U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22348
Supplement #:	005
Drug Name:	Caldolor (intravenous ibuprofen) 10 mg/kg
Indication(s):	Reduction of fever in pediatric patients
Applicant:	Cumberland Pharmaceuticals, Inc.
Date(s):	Received date: January 29, 2015 PDUFA date: November 29, 2015
Review Priority:	Standard
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Keywords: Clinical Study; Pediatric Indication

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1 EXECUTIVE SUMMARY

The active ingredient in Caldolor intravenous (IV) injection is ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) approved for the management of pain and reduction of fever. Caldolor currently has indications for IV use for pain in adults and children, and for fever in adults. The goal for this supplemental application is the addition of an indication for reduction of fever in children. The proposed dosing is 10 mg/kg up to 400 mg intravenously over 10 minutes every 4 to 6 hours as necessary.

This application includes two clinical studies to provide evidence of efficacy. Study CPI-CL-005 was a phase 2, multicenter, randomized, parallel, open-label, active-controlled dose-selection study. The primary objective of this study was to determine the clinical equivalence of a single dose of intravenous ibuprofen 10 mg/kg compared to acetaminophen (APAP) 15 mg/kg oral solution or rectal suppository for the treatment of fever as measured by the AUC-Tº within the first 6 hours of treatment (as compared to a target temperature of 98.6 ºF [37.0 ºC]). A total of 30 pediatric patients, between the ages of 6 months and 17 years of age were enrolled, 15 per treatment arm. While the planned primary endpoint was average change in temperature over the 6 hours post-dosing period, further analyses of the change in temperature over time indicated 4 hours instead of 6 hours was a more appropriate timeframe to compare IV ibuprofen to oral/rectal acetaminophen dosing in these patients. The results of this study provided supportive evidence that IV ibuprofen reduced fever, but did not accommodate direct comparison to the APAP treatment arm under the 4-hour dosing interval the applicant decided to follow in the later phase 3 efficacy study.

The single primary efficacy study was CPI-CL-012. This was a phase 3 clinical study conducted at 14 sites in the US. It was a randomized, open-label, parallel arm, fixed-dose, active-comparator study. The two treatment arms were Caldolor IV ibuprofen (10 mg/kg over 10 minutes) and APAP 10 mg/kg oral solution or rectal suppository. Treatment was administered every 4 hours as needed for fever for up to 24 hours. Patients were hospitalized pediatric patients (ages birth to 16 years) with a fever of at least 38.3 °C (≥101.0 °F) at baseline.

Temperature was recorded prior to first dosing (baseline); at 15-minute intervals through the 2-hour timepoint; at 30-minute intervals through the 4-hour timepoint; and at 2-hour intervals through 24 hours. The single primary efficacy endpoint was the area under the change in temperature versus time curve during the first 2 hours of treatment (AUC_{0-2}). This is a weighted average of the change from baseline to each temperature measurement timepoint over the first 2 hours on study drug.

Other assessments of reduction of fever were calculated as secondary endpoints. These included change in temperature from baseline to 30 minutes; to 60 minutes, and to 4 hours; and percent of patients who were afebrile at 4 hours, defined as temperature <38.0 °C (<100.4 °F). The secondary endpoints were not intended to support an efficacy labeling claim. The protocol specified that no adjustment for multiple endpoints would be made.

The protocol planned for an Analysis of Covariance (ANCOVA) model with terms for treatment, age group (<6 months; 6 months to 16 years) and baseline temperature as the covariate. This was modified in the final statistical analysis plan to an Analysis of Variance (ANOVA) model with treatment as the single factor. The change in model was justified for the following reasons. There were only three patients < 6 months of age enrolled, rendering the defined Age Group term inefficient for modelling. The inclusion of Baseline temperature value in the linear calculation of the AUC_{0-2} and Change from Baseline endpoints meant that term could also be dropped from the model without changing the results of the statistical significance of the between-group comparisons. The resulting ANOVA model was simplified and appropriate for analyzing the data from this study for the primary comparison.

The final analysis for the primary efficacy endpoint was an Analysis of Variance (ANOVA) model with treatment as the single factor. The change from baseline secondary endpoints were analyzed using an ANCOVA model with treatment and baseline temperature terms. The percent of patients classified as afebrile at 4 hours was analyzed with a Cochran–Mantel–Haenszel (CMH) test.

The results of the efficacy analyses showed that Caldolor IV injection (10 mg/kg) was statistically significantly better than acetaminophen on average reduction in fever over the first 2 hours of treatment, as measured by the AUC_{0-2} endpoint. The results of all the secondary endpoints were consistently in favor of Caldolor versus acetaminophen for reduction of fever in hospitalized pediatric patients up to 4 hours after first dosing.

My conclusion is that the results of Study CPI-CL-012 show sufficient evidence of efficacy to support an indication of reduction of fever in pediatric patients for Caldolor IV ibuprofen 10 mg/kg administered over 10 minutes. The results indicate that Caldolor reduced fever over the first four hours after administration.

2 INTRODUCTION

2.1 Overview

The active ingredient in Caldolor IV injection is ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) approved for the management of pain and reduction of fever. Caldolor currently has indications for IV use for pain in adults and children, and for fever in adults. The goal for this supplemental application is the addition of an indication for reduction of fever in children. The proposed dosing is 10 mg/kg up to 400 mg intravenously over 10 minutes every 4 to 6 hours as necessary.

A phase 2 dose selection study, CPI-CL-005, compared Caldolor IV ibuprofen 10 mg/kg compared to acetaminophen (APAP) 15 mg/kg oral solution or rectal suppository for the treatment of fever. It was a randomized, open-label, parallel arm, fixed-dose, active-comparator study. The redosing interval in this study was 6 hours, for up to 24 hours. The primary efficacy endpoint was AUC-T^{o}_{0-6}. This is the area under the curve of the difference between the observed temperature and target temperature of 98.6ºF [37.0ºC] across all temperature measurements observed during the 6 hours after first dose. The primary analyses did not show statistical significance. Further analyses of the change in temperature over time indicated 4 hours instead of 6 hours was a more appropriate timeframe to compare IV ibuprofen to oral/rectal acetaminophen dosing in these patients. The results of this study provided supportive evidence that IV ibuprofen reduced fever, but did not accommodate direct comparison to the APAP treatment arm under the 4-hour dosing interval the applicant decided to follow in the later Phase 3 efficacy study.

The applicant subsequently conducted a single phase 3 study (CPI-CL-012) in hospitalized pediatric patients with redosing every 4 hours up to 24 hours. It was a randomized, open-label, parallel arm, fixed-dose, active-comparator study conducted at 14 sites in the United States. The two treatment arms were Caldolor IV ibuprofen (10 mg/kg over 10 minutes) and APAP 10 mg/kg oral solution or rectal suppository. Patients were hospitalized pediatric patients (ages birth to 16 years) with a fever of at least 38.3 °C (≥101.0 °F) at baseline.

Because of the different redosing intervals in these two studies, and corresponding timeframes for the primary efficacy assessments, Dr. Fang considers Study CPI-CL-012 the single study to provide evidence of efficacy in terms of the superiority comparisons to acetaminophen. Study CPI-CL-005 adds supportive evidence for the reduction of fever over 6 hours post-dosing, but is not appropriate for between-group comparisons to acetaminophen.

2.2 Data Sources

The clinical study reports were included with the initial submission on January 29, 2015, delivered to the electronic document room: \\CDSESUB1\EVSPROD\NDA22348\0065. The datasets for studies 005 and 012 were submitted at our request on March 20, 2015 to: \\CDSESUB1\EVSPROD\NDA22348\0070. All the necessary information to complete my review was provided.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data for the efficacy study were submitted in a format described as "legacy", meaning that the data was cleaned and summarized for analyses of the planned endpoints but was not in the standard CDISC format. The area under the curve (AUC) and change from baseline (CFB) endpoints were calculated in the effsum.xpt dataset with one record per subject. Actual temperature measurements at all observed times were also submitted in SAS transport files. There was sufficient documentation for me to conduct my review.

3.2 Evaluation of Efficacy: Study CPI-CL-012

3.2.1 Study Design and Endpoints

Objective: The objective of Study CPI-CL-012 was to determine the superiority of a single dose of intravenous ibuprofen compared to acetaminophen (APAP) (oral solution or suppository) for the treatment of fever. Assessment of efficacy was focused on the first 4 hours after the first dose, although additional doses could be administered at 4 hour intervals for up to 24 hours, if needed for fever.

Design: Study CPI-CL-012 was a phase 3 randomized, open-label, parallel arm, fixed-dose, active-comparator study. It was designed as an open-label unblinded trial because the active comparator was APAP administered in an oral solution or rectal suppository. A double-dummy design was not viable. All efficacy endpoints were derived from temperature measurements which should not be impacted by unblinding.

The two treatment arms were Caldolor IV ibuprofen (10 mg/kg over 10 minutes) and APAP 10 mg/kg oral solution or rectal suppository. Treatment was administered every 4 hours as needed for fever for up to 24 hours. Patients were hospitalized pediatric patients (ages birth to 16 years) with a fever of at least 38.3 °C (≥101.0 °F) at baseline. Eligible patients were randomized at a 1:1 ratio to the two treatment groups. It was conducted at 14 sites in the U.S.

Temperature was recorded prior to first dosing (baseline); at 15-minute intervals through the 2-hour timepoint; at 30-minute intervals through the 4-hour timepoint; and at 2-hour intervals through 24 hours. The single primary efficacy endpoint was the area under the change in temperature versus time curve during the first 2 hours of treatment (AUC_{0-2}). This is a weighted average of the change from baseline to each temperature measurement timepoint over the first 2 hours on study drug.

Other assessments of reduction of fever were calculated as secondary endpoints. These included change in temperature from baseline to 30 minutes; to 60 minutes, and to 4 hours; and percent of patients who were afebrile at 4 hours, defined as temperature <38.0 °C (<100.4 °F). The secondary endpoints were not intended to support an efficacy labeling claim. The protocol specified that no adjustment for multiple endpoints would be made.

Sample size: The applicant originally planned to enroll 200 patients in the study, with a goal of 100 patients in the birth to < 6 months age group and 100 patients' ages 6 months to 16 years. This sample size was determined to detect a minimal difference of 0.5 °C at a two-sided 0.05 level of significance on the AUC_{0-2} endpoint between the Caldolor treatment group and APAP group with at least 80% power (assumed standard deviation of 1.2). This was planned as a superiority comparison. A total of 184 patients would have been needed to meet that goal.

After the study was initiated, investigators experienced difficulty enrolling patients. The applicant's description from the clinical study report follows:

> Investigators and IRB expressed concern with the study design especially with regards to treating subject in the birth to less than 6 months of age group. Some investigators were limited to enrolling subjects greater than 6 months of age by their institutional IRBs, by institutional policy and procedures related to antipyretic use in their neonatal patient population, or by concerns expressed by their neonatal and pediatrician physician peers. Cumberland allowed enrollment to progress in both age groups until the target enrollment of 100 subjects was achieved in the greater than 6 month's age group. At that time, enrollment in the less than 6 month's age group was three subjects.

The applicant submitted data for the full 103 patients enrolled, but all efficacy analyses were restricted to the 6 months to 16 years age group (n=100).

Endpoints: The primary efficacy endpoint was defined as AUC_{0-2}, the area under the change in temperature versus time curve from baseline (Study Hour 0) to 2 hours after the start of the initial dose of clinical trial material (CTM). The baseline temperature was recorded just prior to initiation of study treatment. Temperature recordings were collected every 15 minutes for the first 2 hours post dosing. The change from baseline was calculated at each timepoint, and then the weighted average was calculated as the area under the curve over the 2 hour timeframe. A negative value represents decrease in temperature, i.e. reduction in fever, and is the desirable outcome from the treatment.

The change from baseline (CFB) in temperature to 30 minutes post-dose, CFB to 60 minutes post-dose, and CFB to 4 hours post-dose were defined as secondary endpoints. A responder endpoint was defined as percent of patients who were afebrile (temperature less than 100.4 ºF [38 ºC]) at 4 hours. All these endpoints only refer to the time after the first dose was administered. The secondary endpoints were not intended to support an efficacy labeling claim. The protocol specified that no adjustment for multiple endpoints would be made.

The efficacy analysis dataset was the intent-to-treat (ITT) population that included all randomized patients in the 6 month to 16 years age group.

3.2.2 Statistical Methodologies

Due to the study design, with patients hospitalized and frequent observations, missing data for temperature during the first 4 hours (first dosing interval) were minimal. Linear interpolation was used to impute missing values bracketed by non-missing values. Missing data after the last available value were not imputed.

Analysis of the primary efficacy endpoint - the area under the change in temperature versus time curve from baseline to 2 hours post first dose (AUC_{0-2})

The protocol planned for an Analysis of Covariance (ANCOVA) model with terms for treatment, age group (<6 months; 6 months to 16 years) and baseline temperature as the covariate for the primary efficacy endpoint (AUC_{0-2}). This was modified in the final statistical analysis plan to an Analysis of Variance (ANOVA) model with treatment as the single factor.

The Age Group factor was dropped from the model because there were only 3 patients under 6 months of age enrolled, as discussed in the Sample Size heading in Section 3.2.1. The primary analysis was modified to only include patients with ages 6 months to 16 years in the ITT population for the efficacy analyses.

The Baseline temperature value is included in the linear functions used to calculate the AUC and Change from Baseline endpoints. Therefore the covariate for baseline value could be dropped from the model without changing the results of the statistical significance of the between-group comparisons. The resulting ANOVA model was simplified and appropriate for analyzing the data from this study for the primary comparison.

Secondary efficacy endpoints
In the protocol the applicant defined secondary endpoints and pre-specified associated analyses. Superiority comparisons to APAP were planned. There was no adjustment for testing of multiple endpoints in order to control the overall Type I error rate for the study. Efficacy labeling claims based on these secondary endpoints are not appropriate.

Analysis of secondary efficacy endpoints – Change from Baseline:
The Change from Baseline to 30 minutes; to 60 minutes, and to 4 hours endpoints were calculated and analyzed using an ANCOVA model, with treatment as the factor and baseline temperature as the covariate term.

Analysis of secondary efficacy endpoint – Percent Patients Afebrile at 4Hours:
Patients were classified as responders on this endpoint at a single time point of 4 hours. Temperature results before or after that cutpoint were not considered. The applicant planned a Cochran–Mantel–Haenszel (CMH) test to compare the two treatment arms.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Eligible patients were randomized on a 1:1 basis to the two treatment arms. The disposition of patients is shown in Table 1. The 3 patients under 6 months in age were not included in the ITT patient population. The treatment period was up to 24 hours, with dosing of study drug every 4 hours as needed for fever. Study Completion was defined as participation through the 7-day follow-up period. Only a quarter of patients completed the full 7 days of follow-up.

There was some imbalance in the reasons for discontinuation, primarily due to the method of administration for study treatment. There were no discontinuations related to IV access or Physician Decision (surgery; burns) in the APAP group because an IV was not needed and APAP is not contraindicated for surgery or burn care.

For this study design, not all reasons for discontinuation necessarily represent a negative outcome. I have listed two categories separately: Fever No Longer Needed Treatment, and Discharged from Hospital or Emergency Room (ER). Ninety-five of the 100 ITT patients had fever data collected through 4 hours. Of the 5 who did not, one was discontinued from IV ibuprofen to go to surgery, and the other four were discharged prior to the 4-hour time point.

Table 1: Patient Disposition: Study CPI-CL-012

	Caldolor 10 mg/kg	**Acetaminophen 10 mg/kg**
Randomized	48	54
Age < 6 months (excluded form ITT)	1	2
Received Study Treatment (ITT)	47 (100%)	53 (100%)
Discontinued Prior to 7-day end of Study	35 (74%)	40 (75%)
Reason for Discontinuation:		
Adverse Event	3 (6%)	1 (2%)
IV Access Discontinued	4 (8%)	0
Lack of Efficacy	0	2 (4%)
Physician Decision (surgery; burn care)	5 (11%)	0
Protocol Violations	1 (2%)	0
Withdrew Consent	3 (6%)	6 (11%)
Other	2 (4%)	2 (4%)
Fever No Longer Needing Treatment	9 (19%)	5 (9%)
Discharged from ER/Hospital	8 (17%)	24 (45%)
Completed 24-hours Treatment Period	12 (26%)	13 (25%)

Source: SAS dataset: Basic.xpt

The demographic characteristics for the two groups are shown in Table 2. The only notable imbalance among the groups is for the youngest age category (6 months up to 2 years). Age was not included as a stratification variable in the randomization. In the Acetaminophen group, 26% were in the youngest age group, versus 13% in the Caldolor group. I did a subgroup analysis by age group, which showed no notable difference in treatment effect. The moderate imbalance in weight coincides with the same imbalance across age.

Table 2: Demographic Characteristics: Study CPI-CL-012

	Caldolor 10 mg/kg N=47	**Acetaminophen 10 mg/kg N=53**
Age (years)		
Mean (SD)	7 (4.6)	6 (4.4)
Median	7	6
Min, Max	0.5, 16	0.5, 15
Age Category n (%)		
6 mos. up to < 2 years	6 (13%)	14 (26%)
2 years up to < 6 years	13 (28%)	14 (26%)
6 to 16 years	28 (60%)	25 (47%)
Gender n (%)		
Male	27 (57%)	26 (49%)
Female	20 (43%)	27 (51%)
Race n (%)		
Caucasian	42 (89%)	42 (79%)
African American	5 (11%)	8 (15%)
Other	0	3 (6%)
Weight (kg)		
Mean (SD)	30 (19.5)	24 (15.2)
Median	23	20
Min, Max	7, 80	7, 63

Source: Clinical Study Report Table 11-2 and Basic.xpt dataset

3.2.4 Results and Conclusions

Analysis of the primary efficacy endpoint - the area under the change in temperature versus time curve from baseline to 2 hours post first dose (AUC_{0-2}):

The results from the applicant's analysis for the primary efficacy endpoint, AUC_{0-2}, are presented in Table 3. The mean represents the average reduction in fever (°C) across the two hours timeframe after the first dose.

There was no discussion in the protocol regarding what alternative approach would be used if the assumptions for the ANOVA model were not met. In the study report the applicant described the following "The nonparametric method of Wilcoxon rank-sum test was also performed. If the endpoint was not normally distributed (i.e., if the Kolmogorov-Smirnov p-value is greater than 0.05), the result from the non-parametric method was used." That was considered an appropriate methodology. The Wilcoxon rank-sum test results are reported in Table 3. The p-value from the planned ANOVA model was .0033.

The results indicate that the Caldolor IV ibuprofen group is statistically superior to the APAP group for reduction in fever (p-value < 0.01)

Table 3: Applicant's Primary Efficacy Analysis of Study CPI-CL-012:

Table 11-6 Summary of AUC0-2 by Treatment Group, ITT

AUC_{0-2}	**Intravenous ibuprofen** n=47	**Acetaminophen** n=53
N	46	50
Mean (SD)	-1.5 (1.11)	-0.9 (0.89)
LS Means (SE)[1]	-1.5 (0.15)	-0.9 (0.14)
Median	-1.4	-0.9
Min, Max	-4.4, 0.1	-3.0, 0.7
Comparison to Acetaminophen		
p-value[2]	0.005	

Missing values at time t are imputed using linear interpolation prior to calculating AUC_{0-t}.

[1] LS Means are from an ANOVA model with fixed effect for treatment.

[2] The data are not normally distributed. The p-value is based on Wilcoxon Rank-Sum test for differences in treatment.

Source: Clinical Study Report Table 11-6

Four subjects were dropped from the applicant's analysis due to discontinuation prior to the 2-hour timepoint. Unbracketed missing data was not imputed by the applicant. This was not specified in the protocol, but was described in the clinical study report.

One subject in the Caldolor group (ID #22.2105) was discontinued due to Medical Decision (taken to surgery). Three subjects in the APAP group (ID# 14.2115; 20.2067; 20.2068) were discharged. I calculated the AUC weighted average over the actual length of time in study using only observed data. Including those four subjects in the analysis did not change the results or conclusions.

Secondary efficacy endpoint - Change from Baseline to 30 minutes; 60 minutes; and 4 hours

The results of the analyses of the Change from Baseline to Timepoint (30 minutes; 60 minutes; 4 hours) after the first dose was administered are shown in Table 4. Data was not imputed if a specific timepoint was missing.

For all three timepoints, the normality assumption for the ANCOVA (or ANOVA) model was not met, and the Wilcoxon Rank Sum test was applied instead. The results are consistently in favor of Caldolor over APAP for reduction of fever at all three timepoints.

Table 4: Study CPI-CL-012; Secondary Efficacy Analysis [Change from Baseline Endpoints]

Secondary Endpoint: Change from Baseline (°C)	**Caldolor 10 mg/kg N=47**	**Acetaminophen 10 mg/kg N=53**
Change from Baseline to 30 minutes:		
	n=45	n=53
Mean	-0.5	-0.3
Std. Dev.	0.50	0.49
p-value [a]	.02	
Change from Baseline to 60 minutes:		
	n=45	n=53
Mean	-0.9	-0.5
Std. Dev.	0.69	0.50
p-value [a]	.01	
Change from Baseline to 4 hours:		
	n=43	n=37
Mean	-1.5	-0.9
Std. Dev.	0.92	0.92
p-value [a]	.03	

[a] Wilcoxon Rank Sum results reported. ANCOVA model with terms for treatment and baseline pain was tested; normality assumption was not met.

Source: SAS dataset dertemp.xpt; CSR Table 11-8.

Secondary efficacy endpoint – Percent of Patients who were Afebrile at 4 Hours

Patients whose temperature decreased and remained below 100.4°F [38°C] up to the 4 hour timepoint were classified as being afebrile at 4 hours. Table 5 shows the results for this responder endpoint, and demonstrates that the proportion of patients who were afebrile at 4 hours after the first dose was higher in the Caldolor group than the APAP group. The Cochran–Mantel–Haenszel (CMH) test showed superiority for Caldolor (p-value <.02).

Table 5: Study CPI-CL-012; Secondary Efficacy Analysis [Percent Afebrile at 4 Hours]

Percent Afebrile at 4 Hours n (%)	**Caldolor 10 mg/kg N=47**	**Acetaminophen 10 mg/kg N=53**
Applicant's Results		
Yes	43 (91%)	40 (75%)
No	3 (6%)	11 (21%)
Missing	1 (2%)	2 (4%)
Results with Afebrile Status Imputed [a]		
Yes	44 (93%)	42 (79%)
No	3 (7%)	11 (21%)

[a] The three subjects excluded from the applicant's results were all afebrile prior to discontinuing before the 2 hour timepoint.
Source: SAS dataset effsum.xpt

3.3 Evaluation of Safety

The evaluation of safety has been completed by Dr. Fang. She did not request any additional safety analyses for my review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Race

Table 6 shows mean treatment effects for the AUC_{0-2} endpoint by treatment arm for the age, gender, and race subgroups. All study sites were in the US so a regional subgroup analysis was not necessary. The study was not designed or powered to make any comparative statements on subgroups. Although the mean treatment response is not the same across all subgroups, the groups are too small to identify any notable trends.

Table 6: Subgroup Analyses: Age, Gender, and Race – Reviewer's Results

Primary Endpoint: AUC $_{0-2}$ Hours				
	Caldolor 10 mg/kg N=47		**Acetaminophen 10 mg/kg N=53**	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Age group				
6 months to < 2 years	6	-1.7 (1.2)	14	-1.4 (0.9)
2 years to < 6 years	13	-1.6 (1.5)	14	-0.7 (0.9)
6 to 16 years	28	-1.4 (0.9)	24	-0.8 (0.8)
Gender				
Female	20	-1.2 (0.9)	27	-1.1 (0.9)
Male	27	-1.8 (1.2)	26	-0.7 (0.9)
Race				
Caucasian	42	-1.5 (1.1)	42	-0.8 (0.8)
Non-Caucasian	5	-1.7 (1.6)	11	-1.3 (0.9)

Source: SAS dataset effsum.xpt

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The protocol for study CPI-CL-012 did not include details on two aspects of the analyses presented in the clinical study report. First, missing data, was minimized by the study design and the fact of patients being in a hospital setting. The applicant provided the datasets with all the observed temperature records, which enabled me to apply a reasonable alternative to those few subjects with missing data dropped from the analyses. Though not prespecified methods, I was able to confirm the results were not impacted by the missing data.

The second topic not covered in the protocol was the alternative analyses if the normality assumption for the ANOVA or ANCOVA models were not met. The applicant used nonparametric test in this instance, which were considered appropriate. Although changing the primary analysis model or adding an alternative model after the trial initiation is not encouraged, the results based on the alternative approach in this trial were reliable given the large treatment effect observed and the consistent evidence gathered from all pre-specified efficacy endpoints.

5.2 Collective Evidence

Study CPI-CL-005 was intended as a phase 2 dose selection study. The planned assessments of temperature over a 6-hour timeframe after dosing suggested that 6 hours was not the appropriate length of time between doses. The results from that study are supportive of the efficacy of Caldolor but do not allow direct comparison to acetaminophen.

Study CPI-CL-012 was planned as a phase 3 confirmatory study, with a 4-hour redosing schedule and a 4-hour timeframe for efficacy comparisons. The single primary and four secondary endpoints all showed Caldolor was superior to acetaminophen for the reduction of fever in pediatric patients across that timeframe. Results were consistent across subgroups.

5.3 Conclusions and Recommendations

The results of Study CPI-CL-012 indicate that Caldolor is statistically significantly better than Acetaminophen for the reduction of fever in hospitalized pediatric patients. Supportive evidence was provided by the secondary endpoints (Change from Baseline to 30 minutes; to 60 minutes; and to 4 hours after first dosing; proportion of patients who were afebrile by 4 hours after first dosing) which were consistently favoring the Caldolor group.

My conclusion is that the results of Study CPI-CL-012 provide sufficient evidence of efficacy for reduction of fever in hospitalized pediatric patients, ages 6 months to 16 years.

5.4 Labeling Recommendations

In the proposed labeling, Study CPI-CL-012 is described accurately and concisely in the Clinical Studies section (14.2). The results for the single primary endpoint, AUC_{0-2}, are included without specifying the active comparator. Dr. Fang also wants to include two descriptive statements from the secondary endpoints, as important information for providers. The proposed text, shown below, is acceptable to me.

> In a multi-center, open-label study, 100 hospitalized pediatric patients 6 months of age and older with temperatures of 101.0ºF or greater were randomized and treated with 10 mg/kg of CALDOLOR or a low dose of an active comparator every 4 hours as needed for fever.
>
> Efficacy was demonstrated as a statistically significant greater reduction in temperature for the primary endpoint, an area under the curve analyses of temperature versus time for the first 2 hours, as well as over the entire dosing interval. Seventy-four percent of CALDOLOR-treated patients became afebrile (temperature <99.5ºF) by the end of first dosing interval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE B MEAKER
11/16/2015

FREDA COONER
11/16/2015
I concur