)	4 (5.9)	-3.0
Hyperkalemia	2 (2.9)	4 (5.9)	-3.0
Convulsion neonatal	1 (1.5)	4 (5.9)	-4.4
Acidosis	0 (0.0)	4 (5.9)	-5.9

There were substantially more reports of anemia, sepsis and pneumonia from the ibuprofen group compared to the placebo groups (placebo-subtracted rates of 9.5%, 8.0% and 5.8%, respectively).

Clinical laboratory parameters

Baseline laboratory tests were obtained within 48 hours prior to study drug administration and included
-complete blood count (hemoglobin, hematocrit, total white cell count and platelet count);
-liver enzyme tests (ALT, AST, GGT); serum bilirubin (total and direct)
-BUN; creatinine; and
-electrolytes (sodium, potassium, chloride, and carbon dioxide (or bicarbonate where reported)).

Complete blood count (hemoglobin, hematocrit, total WBC, and platelet count) was required on day 4. Liver enzyme tests (ALT, AST, and GGT) were required on day 14.

Optional Laboratory Tests

Daily BUN, creatinine, serum bilirubin (total and direct), and electrolytes were recorded from Study Day 1 through Study Day 6. These measurements were recorded only if available from laboratory work completed as per standard of care.

Hematology
Subject (#8901013) randomized to ibuprofen reported thrombocytopenia (platelet count of 38,000/mm3) that led to premature discontinuation. This subject later died of sepsis (see Deaths). In addition to the case just cited, there were 4 ibuprofen subjects and 5 placebo subjects reporting (nonserious) neonatal thrombocytopenia (table 1002).

Anemia was reported as an adverse event in 21/68 (30.9%) ibuprofen subjects compared to 14/68 (20.6%) placebo subjects. The incidence rates for subjects needing blood transfusions up to study day 14 were 94% for ibuprofen and 97% for placebo (table 7). Positive fecal occult blood was the reported less often in the ibuprofen group.

Mean hematocrit and hemoglobin values at study day 1 and study day 4 are shown below by treatment group.

Mean values

	hematocrit (%)		hemoglobin (g/dl)	
	ibuprofen	placebo	ibuprofen	placebo
study day 1	42.5	42.5	14.1	14.2
study day 4	35.4**	38.1	12.0**	12.9

**hematocrit: p=0.0066 and hemoglobin: p=0.0043 for differences between treatment groups.

Mean values at study day 1 were similar for both treatment groups. However, there were statistically significantly lower mean values at study day 4 in the ibuprofen group compared to placebo. Since there were slightly more blood transfusions reported by the placebo group this drop in hemoglobin/hematocrit in the ibuprofen group are likely to be irrelevant.

Mean platelet and WBC values at study day 1 and study day 4 are shown below by treatment group.

Mean values

	platelets (K/mm3)		WBC (K/mm3)	
	ibuprofen	placebo	ibuprofen	placebo
study day 1	231.5	227.4	12.5	14.3
study day 4	199.3	175.2	15.0	13.8

Mean changes from baseline at last evaluation for platelets were -3.3 K/mm3 and -2.4 K/mm3 for ibuprofen and placebo, respectively. Mean changes for WBC were 1.9 K/mm3 and 0.4 K/mm3, respectively.

Platelet changes appear to be similar for the 2 treatment groups. However, there was a larger increase in WBC at endpoint for the ibuprofen group (1.9 K/mm3) compared to placebo (0.4 K/mm3), consistent with the greater number of adverse event reports of sepsis/pneumonia (shown below). Overall, there were more infections and infestations reported for the ibuprofen group (55.9%) compared to the placebo group (42.6%). (table 1002).

No. and (percent) of subjects

	Ibuprofen	Placebo	placebo

	(N=68)	(N=68)	subtracted %
Preferred Term			
Sepsis neonatal	21 (30.9)	15 (22.1)	8.8
Neonatal pneumonia	9 (13.2)	5 (7.4)	5.8

The percents of subjects with at least one abnormal hematocrit, hemoglobin, platelet, or WBC value are shown below.

Percentage of Infants With Abnormal Hematocrit, Hemoglobin, Platelet, or WBC Values

Hematology Parameter	Ibuprofen Lysine IV (N=68) % (n/N)	Placebo (N =68) % (n/N)
Hematocrit (%)	47.1 (32/68)	51.5 (35/68)
Hemoglobin (g/dL)	42.6 (29/68)	48.5 (33/68)
Platelets (k/mm')	26.5 (18/68)	32.4 (22168)
WBC (k/mm3)	60.3 (41/68)	60.3 (41/68)

Only nonmissing, available data points were included in the analysis.

The ibuprofen group had a larger decrease from baseline in hematocrit/hemoglobin (consistent with more reports of anemia) and a greater increase in WBC (consistent with more reports of sepsis/pneumonia) compared to the placebo group.

Hepatobiliary

The numbers and percents of subjects reporting hyperbilirubinemia and/or jaundice are shown below by treatment groups.

No. and (percent) of subjects

	Ibuprofen (N=68)	Placebo (N=68)	placebo subtracted %
Hyperbilirubinemia neonatal	11 (16.2)	10 (14.7)	1.5
Jaundice neonatal	4 (5.9)	5 (7.4)	-1.5

There were 11 (16.2%) reports of hyperbilirubinemia in the ibuprofen group compared to 10 (14.7%) reports in the placebo group. Neonatal jaundice was reported in 4 (5.9%) ibuprofen subjects and 5 (7.4%) placebo subjects.

Subjects with at least one abnormal SGOT, SGPT, GGT value during the study.

Number and (percent) of subjects

	Ibuprofen	Placebo
abnormal SGOT (67/68)+	23 (34.3)	23 (33.8)
abnormal SGPT (67/68)	1 (1.5)	0
abnormal GGT (67/66)	47 (70.1)	41 (62.1)

+total number of ibuprofen/placebo subjects

The incidence rate of abnormal GGT values was higher in the ibuprofen subjects compared to placebo (70.1% and 62.1%, respectively). The one abnormal SGPT value was reported in the ibuprofen group. The incidence rate for abnormal SGOT values was similar across treatment groups.

Means at study day 1 and 14 for SGOT, SGPT, and GGT are shown below by treatment group. The number of subjects with missing values are shown in the subsequent table.

Means (U/L) for liver function tests

	study day 1		study day 14	
	Ibuprofen Lysine IV	Placebo	Ibuprofen Lysine IV	Placebo
Liver function test				
SGOT	54.4	55.9	27.6	27.9
SGPT	15.8	14.9	15.3	15.2
GGT	91.8	103.0	51.0	47.9

Overall, there is little difference between treatment groups. By day 14, the GGT values in both groups dropped to about one half the baseline value.

Number of subjects with available values

	study day 1		study day 14	
	Ibuprofen	Placebo	Ibuprofen	Placebo
Liver function test				
SGOT (U/L)	63	66	58	57
SGPT (U/L)	64	66	57	56
GGT (U/L)	60	61	55	55

SGOT, SGPT, and GGT values at day 1 and day 14 are similar for the two treatment groups. There were subjects with missing values in both treatment groups.

A more complete table showing LFTs is displayed below.

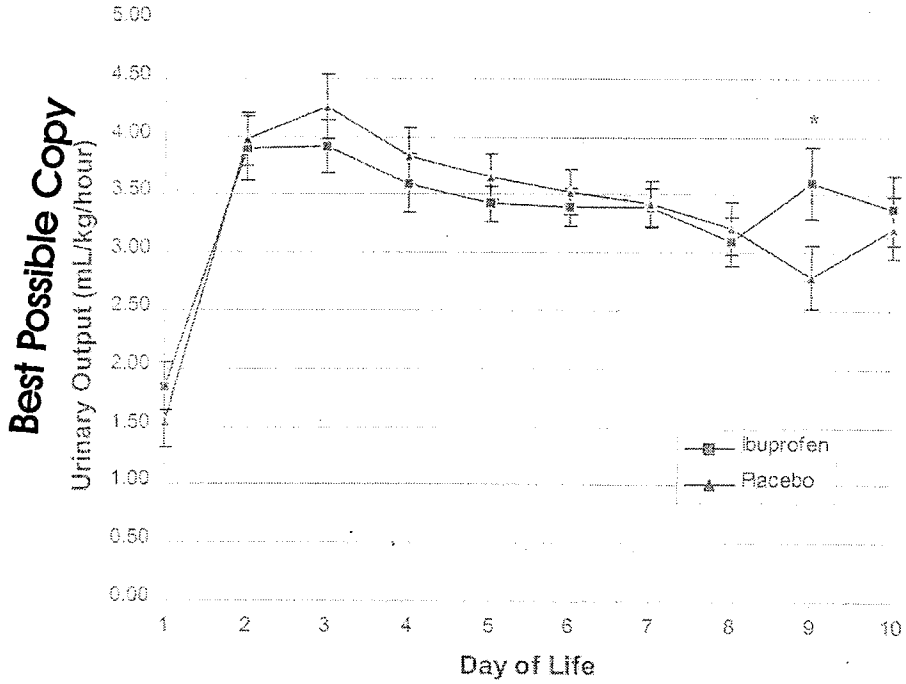
TABLE 10
LIVER ENZYMES (FORM 11) -- BY STUDY DAY

Treatment Group	Study Day		SGOT (U/L)	SGPT (U/L)	GGT (U/L)
IBUPROFEN	1	Mean	54.4	15.8	91.8
		Median	42.0	16.0	84.5
		STD	39.71	10.47	46.56
		SEM	5.00	1.31	6.01
		Minimum	17.0	3.0	30.0
		Maximum	289.0	61.0	236.0
		Missing	5	4	8
		N	63	64	60
IBUPROFEN	14	Mean	27.6	15.3	51.0
		Median	26.0	15.0	37.0
		STD	11.71	7.79	59.37
		SEM	1.54	1.03	8.01
		Minimum	9.0	3.0	14.0
		Maximum	69.0	34.0	425.0
		Missing	5	6	8
		N	58	57	55
PLACEBO	1	Mean	55.9	14.9	103.0
		Median	46.0	15.0	84.0
		STD	38.87	8.95	73.23
		SEM	4.78	1.10	9.38
		Minimum	17.0	3.0	27.0
		Maximum	284.0	42.0	430.0
		Missing	2	2	7
		N	66	66	61
PLACEBO	14	Mean	27.9	15.2	47.9
		Median	25.0	15.0	35.0
		STD	12.65	7.36	39.31
		SEM	1.81	0.98	4.49
		Minimum	11.0	3.0	14.0
		Maximum	82.0	33.0	179.0
		Missing	6	7	8
		N	57	56	55

Renal function

Mean urinary output is shown in the figure below by treatment group.

Figure 3 Mean Urinary Output Over Time



Compared to the ibuprofen group, there was a higher urinary output in the placebo group starting at day 2. By day 6, the means were similar and at day 9, the mean output was significantly higher for ibuprofen compared to placebo. The cumulative urinary output for days 1-5 days of life, shown below, are lower in the ibuprofen group compared to placebo.

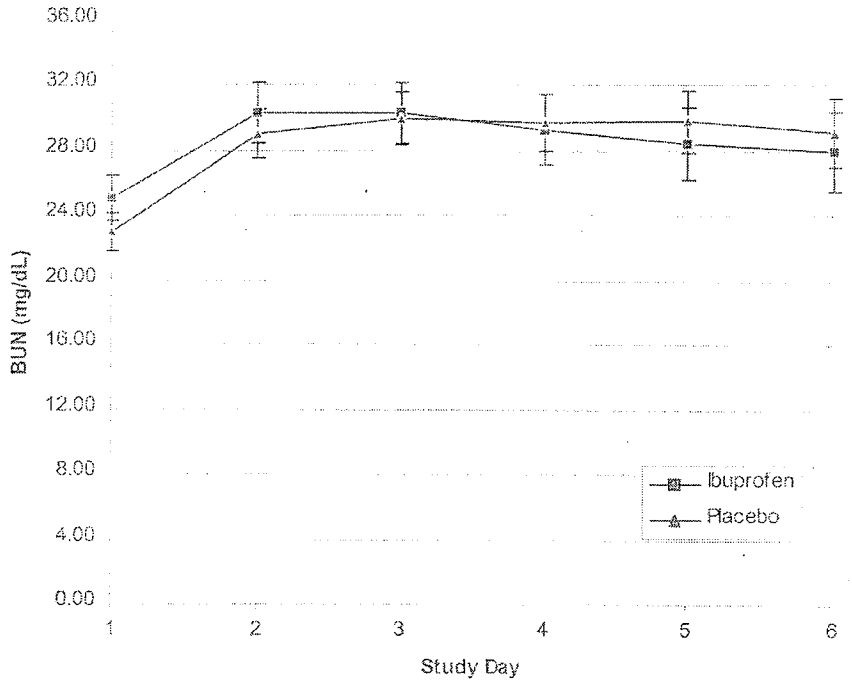
Mean urinary output (mL)

Cumulative urinary output (mL)	Ibuprofen (n=68)	Placebo (n=68)
Mean (SD)	291.9 (98.29)	301.8 (108.58)
Median	291.5	299.0
Minimum, Maximum	80.0,575.0	62.0, 599.0

SD=standard deviation; Appendix Table 17 and Appendix 16.1_9

Since mean fluid intake was similar over time (figure 4, study report), there may be fluid accumulation in subjects receiving ibuprofen. Mean BUN values for study days 1-6 are shown in the figure below by treatment group.

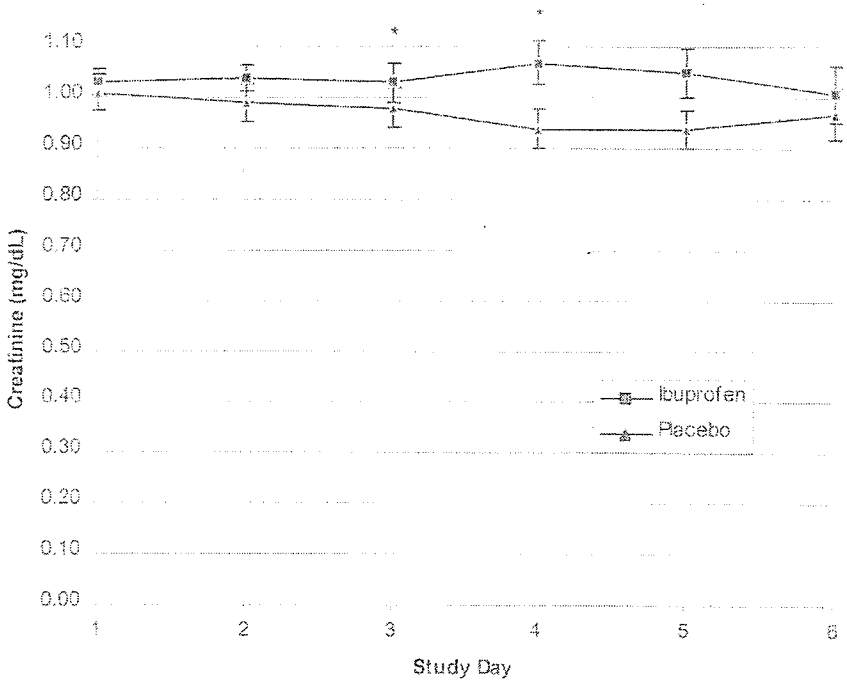
Figure 5 **Mean BUN Values Over Time**



Error bars represent SEM

The figure below shows mean creatinine values study day 1-6.

Figure 6 Mean Creatinine Values Over Time



*statistically significant difference versus placebo. There were significant differences in mean creatinine values collected at study day 3 and 4.

Mean creatinine values by day of life are shown below.

Mean creatinine (mg/dL)

(n=ibuprofen/placebo)	ibuprofen n=68	placebo n=68
day 1 (41/43)	1.03	1.03
day 2 (49/42)	1.04	0.99
day 3 (49/49)	1.08	0.97
day 4 (47/49)	1.08	0.98
day 5 (49/42)	1.04	0.95
day 6 (36/42)	1.04	0.96

Table 18

The mean creatinine values were clearly higher in the ibuprofen group compared to the placebo group, with the exception of study day 1. By day 5, the mean for the ibuprofen group started to decrease. There are many subjects without available data. The use of ibuprofen is linked to the not unexpected and seemingly temporary occurrence of oliguria and higher creatinine values.

Electrolytes

Mean sodium and chloride values obtained study days 1-6 are shown by treatment group.

Mean sodium and chloride (mmol/L)

(n=ibuprofen/placebo)	ibuprofen	placebo

	sodium/chloride	sodium/chloride
day 1 (40/44)	141/112	140/110
day 2 (59/55)	145/114	145/113
day 3 (65/66)	145/115	146/115
day 4 (64/66)	143/112	142/112
day 5 (63/57)	141/112	139/109
day 6 (53/56)	139/108	138/108

Table 18

There were minor differences in mean sodium and chloride values.

Mean baseline and changes from baseline for sodium, chloride, potassium, bicarbonate are shown below.

Mean Baseline (SD) and Change from Baseline for electrolytes

		Mean (Standard Deviation)	
Parameter (unit)		Ibuprofen	Placebo
Sodium (mmol/L)		n = 69	n = 67
	First (Baseline)	142.5 (5.8)	139.7 (5.3)
	Change to Worst	3.8 (8.7)	6.0 (9.7)
	Change to Last	-2.2 (7.8)	-1.2 (7.7)
Chloride (mmol/L)		n = 69	n = 67
	First (Baseline)	111.8 (5.5)	109.9 (5.8)
	Change to Worst	4.0 (6.9)	3.7 (9.6)
	Change to Last	-2.2 (7.8)	-1.7 (7.0)
Potassium (mmol/L)		n = 69	n = 67
	First (Baseline)	5.0 (1.1)	4.9 (1.1)
	Change to Worst	-0.9 (1.1)	-0.8 (1.1)
	Change to Last	-0.4 (1.4)	-0.5 (1.3)
Bicarbonate (mmol/L)		(N = 69)	(N = 67)
	First (Baseline)	22.6 (3.3)	22.7 (2.7)
	Change to Worst	1.8 (2.7)	1.9 (3.2)
	Change to Last	-0.8 (4.1)	-1.2 (4.9)

Vital signs

The percents of subjects who had normal values at baseline that became "severe or life threatening" for systolic blood pressure, mean arterial pressure, pulse, and weight loss are shown below.

Percentage of subjects

		Percentage of Infants with Normal First Value[a] and Change to Severe or Life Threatening Value		Percentage of Infants with Increase to Severe or Life Threatening Value	
		Ibuprofen	Placebo	Ibuprofen	Placebo
Parameter	Change to:	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Systolic SP	Worst Value	14.8 (8/54)	11.1 (6/54)	14.7 (10/68)	14.1 (9/64)
	Last Value	1.9 (1/54)	1.9 (1/54)	2.9 (2/68)	6.3 (4/64)
MAP	Worst Value	3.7(1/27)	0.0 (0/26)	3.6 *(1/28)*	0.0 (0/29)

	Last Value	0.0 (0/27)	0.0 (0/26)	0.0 (0/28)	0.0 (0/29)
Pulse	Worst Value	0.0 (0/49)	2.2 (1/45)	0.0 (0/69)	1.5 (1/67)
	Last Value	0.0 (0/49)	0.0 (0/45)	0.0 (0/69)	0.0 (0/67)
Weight loss	Worst Value	22.0 (13/59)	9.7 (6/62)	18.8 (13/69)	9.0 (6/67)
	Last Value	5.1 (3/59)	0.0 (0/62)	4.3 (3/69)	0.0 (0/67)

a for weight loss, corresponds to no weight loss at first value

Only weight loss is "worse" in the ibuprofen group.

Appears This Way
On Original

CB88A Clinical Study Review
This was a partially randomized, open label, prospective, multicenter study which enrolled preterm infants (gestational age < 33 weeks) with an echocardiographically confirmed PDA and respiratory distress syndrome (RDS). The study was conducted exclusively in Belgium and not under the IND. A re-analysis of results was performed in support of the NDA.

Study Objectives
In support of the NDA, the primary objective was altered to the comparison of the efficacy of ibuprofen, indomethacin, and no treatment for the treatment of PDA on the 2^{nd}-3^{rd} day of life in preterm infants with RDS. The primary analysis considered the proportion of infants requiring rescue treatment for PDA on or prior to Study day 14.

The original primary objectives were: 1) to compare the efficiency of ibuprofen to indomethacin and controls for the treatment of PDA at the 2^{nd}-3^{rd} day of life in preterm infants with RDS; 2) to compare the difference in closure rate of PDA and in pulmonary outcome after "early" versus "late" indomethacin treatment of PDA in preterm infants with RDS.

Inclusion Criteria
1. gestational age of 33 weeks or less,
2. age of 37 to 84 hours (1.5 to 3.5 days),
3. RDS necessitating respiratory support (intermittent mandatory ventilation, high frequency oscillatory ventilation, continuous positive airway pressure or fraction of inspired oxygen > 30% (or HFOV:FiO2 > 21%) at second to third day,
4. (verbal) informed parental consent.

Exclusion Criteria
1. major congenital anomalies,
2. chromosomal anomalies,
3. congenital infection,
4. pulmonary hypertension,
5. rapidly progressive amelioration of respiratory status on the second day of life (i.e., if complete weaning from the ventilator or CPAP with FiO2 < 30% was expected on the third day of life),
6. had contraindications for ibuprofen or indomethacin administration including thrombocyte count < 60,000/mm3, IVH detected by cranial ultrasound within the previous 24 hours, clinical bleeding tendency, oliguria $\leq$ 0.5 mL/kg/hr during the preceding eight hours, had a serum creatinine concentration of $\geq$ 1.8 mg/dL or increasing and > 1.6 mg/dL, hyperbilirubinemia necessitating exchange transfusion, hepatic insufficiency (AST and ALT > two times normal values), necrotizing enterocolitis (NEC).

Study plan
The infants were randomly assigned to receive, in an open label method, three intravenous doses infused over 15 minutes of either
-indomethacin (0.2 mg/kg of body weight, given at 12-hour intervals), or
-ibuprofen (first dose of 10 mg/kg, followed at 24-hour intervals by two doses of 5 mg/kg each), starting on the second or third day of life,
-non-randomized no treatment group was studied in the reanalysis.

If the ductus arteriosus remained patent after the randomly assigned treatment and the subject still required respiratory support, indomethacin (three doses of 0.2 mg/kg at 12-hour intervals) was given as a nonrandomized rescue treatment. Surgical ligation of the ductus was also an option.

Physicians who were blinded to the infant's treatment assignments performed color Doppler echocardiography to evaluate patency of the ductus arteriosus and shunting at the time of inclusion and after the last dose of the study drug was given. A third echocardiographic evaluation was performed to evaluate the effect of a second nonrandomized rescue treatment or whenever there was suspicion on clinical grounds that the ductus had reopened after closure.

Infants received respiratory support (conventional or primary high-frequency oscillatory ventilation), oxygen supplements, and early rescue therapy with surfactant for treatment of RDS. Prophylactic antibiotics were administered upon admission to the neonatal intensive care unit and stopped after three to four days if the results of the bacterial cultures remained negative.

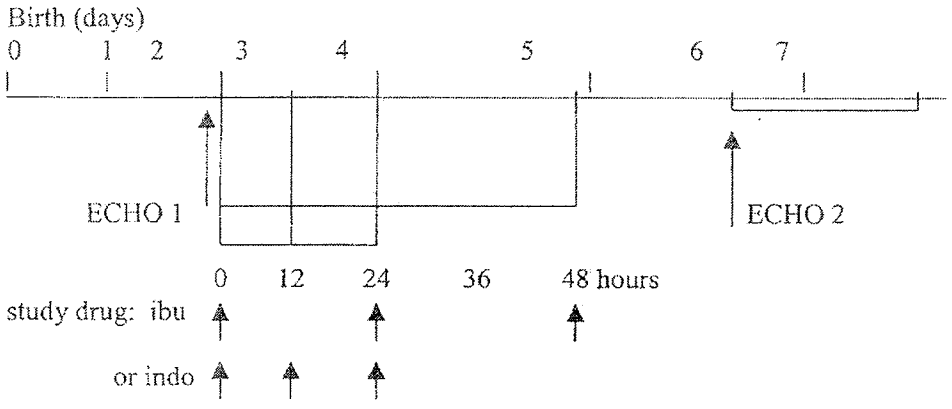
Cranial ultrasound scans were performed during the first three to four days of life, at the end of the first week and weekly thereafter. Infants were evaluated for IVH (grade 1 to 4) and for periventricular leukomalacia (PVL, grade 1 to 3). Serum creatinine concentration, serum sodium concentration, hematocrit, and platelet count were recorded during the first 14 days.

Outcome in surviving subjects was evaluated on the basis of clinical symptoms, the need for respiratory support, and the time required for the infant to regain his or her birth weight and to be ready for full enteral feedings. Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen at 28 days of life, in association with typical radiographic findings. Necrotizing enterocolitis (NEC) was diagnosed when the clinical signs and radiographic findings generally accepted as characteristic of this condition were present.

The need for additional rescue treatment, side effects, and complications were monitored for 14 days. In the reanalysis, adverse events and serious adverse events were documented from the second day of life until 30 days after the last dose of study drug or until day of life 32 for subjects in the no treatment group.

The figure below shows the timing of the echocardiographs and administration of study drug. The timing of the echocardiographs, blood draws, and urine sample collection for infants in the no treatment group was to be similar to that in the ibuprofen and indomethacin groups.

Figure 1 Timing of Echocardiographs and Administration of Study Drug



Results

Number of subjects

There were 210 subjects included in the reanalysis (73 ibuprofen, 73 indomethacin[14], and 64 no treatment).

Completed subjects were defined as those who were observed for the 14-day study period and
-received all three doses of the study drug, or
-were rescued or
-died at any time (during the 14-day study period) after randomization.

There were 70 ibuprofen infants, 62 indomethacin infants, and 58 no treatment infants who completed the study. The table below shows the number and percent of premature discontinuations by reason for discontinuation.

Table 3 Disposition of Subjects

	Ibuprofen	Indomethacin	No Treatment
Intent-to-treat population, n	73	73	64
	n (%)	n (%)	n (%)
Prematurely discontinued the study[a]	8 (11.0)	14 (19.2)	8 (12.5)
Adverse event	0 (0.0)	2 (2.7)	0 (0.0)
Removed by physician	2 (2.7)	1 (1.4)	0 (0.0)
Infant expired	3 (4.1)[b]	3 (4.1)[c]	2 (3.1)
Other	3 (4.1)	8 (11.0)	6 (9.4)

NA = not applicable

a. Primary reason for prematurely discontinuing the study.
b. A fourth infant (# 95) also died during the 14-day study period, but primary reason for premature discontinuation was 'removed by physician' (lung bleeding).
c. A fourth infant (# 56) also died on Study Day 14, so was not considered prematurely discontinued.
Other category included PDA not responding to study drug (1 ibuprofen subject) and subject transferred from facility (remaining infants).

The incidence rate for premature discontinuation was somewhat higher for the indomethacin group (19%) compared to ibuprofen group (11%) and no treatment (13%). The rates for drop outs for adverse event and deaths were similar across treatment groups.

Demographics

Demographics and baseline characteristics are shown below by treatment group.

[14] One additional infant was randomized to this group but permission to use this subject's data was denied.

Table 5 Demographic and Baseline Characteristics

Variable	Ibuprofen (N=73)	Indomethacin (N=73)	No Treatment (N=64)
Birth weight (g)	(n=73)	(n=73)	(n=63)
Mean (SD)	1256.9 (388.0)	1226.4 (389.2)	1268.6 (378.2)
Minimum, Maximum	542.0, 2100.0	600.0, 2060.0	400.0, 2370.0
Gestational age category (wks)	(n=72)	(n=73)	(n=64)
< 27, n (%)	14 (19.4)	15 (20.5)	10 (15.6)
27-28, n (%)	20 (27.8)	21 (28.8)	21 (32.8)
29-30, n (%)	19 (26.4)	23 (31.5)	13 (20.3)
31-32, n (%)	9 (12.5)	9 (12.3)	13 (20.3)
> 32, n (%)	10 (13.9)	5 (6.8)	7 (10.9)
Mean (SD)	29.1 (2.4)	29.0 (2.2)	29.2 (2.1)
Minimum, Maximum	25.0, 33.7	25.0, 33.6	24.9, 33.0
Gender, n (%)			
Male	41 (56.2)	31 (42.5)	37 (57.8)
Female	32 (43.8)	42 (57.5)	27 (42.2)
Race, n (%)			
Caucasian	60 (82.2)	60 (82.2)	49 (76.6)
Not Available	11 (15.1)	5 (6.8)	10 (15.6)
Other	2 (2.7)	6 (8.2)	3 (4.7)
Asian or Pacific Islander	0 (0.0)	2 (2.7)	1 (1.6)
Black	0 (0.0)	0 (0.0)	1 (1.6)
1 Minute Apgar Score	(n=68)	(n=67)	(n=57)
Mean (SD)	5.4 (2.5)	5.4 (2.3)	5.2 (2.6)
Minimum, Maximum	0.0, 9.0	1.0, 9.0	0.0, 9.0
5 Minute Apgar Score	(n=64)	(n=63)	(n=51)
Mean (SD)	7.5 (2.0)	7.7 (1.2)	7.5 (1.7)
Minimum, Maximum	0.0, 10.0	4.0, 10.0	3.0, 10.0
Maternal age (years)	(n=70)	(n=66)	(n=59)
Mean (SD)	27.8 (5.1)	27.1 (5.3)	27.9 (5.2)
Minimum, Maximum	18.0, 39.0	15.0, 41.0	18.0, 39.0
Received Prenatal Steroids, n (%)			
Yes	34 (46.6)	38 (52.1)	27 (42.2)
No	38 (52.1)	30 (41.1)	36 (56.3)
Not Available	1 (1.4)	5 (6.8)	1 (1.6)
Maternal Use of Indomethacin, n (%)			
Yes	11 (15.1)	10 (13.7)	10 (15.6)
No	62 (84.9)	63 (86.3)	54 (84.4)
One of Multiple Birth, n (%)			
Yes	24 (32.9)	25 (34.2)	23 (35.9)
No	49 (67.1)	48 (65.8)	41 (64.1)
Resuscitated in Delivery Room, n (%)			
Yes	72 (98.6)	71 (97.3)	60 (93.8)
No	0 (0.0)	1 (1.4)	3 (4.7)
Not Available	1 (1.4)	1 (1.4)	1 (1.6)
Type of Delivery, n (%)			
Vaginal	30 (41.1)	33 (45.2)	23 (35.9)
C-section	43 (58.9)	40 (54.8)	41 (64.1)

SD=standard deviation
Cross-reference: Appendix Tables 3-6

Mean birth weight was lower for the indomethacin group by about 30 g compared to ibuprofen and 40 g compared to the no treatment group. Overall, the treatment groups were similar for baseline characteristics.

Nearly all subjects in the active treatment groups received all 3 doses of study medication (95% ibuprofen and 93% indomethacin). The percents of subjects observed for the 14 day study period were 92% ibuprofen, 86% indomethacin, and 89% no treatment.

Efficacy

The table below shows the results of the re-analysis.

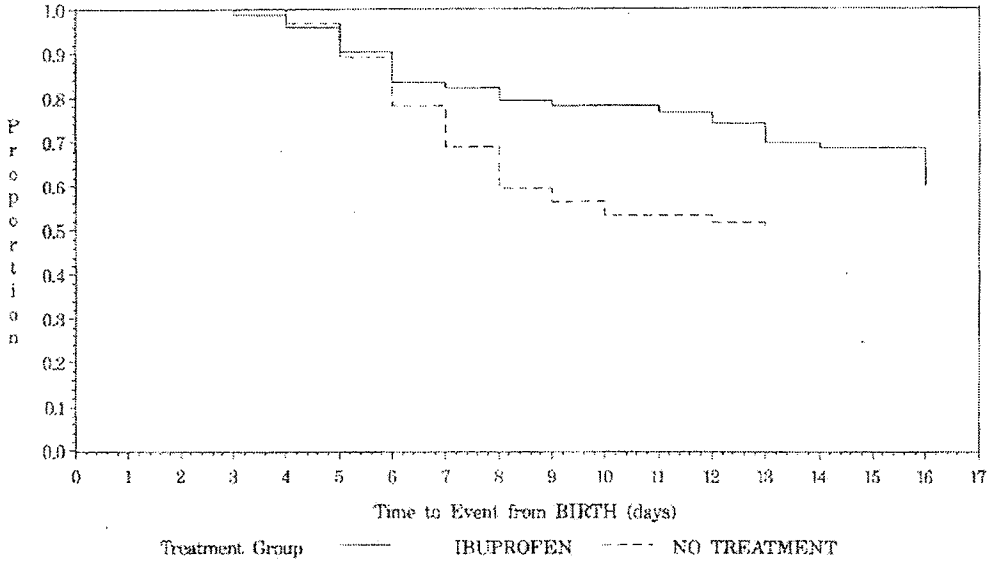
Number and (percent) of subjects needing rescue, died, or dropped out.

	Ibuprofen (N=73) n (%)	Indomethacin (N=73) n (%)	No Treatment (N=64) n (%)
Total rescued, died, or dropped out through Study Day 14	25 (34.2)	24 (32.9)	32 (50.0)
Required rescue through Study Day 14	19 (26.0)	15 (20.5)	25 (39.1)
Died on or prior to Study Day 14 (not rescued prior to death)	4 (5.5)	2 (2.7)	1 (1.6)
Dropped-out on or before Study Day 14 (not rescued prior to dropping out)	2 (2.7)	7 (9.6)	6 (9.4)

The incidence rates for the subjects who required rescue through study day 14 were similar for the active treatment groups (26% and 20.5% for ibuprofen and indomethacin, respectively) and less than for the no treatment group (39.1%). The incidence rates for subjects who needed rescue therapy, or died or dropped out through study day 14 also were similar for the active treatment groups (34% ibuprofen and 33% indomethacin); the incidence rate for the no treatment (non randomized) group was higher (50%). Death rates were the highest in the ibuprofen group.

The figure below shows the Kaplan-Meier survival curves of the proportion of subjects with no event for ibuprofen vs. no treatment.

Figure 4 **Proportion of Infants With No Event (Rescue, Death, or Dropout) to Study Day 14: Ibuprofen vs. No Treatment**



By the 6th day of birth, the no treatment group was starting to require rescue therapy or died or dropped out more often than the ibuprofen group.

For those who required rescue treatment through day 14, the mean age at the start of the first rescue treatment was 8.3 days for the 19 ibuprofen subjects, 5.6 days for the 15 indomethacin subjects and 6.4 days for the 25 no treatment subjects.

The 2 most common signs/symptoms leading to rescue therapy were bounding pulse and systolic murmur.

The table below shows the rescue therapy used (indomethacin/ibuprofen and/or surgery) by treatment group.

Rescue treatment	Ibuprofen (N=20) n (%)	Indomethacin (N=16) n (%)	No Treatment (N=25) n (%)
Indomethacin or ibuprofen	14 (70.0)	12 (75.0)	25 (100.0)
Surgical ligation	10 (50.0)	9 (56.3)	5 (20.0)

NS = not significantly different

Note: Includes two subjects (indomethacin subject 70 and ibuprofen subject 544) rescued after Study Day 14.

Rescue therapy was predominantly medical. It is not stated how many of the subjects who underwent surgery had first failed the medical rescue therapy.

Mean percent $Sa0_2$ ranged from 91.9 to 93.3 during the first 12 hours after the first dose of study drug in the ibuprofen treatment group and from 91.7 to 93.1 in the indomethacin treatment group. Mean percent $Fi0_2$ ranged from 35.0 to 38.1 during the first 12 hours after the first dose of study drug in the ibuprofen

treatment group and from 33.4 to 34.9 in the indomethacin treatment group. These data were not collected for the no treatment group.

Safety
Serious safety

Deaths
The numbers of subjects who died either during to study (through day 14) or after study day 14 are shown below.

	ibuprofen n=73	indomethacin n=73	no treatment n=64
died on or before study day 14	4 (5)	4 (5)	2 (3)
died after study day 14	3 (4)	2 (3)	2 (3)

The deaths rates are similar across treatment groups.

The individual deaths are displayed in the table below.

Subject #/Gender	adverse event considered as resulting in death	Days to Onset/ Time to Death[+]	comments	Age at onset (days)	Gestational Age (weeks) at Birth
Ibuprofen					
#29/male	persistent fetal circulation	8/11	pneumothorax 6 days after enrollment followed by pulmonary hypertension associated with pneumothoraces, hypotension, heart failure. Reported events included bradycardia, thrombocytopenia, sepsis	10	27
#95/female	IVH grade III and cardiorespiratory insufficiency	1/2	poor saturation and bradycardia 1 day after enrollment, ultrasound showed grade III IVH. Died 1 day later.	2	26
#203/male	sepsis, IVH, meningitis	13/18	candida cultured from endotracheal tube day 1, seizures on day 14, IVH diagnosed, treated with antibiotics and died day 18	15	26
#207/female	sepsis	8/21	elevated C reactive protein, antibiotic treatment changed, started ventilation, died after taken off ventilator.	11	29
#216/male	urea plasma infection	13/66	pneumothorax diagnosed, emphysema diagnosed, treated with nitric oxide, relapse, p-positive hematest, candida infection diagnosed, given CPAP, NEC (perforation of bowels) diagnosed, died about 1 week later	15	28
302/male	neonatal IVH	2/5	deterioration of O2 saturation, difficulties with ventilation, IVH diagnosed by ultrasound	3	26
512/male	neonatal IVH	4/4	respiratory distress syndrome at birth, metabolic acidosis and emphysema diagnosed. IVH Grade I diagnosed on study day 2, IVH grade IV diagnosed day 5.	6	29

Indomethacin					
#3/female	sepsis	9/9	rapid deterioration, surgical ligation required, respiratory failure, CPR unsuccessful, sepsis diagnosed at autopsy	11	25
#5/female	IVH and NEC	1/22	IVH diagnosed study day 2, distended abdomen study day 16, NEC diagnosed day 19, died day 22 of NEC and IVH grade III	3	26
#56/male	IVH grade III/IV	1/13	respiratory deterioration and thrombocytopenia study day 2, IVH diagnosed study day 10. Intervention discontinued	5	27
#208/female	multi-organ failure		hyperglycemia and hypotension study day 4, transfusion given, candida infection diagnosed, elevated creatinine, BUN, distended abdomen, poor urinary out put despite furosemide, cholestasis observed, acidosis reported as untreatable. Died study day 17.		
#210/female	multi-organ failure	2/17	surgical ligation on study day 2, hypotension, bleeding, metabolic acidosis, low urine output. IVH grade II diagnosed study day 2. Continued to do poorly and died study day 7.	4	26
#501/male	IVH -1/2	-1/2	diagnosed IVH both sides of brain (grade I study day -1 and grade II on day 2). Evolved into Grades II and III. Indication of pre-existing leukomalacia.	2	28
no treatment					
#61/female	persistent fetal circulation	2/11	cardiac heart failure	2	28
#67/female	sepsis and NEC	5/8	NEC/peritonitis	5	26
#304/male	multi-organ failure	NA/62	multiple organ failure	NA	25
#524/mlae	IVH	3/41	study day 3 IVH grade III diagnosed, dilation of	3	29

			lateral ventricles, meningitis and pneumothorax.		

+days since first dose of study drug or enrollment for no treatment group

Of the seven reported deaths in the ibuprofen group, three were associated with intraventricular hemorrhage, two with sepsis, one with sepsis/NEC and one with persistent fetal circulation with pulmonary hypertension, pneumothorax, and heart failure. Deaths in the other groups were similar in nature.

Discontinuations because of adverse event

There were 3 subjects, all randomized to indomethacin, who discontinued because of an adverse event. The reported events were renal failure, decreased platelet count with death occurring 2 days after start of treatment, and thrombocytopenia.

Serious adverse events

Serious events reported by at least 2% of subjects in any treatment groups are shown below.

Table 13 Common Treatment-Emergent Serious Adverse Events

	Ibuprofen (N=73) n (%)	Indomethacin (N=73) n (%)	No Treatment (N=64) n (%)
Number of subjects with ≥1 serious adverse event	36 (49.3)	30 (41.1)	22 (34.4)
Preferred Term			
Sepsis neonatal	16 (21.9)	11 (15.1)	15 (23.4)
Intraventricular haemorrhage neonatal	8 (11.0)	5 (6.8)	5 (7.8)
Hydrocephalus	3 (4.1)	0 (0.0)	2 (3.1)
Neonatal respiratory distress syndrome	3 (4.1)	1 (1.4)	2 (3.1)
Necrotising enterocolitis neonatal	2 (2.7)	2 (2.7)	1 (1.6)
Catheter sepsis	2 (2.7)	0 (0.0)	0 (0.0)
Neonatal pneumonia	2 (2.7)	2 (2.7)	1 (1.6)
Pneumothorax	2 (2.7)	2 (2.7)	3 (4.7)
Periventricular leukomalacia	1 (1.4)	1 (1.4)	2 (3.1)
Neonatal Candida infection	1 (1.4)	3 (4.1)	0 (0.0)
Neonatal multi-organ failure	0 (0.0)	2 (2.7)	0 (0.0)

Includes preferred terms with an incidence of ≥2.0% in any treatment group. Presentation is in the order of decreasing incidence in the ibuprofen treatment group.

Cross-reference: Appendix Table 1004

Compared to indomethacin, the incidence rates were higher in the ibuprofen groups for several reported events (sepsis, IVH, and hydrocephalus).

Selected serious adverse events
The events listed below were collected at study exit (table 21) or at follow up (table 24).

No. and (percent) of subjects

	ibuprofen n=73	indomethacin n=73	no treatment n=64
observed for 14 days	67 (91.8)	63 (86.3)	56 (87.5)
pulmonary hemorrhage	2 (2.7)	3 (4.1)+	1 (1.6)
pulmonary hypertension	2 (2.7)	0++	2 (3)
serious adverse events during study	29 (39.7)	30 (41.1)	18 (28.1)
follow up data obtained	70 (95.9)	69 (94.5)	61 (95.3)
nec diagnosed at follow up	10 (13.7)#	11 (15.1)#	5 (7.8)@
advanced nec	1	2	1
bronchopulmonary dysplasia (need for O2 at 28 days of life)	44 (60.3)+++	35 (47.9)++++	37 (57.8)!
IVH diagnosed at follow up	12 (16.4)!!	7 (9.6)!!!	10 (15.6)!!!!

+one subject missing
++two subjects missing
#four subjects missing or not available
@three subjects missing or not available
+++five subjects missing or not available
++++six subjects missing or not available
!eight subjects missing or not available

The reporting of these serious adverse events is similar across treatment groups.

Most subjects had follow up data. At follow up, there were more ibuprofen subjects who required oxygen at follow up compared to indomethacin subjects. The numbers are too small to draw conclusions.

The reporting of retinopathy of prematurity and periventricular leukomalacia are similar across treatment groups (table 24).

Intraventricular hemorrhage
The number and percent of subjects with reports of IVH are shown below.

No. and (percent) of subjects

	ibuprofen % (n/N)	indomethacin % (n/N)	no treatment % (n/N)
IVH though study day 14	25 (18/72)	26 (17/66)	17 (10/59)
IVH grade III/IV though study day 14	13 (9/72)	8 (5/66)	7 (4/59)
IVH all study records+	27 (20/73)	29 (20/68)	21 (13/61)
IVH grade III/IV all study records+	12 (9/73)	7 (5/68)	7 (4/61)
IVH diagnosed at	12 (16.4)	7 (9.6)	10 (15.6)

follow up			

+Through day of life 102

There is an indication that IVH could be more likely in subjects receiving ibuprofen or indomethacin compared to no treatment.

Significant but non serious adverse events

Adverse events reported by at least 2% of subjects in any treatment group that were significant[15] but not serious are shown below.

[15] Defined as any unfavorable and unintended sign, symptoms or disease temporally associated with the use of a product whether or not considered related.

Table 10 Common Treatment-Emergent Significant/Nonserious Adverse Events

	Ibuprofen (N=73) n (%)	Indomethacin (N=73) n (%)	No Treatment (N=64) n (%)
Number of subjects with ≥1 significant/ nonserious adverse event	52 (71.2)	50 (68.5)	57 (89.1)
Preferred Term			
Hyperbilirubinaemia neonatal	15 (20.5)	12 (16.4)	31 (48.4)
Jaundice neonatal	6 (8.2)	6 (8.2)	15 (23.4)
Neonatal apnoeic attack	5 (6.8)	5 (6.8)	6 (9.4)
Blood glucose increased	4 (5.5)	3 (4.1)	5 (7.8)
Hypothyroidism	3 (4.1)	2 (2.7)	1 (1.6)
Abdominal distension	3 (4.1)	2 (2.7)	1 (1.6)
Neonatal Candida infection	3 (4.1)	3 (4.1)	1 (1.6)
Neonatal hypotension	2 (2.7)	2 (2.7)	5 (7.8)
Pneumothorax	2 (2.7)	1 (1.4)	2 (3.1)
Bradycardia neonatal	2 (2.7)	1 (1.4)	3 (4.7)
Gastrooesophageal reflux disease	2 (2.7)	2 (2.7)	6 (9.4)
Feeding problem in newborn	2 (2.7)	0 (0.0)	1 (1.6)
Hyperglycaemia	2 (2.7)	3 (4.1)	1 (1.6)
Hypoalbuminaemia	2 (2.7)	2 (2.7)	0 (0.0)
Neonatal hyponatraemia	2 (2.7)	0 (0.0)	1 (1.6)
Renal insufficiency	2 (2.7)	1 (1.4)	0 (0.0)
Hypertension neonatal	2 (2.7)	0 (0.0)	0 (0.0)
Sepsis neonatal	1 (1.4)	2 (2.7)	1 (1.6)
Hypoglycaemia neonatal	1 (1.4)	6 (8.2)	3 (4.7)
Thrombocytopenia neonatal	0 (0.0)	1 (1.4)	2 (3.1)
Patent ductus arteriosus	0 (0.0)	2 (2.7)	0 (0.0)
Neonatal infection	0 (0.0)	2 (2.7)	0 (0.0)
Eye infection	0 (0.0)	0 (0.0)	2 (3.1)
Rash neonatal	0 (0.0)	0 (0.0)	2 (3.1)
Necrotising enterocolitis neonatal	0 (0.0)	5 (6.8)	2 (3.1)

Includes preferred terms with an incidence of ≥2.0% in any treatment group. Presentation is in the order of decreasing incidence in the ibuprofen treatment group.
Cross-reference: Appendix Table 1002

Hyperbilirubinemia and neonatal jaundice were more often reported in the nonrandomized no treatment group compared to either ibuprofen or indomethacin groups. Other events were similar across groups.

Clinical laboratory parameters

There were 3 subjects, all randomized to indomethacin, who discontinued treatment because of abnormal laboratory parameters: high serum creatinine value (#63) and thrombocytopenia (#539 and #501).

Liver enzymes were collected in limited number of subjects (table 9).

Mean total and direct bilirubin values for day 1, day 3, day 6, and day 14 are shown below by treatment group.

Mean total bilirubin (mg/dl)

	day 1	day 3	day 6	day 14
ibuprofen	2.36	7.18	8.01	6.09
indomethacin	2.44	7.47	7.88	6.11
no treatment	2.37	7.16	8.74	7.19

Table 18

Mean direct bilirubin (mg/dl)

	day 1	day 3	day 6	day 14
ibuprofen	0.16	0.27	0.50	0.41
indomethacin	0.13	0.29	0.47	0.44
no treatment	0.26	0.32	0.46	0.38

Table 18

Liver enzymes were collected in limited number of subjects (table 9). While these data are meager, there is no indication that ibuprofen adversely affects the liver.

Renal function

Mean cumulative urinary output is show in the table for days of life 1-5 (subjects were 1.5-3.5 days of age at randomization).

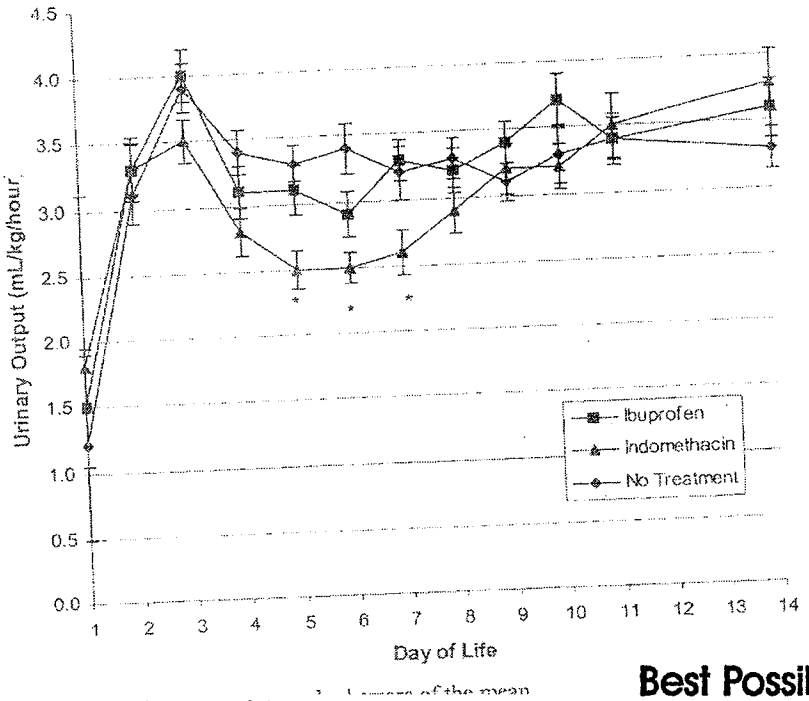
Mean (mL) and SD

Ibuprofen n=73	indomethacin n=73	no treatment n=64
412 (167)	365 (140)	452 (158)

Mean urinary output was higher in the no treatment group.

Mean urinary output over days of life 1-14 is shown in the figure below.

Figure 5 Mean Urinary Output Over Time



error bars are standard errors of the mean

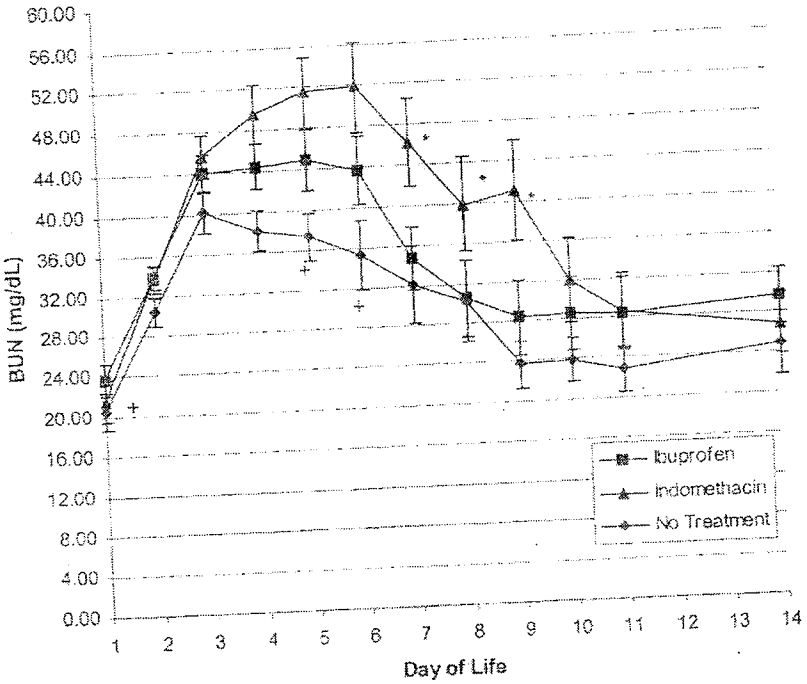
Compared to the non randomized no treatment group, there was less urine output in the 2 active treatment groups, particularly on days 5-7. This was more marked for the indomethacin group. By day 11, urine outputs for all groups were similar.

Mean fluid intake was less for indomethacin, particularly on days 7-10, compared to the other treatment groups. There groups were similar for this parameter by day 11.

BUN and serum creatinine

The figure below shows the mean BUN values from day 1 to day 14 of life for all 3 treatment groups.

Figure 7 Mean BUN Values Over Time



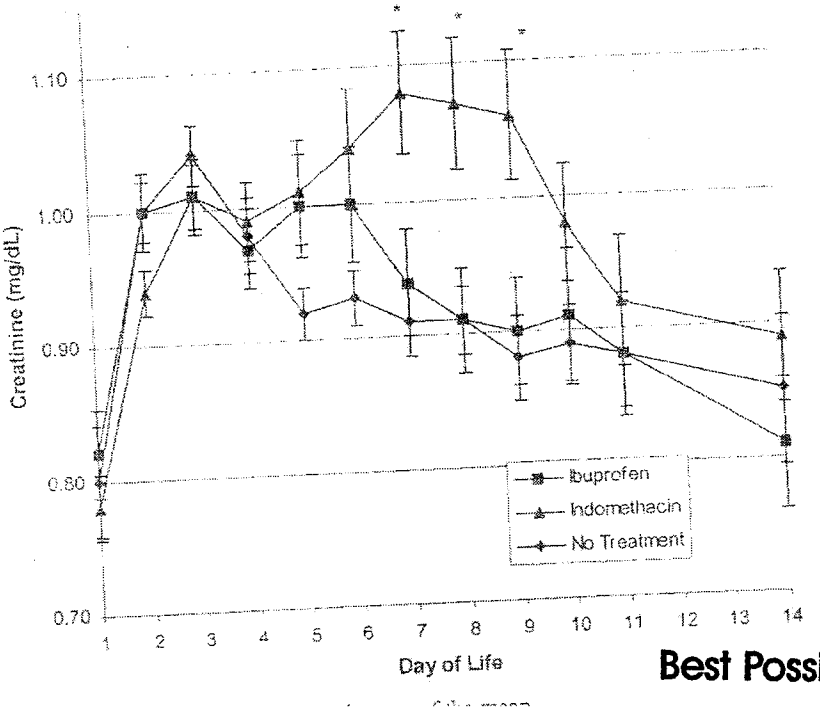
error bars are standard errors of the mean

Mean BUN at baseline was higher in the ibuprofen group compared to the no treatment group. Means increased on third day of life for all 3 treatment groups. By day 4, means either started to decrease (no treatment), plateau (ibuprofen), or continued to increase (indomethacin). On day 6, the mean BUN values started to decrease in both active treatment groups. On day 14, the mean BUN values for the 3 groups were similar.

Mean serum creatinine values over time are shown below.

Appears This Way
On Original

Figure 8 Mean Creatinine Values Over Time



error bars are standard errors of the mean

Similar to BUN, mean serum creatinine values increased, compared to baseline, on day of life 2-3, and then either decreased (no treatment), or flattened (ibuprofen), or continued to increase (indomethacin) starting day 4. By day 14, means for all groups were similar.

Compared to the non randomized no treatment group, subjects receiving ibuprofen showed a decrease in urine output and a rise in BUN and creatinine. By day of life 14, values for these 2 groups became alike. There is an indication that there is less fluid accumulation with lower increases in BUN and serum creatinine in the ibuprofen group compared to indomethacin. These adverse effects on the kidney in both active treatment groups seem to be short-lived. Any definitive conclusions regarding renal effects and the use of ibuprofen compared to indomethacin would first need a confirmatory study.

Hematology

There were 2 subjects (both indomethacin) who discontinued because of thrombocytopenia.

Mean hematology parameters are shown below for days of life 1, 4, and 8.

Mean hemoglobin (g/dl)/hematocrit (%)

	day 1	day 4	day 8
ibuprofen	13.9/41.8	13.5/40.3	13.0/38.6
indomethacin	14.2/42.7	13.7/40.9	13.0/38.4
no treatment	15.1/45.7	13.6/40.5	13.6/40.1

Number of subjects for ibuprofen (range 64-68)
Number of subjects for indomethacin (range 63-69)

Number of subjects for no treatment (range 48-62)

Values are somewhat lower for the active treatment groups compared to no treatment.

Mean platelets (k/mm3)/wbc (k/mm3)

	day 1	day 4	day 8
ibuprofen	201.5/14.4	178.3/9.6	209.5/13.9
indomethacin	204.3/13.1	208.7/12.1	235.0/15.0
no treatment	194.3/9.4	177.7/10.9	214.3/14.4

Number of subjects for ibuprofen (range 64-68)
Number of subjects for indomethacin (range 63-69)
Number of subjects for no treatment (range 48-62)

There are no suggestions of an adverse effect on platelets or WBC.

Weight loss

The maximum mean weight loss during the first 7 days of life was greater in the no treatment group (138g) compared to ibuprofen (107g) and indomethacin (93g).

Respiratory function

The percent of subjects requiring oxygen

Day of Life	Ibuprofen % (n/N)	Indomethacin % (n/N)	No Treatment % (n/N)
Day 1	94.5 (69/73)	97.3 (71/73)	100.0 (61/61)
Day 4	93.2 (68/73)	91.8 (67/73)	100.0 (64/64)
Day 8	79.2 (57/72)	74.6 (53/71)	67.2 (43/64)
Day 14	65.7 (46170)	71.9 (46/64)	70.2 (40/57)
Day 18	69.2 (45/65)	68.3 (41/60)	74.1 (40/54)

Most subjects in all groups required supplemental oxygen.

The percent of subjects requiring intubation

Day of Life	Ibuprofen % (n/N)	Indomethacin % (n/N)	No Treatment % (n/N)
Day 1	97.3 (71/73)	94.5 (69/73)	100.0 (61/61)
Day 4	94.5 (69/73)	91.8 (67/73)	89.1 (57/64)
Day 8	61.1 (44/72)	52.1 (37/71)	62.5 (40/64)
Day 14	30.0 (21/70)	40.6 (26/64)	33.3 (19157)
Day 18	26.2 (17/65)	30.0 (18/60)	29.1 (16155)

By day 14, less than a third of the ibuprofen subjects were intubated.

CB88B Clinical Study Review
This was a randomized[16], double blind, placebo controlled, multicenter study which enrolled preterm infants (gestational age < 30 weeks) aged < 6 hours. The study was conducted exclusively in Belgium and not under the IND. A re-analysis of results was performed in support of the NDA[17]. Case record forms were created and completed in retrospect.

Study Objectives
In support of the NDA, the primary objective was changed to the proportion of infants who received ibuprofen and required rescue treatment for a symptomatic PDA compared to the group who received placebo.

The original primary objectives were to compare: 1) the incidence and severity of intracranial hemorrhage and 2) the incidence and severity of periventricular leukomalacia.

Inclusion criteria
Subjects had to meet all the following to be eligible for enrollment.
-gestational age < 30 weeks);
- age < 6 hours;
-informed parental consent

Exclusion criteria
Subjects who met any of the following exclusion criteria were ineligible for enrollment in the study:
-major congenital anomalies;
-chromosomal anomalies;
-proven severe congenital maternofetal infection or hydrops fetalis;
-maternal use of nephrotoxic medication three days prior to delivery. (aminoglycosides);
-intraventricular hemorrhage or cystic leukomalacia already demonstrable from birth (detectable before administration of the study drug [i.e., by first cranial ultrasound]);
-apparent neurological dysfunction (e.g., convulsions, atonia, asphyxia [five minute Apgar score < 5]);
-shock or life-threatening infection;
-contraindications for ibuprofen administration (platelet count < 60,000/mm3, hyperbilirubinemia obtained from cord blood (> 5 mg/dL), clinical bleeding tendency, oozing from puncture site.

Study plan
The infants were randomly assigned to receive three intravenous doses infused over 15 minutes of either:
-ibuprofen (first dose of 10 mg/kg within the first 6 hours of life, followed at 24-hour intervals by two doses of 5 mg/kg each), or
-placebo (first dose 1mL/kg, followed by 0.5 mL/kg after 24 hours and 48 hours.

Echocardiodoppler was done prior to study inclusion, between 6 and 24 hours after the third dose of study drug, on days of life 7 or 8, and after a second non-randomized treatment, if applicable.

Cranial ultrasonography was done at enrollment prior to the first dose of study drug and on days of life 2, 3, 7, 14, and 28 or before discharge. IVH was graded from 1 to 4. The presence of cystic PVL after age 2 weeks was recorded.

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[16] by a pharmacist at each hospital

[17] CRFs were created and completed in retrospect. Only key variables were source-verified and analyzed.

Study procedures are shown below.

Table 1 Schedule of Study Procedures Under the Reanalysis Plan

Procedure/ Assessment	Baseline[a] (Day of Life 1 [< 6 Hours])	Day of Life 1	Day of Life 3	Day of Life 3/4	Day of Life 7	Days of Life 1 - 7, 14	Days of Life 1-4	Days of Life 1 - 28	Day of Life 28	Follow-Up[b]
Infant Eligibility Criteria	X									
Infant Demographic Data	X									
Infant Medications								X		
Prenatal Treatment	X									
Rescue Assessment								X		
SaO_2/FiO_2 Monitoring		X[c]								
Hematology and Renal Function Parameters	X		X		X					
Serum Bilirubin	X		X		X					
Renal Output and Fluid Intake							X			
Liver Enzymes								X[d]		
Respiratory Function							X		X	
Vital Signs						X			X	
Echocardiogram[e]	X			X	X[f]					
Cranial Ultrasound									X	X
Daily Fluid Intake and Urine Measures							X			
ROP, BPD, PVL, Death										X
Adverse Event Monitoring	Adverse events were reported from six hours of life through 30 days after the last dose of study drug or day of life 30 for infants in the placebo group.									

ROP = retinopathy of prematurity; BPD = bronchopulmonary dysplasia, PVL = periventricular leukomalacia

a Baseline was prior to the first dose of study drug.

b Follow-up was at 36 weeks adjusted gestational age ± 7 days, at time of transfer from facility, time of discharge, or at death.

c Within three hours of the first dose of study drug

d Collected at Weeks 1, 2, 3, and 4 of life.

e An additional echocardiogram was performed if a second nonrandomized rescue treatment was given or whenever there was suspicion that the ductus had reopened after closure.

f At the 7th or 8th day of life.

Laboratories were collected according to the following schedule:

Renal Function Parameters
days of life 1-4: renal output, fluid intake
days of life 1, 3, and 7: BUN, chloride, creatinine, potassium, sodium, bicarbonate,

Hematology Parameters
days of life 1, 3, and 7: platelets, WBC

Liver Enzyme Tests
weeks of life 1-4: ALT, GGT, AST.

Serum Bilirubin
days of life 1, 3, and 7: total bilirubin, direct bilirubin.

Results

Disposition of Subjects

There were 433 subjects randomized to either ibuprofen (215) or placebo (218). The percents of subjects who received all 3 doses of study drug were 87.9% for ibuprofen subjects and 84.4% for placebo subjects. The number of premature discontinuations is shown below by primary reason for the discontinuation.

Number and (percent) of subjects

	Ibuprofen n=215	Placebo n=218
Prematurely discontinued the study	65 (30.2)	76 (34.9)
Adverse event	6	2
Removed by physician	10	15
Infant expired	12b	21c
Otherd	37	38

a Primary reason for prematurely discontinuing the study.
b includes subjects # 316 and 736
c includes subjects # 61, 88, 99, 225, and 331.
d includes discharged, transferred to another facility, ductus closed.

The incidence rate for discontinuation was slightly higher in the placebo group (35%) compared to the ibuprofen group (30%). Death was more common in the placebo group (21 subjects, 9.6%), compared to ibuprofen (12 subjects, 5.6%).

Demographics and baseline characteristics

The demographics and baseline characteristics were similar across treatment groups.

Variable	Ibuprofen (N=215)	Placebo (N=218)
Birth weight (g)		
Mean (SD)	1046.7 (313.9)	1064.6 (323.0)
Minimum, Maximum	425.0, 2165.0	400.0, 2100.0
Gestational age category (wks)		
< 27, n (%)	51 (23.7)	52 (23.9)
27-<29, n (%)	84 (39.1)	87 (39.9)
29-<31, n (%)	80 (37.2)	78 (35.8)
Not available	0	1 (0.5)
Mean (SD)	28.1 (1.7)	28.1 (1.6)
Minimum, Maximum	23.7, 30.9	24.0, 30.9
Gender, n (%)		
Male	109 (50.7)	115 (52.8)
Female	106 (49.3)	103 (47.2)

Infants weighed around 1059 g., were roughly divided equally among the gestational age categories, and were roughly half female. The groups were balanced.

Efficacy

The table below shows the number and percent of subjects needing rescue, died, or dropped out.

Number and (percent) of subjects requiring rescue treatment for PDA

	Ibuprofen Lysine IV (N=215)	Placebo (N=218)	P-values
Total rescued, died, or dropped out through Study Day 14	31 (14.4)	68 (31.2)	<0.0001a
Total rescued, died, or dropped out through Study Day 28	58 (27.0)	102 (46.8)	<0.0001b
Required rescue through Study Day 14	12 (5.6)c	46 (21.1)	
Required rescue through Study Day 28	13 (6.1)c	51 (23.4)	
Died on or prior to Study Day 14 (not rescued prior to death)	11 (5.1)	15 (6.9)	
Died on or prior to Study Day 28 (not rescued prior to death)	14 (6.5)	17 (7.8)	
Dropped-out prior to Study Day 14 (not rescued prior to dropping out)	8 (3.7)	7 (3.2)	
Dropped-out prior to Study Day 28 (not rescued prior to dropping out)	31 (14.4)	34 (15.6)	

a Chi-square test based on logistic regression controlling for site.
b Logistic regression with factors for treatment group, site, birth weight group (0-750 g, 751-1000 g, > 1000 g), gestational age (< 28, >28 weeks), sex, use or non-use of high frequency oscillatory ventilation, maximum weight loss, and site.
c Denominator is 214.

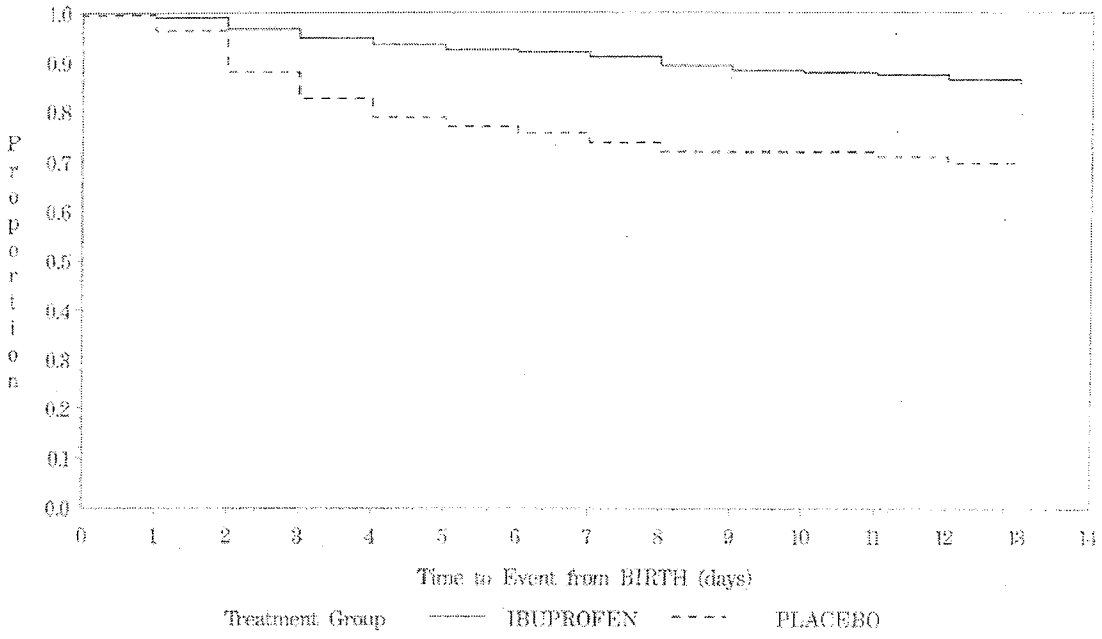
Of the total randomized, 12 ibuprofen (5.6%) and 46 (2.11%) placebo subjects required rescue treatment up to 14 study days and additional 1 ibuprofen and 5 placebo subjects were rescued up to study day 28. The incidence rate for needing rescue was about 4 times for the placebo group compared to the ibuprofen group. When the deaths and dropouts are added in, the difference is about 2-fold (31.2% for placebo and 14.4% for ibuprofen by day 14). It is clear that the use of ibuprofen, a rescue therapy, decreases the need for an additional rescue therapy. There is no effect of using ibuprofen or placebo on the survival rate up to day 28.

The figure below shows the Kaplan-Meier survival cures for the subjects with no rescue, death or dropout to study day 14.

Figure 1

CB88B – PROPORTION OF SUBJECTS WITH NO EVENT (RESCUE, DEATH, OR DROPOUT) TO SDAY 14

Kaplan – Meier Survival Curves



Median SDAY 1 age is 0 days

Curves ending at proportion > 0 show the remaining percentage of subjects that are censored

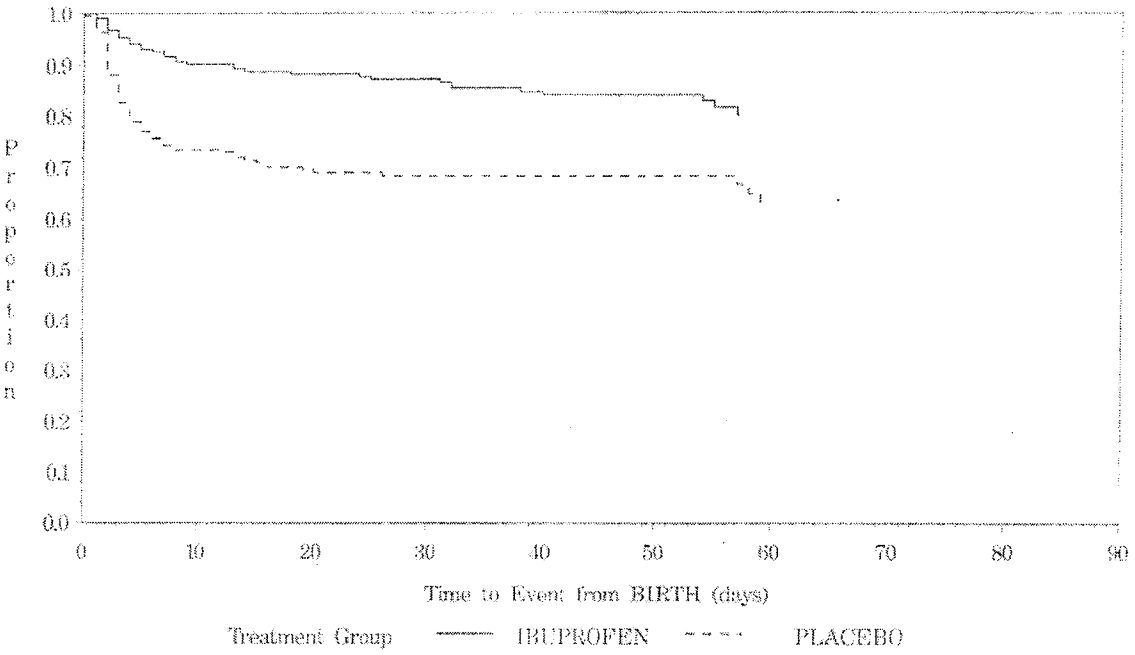
Log rank p-value is <0.0001

The Kaplan-Meier curves for no rescue or death up to 36 weeks adjusted age are shown below.

Figure 3

CBS8B – PROPORTION OF SUBJECTS WITH NO EVENT (RESCUE OR DEATH) TO 36 WEEKS ADJUSTED AGE

Kaplan – Meier Survival Curves



Median SDAY 1 age is 0 days

Curves ending at proportion > 0 show the remaining percentage of subjects that are censored

Log rank p-value is <0.0001

The table below shows the number of subjects who received rescue therapy through day 28 by type of treatment.

No. and (percent) of subjects

	Ibuprofen n=215	Placebo n=218
rescue treatment-any	13 (6.0)	51 (23.4)
medical treatment	13	48
indomethacin	7	31
ibuprofen	8	19
lysine acetylsalicylate	1	6
surgical ligation	6	10+

+3 subjects underwent surgery without prior medical treatment.

Table 12

All but 3 subjects received medical rescue treatment in both randomized groups.

Safety

Serious safety

Deaths

There were 35 reported deaths (14 (6.5%) ibuprofen and 21 (9.6%) placebo) during the 28-day study period. There were 12 reported deaths (8 ibuprofen and 4 placebo) occurring after the 28-day period. All reported deaths are shown in the following table.

Infants Who Died

Subject #/Gender	Preferred Term[a]	Days to onset/ Time to Death[b]	Cause of Death	Age at Death (days)	Gestational Age at Birth (weeks)
Ibuprofen					
12/F	Neonatal respiratory distress syndrome	0/3	Respiratory failure	3	26.9
49/M	Neonatal hypotension	3/3	Pulmonary interstitial emphysema, persistent hypoxemia, and respiratory acidosis, cardiac failure	3	27.0
50/F	IVH	2/4	Coagulation problems; IVH Grade IV	4	29.0
51/F	Coagulation disorder neonatal IVH Platelet count decreased	2/5 2/5 2/5	Coagulation problems; IVH Grade IV	5	29.0
72/F	Capillary leak syndrome	3/54	Cardio-respiratory failure	54	26.7
110/F	Sepsis neonatal	5/6	Sepsis	6	29.0
214/M	IVHc	1/1	Stopped intensive care because of IVH grade III/IV	1	25.6

216/F	Septic shock	3/7	Stop intensive care because of important cerebral hemorrhage	7	28.7
313/F	Sepsis neonatal	27/55	Sepsis	55	24.6
316/M	IVHc	0/25	IVH Grade III	25	28.7
325/F	Neonatal respiratory distress syndrome	31/31	Respiratory failure	32	24.4
343/F	Neonatal respiratory failure	0/57	Immaturity and complications	57	24.4
438/M	Catheter sepsis	20/32	Sepsis, multiple organ failure	32	26.6
465/M	NA	NA/I7	Kidney insufficiency	18	23.7
466/M	IVH	1/1	IVH Grade IV	2	23.7
501/M	Candida sepsis	8/24	Sepsis with Candida albicans	24	24.4
508/M	Respiratory failure	8/8	Insufficient respiration with IVH Grade III	8	29.0
614/F	NA	NA/38	Sepsis, IVH Grade Ill/IV	38	25.4
615/M	IVH	2/4	IVH Grade IV	4	27.0
627/M	Injection site extravasation	23/31	Kidney insufficiency	31	29.7
703/M	Neonatal cardiac failure	26/40	Cardiac failure	40	24.7
736/M	IVH	2/2	IVH Grade IV	2	25.0
Placebo					
27/M	IVH	2/2	Cardio-respiratory arrest	2	25.9
30/Female	Pulmonary hemorrhage	1/1	Cardio-respiratory arrest	2	25.9
40/M	IVH Sepsis neonatal	NA/4 3/4	Cardio-respiratory arrest, E. coli sepsis, possible IVH	4	27.4
44/M	Neonatal hypoxia	0/0	Hypoxemia	0	26.1

58/Male	Sepsis neonatal	-1/0	metabolic acidosis and E. coli sepsis	1	28.0
61/M	IVHc	1/2	IVH Grade IV	3	28.6
88/M	Neonatal respiratory distress syndrome	0/9	Respiratory insufficiency	9	28.0
95/M	Neonatal hypotension	0/26	Cardiovascular failure	26	27.0
99/M	IVHc	1/2	IVH	2	27.0
201/F	IVH	5/5	Intraventricular and intra-parenchymal hemorrhage	6	25.4
206/M	IVHc	1/2	Stopped intensive care because of IVH Grade IV	2	24.9
211/M	IVHc	1/1	Hypovolemic shock and IVH Grade III/IV, stopped intensive care	1	25.7
218/M	NA	NA/58	Peri-operative complications	58	25.6
225/F	Septic shockc	1/4	Septic shock and intracranial bleeding	4	28.0
301/F	Neonatal respiratory distress syndrome Pulmonary hypoplasia	8/8	Respiratory failure	8	27.0
322/F	Neonatal respiratory distress syndromec	1/1	Respiratory and circulatory failure	1	24.9
331/M	Neonatal hypoxia	22/22	Respiratory insufficiency	22	25.0
405/F	NA	NA/41	Septic toxic status	41	26.7

406/F	NA	NA/59	Fulminant enterobacter sepsis	59	29.3
431/F	Pneumothorax	13/13	Respiratory failure and pneumothorax	13	25.1
616/F	IVH	2/4	IVH Grade IV	4	27.0
651/F	Necrotizing enterocolitis	13/16	Multiple organ failure	16	25.6
667/M	IVH	3/5	IVH Grade IV	5	26.7
728/M	Neonatal cardiac failurec	2/2	Cardiac failure	2	25.7
746/Female	NA	NA/56	IVH Grade III/IV /leukomalacia	57	27.7

NA = Not applicable, as no serious adverse event was recorded that had an outcome of death.
a Adverse event with outcome of death.
b Days elapsed since first dose of study drug.
c Event led to premature discontinuation of study drug.

All reported deaths, by time in study at time of death, are shown below. N.B. It is unclear how many subjects had follow up information beyond day 28.

TABLE 18
DIED SUBJECT INFORMATION

	WHEN DIED						TOTAL
	ON/BEFORE SD14		(SD14, SD-28]		AFTER SD28		
	N	%(R)	N	%(R)	N	%(R)	N
Treatment							
IBUPROFEN	11	50.0	3	13.6	8	36.4	22
PLACEBO	18	72.0	3	12.0	4	16.0	25
TOTAL	29	61.7	6	12.8	12	25.5	47

The total number of deaths is slightly higher for placebo. There is no indication that the early use of ibuprofen influences mortality in premature infants.

Other Serious Adverse Events
A total of 196 infants (92 ibuprofen and 104 placebo) experienced serious adverse events during the 28-day study period or within 30 days of the last dose of study drug (or day of life 30 for infants in the placebo group). Serious events reported by at least 2% in either treatment group are shown below.

No. and (percent) of subjects

	Ibuprofen (n=215)	Placebo (n=218)	placebo subtracted (%)
Number of subjects with at least 1 serious adverse event	92 (42.8)	104 (47.7)	-4.9
Preferred Term			
Intestinal perforation	11 (5.1)	4 (1.8)	3.3
Neonatal infection	6 (2.8)	1 (0.5)	2.3
Sepsis neonatal	29 (13.5)	51 (23.4)	-9.9
Intraventricular hemorrhage neonatal	15 (7.0)	17 (7.8)	-0.8
Neonatal respiratory distress syndrome	10 (4.7)	11 (5.0)	-0.3
Catheter sepsis	7 (3.3)	8 (3.7)	-0.4
Necrotizing enterocolitis neonatal	4 (1.9)	11 (5.0)	-3.1
Meconium ileus	3 (1.4)	5 (2.3)	-0.9
Thrombocytopenia neonatal	2 (0.9)	6 (2.8)	-1.9

Table 1004

Events reported more commonly by the ibuprofen group compared to placebo were intestinal perforation and neonatal infection (placebo subtracted incidence rates of 3.3% and 2.3%, respectively).

Discontinuations for adverse events

There were 17 subjects (8 ibuprofen and 9 placebo) whose listed reason for discontinuation of study drug was because of an adverse event. The 14 subjects randomized to ibuprofen who discontinued either for an adverse event or the notes in the case record form (form 26) suggested an adverse event (or no reason found) are listed below.

subject ID	reason for discontinuation	comments
ibuprofen		
101	by physician	low platelet count
112	for AE	high serum creatinine
316	no reason found	probably IVH
333	by physician	renal failure
404	for AE	low platelets
407	other	no explanation found
447	by physician	no explanation found
451	for AE	low urine output
452	for AE	low urine output
466	for AE	bleeding, drop in Hgb
507	for AE	low urine output
627	by physician	oliguria
639	by physician	renal failure
736	for AE	low urine output, bleeding, drop in Hgb

The discontinuations from ibuprofen are mostly for low urine output/signs of renal impairment) or bleeding/low platelets.

Intraventricular hemorrhage
The table below shows the number and percent with reported intraventricular hemorrhage Grade I or higher during the study period (study day 28).

No. and (percent) of subjects with reports of IVH grade I or higher

ibuprofen n=215	placebo n=218
65 (30.2) a, c	69 (31.7) b, d

a missing 3 subjects
b missing 1 subject
c number of IVH reported at any time was 68 (31.6%)
d number of IVH reported at any time was 73 (33.5%)

IVH by grade is shown below for reports of IVH during study period.

No. and (percent) of subjects

	I	II	III	IV
ibuprofen n=212+	37 (17.2)	13 (6.0)	5 (2.3)	10 (4.7)
placebo n=217^	39 (17.9)	12 (5.5)	5 (2.3)	13 (6.0)

+3 missing or absent
^ 1 missing or absent
table 10

The treatment groups have similar reporting rates of IVH regardless of grade.

Necrotizing enterocolitis
The incidence rate for subjects with any NEC diagnosed was 11.2% for the ibuprofen group+ compared to 11.5% for the placebo group^18.

TABLE 20
FOLLOW-UP (FORM 27A)

	NEC Stage								TOTAL
			Pre NEC		Def. NEC		Adv. NEC		
	N	%(R)	N	%(R)	N	%(R)	N	%(R)	N
Treatment									
IBUPROFEN	193	89.8	13	6.0	2	0.9	4	1.9	215
PLACEBO	193	88.5	13	6.0	1	0.5	11	5.0	218
TOTAL	384	88.7	31	7.2	3	0.7	15	3.5	433

+Missing 44 subject
^Missing 56 subjects
There is no evidence of a harmful effect of ibuprofen on the premature intestine.

Leukomalacia
The reporting of leukomalacia is shown below by treatment group.

No. and (percent) of subjects

ibuprofen n=214+	placebo n=216^
47 (22.0)	38 (17.6)

+1 subject missing
^3 subjects missing
Table 11

The incidence rate is slightly higher in the ibuprofen group.

Significant but not serious adverse events
Adverse events described as significant but not serious and reported by at least 2% of either treatment group are shown below.

No. and (percent) of subjects

	Ibuprofen (N=215)	Placebo (N=218)	placebo subtracted %
Number of subjects with at least 1 event	202 (94.0)	206 (94.5)	-0.5
Preferred Term			
Hypotension/neonatal hypotension	37 (17.2)	17 (7.8)	9.4
Urine output decreased/oliguria	13 (6.0)	3 (1.4)	4.6
Jaundice neonatal	23 (10.7)	14 (6.4)	4.3
Sepsis neonatal	18 (8.4)	10 (4.6)	3.8
Necrotizing enterocolitis neonatal	14 (6.5)	9 (4.1)	2.4
Catheter sepsis	7 (3.3)	4(1.8)	1.5
Hyperglycemia	6 (2.8)	3 (1.4)	1.4
Intestinal functional disorder	5 (2.3)	2 (0.9)	1.4
Pneumothorax	7 (3.3)	5 (2.3)	1.0
Neonatal respiratory distress syndrome	5 (2.3)	3 (1.4)	0.9
Neonatal infection	12 (5.6)	11 (5.0)	0.6
Abdominal distension	14 (6.5)	13 (6.0)	0.5
Neonatal Candida infection	6 (2.8)	5 (2.3)	0.5
Staphylococcal infection	5 (2.3)	4 (1.8)	0.5
Blood calcium decreased	5 (2.3)	4 (1.8)	0.5
Intraventricular hemorrhage neonatal	8 (3.7)	8 (3.7)	0
Hyperbilirubinemia neonatal	156 (72.6)	169 (77.5)	-4.9
Blood glucose increased	13 (6.0)	14 (6.4)	-0.4
Feeding problem in newborn	11 (5.1)	15 (6.9)	-1.8
Blood glucose decreased	10 (4.7)	14 (6.4)	-1.7
Neonatal apneic attack	10 (4.7)	23 (10.6)	-5.9
Gastroesophageal reflux disease	7 (3.3)	9 (4.1)	-0.8
Eye infection	4 (1.9)	10 (4.6)	-2.7
Hypothyroidism	3 (1.4)	6 (2.8)	-1.4
Respiratory tract infection	3 (1.4)	5 (2.3)	-0.9
Platelet count decreased	2 (0.9)	5 (2.3)	-1.4

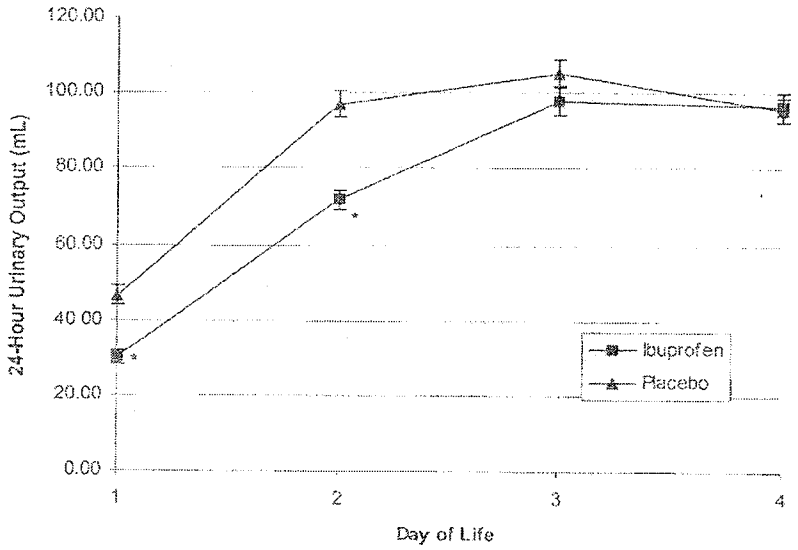
Table 1002

The placebo subtracted incidence rate was the highest for hypotension/neonatal hypotension (9.4%), followed by urine output decreased/oliguria (4.6%), neonatal jaundice (4.3%), and sepsis (3.8%).

Clinical Laboratory

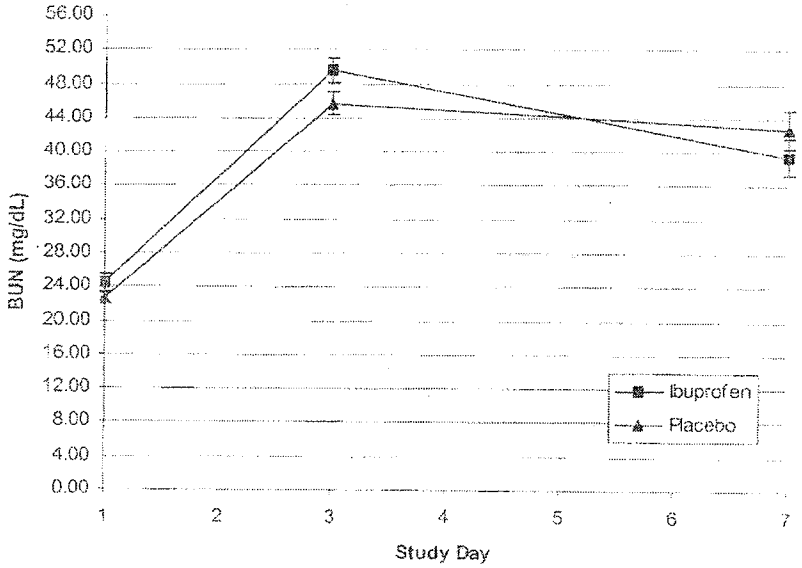
Renal function
While mean fluid intake was similar for the 2 treatment groups, urine output was significantly less for the ibuprofen group compared to placebo study days 1-2.

Figure 3 Mean Urinary Output Over Time



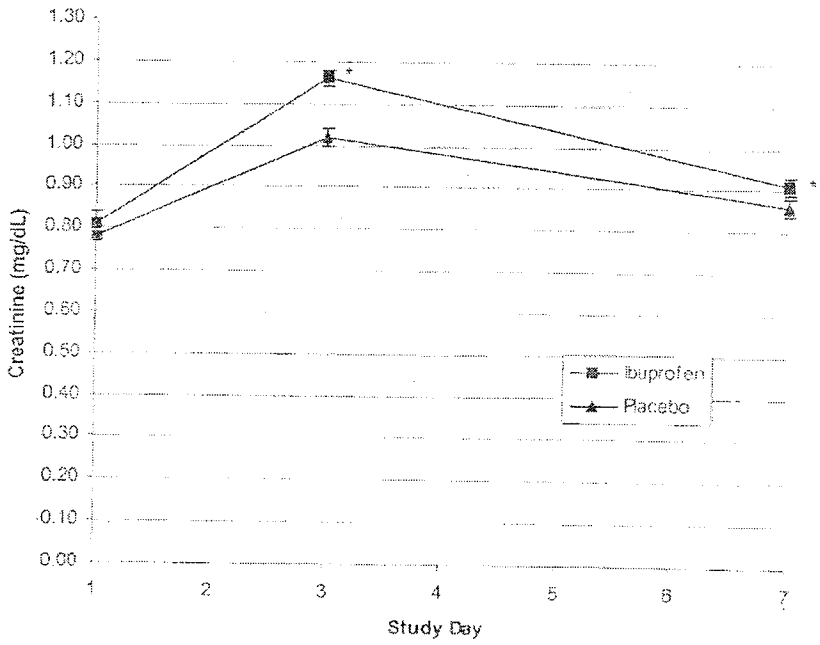
Mean BUN values were higher in the ibuprofen group on study day 7. Difference between groups disappeared rapidly. N.B. Not all subjects had laboratory measurement.

Figure 5 Mean BUN Values Over Time



Mean serum creatinine, however, was higher in the ibuprofen group compared to placebo for the first week of the study. The differences were short-lived.

Figure 6 Mean Creatinine Values Over Time



Mean (SD) creatinine (mg/dl)

day 1		day 3		day 7	
ibuprofen	placebo	ibuprofen	placebo	ibuprofen	placebo
0.81 (0.33)	0.78 (0.18)	1.16 (0.26)	1.02 (0.22)	0.91 (0.23)	0.86 (0.22)

Table 15

By day 7, mean creatinine values were declining in the ibuprofen group and approaching the placebo mean.

Liver function

LFTs were similar for both groups as was total as well as direct bilirubin levels. The incidence rates for abnormal total bilirubin and direct bilirubin were 95.8% and 65.3%, respectively, for ibuprofen, and 91.2% and 64.2%, respectively, for placebo.

The percent of subjects randomized to ibuprofen who had at least one abnormal ALT value was 5.2%. This compares to 1.2% for the subjects randomized to placebo.

Blood Chemistry

There were small variations for serum sodium, chloride, potassium and CO2 for both treatment groups.

Hematology

There was no difference in the percent of subjects with abnormal platelets or WBC values, with the exception of higher WBC in the placebo group on study days 3 and 7. There is no indication that the parameters hemoglobin, hematocrit, or red cell count were collected.

Vital signs

Weight loss is shown below by treatment group.

Table 18 Maximum Weight Loss During the First Seven Days of Life

Maximum Weight Loss (g)	Ibuprofen Lysine IV (N=215)	Placebo (N=218)	P-value
	(n=215)	(n=217)	0.0004
Mean (SD)	81.6 (73.0)	107.9 (79.7)	
Median	73.0	110.0	
Minimum, Maximum	0.0, 405.0	0.0, 370.0	

Cross-reference: Appendix Table 13 and Appendix 16.1.9

The weight loss during first 7 days of life was numerically greater for the placebo group.

Respiratory function

Percentages of subjects requiring oxygen as well as those requiring intubation are shown below by treatment group.

Table 19 Percentage of Infants Who Received Oxygen

Day of Life	Ibuprofen Lysine IV % (n/N)	Placebo % (n/N)
Day 1	92.5 (198/214)	91.7 (200/218)
Day 2	80.0 (172/215)	83.4 (181/217)
Day 3	77.1 (165/214)	83.6 (178/213)
Day 4	68.9 (146/212)	69.2 (144/208)
Day 28	57.1 (97/170)	60.9 (98/161)

Only nonmissing, available data points were included in the analysis.

Table 20 Percentage of Infants Who Were Intubated

Day of Life	Ibuprofen Lysine IV % (n/N)	Placebo % (n/N)
Day 1	82.8 (178/215)	80.7 (176/218)
Day 2	75.3 (162/215)	75.1 (163/217)
Day 3	61.2 (131/214)	63.6 (136/214)
Day 4	55.7 (118/212)	57.9 (121/209)
Day 28	13.5 (23/170)	9.9 (16/161)

Only nonmissing, available data points were included in the analysis.

By day 28, slightly more subjects randomized to ibuprofen were intubated on day 28.

The results of follow up serious adverse events (retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL), and IVH) are shown below.

No. and (percent) with "yes"

	ibuprofen	placebo
ROP	50 (35.2)	50 (40.3)
BPD	112+ (52.1)	107^ (49.1)
PVL	9 (5.3)	6 (3.7)
IVH	74 (43.3)	66 (41.0)

+Missing 44 subjects
^Missing 57 subjects
Table 20

Only minor difference are shown between treatment groups.

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/s/

Maryann Gordon
1/20/2006 09:55:34 AM
MEDICAL OFFICER