CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-903

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	21-903
DRUG NAME:	Ibuprofen Lysinate Injection
INDICATION:	Early treatment of [redacted]
APPLICANT:	Farmacon-IL, LLC
DATE OF RECEIPT:	8/30/05
REVIEW PRIORITY:	Priority
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	Steve Bai, Ph.D. (HFD-710)
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KEY WORDS: PDA

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The current submission is to determine the effect of early treatment with intravenous ibuprofen given to very low birth weight infants with non-symptomatic patent ductus arteriosus (PDA) in the first 72 hours of life to accelerate and maintain ductal closure thereby reducing the need for rescue therapy. The data in the study supports the ibuprofen lysine IV therapy initiated within the first 72 hours of life is significantly more effective than placebo for treatment of PDA in very low birth weight infants (<1000g).

1.2 Brief Overview of Clinical Studies

The study FCR-00-01/CR88 was a phase III, double-blind, placebo-controlled, randomized, multi-centered study evaluating a three-day treatment course with ibuprofen lysine 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. A total of 138 infants (68 in ibuprofen lysine IV and 68 in placebo) from 12 US hospitals and medical centers were included in the study.

1.3 Statistical Issues and Findings

The primary analysis in the study is statistically significant. The statistically significant lower proportion of infants who received ibuprofen lysine IV required rescue treatment for PDA through Study Day 14 compared to infants in the placebo group (25.0% vs. 48.5%). The logistic regression with factors of treatment group and site provided a significant p-value of 0.0028.

2 INTRODUCTION

2.1 Overview

The submitted pivotal study FCR-00-01/CR88 was a phase III, double-blind, placebo-controlled, randomized, multi-centered study evaluating a three-day treatment course with ibuprofen lysine 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. A total of 138 infants (68 in ibuprofen lysine IV and 68 in placebo) from 12 U.S hospitals and medical centers were enrolled in the study.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\n21903\N_000\2005-08-30 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

3.1.1 STUDY OBJECTIVES OF FCR-00-01/CR88

This study aimed to determine the effect of early treatment with ibuprofen lysine IV given to very low birth weight infants with a non-symptomatic PDA in the first 72 hours of life to accelerate and maintain ductal closure thereby reducing the need for rescue therapy (indomethacin or surgical ligation).

3.1.2 STUDY DESIGN

This was a phase III, double-blind, placebo-controlled, randomized, multi-centered study evaluating a three-day treatment course with ibuprofen lysine 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 lysine (first dose of 10 mg/kg, followed at 24-hour intervals by two doses of 5 mg/kg each) or placebo. The medications were infused continuously over a period of 10 to 15 minutes; infants were stratified in two birth weight categories, 500 to 750 g and 751 to 1000 g. Study outcomes were collected through Study Day 14. Follow-up outcomes were collected at 36 weeks adjusted gestation age ±7 days or at the time of discharge or transfer from facility.

3.1.3 EFFICACY MEASURES

The primary endpoint was symptomatic PDA treated with indomethacin or by surgery. The proportion of infants, who were rescued, died or dropped out on or prior to Study Day 14 was considered. The criteria for rescue treatment with indomethacin or surgical ligation included presence of a symptomatic PDA as evidenced by a positive echocardiogram and three of the following five criteria: bounding pulse, hyper dynamic precordium, pulmonary edema, increased cardiac silhouette and systolic murmur or in view of the neonatologist, was deemed to have a hemodynamically significant ductus.

3.1.4 STATISTICAL ANALYSIS PLAN

All infants who were randomized were included in the intent-to-treat analyses. The primary inferences concerning the efficacy of ibuprofen lysine IV were made using the ITT population. The primary efficacy null hypothesis was:

H_0: The proportion of infants requiring rescue treatment for PDA in the group treated with ibuprofen lysine IV will be the same as that of the placebo group:

$$\pi_{\text{ibuprofen}} = \pi_{\text{placebo}},$$

versus the alternative

H_a: The proportion of infants requiring rescue treatment for PDA in the group treated with ibuprofen lysine IV will be different from that of the placebo group:

$$\pi_{ibuprofen} \neq \pi_{placebo.}$$

The primary efficacy hypothesis was tested using a two-sided, 0.01 level test. All other tests of hypotheses were two-sided, 0.05 level tests. The primary variable was analyzed by fitting a logistic regression model with factors for treatment and site.

All infants who were randomized were included in the intent-to-treat population. Missing values were not imputed and were not included in the statistical analyses.

There was one protocol-specified primary efficacy variable in the study. Hence, no adjustment to the significance levels for comparing treatment groups with respect to the primary endpoints.

3.1.5 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The intent-to-treat population comprised 68 infants in the ibuprofen lysine IV group and 68 infants in the placebo group. A total of 17 infants (7 in ibuprofen lysine IV, 10 in placebo group) prematurely discontinued the study (i.e. either did not receive all three doses of study drug or were not observed for the entire 14 days). The most common primary reasons were due to infants expired and removed by physician. The demographical and baseline characteristics, such as Birth weight, infant gender, race, maternal age, or maternal steroid use, were all numerically comparable between ibuprofen lysine IV and placebo (Figure 1).

3.1.6 SPONSOR'S PRIMARY EFFICACY RESULTS

A logistic regression model with factors as treatment and site was analyzed on the primary variable, proportion of infants who were rescued on or prior to Study Day 14. The Sponsor found a statistically significant lower proportion of infants who received ibuprofen lysine IV required treatment, died, or dropped out compared to infants receiving placebo (p=0.0028). See Table 1.

Figure 1 Demographic and Baseline Characteristics

Variable	Ibuprofen Lysine IV (N=68)	Placebo (N=68)
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

[Source: Sponsor Study Report Table 5. Verified by the reviewer]

Table 1 Proportion of Infants Requiring Rescue Treatment for PDA

	Ibuprofen Lysine IV, n (%)	Placebo, n (%)	P-values
Total rescued, died, or dropped out on or prior to Study day 14	21 (30.9)	36 (52.9)	↑
Required rescue through Study day 14	17 (25.0)	33 (48.5)	0.0028
Died on or prior to study day 14 (not rescued prior to death)	4 (5.9)	3 (4.4)	
Dropped-out prior to study day 14 (not rescued prior to dropped out)	0 (0.0)	0 (0.0)	

[Source: Sponsor's Study Report's Table 6. ↑-- Ibuprofen is numerically better than placebo]

3.1.7 CONCLUSIONS

The reviewer validated the applicant's results according to the protocol.

A statistically significantly lower proportion of infants who received ibuprofen lysine IV required rescue treatment through Study Day 14 compared to infants in the placebo group (25% vs. 48.5%).

3.2 Evaluation of Safety

Please read Dr. Gordon's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

There are no summary statistics for the age subgroups because there is no age difference among the infants. Summary statistics for the proportion of infants required rescue treatment for PDA by sex and race are listed in the Tables 2 and 3. Based on the table results, we see that Ibuprofen Lysine IV performed numerically better than the placebo in all subgroups, except the Other in Race category, see Table 3. However, there are so few of infants in that particular subgroup.

Table 2 Proportion of Infants requiring Rescue based on Sex

Parameter	Ibuprofen Lysine IV	Placebo
Male		
No. Infants	32	37
No. required Rescue	7	18
Response Rate	21.88%	48.65%
Female		
No. Infants	36	31
No. required Rescue	10	15
Response Rate	27.78%	48.39%

Table 3 Proportion of Infants requiring Rescue based on Race

Parameter	Ibuprofen Lysine IV	Placebo
Asian (no. Infants)	1	2
No. required Rescue	0	1
Response Rate	0.00%	50.00%
Black (no. infants)	17	18
No. required Rescue	2	8
Response Rate	11.76%	44.44%
Caucasian (no. infants)	23	18
No. required Rescue	8	7
Response Rate	34.78%	38.89%
Hispanic (no. infants)	21	28
No. required Rescue	5	17
Response Rate	23.81%	60.71%
Other (no. infants)	6	2
No. required Rescue	2	0
Response Rate	33.33%	0.00%

4.2 Other Subgroup Populations

The birth weight group (<750 g and > 751 g) and gestational age (<28 weeks, ≥28 weeks) were considered in the logistic regression model. Subgroup summary statistics based on these two variables are listed in the Tables 4 and 5.

Table 4 Proportion of Infants requiring Rescue based on Birth weight

Parameter	Ibuprofen Lysine IV	Placebo
0-750 g (no. infants)	22	24
No. required Rescue	5	11
Response Rate	22.73%	45.83%
751-1015 g (no. infants)	46	44
No. required Rescue	12	22
Response Rate	26.08%	50.00%

Table 5 Proportion of Infants requiring Rescue based on gestational age

Parameter	Ibuprofen Lysine IV	Placebo
<28 wks (no. infants)	61	59
No. required Rescue	16	29
Response Rate	26.23%	49.15%
≥28 wks (no. infants)	7	9
No. required Rescue	1	4
Response Rate	14.29%	44.44%

The Ibuprofen Lysine IV had the favorable numerical results over Placebo in these subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary analysis in the study is statistically significant. The statistically significant lower proportion of infants who received ibuprofen lysine IV required rescue treatment for PDA through Study Day 14 compared to infants in the placebo group (25.0% vs. 48.5%). The logistic regression with factors of treatment group and site provided a significant p-value of 0.0028.

5.2 Conclusions and Recommendations

The results of this study demonstrated that ibuprofen lysine IV therapy initiated within the first 72 hours of life is significantly more effective than placebo for treatment of PDA in very low birth weight infants (<1000g) with non-symptomatic PDA.

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/s/

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