CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-903

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	**21-903 N000**
Submission Dates:	2/10/2006
Brand Name:	**Neoprofen**
Generic Name:	Ibuprofen-L-Lysinate
Dosage Form & Strength:	Solution for IV infusion
Indication:	Patency of Arterial Ductus
Category:	P
Applicant:	Farmacon-IL, LLC
Submission:	Response to Request for Information
Divisions:	DPEI and Cardio-Renal Drug Products, HFD-110
Primary Reviewers:	Elena V. Mishina, Ph.D.
Team Leader:	Patrick Marroum, Ph.D.

BACKGROUND

The sponsor did not provide the assay validation for ibuprofen in the Analytical Section of the original NDA 21-903. This information was requested from the sponsor.
The current submission contains the requested information.

RESULTS

Ibuprofen is a chiral nonsteroidal anti-intlammatory drug with the S-(+)-enantiomer possessing most of the anti-inflammatory activity. Ibuprofen demonstrates distinct stereoselectivity in its pharmacokinetics. Substantial unidirectional inversion of the R-(-) to the S-(+) enantiomer occurs and thus, data generated using non-stereospecific assays may not be extrapolated to explain the disposition of the individual enantiomers. The sponsor assayed only racemic ibuprofen in plasma using the assay method developed in 1984. Therefore, all information presented in the NDA 21-903 regarding the ibuprofen pharmacokinetics in neonates is reflecting the properties of the ibuprofen racemic mixture.
The plasma samples were analyzed for ibuprofen concentration at the [redacted] using high performance liquid chromatography (HPLC) technique.
The assay characteristics are provided in Table 1 below.

Table 1. Assay Characteristics for Racemic Ibuprofen

Parameter	Measure	Reviewer Comment
Linearity	1 mcg/mL to 100 mcg/mL	Satisfactory
Precision (within day), CV %	Between 1.52 and 4.84%	Satisfactory
Accuracy (between days)	between -4.82% and 4.49%	Satisfactory
LLOQ	1 mcg/mL	Satisfactory
Specificity		Satisfactory

The results of the assay validation are acceptable.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the assay validation for NDA 21-903 and finds it acceptable.

_____ Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

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/s/

Elena Mishina
2/21/2006 12:55:43 PM
BIOPHARMACEUTICS

Patrick Marroum
2/21/2006 01:13:33 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	**21-903 N000**
Submission Dates:	8/30, 9/19, 10/26, 11/1, and 12/5, 12/21, 2005 1/12/2006
Brand Name:	**Neoprofen**
Generic Name:	Ibuprofen-L-Lysinate
Dosage Form & Strength:	Solution for IV infusion
Indication:	Patency of Arterial Ductus
Category:	P
Applicant:	Farmacon-IL, LLC
Submission:	Original NDA
Divisions:	DPEI and Cardio-Renal Drug Products, HFD-110
Primary Reviewers:	Elena V. Mishina, Ph.D.
Team Leader:	Patrick Marroum, Ph.D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-903 and finds the clinical pharmacology section and biopharmaceutics sections acceptable provided the labeling comments are adequately addressed.

Ibuprofen lysinate was administered as an IV 10 mg/kg dose followed with two doses of 5 mg/kg per day to premature newborn infants with non-symptomatic PDA (mean age at receipt of first dose was 37.5 hours and the mean birth weight was 791 g). The mean (SD) ibuprofen concentrations achieved at nominal sampling times of 1, 24, 48 and 120 h after the start of the first 10 mg/kg infusion were 34.7 (9.0), 24.7 (7.5), 27.5 (14.0), and 13.5 (11.5) pg/mL, respectively. The population average ibuprofen clearance and volume of distribution values for premature infants on day of birth were 2.96 mL/kg/h (CV 60%) and 320 mL/kg (CV 14%), respectively. Ibuprofen clearance in premature infants significantly correlated with post-natal age; it increased rapidly over time by 0.5 mL/kg/h per day, probably reflecting the maturation of metabolic capacity. The ibuprofen elimination in neonates was markedly slower than in adults.

The sponsor is requested to:

1. Submit for review the ibuprofen assay validation report.

1.2 COMMENTS:

Issue not addressed by the sponsor:

1. The assay used by the sponsor (established in 1984) measured the mixture of both stereoisomers of ibuprofen, therefore, the pharmacokinetics of these isomers and their inter-conversion were not described.

2. The assay validation was not available for review.

3. Although the Agency advised the sponsor how to apply the random time blood sampling and to cover the time frame up to 216 hours after the first dose, the sponsor did not properly perform the pharmacokinetic sampling. The fixed sampling times and termination of the sampling at 120 hours after the first dose did not allow to fully characterize the terminal phase of the ibuprofen pharmacokinetics in neonates.

4. The sponsor reported the ibuprofen half-life on day 1 of the neonate life as 75 hours, diminishing to 41 hour at day 3. The plasma concentrations were obtained at 1 and 24 after the first dose. The drug was administered once a day for three days. The last plasma sample was obtained at 72 hours after the third dose. This plasma sampling scheme does not cover the interval of 3-5 half-lives, therefore, the half-life values do not seem to be estimated correctly.

5. The sponsor attempted to describe the pharmacologic response to ibuprofen by the measurement of the prostanoids (6-ketPGF1α, PGE2, PGE2α and TxB2) in plasma. There were only 3 measurements: pre-dose, 1 hour after the dosing on day 1 and day 3 in the active drug group and placebo group. There were no differences in plasma concentrations of 6-ketPGF1α and PGE2 between the active drug and placebo groups. The group of patients receiving ibuprofen had lower PGE2α levels and much higher thromboxane B2 levels. The sponsor could not explain this fact and speculated that this may reflect some inherent conditions that were not measured during the study. For each of the measurements, the differences between the values obtained pre-dose and post-dose on day 3 were not statistically significant. This information could not be used to link the ibuprofen plasma concentrations and pharmacologic response; therefore, the PK/PD relationship between ibuprofen and prostanoids was not established.

_____ Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on January 25, 2006.

Attendees: Drs. Mehta, Selen, Sahajwala, Stockbridge, Marroum, Mishina, Gordon, Velazquez, Rahman, Bhattaram, Huang, Frueh, Shah, Johal.

cc list: NDA 21-903, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

1.3.1 Background

Farmacom-IL, LLC. is seeking approval of ibuprofen-L-lysinate solution for IV infusion for the treatment of patent ductus arteriosus (PDA) in neonates.
Ibuprofen is a nonsteroidal, anti-inflammatory drug derived from 2-(4-isobutylphenyl) propionic acid. It was developed as an antirheumatic drug in the 1960s and has been available as an over-the-counter analgesic and anti-inflammatory drug in the US since 1984.
Patent ductus arteriosus is a common problem for neonates with low gestational age and low birth weight. PDA results from the failure of the ductus arteriosus to close following the end of intrauterine blood circulation at birth. Current treatment of PDA includes fluid restriction, increased ventilatory support, diuretics, and indomethacin and in case of failure of the above therapy surgical ligation can be performed. The therapy with indomethacin can lead to decrease cerebral, renal, and mesenteric blood flow, which causes periventricular leukomalacia, altered renal function, necrotizing enterocolitis, or isolated intestinal perforation.
Several articles describe the current off label use of IV ibuprofen to treat PDA. The sponsor submitted NDA 21-903 to support the proposed indication.

1.3.2 Current Submission

Item 6 of NDA 21-903 contains the summary of the published literature regarding the pharmacokinetics of ibuprofen in adults and in premature infants and a report of one clinical study of IV ibuprofen lysinate in premature infants including the population PK data analysis. The literature data and the study performed by the sponsor were reviewed.

Pharmacokinetics
Ibuprofen is a chiral nonsteroidal anti-intlammatory drug with the S-(+)-enantiomer possessing most of the anti-inflammatory activity. Ibuprofen demonstrates distinct stereoselectivity in its pharmacokinetics. Substantial unidirectional inversion of the R-(-) to the S-(+) enantiomer occurs and thus, data generated using nonstereospecific assays may not be extrapolated to explain the disposition of the individual enantiomers. The sponsor assayed only racemic ibuprofen in plasma using the assay method developed in 1984. Therefore, all information presented in the NDA 21-903 regarding the ibuprofen pharmacokinetics in neonates is reflecting the properties of the ibuprofen racemic mixture.
In adults, an apparent volume of distribution (Vd/F) determined after oral administration ranges from 0.09 to 0.34 L/kg. Similar results were reported in literature when IV ibuprofen lysinate was administered to premature infants, (Vd from 0.062 to 0.354 L/kg). The population average ibuprofen Vd estimated by the sponsor was 0.320 L/kg (CV=14%), at the high end of the reported range. None of the demographic variables and ventilation status had any significant ($p<0.05$) influence.
CYP2C9 is the major enzyme mediating the 2 and 3-hydroxylations of R- and S-ibuprofen in the liver in adults (two major inactive metabolites and conjugates to acyl glucuronides). The ibuprofen elimination occurs primarily by liver metabolism, renal elimination of unchanged ibuprofen accounts for 10-15% of the dose. The excretion of ibuprofen and metabolites in adults occurs in both urine (80% of the oral dose) and feces. At birth, the glomerular filtration rate is

low; it is about 30% that of adults. The neonate has a low effective renal blood flow (34 to 99 mL/mm/1.73 m^2), which increases twice by 14 to 21 days.
The sponsor estimated the average clearance in premature newborns on the day of birth as 3 mL/kg/h (CV 60%). The post-natal age was the only significant covariate influencing clearance; it increased over time with an average of about 0.5 mL/kg/h per day. In literature, the clearance of racemic ibuprofen after the IV dose in infants on day 3 of life was estimated between 2 and 9 mL/kg/h and half-life between 31 and 43 hours. In adults, the half life values were reported to be between 1 and 3 hours.
The sponsor explained that the decreased clearance and prolonged half-life of ibuprofen in preterm infants may be due to deficient activity of the hepatic CYP450 enzymes and reduced activity of glucuronyl transferase and many UDPGT isoforms. However, none of the ibuprofen metabolites was measured in this study and its metabolic pathway in infants is not described. In addition, reduced renal function, may contribute to the prolonged elimination time of ibuprofen in premature neonates but the urinary excretion of ibuprofen and its metabolites was not measured by the sponsor.

Biopharmaceutics
The proposed commercial IV formulation of ibuprofen L-lysinate for the PDA indication and the formulation used in the PDA clinical study is directly analogous to the commercial formulation supported by the US patent.

Issue not addressed by the sponsor:

1. The assay used by the sponsor (established in 1984) measured the mixture of both stereoisomers of ibuprofen, therefore, the pharmacokinetics of these isomers and their inter-conversion were not described.

2. The assay validation was not available for review.

3. Although the Agency advised the sponsor how to apply the random time blood sampling and to cover the time frame up to 216 hours after the first dose, the sponsor did not properly perform the pharmacokinetic sampling. The fixed sampling times and termination of the sampling at 120 hours after the first dose did not allow to fully characterize the pharmacokinetic profile of ibuprofen in neonates.

4. The sponsor reported the ibuprofen half-life on day 1 of the neonate life as 75 hours, diminishing to 41 hour at day 3. The plasma concentrations were obtained at 1 and 24 after the first dose. The drug was administered once a day for three days. The last plasma sample was obtained at 72 hours after the third dose. This plasma sampling scheme does not cover the interval of 3-5 half-lives, therefore, the half-life values do not seem to be estimated correctly.

5. The sponsor attempted to describe the pharmacologic response to ibuprofen by the measurement of the prostanoids (6-ketPGF1α, PGE2, PGE2α and TxB2) in plasma. There were only 3 measurements: pre-dose, 1 hour after the dosing on day 1 and day 3 in the active drug group and placebo group. There were no differences in plasma

concentrations of 6-ketPGF1α and PGE2 between the active drug and placebo groups. The group of patients receiving ibuprofen had lower PGE2α levels and much higher thromboxane B2 levels. The sponsor could not explain this fact and speculated that this may reflect some inherent conditions that were not measured during the study. For each of the measurements, the differences between the values obtained pre-dose and post-dose on day 3 were not statistically significant. This information could not be used to link the ibuprofen plasma concentrations and pharmacologic response; therefore, the PK/PD relationship between ibuprofen and prostanoids was not established.

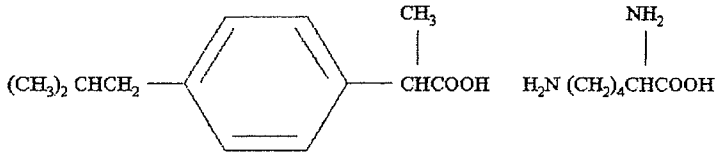
2 QUESTION BASED REVIEW

2.1 General Attributes

What are the highlights of chemistry and physico-chemical properties of ibuprofen?

Ibuprofen-L-Lysinate (or L-Lysinate) Injection is a sterile solution of the L-lysinate salt of (±)-ibuprofen, which is the active ingredient. (±)-ibuprofen is a nonsteroidal anti-inflamrnatory agent (NSAID). L-Lysinate, classified as a nutritional supplement, is used to create a water-soluble drug product salt suitable for intravenous administration. Each mL of Ibuprofen L-Lysinate (or L-Lysine) Injection contains 17.1 mg of Ibuprofen L-Lysinate (or L-Lysine) equivalent to 10 mg of (±)-ibuprofen.

The structural formula of ibuprofen lysinate is presented below:



Ibuprofen L-Lysinate (or L-Lysine) is designated chemically as a-methyl-4- (2- methylpropyl) benzene-acetic acid lysinate salt. Its molecular weight is 352.48 (ibuprofen 206.29 and lysinate 146.19). Its empirical formula is $C_{10}H_{32}N_2O_4$.

History of Ibuprofen Development for the Treatment of PDA

Ibuprofen is a nonsteroidal, anti-inflammatory drug developed as an antirheurnatic drug in the 1960s and has been available as an OTC analgesic and anti-inflammatory drug in the US since 1984. The antipyretic property of ibuprofen in children was initially demonstrated in the mid-1980s, and its pharmacokinetics in children have been studied; however, it has not been well characterized in neonates. Several literature studies report that ibuprofen was used for the closure of PDA in premature infants and changes in blood flow appear to be absent or less pronounced than with indomethacin. Most published studies of intravenous ibuprofen for the treatment of PDA report a dosing regimen of 10 mg/kg on Day 1 of treatment, followed by 5 mg/kg 24 hours and 48 hours after the initial dose. The sponsor submitted three studies with NDA 21-903. Studies CB88A and CB88B provide the results of the reanalysis of two published studies by Van Overmeire, et. al. Study FCR-00-01/CB88, is the pivotal study for efficacy and safety where the information on ibuprofen pharmacokinetics, and results from the ibuprofen population pharmacokinetic evaluation in premature infants in study FCR-00-01/CB88 is summarized.

Was the information about the general attributes of ibuprofen submitted with this sNDA?

The literature information regarding ibuprofen pharmacokinetics (ADME) studied previously in adults and pharmacokinetic studies in premature infants were summarized by the sponsor.

2.2 Pediatric Study Decision Tree

What are the design features of the clinical pharmacology study used to support dosing and claim?

The following scheme Figure 1 illustrates the regulatory basis for requiring the sponsor to perform the safety/efficacy study in pediatrics.

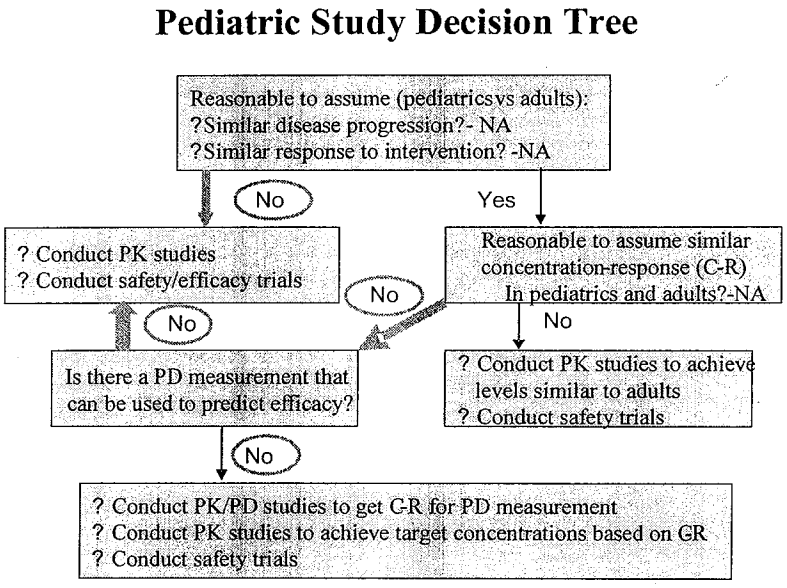


Figure 1: Pediatric Study Decision Tree

The target population is neonates, and the adult's data cannot be used to predict the safety and efficacy of ibuprofen in neonates. Therefore, the safety and efficacy study in the target population need to be conducted.

2.3 General clinical pharmacology

What is the rationale for dose selection?

The sponsor used only one dose regimen: 10 mg/kg dose on day 1 and two doses of 5 mg/kg at days 2 and 3. The rational for the selection of this regimen is that the same regimen was used in the majority of the published studies which led to the PDA closure. Only one reference (abstract) described the use of 4 different doses with a dose regimen of 15-7.5-7.5 mg/kg showing a higher response. Since the other dose regimens were not studied in the well controlled studies, the dose-response curve could not be characterized.

Was the exposure response relationship described for efficacy?

No.

It is recognized that non-steroidal anti-inflammatory drugs like ibuprofen act to reduce inflammation and pain by interupting the synthesis of prostaglandins. The levels of prostanoids could be a possible determinant of the pharmacologic response. The sponsor measured the prostanoids plasma concentrations (6-keto prostaglandin F1 [6-ketPGF1α], prostaglandin E2 [PGE2], prostaglandin Fl [PGF PGF2α], and thromboxane B2 [TxB2]). However, the relationship between the plasma concentrations of ibuprofen and prostanoids could not be rulled out based on the obtained data.

Table 1. Plasma prostanoid concentrations

Treatment Group	6-ketoPGF1 alpha (pg/mL)	PGE2 levels x 2 (pg/mL)	PGF2alpha (pg/mL)	TxB2 Levels x 2 (pg/mL)
Ibuprofen Lysine IV				
Prior to dose 1	(n=31)	(n=30)	(n=31)	(n=31)
Mean (SE)	8286.77 (1426.40)	3861.54 (773.13)	1450.42 (201.90)	2260.11 (278.71)
Median	5101.18	1671.32	1095.88	1851.07
Minimum, maximum	[redacted]			
One hour post dose 1	(n=32)	(n=32)	(n=32)	(n=32)
Mean (SE)	8882.87 (1857.96)	3922.44 (733.38)	1477.75 (211.67)	2411.20 (313.35)
Median	3969.56	1926.19	1074.30	2051.86
Minimum, maximum	[redacted]			
One hour post dose 3	(n=33)	(n=33)	(n=33)	(n=33)
Mean (SE)	7576.67 (1301.77)	3728.60 (571.29)	1254.59 (181.94)	1813.64 (199.39)
Median	3883.53	2754.45	778.13	1537.69
Minimum, maximum	[redacted]			
Placebo				
Prior to dose 1	(n=37)	(n=37)	(n=37)	(n=37)
Mean (SE)	9412.68 (1107.56)	3666.07 (606.73)	2457.82 (333.11)	19468.05 (9498.22)
Median	7130.57	2336.53	1776.61	3559.29
Minimum, maximum	[redacted]			
One hour post dose 1	(n=37)	(n=37)	(n=37)	(n=37)
Mean (SE)	9730.69 (1245.32)	3561.48 (583.46)	2380.03 (319.49)	19037.49 (9542.48)
Median	7292.23	2223.20	1833.81	2581.72
Minimum, maximum	[redacted]			
One hour post dose 3	(n=34)	(n=34)	(n=34)	(n=34)
Mean (SE)	8145.38 (1262.74)	4261.54 (677.59)	2158.27 (327.54)	13287.60 (4528.86)
Median	5330.34	2599.36	1466.28	2432.60
Minimum, maximum	[redacted]			

There were only 3 measurements: pre-dose, and 1 hour after dosing on day 1 and day 3 in the active drug group and placebo group. There were no differences in plasma concentrations of 6-ketPGF1α and PGE2 between the active drug and placebo groups. The group of patients receiving ibuprofen had lower PGE2α levels and much higher thromboxane B2 levels. The difference in mean thromboxane levels between the baseline values in placebo and ibuprofen groups is 5 fold. The sponsor could not explain this fact and speculated that this may reflect some inherent conditions that were not measured during the study. For each of the measurements, the differences between the values obtained pre-dose and post-dose on day 3 were not statistically significant. This information could not be used to link the ibuprofen

plasma concentrations and pharmacologic response; therefore, the PK/PD relationship between ibuprofen and prostanoids was not established in this study.

What was the primary efficacy endpoint?

The primary efficacy endpoint was symptomatic PDA treated with indomethacin or by surgery. Efficacy was evaluated using four outcomes defined as follows:

1. Proportion of infants who were rescued, died or dropped out on or prior to Study Day 14,
2. Proportion of infants who were rescued to Study Day 14,
3. Proportion of infants who were rescued at any time, and
4. Overall proportion of infants who were rescued, died, or dropped out at any time during the study.

Including infants that died on or prior to Study Day 14 and infants that dropped out on or prior to Study Day 14, a statistically significantly lower proportion of infants who received ibuprofen lysine IV required rescue treatment, died, or dropped out compared to infants receiving placebo ($p = 0.0052$).

Was the exposure response relationship described for safety?

No.

The measurement for safety was the occurrence of adverse events. The sparse data do not allow to describe this relationship.

What is the ibuprofen protein binding in adults and in neonates?

Ibuprofen is extensively bound to whole human plasma and purified albumin at therapeutic concentrations. Ibuprofen protein binding is stereoselective and non-linear; unbound fraction ranges from 0.033 at a concentration of 2 pg/mL to 0.042 at 50 pg/mL.

In the literature, the percentage of bound ibuprofen premature infants was significantly lower in full term cord plasma (mean + SE = 94.98 ± 0.39%, n=26) compared with adults (mean + SE = 98.73 ± 0.31%, n=8, $p < 0.0001$).

The protein binding was not assessed in the sponsor's study.

What are the distribution characteristics of ibuprofen in neonates?

In the sponsor's study, the population average ibuprofen volume of distribution value was reported as 0.320 L/kg (CV=14%). None of the demographic variables and ventilation status had a significant ($p<0.05$) influence. In the literature articles, the same IV dosage regimen of ibuprofen lysinate in premature infants led to the estimation of the volume of distribution in the range of 0.062 to 0.354 L/kg after IV dosing.

Was the ibuprofen pharmacokinetic study in neonate patients properly designed?

No.

The Agency recommended to the sponsor to obtain random blood sampling up to 216 hours after the first dose (168 hours post last dose). However, the sponsor obtained 4 plasma samples per patient at fixed times and terminated the sampling at 120 hours after the first dose (72 hours post last dose). This sampling schedule did not allow to fully characterize the pharmacokinetic profile of ibuprofen in neonates.

What was the exposure to ibuprofen in neonates?

In study CB88, the mean plasma concentrations achieved at sampling times of 1, 24, 48 and 120 h after the start of the first 10 mg/kg infusion were 34.7 ± 9.0, 24.7 ±7.5, 27.5 ± 14.0, and 13.5 ± 11.5 mcg/mL, respectively. Figure 2 shows the individual observed ibuprofen plasma concentrations. After the last dose, the plasma concentrations decreased very slowly. These concentrations were similar to the ibuprofen plasma concentrations of 43.5 mcg/mL described in premature neonates who received the same dose regimen of the drug; however, in one study, the premature newborns had the ibuprofen Cmax (1 hour) of 180 mcg/mL and 117 and 114 mcg/mL on days 2 and 3 (same 3-days IV dose regimen).

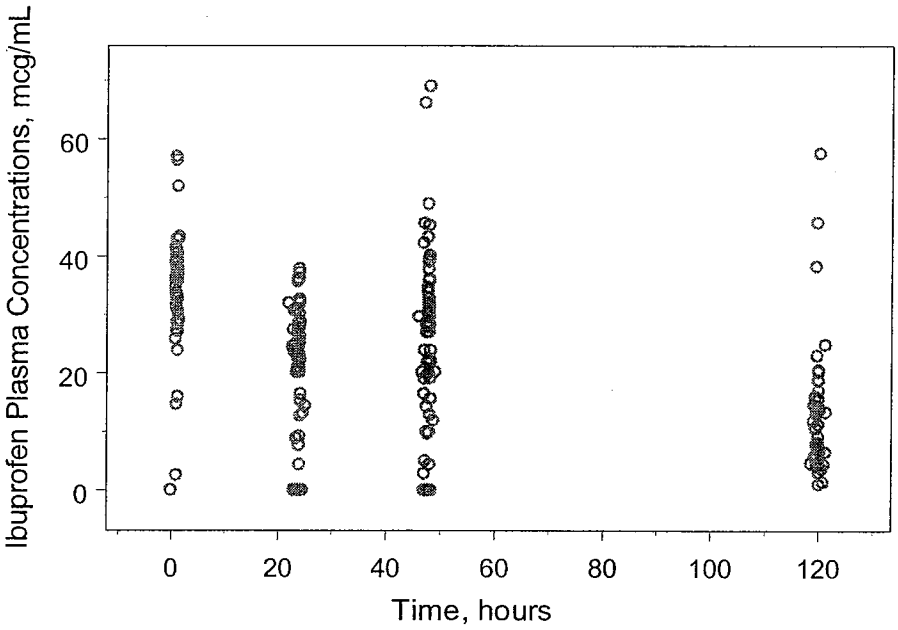


Figure 2. Observed ibuprofen plasma concentrations vs. time

What are the characteristics of ibuprofen metabolism in adults?

Ibuprofen is metabolized into two major inactive metabolites: 2-[4-(2-hydroxy-2-methyl propyl)phenyl]propionic acid and 2-[3-(2-carboxypropyl)phenyl] propionic acid. CYP2C9 is the major enzyme mediating the 2 and 3-hydroxylations of R- and S-ibuprofen in the liver. Ibuprofen and its metabolites are further conjugated to acyl glucuronides.

Were the metabolites of ibuprofen characterized in neonates?

None of the ibuprofen metabolites was measured in this study.

In infants the CYP450 enzymatic system is not developed, in mid-gestation fetal liver CYP450 represents 20 to 40% of the adult values. The sponsor speculated that due to the low enzyme activity, ibuprofen is metabolized and excreted in preterm neonates more slowly than in adults. However, since the ibuprofen metabolites were not measured, the metabolic profile in infants was not characterized.

What are the characteristics of ibuprofen elimination in adults?

In adults, ibuprofen is eliminated primarily by liver metabolism, renal elimination of unchanged ibuprofen accounts for 10-15% of the dose. Renal elimination occurs primarily by glomerular filtration and tubular secretion, with tubular reabsorption playing a minor role. The excretion of ibuprofen and metabolites occurs in both urine (80% of the oral dose) and feces.
In adults, the half life values reported between 1 and 3 hours.

How the renal function in neonates may influence the ibuprofen elimination?

At birth, the glomerular filtration rate (GFR) is low; it is about 30% that of adults. During the first one to two days of life, there is a rapid increase in GFR and natriuresis/diuresis that is accompanied by a contraction of the extra-cellular compartment. GFR is about 25 mL/min/1.73m^2 during the first two to three postnatal days in healthy infants and increases approximately two-fold during the first week of life. At birth, the neonate has a low effective renal blood flow (34 to 99 mL/mm/1.73 m^2), which increases twice in 14 to 21 days. Tubular function is more immature than GFR at birth and maturation occurs more slowly. During the immediate postnatal period, there is an abrupt increase in tubular function in term infants, which continues to increase at a slow rate until adult levels are reached by 3 to 5 months of age.
The reduced renal function may contribute to the prolonged elimination time of ibuprofen in premature neonates but the urinary excretion of ibuprofen and its metabolites was not measured by the sponsor.

Were the characteristics of the ibuprofen pharmacokinetics in neonates properly assessed?

The sponsor estimated the average clearance in premature newborns on the day of birth as 3 mL/kg/h (CV 60%) which is in the same range as it was reported previously. The post-natal age was the only significant covariate influencing clearance with an average increase of about 0.5 mL/kg/h per day. The clearance values estimated by the sponsor were similar to the same values reported in the literature (between 2 and 9 mL/kg/h). The dose and sampling schedule applied in the sponsor's study was similar to the studies reported in the literature.
The sponsor explained that the decreased clearance of ibuprofen in preterm infants may be due to the deficient activity of the hepatic CYP450 enzymes and reduced activity of glucuronyl transferase and many UDPGT isoforms. However, the metabolites of ibuprofen were not measured in this study, and therefore the sponsor's explanation could not be confirmed.
The sponsor reported the ibuprofen half-life on day 1 of the neonate life as 75 hours, diminishing to 41 hour at day 3. This value does not seem to be correctly estimated. The plasma concentrations were obtained at 1 and 24 after the first dose. The drug was administered once a day for three days. The last plasma sample was obtained at 72 hours after the third dose. This plasma sampling scheme does not cover the interval of 3-5 half-lives. The comparison of the plasma concentration profiles in neonates and adults leads to the conclusion that the elimination of ibuprofen in neonates is much slower; however, the sponsor could not properly characterize the ibuprofen elimination in neonates.

Was the data analysis for the evaluation of ibuprofen pharmacokinetics properly performed?

Yes. The population PK data analysis (Appendix) was properly performed by the sponsor. The one-compartmental model proposed by the sponsor described the pharmacokinetic data obtained in this study satisfactorily.

Are the results of the population data analysis accurate?

No. The sponsor failed to properly characterize the terminal elimination phase of ibuprofen pharmacokinetics in neonates due to an early cutoff of the blood sampling. Although the model adequately described the obtained data, the parameters estimated based on these data are not accurate due to the quality of the data. The sponsor reported that the parameters estimated in this study were similar to the earlier reported PK parameters for ibuprofen in neonates. However, all reported studies applied the same dose regimen and blood sampling scheme; therefore, none of the available studies properly characterized the ibuprofen pharmacokinetics in neonates.

Is the dose and dosing regimen selected by the sponsor acceptable?

Yes.

The proposed dosage regimen is acceptable because sufficient efficacy and safety were shown in the pivotal clinical trials using the proposed regimen.

2.4 Intrinsic Factors

What is the inter- and intra-subject variability of the ibuprofen PK parameters in neonates, and what are the major causes of variability?

Ibuprofen is a moderately variable drug. The inter-individual coefficients of variation were 55% for clearance and 14% for volume of distribution. Because an exponential error distribution model was assumed for clearance and volume of distribution, the actual coefficients of variation were 60% and 14%, respectively. The inter-subject variability of the apparent clearance was explained by the incorporation the covariate "post-natal age" into the model. The inter-occasion variability was not evaluated in the model.

What intrinsic factors influence the pharmacokinetics of ibuprofen in neonates?

The ibuprofen dose was administered based on body weight; therefore, clearance and volume of distribution values were already corrected by body weight and the influence of the body size covariates were not significant. None of the other explanatory variables (sex, race, gestational age, birth weight, creatinine, bilirubin) were found to be significant ($p < 0.05$). The only significant covariate was the influence of the post-natal age on the clearance. The relationship between clearance and post-natal age was linear. The ibuprofen clearance was estimated on day of birth for premature newborns as 2.96 mL/kg/h with an average increase of approximately 0.0200 mL/kg/h or about 0.5 mL/kg/h per day.

Renal impairment

Not applicable.

Hepatic impairment

Not applicable.

What pharmacogenetics information is there in the application and is it important or not?

Ibuprofen is cleared predominantly by the CYP2C9 hepatic microsomal isoenzyme. A blood sample for CYP2C9 genotyping was obtained from infants who received all three doses of the study drug. The CYP2C9 genotyping report is included in the clinical study report but this information was not used for any of the data analysis, therefore, the sponsor considered this information not important.

2.5 Extrinsic Factors

What extrinsic factors influence the pharmacokinetics of ibuprofen in neonates?

The influence of the ventilation status was evaluated in the population PK model. This influence was found not to be statistically significant. None of the other extrinsic factors were assessed in the model.

Drug-Drug and Drug-Disease Interactions

No analyses of drug-drug and drug-disease interactions were planned or performed.

Is there a need for dose adjustments when ibuprofen is coadministered with the other drugs?

The impact of the concomitant medications on the pharmacokinetics of ibuprofen in neonates was not studied. The neonates who received any NSAIDs were excluded from the study.

What are the proposed dosages and route of administration?

The recommended dose of IV ibuprofen in neonates: 10 mg/kg on day 1, followed by two daily doses of 5 mg/kg.

Are the doses proposed by the sponsor justified?

No. The only justification of the proposed dose regimen is that this regimen was studied previously when the drug was used for PDA in off label studies.

Is the dose and dosing regimen selected by the sponsor acceptable?

Yes. The proposed dosage regimen is acceptable because sufficient efficacy and safety were shown in the pivotal clinical trials using the proposed regimen.

Was the ibuprofen formulation for PDA equivalent to the previously approved drug strengths?

The proposed commercial formulation for the PDA indication and the formulation used in the PDA clinical studies is directly analogous to the commercial formulation. Manufacturers: [redacted] (final drug product). The commercial Neoprofen product will be a 2 mL vial containing 34.18 mg of the ibuprofen lysine salt, which is equivalent to 20.0 mg of ibuprofen (free acid), dissolved in Water for Injection. The pH is balanced with sodium hydroxide and hydrochloric acid.

The composition and components are presented in Table 2 below.

Table 2: Drug Product Components and Composition/2 ml vial

Ingredient	Standard	Function	Quantity/Vial
(±) Ibuprofen L-lysinate	BVL spec	API	34.18 mg salt 20.0 mg ibuprofen
Sodium hydroxide	NF	pH	*q.s.*
Hydrochloric acid	NF	pH	*q.s.*
Water for Injection	USP	Solvent	*q.s.*
[redacted]			*q.s.*

2.6 Analytical Section

Were the proper moieties identified and measured in plasma?

Ibuprofen is a chiral nonsteroidal anti-intlammatory drug with the S-(+)-enantiomer possessing most of the anti-inflammatory activity. Ibuprofen demonstrates distinct stereoselectivity in its pharmacokinetics. Substantial unidirectional inversion of the R-(-) to the S-(+) enantiomer occurs and thus, data generated using nonstereospecific assays may not be extrapolated to explain the disposition of the individual enantiomers. The sponsor assayed only racemic ibuprofen in plasma using the assay method developed in 1984. Therefore, all information presented in the NDA 21-903 regarding the ibuprofen pharmacokinetics in neonates is reflecting the properties of the ibuprofen racemic mixture.

The plasma samples were analyzed for ibuprofen concentration at the [redacted], using high performance liquid chromatography (HPLC) technique.

Were the validation characteristics of the assay acceptable?

The assay validation is not available for the review.

What is the overall conclusion regarding NDA 21-903?

Overall the clinical pharmacology and biopharmaceutics section is acceptable.

2.7 References

1. Aravind MK, Miceli JN, Kauffman RE. Determination of ibuprofen by high-performance liquid chromatography. J Chromatogr 1984;308:350-3.
2. Aranda J, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, Papageorgiou A, Chemtob S. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediatr 1997;86(3):289-93.
3. Van Overmeire B, Touw D, Schepens P J, Kearns GL, van den Anker JN. Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther 2001;70:336-343.

3 DETAILED LABELING RECOMMENDATIONS

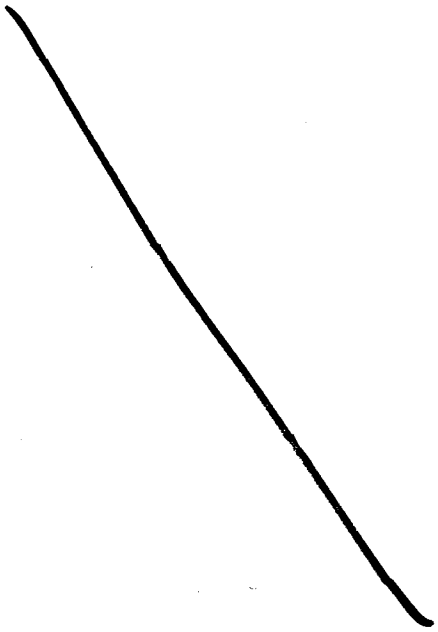
GENERAL

The Agency considered that the information provided in the original NDA 21-903 ibuprofen lysinate was appropriate to evaluate the pharmacokinetic of this drug for the use in PDA therapy.

CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

CLINICAL PHARMACOLOGY Section



12 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 4

4.2 Individual Study Reviews

4.2.1 POPULATION PHARMACOKINETICS OF IBUPROFEN L-LYSINATE INTRAVENOUS SOLUTION DURING EARLY TREATMENT OF PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS

Investigator(s): 17 investigator sites enrolled subjects
Study Site(s): Multi-center (United States)
Study Period
Date First Subject Dosed: 27 July 2001
Date Last Subject Completed Dosing: 15 May 2002

OBJECTIVES:

To determine the effect of early treatment with intravenous (IV) ibuprofen given to very low birth weight infants with non-symptomatic patent ductus arteriosus (PDA) at less than 72 hours of life to accelerate and maintain ductal closure, thereby reducing the need for rescue therapy. This report discusses the pharmacokinetic data obtained during the study.

DRUG FORMULATION:

Ibuprofen-L-Lysinate IV was dispensed in clear glass vials, each vial contained 2 mL sterile solution of 10 mg/mL ibuprofen base.

Lot Number 2140-41- 552659 [redacted]

Lot Number 2140-41- 266672 [redacted]

Placebo IV was dispensed in clear glass vials, each vial contained 2 mL sterile saline solution matching the ibuprofen IV solution in color, consistency and packaging

Lot Number 0927-99-552658 [redacted]

Lot Number 0927-99-333752 [redacted]

Manufactured for Farmacon-IL, LLC, Westport, CT, USA).

STUDY DESIGN AND DOSE ADMINISTRATION:

This was a Phase 3, double-blind, placebo- controlled, randomized, multicenter study evaluating a three-day treatment course with Ibuprofen Lysinate 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. Enrollment was to continue until 60 infants in each group completed the study.

The infants were randomly assigned to receive three IV doses of either ibuprofen lysinate (first dose of 10 mg/kg, followed at 24-hour intervals by two doses of 5 mg/kg each) or placebo. Infants were stratified in two birth weight categories, 500 to 750 g and 751 to 1000 g. Infants were less than 72 hours of age at the time of randomization.

Intravenous infusion of 1 mL/kg Ibuprofen L-Lysinate or placebo was administered over 10 to 15 minutes. The first dose of study drug was administered within 4 hours post confirmation of echocardiogram results. The second and third doses of study drug were

administered 24 (±1 hour) and 48 hours (±1 hour) after the first dose. Study drug administration times for Dose 2 and Dose 3 were determined based on the time of administration of the first dose of study drug. In the event that the administration of Dose 2 was delayed, Dose 3 should have been at least 12 hours after Dose 2.

DOSING SCHEDULE

Dosing Day	Group 1	Group 2
Study Day 1 (0 h)	0 mg/kg (placebo)	10 mg/kg (ibuprofen)
Study Day 2 (24 ±1 h)	0 mg/kg (placebo)	5 mg/kg (ibuprofen)
Study Day 3 (48 ±1 h)	0 mg/kg (placebo)	5 mg/kg (ibuprofen)

An infant was considered a completer if he/she: 1a) received all three doses of study drug or 1b) was rescued or died at any time (during the 14-day study period) after randomization and 2) was observed for the 14-day study period, unless he/she died.
Infants were not to be given any other NSAIDs while in the study unless it was indomethacin for rescue therapy.

SUBJECTS: Premature newborn infants (n = 136) with non-symptomatic PDA were enrolled in the study with 133 infants (67 males and 66 females) completing the study. Fifty-four premature infants (26 males and 28 females) were included in the pharmacokinetic analyses; 15 were Caucasian, 17 were Black, 20 were Hispanic, 1 was Asian/Pacific Islander and 1 was of other race. The mean age at receipt of first dose of study drug was 37.5 hours and the mean birth weight was 791 g.

SAMPLE COLLECTION: For each subject, four blood samples (0.3 mL) were collected from a central line (arterial/venous) or heel stick into 0.6 mL microvacutainer ethylene diaminetetraacetic acid tubes at 1 hour (±30 minutes) post Dose 1; at 24 hours (±1 hour) post Dose 1 (just prior to adrninistration of Dose 2); 48 hours (±1 hour) after Dose 1 (just prior to Dose 3); and 120 hours (±1 hour) after Dose 1 (72 hours after Dose 3).

ANALYTICAL METHODOLOGY:
The plasma samples were analyzed for racemic ibuprofen concentration at the [redacted] using high performance liquid chromatography (HPLC) technique. However, the assay validation was not available for review.

POPULATION PHARMACOKINETIC ANALYSES:
Nonlinear mixed effects models were explored to characterize the population pharmacokinetics of IV ibuprofen for premature newborn subjects using the NONMEM program (DOUBLE PRECISION NONMEM VERSION V LEVEL 1.0) on a Hewlett Packard workstation using the Unix operating system.

Model Building

Step 1 – Base Model: The base model was selected: the number of compartments, random effects, the structure of random effect, and the possibility of a nonzero correlation between the random components of the pharmacokinetic parameters.
Step 2 – Validation of the Base Model: The stability of the parameters estimates from the base model was tested by perturbing the initial estimates and running the model with portions of the data excluded.
Step 3 – Full Model Development/Forward Selection: A forward selection procedure was applied to determine if any demographic or laboratory variables, or ventilation status, significantly improved the base model. The forward selection procedure was conducted for each parameter (clearance and volume of distribution) in the base model separately. The new variable entered the model linearly and if the assumption of linearity was questionable, residual plots were used to confirm the validity of the assumption. Each explanatory variable was tested individually at the 0.05 significance level. The error terms and random components were assumed to have normal probability distributions. Those explanatory variables that significantly reduced the objective function of the base model were added sequentially to the model. This process was continued until none of the remaining explanatory variables significantly improved the model from the previous step.
Step 4 – Final Model Development/Backward Elimination: The full model was subjected to a backward elimination process. To carry out the backward elimination process, variables were eliminated from the full model, one at a time. At each step of this process, the variable producing the smallest reduction in the objective function value was the one considered for elimination. The chi-square test was used to evaluate if the change in the objective function as a result of dropping the explanatory variable from the model was significant at the 0.005-level.
Step 5 – Validation of the Final Model: Once an optimal full model was developed, the stability of the parameter estimates from this model was tested by perturbing the initial estimates and running the analysis with portions of the data excluded.

Explanatory Variables (Covariates)
The relationship between clearance and the following explanatory variables was explored: post-natal age, race, weight, birth weight, gestational age, ventilation status and earliest, non-missing on-study laboratory values for serum creatinine and bilirubin. The relationship between volume of distribution and the following explanatory variables was explored: post-natal age, race, weight, birth weight, gestational age and ventilation status. The explanatory variables weight and post-natal age were incorporated as time varying (multiple values for a given subject across time) variables. For all other explanatory variables a single value (earliest available non-missing value) was used for each subject. Some subjects had no serum creatinine and/or no bilirubin values reported. These missing values were replaced by the sample mean.
There were five categories of race (Caucasian, Black, Hispanic, Asian/Pacific Islander, and Other). There was only a single Asian/Pacific Islander and only one whose race was identified as 'Other'. For the modeling steps at which a test was performed on the race

factor, the two subjects with race identified as 'Other' and Asian/Pacific Islander were excluded. For all other modeling steps, data from these two subjects were included.

Pharmacokinetic Results:
All subjects (26 males and 28 females) who received at least one dose of active study drug and had any concentration data were included in the pharmacokinetic analysis. Summary Statistics is shown in .

Table 3: Summary Statistics for Concentration-Time Data, Dosing Information, Demographic and Explanatory Variable Data and Post-Hoc Estimates of Clearance and Volume of Distribution

	Mean ± SD (N)			
	Sample No. 1	**Sample No. 2**	**Sample No. 3**	**Sample No. 4**
Actual Sampling Time (h)	1.1 ± 0.2 (52)	23.7 ± 0.4 (49)	47.7 ± 0.5 (49)	120.0 ± 0.6 (41)
Concentration (µg/mL)	34.7 ± 9.0 (52)	24.7 ± 7.5 (49)	27.5 ± 14.0 (49)	13.5 ± 11.5 (41)
CL (mL/kg/h)*	4.31 ± 2.06 (52)	4.72 ± 2.28 (49)	5.39 ± 2.48 (49)	6.54 ± 2.92 (41)
V (mL/kg)*	315 ± 25 (52)	314 ± 25 (49)	315 ± 26 (49)	315 ± 27 (41)
	Day 1	**Day 2**	**Day 3**	**Day 4**
Actual Dosing Time (h)	0.0 ± 0.0 (54)	24.0 ± 0.3 (53)	47.9 ± 0.3 (52)	--
Body Weight (kg)	0.746 ± 0.147 (54)	0.753 ± 0.127 (53)	0.737 ± 0.139 (52)	0.742 ± 0.140 (41)
Dose (µg/kg)**	10790 ± 1311 (54)	5334 ± 456 (53)	5468 ± 560 (52)	--
Rate (µg/kg/h)	51096 ± 12327 (54)	25479 ± 6095 (53)	26334 ± 7134 (52)	--
Duration (h)	0.22 ± 0.04 (54)	0.22 ± 0.05 (53)	0.22 ± 0.05 (52)	--
	Demographic Information			
Age at 1st Dose (min)	2249 ± 1026 (54)			
Gestational Age (week)	25.9 ± 1.2 (54)			
Birth weight (g)	791 ± 125 (54)			
Creatinine (mg/dL)	1.0 ± 0.2 (42)			
Direct Bilirubin (mg/dL)	0.3 ± 0.2 (34)			
	Categorical Explanatory Variables			
Gender	Male = 26, Female = 28			
Race	Asian/Pacific Islander = 1, Black = 17, Caucasian = 15, Hispanic = 20, Other = 1			
Ventilation status	Ventilator = 43, CPAP = 8, Hood/Nasal = 3			

Some observed plasma concentration data were excluded based on physiologic and pharmacokinetic expectations, all exclusions are acceptable.

The sponsor reported all steps of the population model building with explanation why the particular model was accepted or rejected. The results of the run for the base model are shown below.

Table 4: Summary of Model Selection Procedure Used to Find the Base Model (Not Including AnyCovariates)

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
1	$CL = \theta_1 * (1+\eta_1)$ $V = \theta_2 * (1+\eta_2)$ $Y = F + \varepsilon_1$	CL (θ_1)	5.83	0.681	1094.015	Proportional random component for inter-individual variability for clearance (CL) and volume of distribution (V), but additive residual error. Method = 0 converged, but Method = 1 (run 1.1) did not converge.
		V (θ_2)	306	11.8		
		CL (Var[η_1])	0.248	0.0941		
		V (Var[η_2])	0.0212	0.0103		
		Var[ε]	63.9	16.3		
2	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F + \varepsilon_1$	CL (θ_1)	5.83	0.681	1094.015	Exponential random component for inter-individual variability, but additive residual error; Method = 0.
		V (θ_2)	306	11.8		
		CL (Var[η_1])	0.248	0.0941		
		V (Var[η_2])	0.0212	0.0103		
		Var[ε]	63.9	16.3		
3	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F + \varepsilon_1$	CL (θ_1)	5.64	0.494	1091.215	Same as run #2, but with Method = 1.
		V (θ_2)	304	12.1		
		CL (Var[η_1])	0.257	0.0956		
		V (Var[η_2])	0.0225	0.00823		
		Var[ε]	60.7	15.4		
4	**$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$**	**CL (θ_1)**	**5.11**	**0.457**	**1082.057**	**Same as run #3, but with exponential residual error; Method = 1. OPTIMAL BASE MODEL**
		V (θ_2)	**302**	**13.1**		
		CL (Var[η_1])	**0.230**	**0.0767**		
		V (Var[η_2])	**0.0155**	**0.00935**		
		Var[ε]	**0.0887**	**0.0212**		
5	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ Positive (η_1,η_2) correl. $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.14	0.470	1081.645	Exponential random components for inter-individual variability assumed to be correlated. No significant improvement over previous model. Method = 1.
		V (θ_2)	302	12.6		
		CL (Var[η_1])	0.224	0.0745		
		V (Var[η_2])	0.0156	0.00908		
		Cov. (η_1,η_2)	0.0121	0.0209		
		Var[ε]	0.0898	0.0214		
6	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.11	0.457	1082.057	Same as run #4, but with very high initial estimates; Method = 1. Parameter values almost identical; SE similar to run #4.
		V (θ_2)	302	13.1		
		CL (Var[η_1])	0.230	0.0767		
		V (Var[η_2])	0.0155	0.00937		
		Var[ε]	0.0887	0.0212		
7	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.11	0.457	1082.057	Same as run #4, but with very low initial estimates; Method = 1. Parameter values almost identical; SE similar to run #4.
		V (θ_2)	302	13.1		
		CL (Var[η_1])	0.230	0.0768		
		V (Var[η_2])	0.0155	0.00938		
		Var[ε]	0.0887	0.0212		
8	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Q = \theta_3$ $VSS = \theta_4$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	4.88	0.434	1094.123	Two compartment model; Method = 0. Parameter estimates were not reasonable.
		V (θ_2)	4.43	31.3		
		Q (θ_3)	14700	12100		
		VSS (θ_4)	312	13.5		
		CL (Var[η_1])	0.183	0.0626		
		V (Var[η_2])	0.00999	0.422		
		Var[ε]	0.109	0.0235		
9	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.08	0.557	856.358	Model Validation: Same as run #4, but 25% of data excluded to test the stability of the parameter estimates. SAS Seed = 12456
		V (θ_2)	300	15.7		
		CL (Var[η_1])	0.292	0.0103		
		V (Var[η_2])	0.0169	0.0115		
		Var[ε]	0.100	0.0267		

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
10	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.12	0.440	876.868	Model Validation: Same as run #4, but a different 25% of data excluded to test the stability of the parameter estimates. SAS Seed = 98765
		V (θ_2)	307	16.0		
		CL (Var[η_1])	0.124	0.0433		
		V (Var[η_2])	0.0157	0.0111		
		Var[ε]	0.104	0.0259		
11	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.21	0.419	1008.901	The optimal base model (run #4) excluding the following data based on subjective assessment: [redacted]
		V (θ_2)	294	9.91		
		CL (Var[η_1])	0.211	0.0719		
		V (Var[η_2])	0.0162	0.00867		
		Var[ε]	0.0664	0.0136		
12	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.37	0.412	1009.662	The optimal base model (run #4) excluding the concentration data using the objective exclusion criteria of any concentration at 1 h < 24 h or 48 h < 120 h.
		V (θ_2)	285	9.70		
		CL (Var[η_1])	0.198	0.0718		
		V (Var[η_2])	0.0144	0.0853		
		Var[ε]	0.0680	0.0149		
12.5	$CL = \theta_1 * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.32	0.481	1015.373	Base model excluding RACE = Other & Asian/Pacific Islander
		V (θ_2)	306	13.2		
		CL (Var[η_1])	0.249	0.0816		
		V (Var[η_2])	0.00948	0.00848		
		Var[ε]	0.0811	0.0203		

The sponsor presented the results of the forward selection procedure for choosing important explanatory variables for clearance (Table 5).

Table 5: Summary of Explanatory Variable Forward Selection Procedure for Clearance

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
13	WEIGHT $CL = (\theta_1 + \theta_3 * WT) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.08	2.56	1082.056	Clearance modeled as a function of weight (WT). No significant improvement over the base model because clearance was body weight normalized
		V (θ_2)	302	12.8		
		CL WT (θ_3)	0.0476	3.32		
		CL (Var[η_1])	0.230	0.0765		
		V (Var[η_2])	0.0155	0.00958		
		Var[ε]	0.0887	0.0212		
14	SEX $CL = (\theta_1 + \theta_4 * SEX) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	4.89	0.705	1081.522	Clearance modeled as a function of sex. No significant improvement over the base model.
		V (θ_2)	301	12.9		
		CL SEX (θ_4)	0.460	0.952		
		CL (Var[η_1])	0.234	0.0802		
		V (Var[η_2])	0.0153	0.00948		
		Var[ε]	0.0881	0.0209		
15	RACE $CL = (\theta_1 + \theta_5 * R2 + \theta_6 * R3) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL-R1(θ_1)	6.54	0.595	1000.954	Clearance modeled as a function of race (R1=Caucasian, R2=Black, R3=Hispanic). No significant improvement over the base model (run #12.5 from Table 1).
		V (θ_2)	308	13.7		
		CL-R2 (θ_5)	-1.48	0.924		
		CL-R3 (θ_6)	-1.89	1.06		
		CL (Var[η_1])	0.222	0.0713		
		V (Var[η_2])	0.0102	0.00904		
		Var[ε]	0.0809	0.0194		
16	GESTATIONAL AGE $CL = (\theta_1 + \theta_7 * GAGE) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	-4.46	10.7	1080.474	Clearance modeled as a function of gestational age (GAGE, weeks). No significant improvement over the base model.
		V (θ_2)	300	12.4		
		CL GAGE (θ_7)	0.371	0.412		
		CL (Var[η_1])	0.239	0.0796		
		V (Var[η_2])	0.0104	0.00966		
		Var[ε]	0.0861	0.0198		

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
16.1	GESTATIONAL AGE $CL = (\theta_1 + \theta_4 * [GAGE - mean\ GAGE]) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.15	0.452	1080.474	Clearance modeled as a function of gestational age (GAGE, weeks) centered on mean GAGE. No significant improvement over the base model.
		V (θ_2)	300	12.4		
		CL GAGE (θ_4)	0.371	0.390		
		CL (Var[η_1])	0.239	0.0795		
		V (Var[η_2])	0.0164	0.00962		
		Var[ε]	0.0861	0.0198		
17	BIRTH WEIGHT $CL = (\theta_1 + \theta_3 * BWT) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.19	1.38	1082.055	Clearance modeled as a function of birth weight (BWT, grams). No significant improvement over the base model.
		V (θ_2)	302	13.1		
		CL BWT (θ_3)	-0.0000976	0.00187		
		CL (Var[η_1])	0.230	0.0768		
		V (Var[η_2])	0.0154	0.00925		
		Var[ε]	0.0888	0.0213		
17.1	BIRTH WEIGHT $CL = (\theta_1 + \theta_3 * [BWT - mean\ BWT]) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.11	0.457	1082.055	Clearance modeled as a function of birth weight (BWT, grams) centered on mean BWT. No significant improvement over the base model.
		V (θ_2)	302	13.1		
		CL BWT (θ_3)	-0.0000962	0.00310		
		CL (Var[η_1])	0.230	0.0777		
		V (Var[η_2])	0.0154	0.00928		
		Var[ε]	0.0888	0.0216		
18	CREATININE $CL = (\theta_1 + \theta_3 * CREA) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	6.07	2.75	1081.827	Clearance modeled as a function of creatinine (CREA). No significant improvement over the base model.
		V (θ_2)	302	13.3		
		CL CREA (θ_3)	-0.933	2.57		
		CL (Var[η_1])	0.230	0.0769		
		V (Var[η_2])	0.0156	0.00945		
		Var[ε]	0.0887	0.0210		
18.1	CREATININE $CL = (\theta_1 + \theta_3 * [CREA - mean\ CREA]) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.10	0.456	1081.827	Clearance modeled as a function of creatinine (CREA) centered on mean CREA value. No significant improvement over the base model.
		V (θ_2)	302	13.3		
		CL CREA (θ_3)	-0.932	2.48		
		CL (Var[η_1])	0.230	0.0768		
		V (Var[η_2])	0.0156	0.00944		
		Var[ε]	0.0887	0.0210		
19	BILIRUBIN $CL = (\theta_1 + \theta_3 * DBIL) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.17	0.956	1082.052	Clearance modeled as a function of direct bilirubin (DBIL). No significant improvement over the base model.
		V (θ_2)	302	13.1		
		CL DBIL (θ_3)	-0.178	2.68		
		CL (Var[η_1])	0.231	0.0773		
		V (Var[η_2])	0.0155	0.00934		
		Var[ε]	0.0887	0.0211		
19.1	BILIRUBIN $CL = (\theta_1 + \theta_3 * [DBIL - mean\ DBIL]) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	5.11	0.457	1082.052	Clearance modeled as a function of direct bilirubin (DBIL) centered on mean DBIL. No significant improvement over the base model.
		V (θ_2)	302	13.1		
		CL DBIL (θ_3)	-0.179	1.35		
		CL (Var[η_1])	0.231	0.0771		
		V (Var[η_2])	0.0155	0.00937		
		Var[ε]	0.0887	0.0211		
20	**POST-NATAL AGE** **$CL = (\theta_1 + \theta_4 * PAGE) * EXP(\eta_1)$** **$V = \theta_2 * EXP(\eta_2)$** **$Y = F * EXP(\varepsilon_1)$**	**CL INT (θ_1)**	**2.96**	**0.942**	**1072.954**	**Clearance modeled as a function of post-natal age (PAGE). Significant improvement; change in object function of 9.103 ($p < 0.005$) over the base model. OPTIMAL FULL MODEL**
		V (θ_2)	**320**	**11.3**		
		CL PAGE (θ_4)	**0.0200**	**0.00870**		
		CL (Var[η_1])	**0.308**	**0.0929**		
		V (Var[η_2])	**0.0198**	**0.00810**		
		Var[ε]	**0.0781**	**0.0187**		
21	RANDOM SLOPE ON POST-NATAL AGE $CL = (\theta_1 + \theta_4 * \eta_3 * PAGE) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	3.01	0.942	1072.832	Clearance modeled as a function of post-natal age with a random component. No significant improvement over run #21.
		V (θ_2)	319	11.3		
		CL PAGE (θ_4)	0.0197	0.00876		
		CL (Var[η_1])	0.289	0.0876		
		V (Var[η_2])	0.0199	0.00812		
		CL PAGE-(Var[η_3])	0.0101	0.153		
		Var[ε]	0.0779	0.0188		
22	VENTILATION STATUS $CL = (\theta_1 + \theta_3 * VS2 + \theta_4 * VS3) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL-VS1 (θ_1)	5.29	0.467	1080.123	Clearance modeled as a function of ventilation status (VS1, VS2 & VS3). No significant improvement over the base model.
		V (θ_2)	300	11.6		
		CL-VS2 (θ_3)	-1.03	1.52		
		CL-VS3 (θ_4)	0.474	1.03		
		CL (Var[η_1])	0.220	0.0663		
		V (Var[η_2])	0.0142	0.00977		
		Var[ε]	0.0887	0.0215		
22.1	VENTILATION STATUS $CL = (\theta_1 + \theta_3 * VS1) * EXP(\eta_1)$ $V = \theta_2 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	4.54	1.38	1080.968	Reduced covariate model for clearance-modeled as a function of whether ventilation status = 1 or ≠1. No significant improvement over the base model.
		V (θ_2)	301	12.0		
		CL-VS1 (θ_3)	0.763	1.30		
		CL (Var[η_1])	0.220	0.0674		
		V (Var[η_2])	0.0147	0.00958		
		Var[ε]	0.0893	0.0216		

None of the demographic (weight, sex, race, gestational age, birth weight) or laboratory (creatinine, bilirubin) variables were found to have significant ($p < 0.05$) explanatory value except for post-natal age for clearance. The relationship between post-natal age and clearance were explored with random slope effect model however, that did not significantly improve the model fit. After post-natal age was added to the model, the influence of the other explanatory variables were tested again however, none of them were significant at the 0.05-level. Since post-natal age was the only explanatory variable for clearance that was identified as significant at the 0.005-level, the backward elimination procedure was unnecessary. The output results for all runs were shown.
The model estimated average clearance on day of birth was 2.96 mL/kg/h for premature newborns with an average increase of approximately 0.0200 mL/kg/h or about 0.5 mL/kg/h per day (Run 20).

The same procedure was repeated for the relationship between volume of distribution and the explanatory variables.

Table 6: Summary of Explanatory Variable Forward Selection Procedure for Volume of Distribution

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
23	**WEIGHT** $CL = \theta_1 * EXP(\eta_1)$ $V = (\theta_2 + \theta_3 * WT) * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.11	0.457	1082.057	Volume modeled as a function of weight (WT). No significant improvement over the base model because volume of distribution was body weight normalized.
		V INT (θ_2)	302	13.1		
		V WT (θ_3)	-0.0000980	0.00000854		
		CL (Var[η_1])	0.230	0.0767		
		V (Var[η_2])	0.0155	0.00931		
		Var[ε]	0.0887	0.0212		
24	**SEX** $CL = \theta_1 * EXP(\eta_1)$ $V = (\theta_2 + \theta_3 * SEX) * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.10	0.452	1081.348	Volume modeled as a function of sex. No significant improvement over the base model.
		V INT (θ_2)	311	19.2		
		V SEX (θ_3)	-17.9	22.2		
		CL (Var[η_1])	0.227	0.0756		
		V (Var[η_2])	0.0140	0.00920		
		Var[ε]	0.0893	0.0212		
25	**RACE** $CL = \theta_1 * EXP(\eta_1)$ $V = (\theta_2 + \theta_3 * R2 - \theta_4 * R3) * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.32	0.481	1012.536	Clearance modeled as a function of race (R1=Caucasian, R2=Black, R3=Hispanic). No significant improvement over the base model (run #12.5 from Table 1).
		V-R1(θ_2)	303	17.5		
		V-R2 (θ_3)	-17.0	19.3		
		V-R3 (θ_4)	23.5	24.9		
		CL (Var[η_1])	0.243	0.0789		
		V (Var[η_2])	0.00350	0.00681		
		Var[ε]	0.0839	0.0214		
26	**GESTATIONAL AGE** $CL = \theta_1 * EXP(\eta_1)$ $V = (\theta_2 + \theta_3 * GAGE) * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL (θ_1)	5.12	0.453	1081.329	Volume modeled as a function of gestational age (GAGE, weeks). No significant improvement over the base model.
		V INT (θ_2)	509	203		
		V GAGE (θ_3)	-8.04	7.81		
		CL (Var[η_1])	0.229	0.0757		
		V (Var[η_2])	0.0128	0.00925		
		Var[ε]	0.0897	0.0212		

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
26.1	GESTATIONAL AGE CL =θ_1*EXP(η_1) V = (θ_2+θ_3*(GAGE – mean GAGE)) *EXP(η_2) Y = F * EXP(ε_1)	CL (θ_1)	5.12	0.454	1081.329	Volume modeled as a function of gestational age (GAGE, weeks) centered on mean GAGE. No significant improvement over the base model.
		V INT (θ_2)	309	14.8		
		V GAGE (θ_3)	-8.04	7.79		
		CL (Var[η_1])	0.229	0.0757		
		V (Var[η_2])	0.0128	0.00927		
		Var[ε]	0.0897	0.0212		
27	BIRTH WEIGHT CL =θ_1*EXP(η_1) V = (θ_2+θ_3*BWT) *EXP(η_2) Y = F * EXP(ε_1)	CL (θ_1)	5.11	0.458	1080.145	Volume modeled as a function of birth weight (BWT, grams). No significant improvement over the base model.
		V INT (θ_2)	403	59.4		
		V BWT (θ_3)	-0.127	0.0716		
		CL (Var[η_1])	0.229	0.0756		
		V (Var[η_2])	0.0124	0.00933		
		Var[ε]	0.0893	0.0214		
27.1	BIRTH WEIGHT CL =θ_1*EXP(η_1) V = (θ_2+θ_3*[BWT -mean BWT]) *EXP(η_2) Y = F * EXP(ε_1)	CL (θ_1)	5.11	0.458	1080.145	Volume modeled as a function of birth weight (BWT, grams) centered on mean BWT. No significant improvement over the base model.
		V INT (θ_2)	302	12.8		
		V BWT (θ_3)	-0.127	0.0717		
		CL (Var[η_1])	0.229	0.0756		
		V (Var[η_2])	0.0124	0.00933		
		Var[ε]	0.0893	0.0214		
28	POST-NATAL AGE CL =θ_1 *EXP(η_1) V = (θ_2+θ_3*PAGE) *EXP(η_2) Y = F * EXP(ε_1)	CL (θ_1)	5.16	0.394	1076.671	Volume modeled as a function of post-natal age (PAGE). No significant improvement over the base model.
		V INT (θ_2)	340	18.7		
		V PAGE (θ_3)	-0.700	0.285		
		CL (Var[η_1])	0.188	0.0596		
		V (Var[η_2])	0.0251	0.0145		
		Var[ε]	0.0818	0.0198		
29	VENTILATION STATUS CL =θ_1*EXP(η_1) V = (θ_2+θ_3*VS2 +θ_4* VS3) *EXP(η_2) Y = F * EXP(ε_1)	CL (θ_1)	5.11	0.455	1081.092	Volume modeled as a function of ventilation status (VS1, VS2, VS3). No significant improvement over the base model.
		V-VS1 (θ_2)	298	12.1		
		V-VS2 (θ_3)	26.3	29.2		
		V-VS3 (θ_4)	-12.6	27.5		
		CL (Var[η_1])	0.234	0.0791		
		V (Var[η_2])	0.0147	0.00813		
		Var[ε]	0.0878	0.0208		
29.1	VENTILATION STATUS CL =θ_1*EXP(η_1) V = (θ_2+θ_3*VS1) *EXP(η_2) Y = F * EXP(ε_1)	CL (θ_1)	5.11	0.457	1082.057	Reduced covariate model for volume- modeled as a function of whether ventilation status =1 or ≠1. No significant improvement over the base model.
		V INT (θ_2)	302	13.1		
		V-VS1 (θ_3)	0.000846	0.000359		
		CL (Var[η_1])	0.230	0.0768		
		V (Var[η_2])	0.0155	0.00936		
		Var[ε]	0.0887	0.0212		

None of the demographic variables were found to have significant ($p < 0.05$) explanatory value for volume of distribution. None of the tested covariates were significant at the selected level.

The mean + SD post-hoc estimates of clearance on day 1 (hour-1), 2 (hour-24), 3 (hour-48), and 6 (hour-120) were 4.31 ± 2.06, 4.72 ± 2.28, 5.39 ± 2.48, and 6.54 ± 2.92 mL/kg/h, and the mean post-hoc estimate of volume of distribution were 315 ± 25, 314 ± 25, 315 ± 26, 315 ± 27 mL/kg, respectively.

The reviewer repeated the final run of the optimal model and created the diagnostic plots using the post-hoc Tables. Figure 3 below shows the observed vs. population predicted ibuprofen plasma concentrations. The line is identity line. The model predicts the ibuprofen plasma concentrations satisfactory with under-prediction at high values.

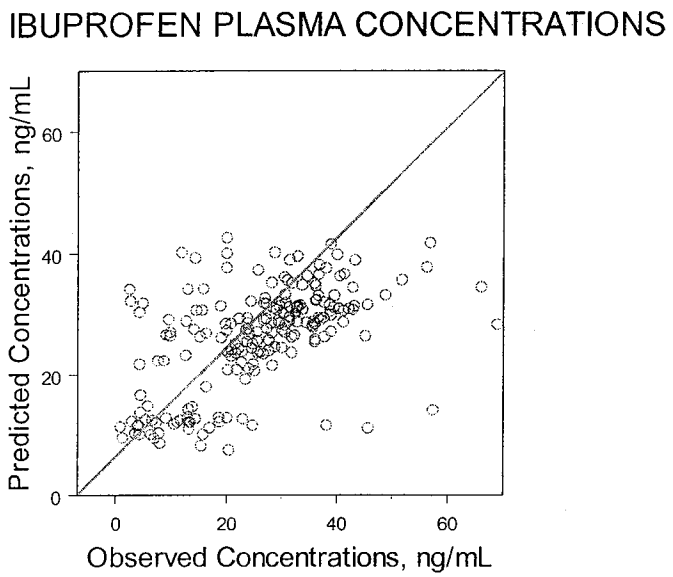


Figure 3. Observed vs population predicted ibuprofen plasma concentrations.

The individual predictions of the observed ibuprofen plasma concentrations (not shown) were good. Weighted residuals vs. ibuprofen concentration are shown in Figure 4. The distribution around zero is reasonably good.

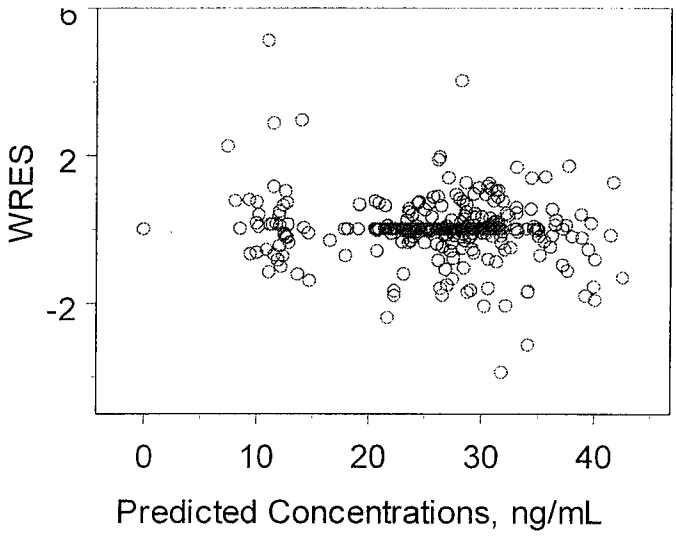


Figure 4. Weighted residuals vs. ibuprofen plasma concentrations

The example of observed, population predicted and individual predicted ibuprofen plasma concentrations are shown in Figure 5.

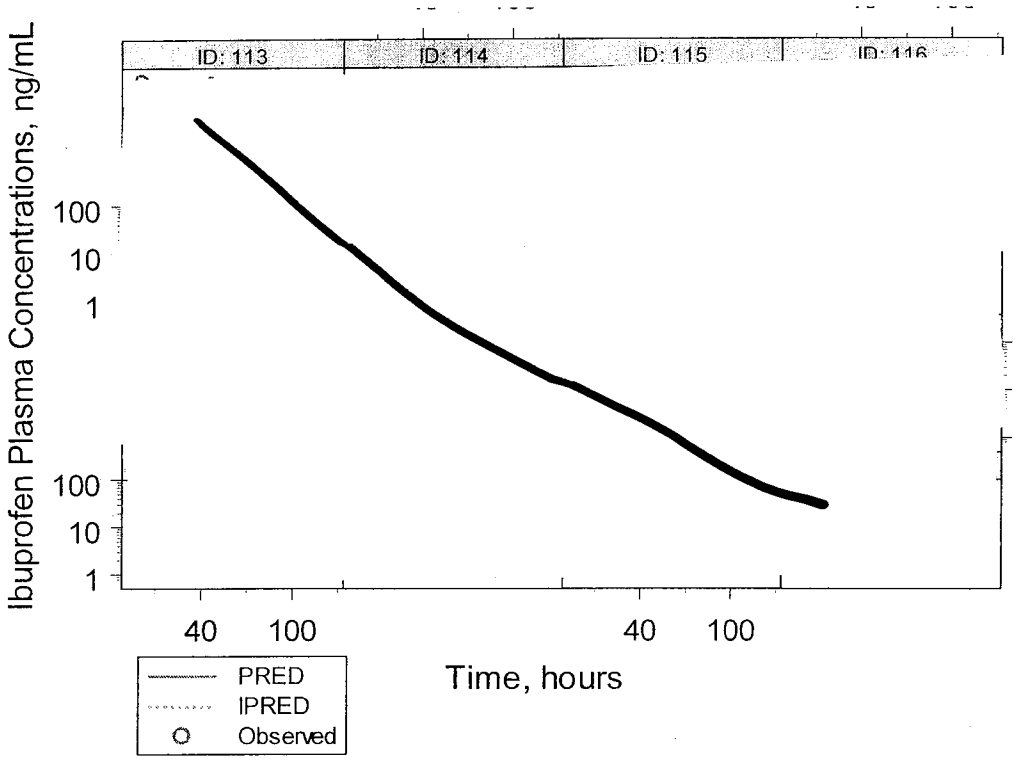


Figure 5. Observed, population predicted (PRED) and individual predicted (IPRED) ibuprofen plasma concentrations vs time.

The sponsor validated the optimal model using the random portions (25%) of the data (Table 7).

Table 7: Validation of the Optimal Final Model

Run #	Model	Parameter Description	Parameter Estimate	Standard Error of Estimate	Objective Function	Comments
30	POST-NATAL AGE $CL = (\theta_1 + \theta_2 * PAGE) * EXP(\eta_1)$ $V = \theta_3 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	3.10	1.16	851.092	Validation optimal final model, same as run #20, but 25% of data excluded to test the stability of the parameter estimates. SAS Seed = 12456
		V (θ_3)	317	13.6		
		CL PAGE (θ_2)	0.0184	0.0105		
		CL (Var[η_1])	0.381	0.0121		
		V (Var[η_2])	0.0212	0.00972		
		Var[ε]	0.0907	0.0236		
31	POST-NATAL AGE $CL = (\theta_1 + \theta_2 * PAGE) * EXP(\eta_1)$ $V = \theta_3 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	2.80	1.06	869.620	Validation optimal final model, same as run #20, but a different 25% of data excluded to test the stability of the parameter estimates. SAS Seed = 98765
		V (θ_3)	326	12.8		
		CL PAGE (θ_2)	0.0212	0.0105		
		CL (Var[η_1])	0.195	0.0627		
		V (Var[η_2])	0.0202	0.0100		
		Var[ε]	0.0889	0.0229		
32	POST-NATAL AGE $CL = (\theta_1 + \theta_2 * PAGE) * EXP(\eta_1)$ $V = \theta_3 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	2.96	0.948	1072.954	Optimal final model, same as run #20, but with very low initial estimates; Method = 1. Parameter values almost identical; SE similar to run #20.
		V (θ_3)	320	11.3		
		CL PAGE (θ_2)	0.0200	0.00877		
		CL (Var[η_1])	0.308	0.0931		
		V (Var[η_2])	0.0198	0.00813		
		Var[ε]	0.0781	0.0187		
33	POST-NATAL AGE $CL = (\theta_1 + \theta_2 * PAGE) * EXP(\eta_1)$ $V = \theta_3 * EXP(\eta_2)$ $Y = F * EXP(\varepsilon_1)$	CL INT (θ_1)	2.97	0.947	1072.954	Optimal final model, same as run #20, but with very high initial estimates; Method = 1. Parameter values almost identical; SE similar to run #20.
		V (θ_3)	320	11.3		
		CL PAGE (θ_2)	0.0200	0.00875		
		CL (Var[η_1])	0.308	0.0931		
		V (Var[η_2])	0.0198	0.00812		
		Var[ε]	0.0781	0.0187		

SPONSOR'S CONCLUSIONS

The population average ibuprofen clearance and volume of distribution values estimated by the final optimal model for premature infants on day of birth were 2.96 mL/kg/h and 320 mL/kg, respectively. As hepatic function, predominantly cytochrome P450 2C9 activity, matures in premature infants the model predicted ibuprofen clearance increases by approximately 0.5 mL/kg/h per day and reaches 5.36 mL/kg/h by day 6. Consequently, ibuprofen terminal elimination half-life is expected to decrease from 75 h on day of birth to 65, 57, 50, 46 and 41 h on days 2, 3, 4, 5 and 6 of the life of an average newborn infant, irrespective of gestational age or birth weight, consistent with previous literature reports.

The estimates of the variances of the random components of variation of 55% and 14% for clearance and volume of distribution, respectively. Because an exponential error distribution model was assumed for clearance and volume of distribution, the actual coefficients of variation were 60% and 14%, respectively.

Compared with adults and older children, the significantly longer elimination half-life in premature infants is probably due to decreased hepatic biotransformation. Therefore, the design of any therapeutic dosing regimen of ibuprofen for premature infants should consider the significantly lower elimination rate compared with adults to ensure safe and effective therapy.

COMMENTS

1. Although the assay method for determination of racemic ibuprofen in plasma is well established, the method validation was not submitted for review. The sponsor should submit the ibuprofen assay validation report for review.

2. The population PK model predicts the ibuprofen plasma concentrations satisfactory with slight under-prediction at high values. The average population clearance value estimated by the sponsor (2.96 ± 0.94 mL/kg/h) was similar to the reported in the literature values obtained in premature infants (2.06 ± 0.33 mL/kg/h, Aranda; 9.49 ± 6.82 and 10.8 ± 6.52 mL/kg/h on days 3 and 5 after birth, Van Overmeire). The first study used a one-compartment model to characterize ibuprofen concentration-time profile following a single 10 mg/kg intravenous dose over 2-3 minutes. The latter study used 2-compartmental model. The data in the current study did not permit the robust estimation of the parameters of a two-compartment model. Nevertheless, the differences are of the same order of magnitude and these studies showed that the pharmacokinetics of ibuprofen in infants is markedly different from the adults with much slower elimination of the drug.

3. Van Overmeire reported a significant decrease in volume of distribution of the central compartment (Vd,) (244 versus 171 mL/kg; p = 0.03) and area under the plasma concentration-time curve (534 versus 447 mg.h/L; p = 0.01) between the first and third doses (day 3 and day 5). The decrease in volume of distribution of the central compartment was most pronounced in infants with a closing ductus. The apparent volumes of distribution at steady state (Vdss) were not different on days 3 and 5 (357 versus 349 mL/kg). Total body clearance and plasma half-life did not change significantly. Van Overmeire postulated that the presence of a hemodynamically significant PDA may alter drug disposition by causing hypoperfusion of drug-eliminating organs (liver and kidney), introducing quick overload, or inducing systemic hypoxia and acidosis. Closure of the ductus may have improved these physiologic effects and resulted in a decrease in Vd. In the sponsor's study, the population average ibuprofen volume of distribution estimated by the final optimal model for premature infants was 320 mL/kg with no changes during the 3 day dosing. It is possible, that the changes in Vd over the three day period could not be assessed in this study due to the early termination of blood sampling and use only a one-compartmental model to describe the data.

4. The raw data suggest that the ibuprofen disposition is very delayed relative to the adults. FDA advised the sponsor to apply a random time sampling across the population and to extend sampling up to 168 hours post last dose. Nevertheless, the sponsor completed study using the blood sampling with 4 fixed time points up to 72 hours post last dose. The sponsor reported the ibuprofen elimination half-life in an average newborn infant from 75 h on day of birth with decrease to 65, 57, 50, 46 and 41 h on days 2, 3, 4, 5 and 6 of the life. Normally, the plasma sampling should be scheduled up to 3-5 half-lives. Due to an inadequate blood sampling schedule used in

this study, the sponsor could not properly describe the terminal elimination phase of ibuprofen pharmacokinetics in neonates. Therefore, since the last plasma sample was obtained only 72 hours post last dose, the half-life value of 75 hours seems inaccurate and should not be reported in the Package Insert.

5. The sponsor attempted to describe the pharmacologic response to ibuprofen by the measurement of the prostanoids (6-ketPGF1α, PGE2, PGE2α and TxB2) in plasma. The plasma concentrations of the prostanoids may be surrogate markers for COX inhibition and drug effect on the ductus and organs such as the gastrointestinal and kidney organ systems. There were only 3 measurements: pre-dose, 1 hour after the doses on day 1 and day 3 in the active drug group and placebo group. There were no differences in plasma concentrations of 6-ketPGF1α and PGE2 between the active drug and placebo groups. The group of patients receiving ibuprofen had lower PGE2α levels and much higher thromboxane B2 levels. The sponsor could not explain this fact and speculated that this may reflect some inherent conditions that were not measured during the study. For each of the measurements, the differences between the values obtained pre-dose and post-dose on day 3 were not statistically significant. This information could not be used to link the ibuprofen plasma concentrations and pharmacologic response; therefore, the PK/PD relationship between ibuprofen and prostanoids was not established.

4.3 Biopharmaceutics

Ibuprofen-L-Lysinate Injection is a sterile solution of the L-Lysinate salt of (±)-ibuprofen, which was dispensed in clear glass vials, each vial contained 2 mL sterile solution. (±)-Ibuprofen is the active ingredient; L-Lysine, classified as a nutritional supplement, is used to create a water-soluble drug product salt suitable for intravenous administration.

The proposed commercial formulation for the PDA indication and the formulation used in the PDA clinical studies is directly analogous to the commercial formulation. Manufacturers: [redacted] (final drug product). The commercial Neoprofen product will be a 2 mL vial containing 34.18 mg of the ibuprofen lysine salt, which is equivalent to 20.0 mg of ibuprofen (free acid), dissolved in Water for Injection. The pH is balanced with sodium hydroxide and hydrochloric acid.

The composition and components table below.

Table 8: Drug Product Components and Composition

Ingredient	Standard	Function	Quantity/Vial
(±) Ibuprofen L-lysinate	BVL spec	API	34.18 mg salt 20.0 mg ibuprofen
Sodium hydroxide	NF	pH	*q.s.*
Hydrochloric acid	NF	pH	*q.s.*
Water for Injection	USP	Solvent	*q.s.*
[redacted]			

4.4 Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-903	Brand Name	neoprofen
OCPB Division (I, II, III)	DIV-1	Generic Name	Ibuprofen lysinate
Medical Division	CARDIORENAL	Drug Class	
OCPB Reviewer	ELENA MISHINA	Indication(s)	PDA
OCPB Team Leader	P. Marroum	Dosage Form	Solution for IV ifusion
		Dosing Regimen	
Date of Submission	August 30, 2005	Route of Administration	IV
Estimated Due Date of OCPB Review	January 30, 2006	Sponsor	Farmacon IL LLC
PDUFA Due Date	February 28, 2006	Priority Classification	P
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting /non-fasting single dose:				
fasting /non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	X	1		
Data rich:				
Data sparse:	X	1		

II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single /multi dose:				
replicate design; single /multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Electrophysiololgy Study				
Pharmacodynamic studies				
Total Number of Studies Reviewed	1			

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-903, HFD-850(Lee), HFD-860 (Marroum, Mehta, Mishina), Biopharm (CDER)

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/s/

Elena Mishina
1/25/2006 07:23:02 PM
BIOPHARMACEUTICS

Patrick Marroum
1/26/2006 09:42:08 AM
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