CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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/Serial Number:	22-450/0000
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Keywords: Clinical trials, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Cadence Pharmaceuticals, Inc. (CPI) has submitted an application evaluating intravenous acetaminophen (IV APAP) for the treatment of acute pain. Based on my review of the data from two controlled clinical trials, Studies RC 210 3 002 and CPI-APA-304, I conclude there is statistical evidence of the efficacy of IV APAP 1000 and 650 mg to treat acute post-operative pain. For both studies, the predefined primary endpoint was statistically significant. Further, when the data from Study RC 210 3 002 was reevaluated using the currently preferred endpoint, sum of pain intensity difference scores through 24 hours (SPID24), there was a significant treatment effect in favor of APAP 1000 mg.

1.2 Brief Overview of Clinical Studies

The Applicant is relying on two clinical trials to support the efficacy of IV APAP to treat acute pain. These trials are described briefly below.

Study RC 210 3 002 was a randomized, double-blind, placebo- and active-controlled, multi-center, Phase 3, parallel-group, repeat dose clinical trial that was conducted from 1999-2000 at nine sites in the United States. This study was designed to evaluate the efficacy and safety of single and repeated doses of IV APAP for the treatment of acute post-operative pain in adult patients following either unilateral or bilateral total hip or knee arthroplasty. Following surgery, post-operative Day 1, patients were instructed to stop taking pain medication. When their pain intensity (PI) was at least moderate on a four point scale, patients were randomized to either placebo, APAP 1000 mg, or proacetamol (PPA) 2000 mg. The protocol-defined primary efficacy endpoints were the comparisons of pain relief (PR) scores from 0.25 to 6 hours. Data were analyzed using an analysis of covariance (ANCOVA) model with treatment and center as fixed effects and the baseline pain score as a covariate. Repeat dosing was evaluated using mean pain intensity over 24 hours adjusted for rescue medication. Since the time this study was conducted, the preferred primary efficacy endpoint has changed. Post-hoc, the Applicant reevaluated the data using the sum of pain intensity difference scores through 24 hours (SPID24) as the efficacy endpoint.

The second study, CPI-APA-304, evaluated APAP 1000 and 650 mg in patients that were recovering from abdominal laparoscopic surgery. On post-operative Day 1, patients stopped taking pain medicine and those that had sufficient PI scores within 4 hours were randomized to either placebo or APAP (1000 or 650 mg). PI and PR scores were measured out to 24 hours and at the time of withdrawal or use of rescue medication. The primary efficacy endpoint was defined as SPID24. Data were analyzed using an ANCOVA model with treatment, randomization period, and center as fixed effects and baseline PI score as the covariate.

1.3 Statistical Issues and Findings

The two studies submitted by the Applicant demonstrated that IV APAP 1000 mg was significantly better than placebo in relieving acute postoperative pain according to the predefined primary efficacy endpoints. In Study RC 210 3 002, the defined primary endpoint was the comparison of PR scores from 0.25 to 6 hours. There were no adjustments incorporated into the

analyses to account for the comparison at each time point. Post-hoc, I examined three methods; the Bonferroni adjustment, the Hochberg step-down approach, and the Intersection-Union test. Only the most conservative method, Bonferroni, lacked significance at 15 and 30 minutes post-dose. Based on these results and the fact that it has been shown that multiplicity is less of a concern when endpoints are correlated, I conclude that multiplicity is not a concern in this study. Further evidence of a treatment effect was provided when the Applicant reanalyzed the data using SPID24 and observed a significant treatment effect in favor of IV APAP.

In study CPI-APA-304, there were concerns regarding the pooling of placebo groups and an allocation error that occurred during the randomization of patients to treatment. I examined both of these concerns and determined that it was appropriate to pool placebo patients and that the treatment effect was not different during the two randomization periods. The Applicant also evaluated a 650 mg dose in Study CPI-APA-304 and included it in the proposed label. However, the Applicant's analysis did not account for multiple comparisons. Typically any secondary claims or doses that are allowed on the label should incorporate some type of adjustment for multiple comparisons. Post-hoc, I repeated the analysis using three different multiplicity adjustment methods; Bonferroni, Hochberg, and the Inter-Section Union test. A significant treatment effect was observed for all three methods.

2. INTRODUCTION

2.1 Overview

While oral APAP has been approved since 1951, there are no approved IV formulations of APAP marketed in the United States. An IV formulation, Perfalgan, has been approved in Europe since 2001 and is currently marketed in approximately 80 countries by Bristol-Myers Squibb Pharmaceuticals Ltd (BMS). In March of 2006, CPI obtained the rights to develop and market IV APAP in the United States from BMS. The formulation of the product submitted for approval is identical to the Perfalgan formulation marketed in Europe. There have been numerous correspondences between FDA and CPI regarding the clinical development plan (CDP). Key statistical issues are listed below.

In an end-of-phase 2 (EOP2) meeting held on August 14, 2006 for IND 58,362, there were several comments that directly applied to the two studies I am reviewing. FDA clearly stated that the analgesic efficacy of IV APAP must encompass a 48-hour period and if different, CPI would need to provide rational while 24-hours would be more appropriate. It was further explained that pain should be evaluated at the end of each dosing period. The Applicant stated they would reconsider the design of their study.

CPI submitted a revised CDP in March, 2008 and requested advice from FDA. The Applicant sought clarification that studies RC 210 3 002 and CPI-APA-304 would support the approval of IV APAP to treat acute pain. FDA's response indicated the Applicant had a sufficient package to submit an application but whether or not the studies would support an indication for treatment of acute pain would be a review issue.

2.2 Data Sources

All data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

\\cdsesub1\evsprod\NDA022450\0000\m5\datasets\rc210-3-002
\\cdsesub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-304

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Applicant has submitted two Phase 3 trials, RC 210 3 002 and CPI-APA-304, that evaluate the efficacy of IV APAP in treating patients with post-operative acute pain. These two studies will be the focus of my review.

Study RC 210 3 002 was conducted from September 1999 to June 2000 by BMS. At the time this study was conducted the preferred primary efficacy endpoint was PR scores from zero to six hours. The current preferred endpoint is the sum of pain intensity difference through 48 hours (SPID48). Since this study only accessed patients out to 24 hours, the Applicant re-analyzed the data evaluating SPID24 as the endpoint. While there was a positive control included in this study, PPA, it is not approved for use in the United States and was not included in my review of the efficacy of IV APAP.

Study CPI-APA-304 was reviewed in October, 2007 by the statistical review team. It was noted that the sample size and statistical methods proposed were adequate. However, there was a concern about the appropriateness of the pooling of placebo groups. The Division stated that a statistical method should be used to evaluate the appropriateness of pooling the placebo groups or else each active treatment group should be compared to its respective placebo. Further, in May 2008, FDA was notified by the Applicant of a randomization issue with this study. Due to an error in the drug allocation process, patients were only being randomized to two treatment groups instead of four. A new randomization scheme was implemented to adjust for this error. FDA was concerned that the treatment under the initial randomization might not perform the same way as it would under the new randomization scheme. The Applicant was advised to develop a plan to evaluate the randomization error and propose a method to account for this in the statistical analyses. This issue is discussed in section 3.1.3.

3.1.1 Study Design and Endpoints

Study RC 210 3 002

After undergoing either total hip or knee replacement, in-hospital patients were randomized to placebo, APAP 1000 mg, or PPA 2000 mg; 52, 49, and 50, respectively. On the morning following surgery, all opioid medication was ceased and patients were monitored for pain intensity using a 4-point scale; 0=no pain, 1=mild, 2=moderate, 3=severe pain. Only patients with moderate or severe pain were randomized to treatment. Once randomized, all patients received a 15-minute infusion of study drug every six hours in a double-blind fashion. A total of

four doses were administered. Patients that experienced inadequate pain relief after the first administration of study drug were allowed to use rescue medication but were encouraged to wait at least 30 minutes before requesting. The time and amount of rescue medication administered was recorded for each patient.

The primary measure of efficacy was pre-specified as the comparison of PR scores at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours. PR was measured on a 5-point scale with 0= no relief, 1=a little, 2=moderate, 3=a lot, and 4=complete relief. Secondary measures included PI scores, patient's global evaluation of study medication, time of first rescue medication use, and amount of rescue medication used over 24 hours. PI scores were measured from 0.25 to 6 hours and at 18, 20, and 24-hours post-dose using a 4-point categorical scale and a 100 mm VAS scale. Patient's global evaluation of study medication was assessed at 6 and 24 hours using a 4-point scale where 0=poor, 1=fair, 2=good, and 3=excellent. If applicable, PI, PR, and patients' global evaluation of study medication were measured before a patient used rescue medication or discontinued from the study.

Based on a PR score of 1 for the placebo and 1.7 for active treatment, the Applicant determined that a sample size of 50 patients per treatment group would result in at least 90% power for the overall comparison of the 3 treatment groups, i.e. testing the null hypotheses that $\mu_1 = \mu_2 = \mu_3$.

Study CPI-APA-304
To assess the analgesic efficacy of APAP 650 and 1000 mg in treating acute pain associated with abdominal laparoscopic surgery, 244 patients were randomized to APAP 1000 mg, APAP 650 mg, or placebo. Since the 1000 mg dose was administered every 6 hours and the 650 mg dose was administered every 4 hours, each dose group had a matching placebo group, P1000 and P650, respectively. On post-operative Day 1, opioid medication was stopped and patients were randomized when they had a pain score of moderate or severe on 4-point scale. Treatment was administered to all patients as 15 minute IV infusion. Patients on the 1000 mg dosing regimen received 4 doses, 1 every 6 hours, while patients on the 650 mg dosing regimen received 6 doses, 1 every 4 hours. Patients not achieving sufficient PR after the first dose were allowed to request rescue medication, but before rescue medication was given, PI and PR scores were recorded. Time of rescue and amount of rescue medication given were noted in a patient's record. CPI defined the primary efficacy endpoint as SPID24 based on VAS PI scores. Secondary efficacy endpoints included sum of PR scores (TOTPAR), PR scores, time to rescue medication use, amount of rescue medication used, and subject's global evaluation of study medication.

Based on a previous study, the Applicant used a treatment effect size of -160 for SPID24 and a standard deviation of 290 to estimate that 207 subjects would provide 90% power to detect a significant treatment effect.

3.1.2 Patient Disposition and Demographics

Study RC 210 3 002
This study randomized 156 patients but only 151 of these received treatment. Descriptive information regarding demographic characteristics was summarized based on treatment assignment in Table 1.

Table 1. Patient demographics and baseline characteristics for patients enrolled in Study RC 210 3 002

Characteristic	Placebo	APAP 1000 mg	PPA	total
Number of Patients	49	50	52	151
Age in years				
Mean (SD)	59 (13)	62 (17)	60 (14)	60 (15)
Median	61	66	64	63
[range]	[24, 81]	[22, 87]	[25, 82]	[22, 87]
Gender (%)				
Female	30 (58)	21 (43)	23 (46)	74 (49)
Male	22 (42)	28 (57)	27 (54)	77 (51)
Race (%)				
Caucasian	46 (88)	42 (86)	42 (84)	130 (86)
Black	4 (8)	4 (8)	3 (6)	11 (7)
Asian	0 (0)	0 (0)	0 (0)	0 (0)
Other	2 (4)	3 (6)	5 (10)	10 (7)
Baseline Pain Score Mean (SD)	56 (17)	62 (19)	58 (18)	58 (18)

Source: Reviewer

While 151 patients were randomized and received study drug, 137 completed the study. The reasons listed for withdrawal are shown in Table 2.

Table 2. Disposition of patients enrolled in study RC 210 3 002.

		Treatment groups			
	Statistic	Inj APAP	PPA	Placebo	Overall
Total nbr of patients randomised	n	51	52	53	156
Total nbr of pts who received study medication		49a	50bc	52d	151
Nbr of patients who completed the study	n (%)	46 (90.2)	44 (84.6)	47 (88.7)	137 (87.8)
Nbr of patients who withdrew from the study	n (%)	5 (9.8)	8 (15.4)	6 (11.3)	19 (12.2)
Reason for study withdrawal					
Withdrawal of consent	n	2	3	2	7
Adverse event	n	0	3	1	4
Lack of compliance	n	1	1	0	2
All eligibility criteria not met	n	0	0	2	2
Other	n	2a	1c	1e	4

Inj APAP: injectable acetaminophen; PPA: propacetamol
a.Patients # 52 finally had an implanted morphine pump, for patient # 146 the pain intensity decreased from moderate to mild while the treatment was prepared; b Patients # 77 withdrew consent ; c for patient # 429, the surgery was cancelled; d. patient # 457 had no pain; e patient # 109 was given oral acetaminophen for fever.

Source: Table 10.1 from the Applicant's final study report.

Study CPI-APA-304

Descriptive information regarding demographic characteristics was summarized based on treatment assignment in Table 3.

Table 3. Patient demographics and baseline characteristics for Study CPI-APA-304

Characteristic	Placebo 1000 mg	Placebo 650 mg	APAP 1000mg	APAP 650 mg	total
Number of Patients	43	67	92	42	244
Age in years					
Mean (SD)	46 (12)	47 (13)	45 (12)	47 (13)	46(13)
Median	45	45	43	47	45
[range]	[18, 72]	[21, 78]	[19, 73]	[21,71]	[18, 78]
Gender (%)					
Female	37 (86)	54 (81)	74 (80)	33 (79)	198 (81)
Male	6 (14)	6 (19)	18 (20)	9 (21)	46 (19)
Race (%)					
Caucasian					
Black	37 (86)	61 (91)	76 (82)	39 (93)	213 (87)
Asian	5 (12)	3 (4)	15 (16)	1 (2)	24 (10)
Other	0 (0)	2 (3)	1 (2)	1 (2)	4 (2)
	1 (2)	1 (2)	0 (0)	1 (3)	3 (1)
Baseline Pain Score Mean (SD)	58 (12)	50 (16)	52 (13)	57 (15)	53 (14)

Source: Reviewer

Since this was an in-patient study, relatively few patients discontinued prematurely, Table 4.

Table 4. Patient disposition for Study CPI-APA-304

Reason for Discontinuation	Placebo 1000 mg	Placebo 650 mg	APAP 1000 mg	APAP 650 mg	Total
Adverse event	1	-	3	-	4
Withdrew consent	4	4	-	-	8
Investigator judgment	-	-	1	-	1
Early discharge from hospital	-	1	-	1	2
Other	1	-	-	1	2

Source: Adapted from Table 7 of final study report

3.1.3 Statistical Methodologies

Study RC 210 3 002

The primary efficacy endpoint was defined as PR scores at each assessed time point. Mean PR scores for placebo were compared to APAP using an ANCOVA model with treatment and center as main effects and the baseline PI score as a covariate. While seven sites enrolled patients, due to small sample sizes at several sites only two sites were included individually. All others were pooled for the analyses. There were no multiplicity adjustments in the analyses to account for comparisons made at each time point. While not specified in the study protocol, the Applicant examined the data using SPID24 as the efficacy endpoint. Data was analyzed using the same ANCOVA model described for PR scores.

Analyses of secondary endpoints were conducted to provide additional support for efficacy. The endpoints examined in my review are SPID6, time to first use of rescue medication, patient's global evaluation of study drug, total amount of rescue medication used, and mean pain scores adjusted for rescue medication at 24 hours (MPAI24). SPID6 was analyzed using an ANCOVA model with treatment and site as fixed effects and baseline pain score as a covariate. Time to first use of rescue medication was examined using survival analysis techniques. The Log-Rank test was used to compare time-to-event curves between placebo and APAP. Global evaluation of pain regimen was compared using the Cochran-Mantel-Haenszel (CMH) test stratified by site. MPAI24 scores were computed by ranking PI scores and ranking total amount of rescue medication at 24 hours using all patients. Ranks were then standardized by calculating the percent difference from the over-all mean. Standardized ranks were then added together for each subject. These combined ranks were analyzed using an ANCOVA model with treatment and site as main effects and baseline PI as a covariate[1].

The Applicant's method for handling missing data in Study RC 210 3 002 depended on the specific endpoint. For the 6-hour time point, PR, PI, and patient's global evaluation of study drug were measured prior to any patient withdrawing or using rescue medication. These scores were then imputed for the remaining time points. If a patient withdrew early but did not have a measured score at the time of withdrawal, the last measured observation was carried forward (LOCF). If a patient received rescue medication but failed to have a score measured prior to use, the worst observed score was carried forward (WOCF). For the 24-hour time point, missing PI scores during a dosing period were considered to be the mean of the PI scores available during that period. If a patient's score for global assessment of study medication was missing, the score evaluated at the time of withdrawal or use of rescue medication was used.

Study CPI-APA-304

The Applicant's original allocation scheme was to randomize patients in a 2:2:1:1 ratio to APAP 1000 mg, APAP 650 mg, P1000, or P650. However, during a scheduled quality check by the Applicant's contract research organization (CRO), it was discovered that patients were only being randomized to APAP 1000 mg and P650 in a 1:1 fashion. The Applicant explained this was due to a programming error in the integrated voice response system (IVRS). The CRO implemented an interim randomization scheme where a subset of patients (selected randomly) had the yes /no field for APAP 1000 mg and P650 changed to yes. Meanwhile, the Applicant implemented a new randomization scheme that allocated patients to APAP 1000mg, APAP 650 mg, P1000, P650 in a 6:5:5:2 ratio. The number of patients enrolled during each randomization period is shown in Table 5.

[1] Silverman DG, O'Conner TZ, Brull SJ. Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy.Anesth Analg 1993;77:168-70

Table 5. Number of patients enrolled during the different randomization periods in Study CPI-APA-304

Treatment	Randomization Period (dates)			
	Initial (Nov07-May08)	Interim (May-June)	Final (June-Sept)	total
APAP 1000mg	54	8	30	92
APAP 650mg	-	16	26	42
Placebo -1000	-	14	29	43
Placebo- 650	55	2	10	67

Source: Reviewer

In communications with the statistics group at FDA, there was concern that the treatment groups might respond differently during each randomization period. To explore this, the Applicant used an ANCOVA model to examine the influence of enrollment timing (period) on the primary efficacy endpoint, SPID24. They also included regimen in the analysis to examine the appropriateness of combining the placebo groups.

The Applicant defined the modified intent-to-treat (mITT) population two different ways. In the synopsis section of the final study report, it was defined as those subjects who received at least one complete dose of study drug prior to requesting rescue medication and had at least one completed PI assessment after time 0. In section 11.1 of the study report, the mITT was defined as those subjects who received at least one complete dose of study drug prior to requesting rescue medication. The second definition is preferred; the mITT should not depend on post-treatment assessments. While 244 patients were randomized and received treatment the Applicant indicated the mITT population consisted of 241 patients. Three patients, two placebo and one APAP 650 mg were not included in the analyses. Since these patients were randomized and received study drug, they should be included in the mITT population.

The primary efficacy comparison was defined as SPID24 (VAS) for the pooled placebo group versus the APAP 1000 mg dose group. Data was analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization period, and site as main effects and baseline PI scores as a covariate.

Secondary variables examined in my review included time to meaningful pain relief (T-MPR) and sum of pain relief scores after 24 hours (TOPAR24). To examine the treatment effect on TOPAR24, the applicant used an ANCOVA model with treatment as the main effect and baseline PI score as a covariate. Results for T-MPR were compared using a log-rank test. Since the reviewing medical officer was concerned about the duration of effect, I also examined the mean PID scores at the end of each dosing interval.

The Applicant's method's for handling missing data are shown in Table 6.

Table 6. Applicant's methods for handling missing data in study CPI-APA-304

Efficacy Variable Type	Variables	Type of Missing Data[1,2,3]		
		Prior to Receiving First Rescue Medication	**From the Time of First Rescue Medication Administration**	**After Early Discontinuation (for reasons other than rescue)**
Primary	SPID24	LOCF[3] imputation for missing data	WOCF[3] imputation applied in place of actual assessments after the time of first rescue administration to T24 disregarding actual data and "Early Discontinuation" imputation rules[4]	If no rescue, then use the following imputation methods: LOCF imputation applied in place of all scheduled assessments after the time of the early hospital discharge to T24 (hereinafter referred to as LOCF post early d/c) BOCF[3] imputation applied in place of all scheduled assessments after the time of an early termination due to an AE or for reasons other than early hospital discharge using the baseline observation taken from the beginning of the dosing interval during which the AE or other reason (excluding early discharge) started or occurred (hereinafter referred to as BOCF post early term)
Secondary and Other	Analyses disregarding data after time of rescue	LOCF	LOCF	LOCF for those that were discharged early from the hospital. BOCF for all subjects that discontinued early from the study due to AEs or for reasons other than early discharge.
	Analyses including data after time of rescue	LOCF	WOCF from the time of rescue medication administration	LOCF for those that were discharged early from the hospital. BOCF for all subjects that discontinued early from the study due to AEs or for reasons other than early discharge.

[1] If no observation was collected, a value of 0 was carried forward for PR score and a value of 0 was carried forward for each of the Global Evaluations scores
[2] If the PI value was missing at T0, the randomization value was used
[3] For other missing data LOCF was used

Source: Table 19 from the Applicant's final study report.

3.1.4 Results

Study RC 210 3 002

Primary Efficacy Endpoint

Using the datasets provided by the Applicant, three patients did not discontinue but had intermittent missing data. In my primary analysis, to be conservative, I used WOCF for these values. To examine the impact of these patients, I also used LOCF. When comparing mean PR scores at each time point, there was a statistically significant difference between placebo and APAP 1000 mg at each time point, Table 7. The maximum difference is seen at approximately 3 hours. The three patients with missing data did not have an impact of results of the analyses.

Table 7. Mean PR scores for patients enrolled in study RC 210 3 002

Hours Post-dose	Mean PR score (stdev)		Difference	p-value
	Placebo	APAP 1000 mg	(APAP-Placebo)	
0.25	0.6 (0.8)	1.0 (1.0)	0.4	0.01
0.5	0.7 (1.0)	1.2 (1.1)	0.5	0.02
0.75	0.7 (1.0)	1.5 (1.3)	0.8	0.0003
1	0.7 (1.1)	1.6(1.3)	0.9	< 0.0001
2	0.5 (1.0)	1.4 (1.3)	0.9	< 0.0001
3	0.3 (0.7)	1.3 (1.3)	1.0	< 0.0001
4	0.3 (0.7)*	1.0 (1.2)	0.7	0.0003
5	0.2 (0.5)*	0.8 (1.1)	0.6	0.0005
6	0.2 (0.4)*	0.8 (1.1)*	0.6	0.0009

Source: Reviewer
* WOCF or LOCF used for missing data

The Applicant's analysis did not account for multiple comparisons. Generally, when multiple comparisons are made, some type of multiplicity adjustment is required to avoid increasing the probability of a Type I error. This could be a procedure such as a Bonferroni adjustment, a stepwise procedure such as the Hochberg test, or the intersection-union test where all comparisons must be significant. Using the conservative Bonferroni method, there was not a significant difference at 15 and 30 minutes post-dose. The other two methods resulted in significance at all time points. Further, multiplicity is less of a concern when endpoints are correlated. Since the same endpoint was evaluated at each time point, there would be correlation.

Secondary Efficacy Endpoints

To evaluate the efficacy of repeat dosing of APAP, the Applicant examined mean PI scores at 24 hours (VAS) when adjusted for amount of rescue medication used according to the method of Silverman et al. I was able to duplicate the Applicant's analysis and did show a significant difference between APAP and placebo, p-value < 0.0001. Placebo patients had a larger mean combined rank than APAP patients which agrees with the results from the individual analyses of total amount of rescue medication used and PI scores. Patients treated with IV APAP 1000 mg were significantly better than placebo treated patients. Further evidence was provided when the Applicant reanalyzed the data using SPID24 as the efficacy endpoint. There was a significant difference between placebo treated patients and APAP treated patients. Of note, although the final study report defined pain intensity difference (PID) as $PI_{Ti} - PI_{T0}$, the results were not in the right direction. Upon confirming the Applicants analyses, I confirmed that indeed PID was defined incorrectly. The results support PID = $PI_{T0} - PI_{Ti}$. As shown in Table 8, there was a significant treatment effect regardless of the imputation method utilized.

Table 8. Analysis of SPID24 (PID/hr) using different imputation methods for Study RC 210 3 002

Imputation Method	AUC (stdev)		p-value
	Placebo	APAP	
LOCF	407 (341)	658 (423)	0.005
BOCF	374 (334)	640 (422)	< 0.001
Rescue/Withdrawal Score/LOCF	-162 (343)	227 (403)	< 0.001

Source: Reviewer

The sum of PID scores was also evaluated at six hours post dosing (SPID6). Missing data was imputed using BOCF. Mean SPID6 values were 61 and 173 PID/hour for placebo and APAP, respectively. Using ANCOVA procedures with treatment and baseline pain scores, there was a significant difference between placebo and APAP.

Time to first request of rescue medication was compared between treatment groups using survival analysis techniques. The median time to use of rescue medication for placebo and APAP 1000 mg was 0.9 and 3.1 hours, respectively. The Log-Rank test indicated there was a significant difference between placebo and APAP. Note there was only one patient in the APAP group that did not use rescue medication before 24 hours.

Total amount of rescue medication used through 24 hours was calculated for each patient and compared, placebo versus APAP. I found that the mean amount of rescue medication (morphine equivalent) used by placebo and APAP was 80 and 44 mg, respectively. This was not in agreement with the Applicant's results. They reported 57 and 38 mg for placebo and APAP, respectively. After communicating this discrepancy to the Applicant, an error in the dataset was noted. Four patients did not have the correct units of rescue medication recorded, i.e. volume (mL) was recorded instead of weight (mg). Using the revised dataset, I was able to confirm the Applicant's analyses and conclusions. A significant treatment effect was observed for total amount of rescue medication used through 24 hours.

Global evaluation of pain regimen was evaluated at the end of the first dosing period or six hours post-dose. If a patient used rescue medication prior to six hours, the score taken prior to use was imputed as the six hour score. The distribution of scores is shown in Table 9.

Table 9. Patient's assessment of study medication at 6 hours post-dose in Study RC 210 3 002.

Treatment Group	Patient's Global Assessment of Study Medication at 6 hours Post-Dose, n (%)			
	Poor	Fair	Good	Excellent
Placebo (N=49)	10 (21)	19 (40)	11 (23)	8 (17)
APAP 1000 mg (N=48)*	16 (33)	22 (45)	11 (22)	0 (0)

Source: Reviewer

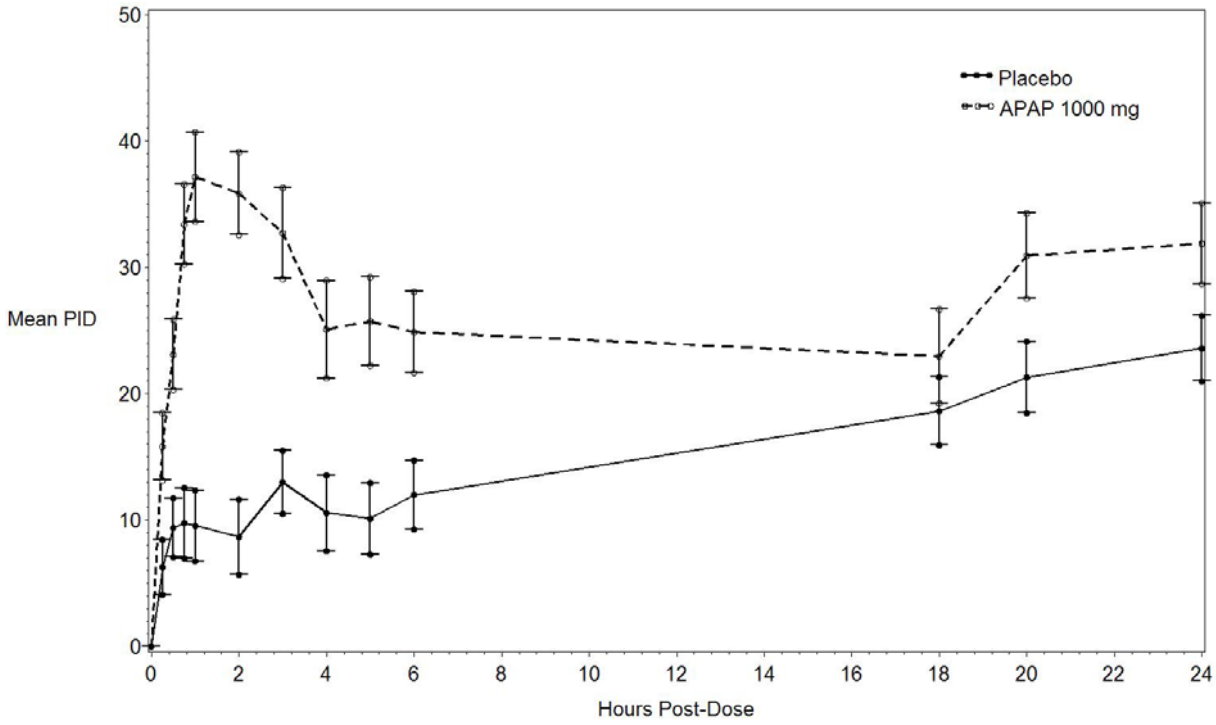
* p-value=0.009 for CMH test "Row Mean Scores Differ"

While significance was noted at six hours post-dose, there was not a significant difference at 24 hours-post dose, data not shown.

Other Analyses

Dr. Christina Fang requested a graph of the mean PID over time. Figure 1 examines PID scores out to 24 hours. Missing data was imputed using BOCF methods.

Figure 1. Mean PID scores by time in Study RC 210 3 002



Source: Reviewer

Clearly, mean PID scores are larger for APAP with the largest treatment effect occurring from zero to four hours. However, by 18 hours the treatment effect is minimal. Note, although it was suggested in the EOP2 meeting to measure PR and PI scores at the end of each dosing interval, this was not done.

Study CPI-APA-304

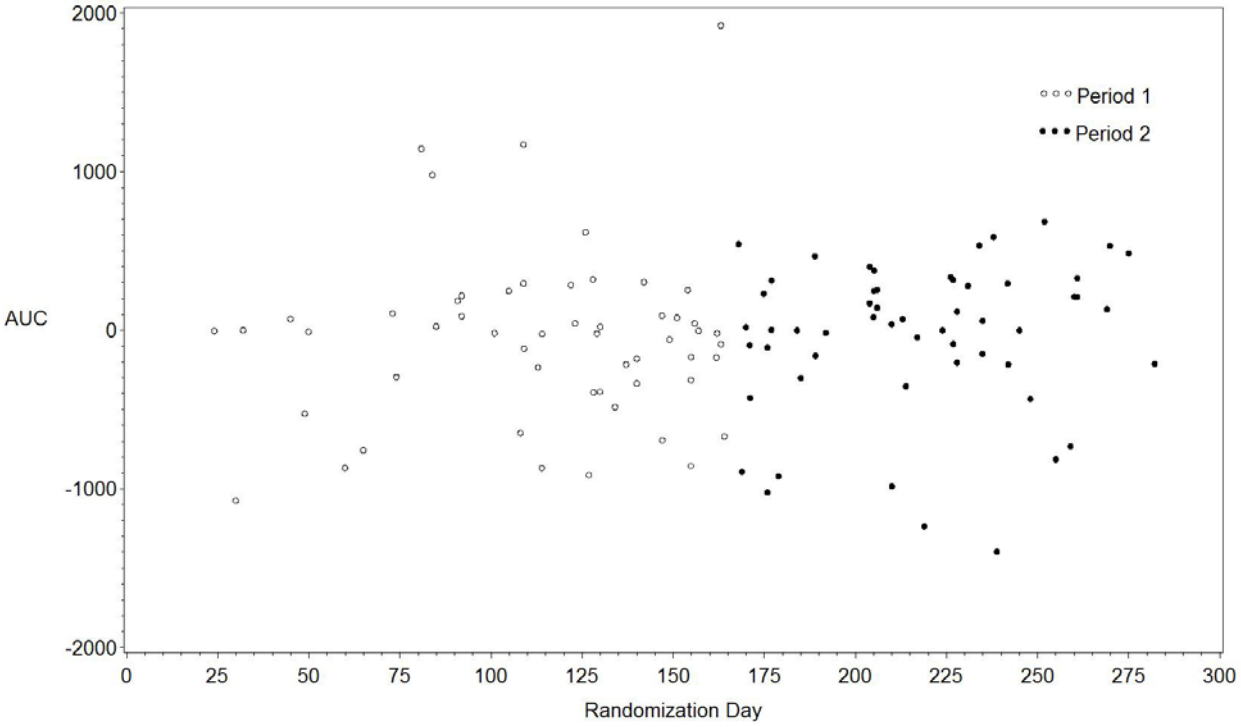
While the applicant excluded three patients because they did not have any post-randomization assessments, they were included in my analyses as they were randomized and did receive treatment, i.e. ITT principle.

Primary Efficacy Endpoint

The protocol defined primary comparison of interest was SPID24 of placebo (pooled) versus APAP 1000 mg. I had two concerns regarding the pooling of placebo groups. First, the two placebo groups used different dosing regimens, P1000 was dosed every six hours and P650 was dosed every four hours. Second, there were two separate randomization periods and the first randomization period only examined the P650 treatment group. To explore potential differences between the dosing regimen and randomization periods, I examined the primary endpoint

SPID24. In Figure 2, I graphed the placebo groups versus the time from when the first patient was randomized.

Figure 2. SPID24 for placebo patients in Study CPI-APA-304



Source: Reviewer

From this figure, there do not appear to be any differences in SPID24 based on the randomization period. I also compared the mean SPID24 for P1000 and P65 and did not observe significant difference in SPID24. Based on this information, I deemed it was appropriate to pool the placebo groups.

In Table 10 each IV APAP dose group is compared to the pooled placebo group. Missing data for patients that were discharged early from the hospital used LOCF and missing data for patients that used rescue medication or discontinued early used BOCF. Note, the Applicant had the p-values reversed in their study report. While both APAP doses were statistically significant, the more significant comparison was noted for the 650 mg dose not the 1000 mg dose.

Table 10. Comparison of SPID24 (PID/hr) -in Study CPI-APA-304

Treatment Group, (n)	Mean AUC, (SD)	Range	P-value of comparison to placebo
Pooled placebo, (n=110)	-44 (509)	[-1396, 1921]	-
APAP 1000 mg, (n= 92)	-194 (593)	[-1432, 1589]	0.02
APAP 650 mg, (n=42)	-315 (613)	[-1673, 848]	0.009

Source: Reviewer

Although the sponsor is including the 650 mg dose in the label, there were no adjustments in the statistical analyses to adjust for multiple comparisons. However, any method applied post-hoc such as a Bonferroni adjustment or the Intersection-Union test would still result in a significant treatment effect.

Secondary Efficacy Endpoints

Time to meaningful pain relief (T-MPR) was examined using survival analysis techniques. The Log-Rank test was used to determine if the time to meaningful pain relief for the placebo group was statistically different from the APAP groups, Table 11. While there was a significant treatment effect for the APAP 1000 mg dose, there was not for the 650 mg dose.

Table 11. Time to meaningful pain relief for patients enrolled in Study CPI-APA-304

Treatment Group	Median Time to Meaningful Pain Relief (minutes)	p-value for log rank test
P1000	59	-
APAP 1000 mg	27	0.001
P650	33	-
APAP 650 mg	27	0.14

Source: Reviewer

Sum of pain relief scores at 24 hours (TOTPAR) was examined using ANCOVA procedures with treatment group as a main effect and the baseline PI score as the covariate. Note, the analysis of the derived dataset was not consistent with the study report. However, when TOTPAR was derived from the raw data, the results were consistent with the study report. There was a significant treatment effect observed for both APAP 1000 and 650 mg when compared to pooled placebo, p-values 0.007 and 0.005, respectively.

Other Analyses

The reviewing medical officer requested information regarding PI and PR scores at the end of each dosing interval. To examine this, PID and PR scores for APAP 650 mg were evaluated at 4, 8, 12, 16, 20, and 24 hours and for APAP 1000 mg, the scores were evaluated at 6, 16, 18, and 24 hours, Tables 12 and 13. I also included the scores of the respective placebo groups for comparison.

Table 12. Mean PID scores for APAP 1000mg and its respective placebo group in Study CPI-APA-304

Treatment	Time (hours)																	
	1	2	3	4	5	6*	7	8	9	10	11	12*	14	16	18*	20	22	24*
APAP	-23	-20	-17	-11	-7	-5	-10	-10	-9	-9	-5	-1	-6	-6	-6	-8	-8	-8
Placebo	-13	-17	-10	-3	-1	-3	-4	-3	-3	-2	0	0	-1	0	-2	-2	-3	-5
Difference	10	3	7	9	6	2	6	7	6	7	5	2	5	6	4	6	5	3

* end of dosing period
Source: Reviewer

Table 13. Mean PID scores for APAP 650 mg and its respective placebo group in Study CPI-APA-304

Treatment	Time (hours)																	
	1	2	3	4*	5	6	7	8*	9	10	11	12*	14	16*	18	20*	22	24*
APAP	-20	-23	-18	-12	-19	-18	-15	-13	-17	-19	-14	-12	-11	-13	-13	-14	-14	-16
Placebo	-9	-8	-5	-2	-3	-4	-1	0	-1	0	1	2	1	1	0	-1	-2	-4
Difference	11	15	13	10	16	14	14	13	16	19	13	14	12	14	13	13	12	12

* end of dosing period
Source: Reviewer

The magnitude of the treatment effect is larger for APAP 650 mg compared to placebo.

3.2 Evaluation of Safety

The primary medical officer, Dr. Jacqueline Spaulding, reviewed the safety data for this NDA.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race and Age

Study RC 210 3 002

While the study conducted by BMS in 1999/2000 did not include a subgroup analysis, the Applicant did conduct one post-hoc. Although the Applicant examined multiple endpoints, I focused on SPID24 and examined the data for a treatment interaction with sex, race, or age. Age was categorized as less than 65 years or 65 years and older, and race was examined as Caucasian or not Caucasian. There were no significant interactions noted with SPID6. However, I did note significant treatment interactions with age and race for SPID24. The mean SPID24 for Caucasians, non-Caucasians, patients less than 65 years old, and patients greater than 65 years old are shown in Table 14.

Table 14. Subgroup analysis for age and race for SPID24 in study RC 210 3 002

Treatment	Mean SPID24 (PID/hr) – (n)			
	Caucasian	Non-Caucasian	< 65 years	> 65 years
Placebo	403 (46)	154 (6)	413 (32)	312 (20)
APAP 1000 mg	631 (42)	693 (7)	566 (22)	699 (27)

Source: Reviewer

Study CPI-APA-304

While the Applicant did not conduct a subgroup analysis for this study, I examined the primary endpoint, SPID24, to see if there was a significant treatment interaction with age, sex, or race.

Using an ANCOVA model as above, I did not observe a treatment interaction with sex, age, or race.

While there was a significant treatment interaction with sex and age observed with SPID24 in Study RC 210 3 002, this effect was not observed in the second study. Since the Applicant is not making claims regarding subgroups in the label, the treatment effect is consistent with the overall findings, i.e. APAP treatment patients appear to have less pain than placebo patients, and these interactions were not noted in the second study, further exploration is not warranted.

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were two clinical trials that were reviewed to support the efficacy of IV APAP in treating patients with acute post-operative pain. In the first study, RC 210 3 002, pain resulted from patients undergoing total hip or knee replacement. The Applicant showed a significant treatment effect for the protocol defined primary endpoint, PR scores from 15 minutes to 6 hours. While there were not adjustments for multiple comparisons pre-specified in the protocol, I applied several methods post-hoc. Two of the three methods demonstrated significance. The conservative Bonferroni adjustment method did not show significance at the first two time points. When the data was reanalyzed using the current regulatory endpoint, SPID24, there was a significant treatment effect.

In the second study, CPI-APA-304, pain was the result of patients undergoing abdominal laparoscopic surgery. There was a significant treatment effect noted with the protocol defined primary endpoint, SPID24. While there was an allocation error noted in the randomization procedure, the Applicant revised the procedure to achieve an adequate number of patients in each treatment and included an adjustment in the analyses account to correct for it. I explored a potential treatment difference between the randomization periods using the primary defined endpoint, SPID24. None were noted in my exploration, section 3.1.4. The primary efficacy comparison defined in the protocol, SPID24 for placebo versus APAP 1000 mg. was significant. However, there was no multiplicity adjustment for the secondary comparison of SPID24 for placebo versus APAP 650 mg. However, adjustments made post-hoc were significant.

5.2 Conclusions and Recommendations

CPI requests that IV APAP 1000 and 650 mg be approved to treat patients with acute post-operative pain. Based on my review of two randomized, placebo-control, Phase 3 clinical trials, I conclude that IV APAP is effective in treating patients with acute post-operative pain. However, the appropriate dose and dosing regimen needs to be further evaluated by the review team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

DAVID M PETULLO
10/14/2009

DIONNE L PRICE
10/14/2009
Concur

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/Serial Number:	22-450/ N000
Drug Name:	ACETVANCE (acetaminophen)
Indication(s):	Acute pain and fever
Applicant:	Cadence Pharmaceuticals, Inc.
Date(s):	Letter date: May 12, 2009, PDUFA date: November 13, 2009
Review Priority:	Priority
Biometrics Division:	II
Statistical Reviewer:	Feng Li, Ph.D.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia and Rheumatology Products
Clinical Team:	Christina Fang, M.D., Jacqueline Spaulding, M.D.
Project Manager:	Sharon Turner-Rinehardt
Keywords:	NDA review, Clinical Studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Applicant seeks approval to market ACETAVANCE (acetaminophen intravenous injection) in adult and pediatric populations for the proposed indication of "treatment of acute pain and fever".

This review focuses on the adult fever indication. The review of data supporting the acute pain indication has been reviewed by Mr. David Petullo.

The Applicant conducted a randomized, double-blind, placebo-controlled efficacy study to support the fever indication. Based on my review, there is evidence that ACETAVANCE is effective in the treatment of acute fever. The Applicant also conducted an active-controlled, randomized, double-blind study to support the efficacy, which is included in the clinical study section of the proposed label. Although I have included my review of the active-controlled study, this study is supportive and not needed for making a final regulatory decision.

1.2 Brief Overview of Clinical Studies

The Applicant conducted the two Phase 3 studies in healthy adult males to support the efficacy of 1000 mg intravenous acetaminophen (IV APAP) in the treatment of fever. Both studies were randomized, single-dose, single-site, double-blind and parallel-group studies conducted in subjects with reference standard endotoxin induced fever.

Study CPI-APF-302 was the placebo-controlled study. The Applicant's stated primary objective was to assess the antipyretic efficacy over 6 hours of a single dose of IV APAP compared with IV placebo in the treatment of fever induced by a standard dose of endotoxin. The primary endpoint was the time-weighted sum of temperature difference from baseline during the 6 hours post-dose (WSTD6). The primary endpoint was analyzed using an analysis of covariance model with baseline temperature as the covariate. The efficacy population included all dosed subjects.

Study CPI-APF-303 used a double-dummy design with oral (PO) acetaminophen 1000 mg as the active control. The Applicant's stated primary objective was to assess the rapidity of onset of antipyretic effect and the efficacy of a single dose of IV acetaminophen versus PO acetaminophen in the treatment of fever induced by a standard dose of endotoxin. The primary endpoint was the time-weighted sum of temperature difference from baseline during the 2 hours post-dose, analyzed using an analysis of covariance model with baseline temperature as the covariate. The Applicant's efficacy population included all dosed subjects who didn't vomit within two hours after oral dose.

1.3 Statistical Issues and Findings

There were no statistical issues identified for Study CPI-APF-302.

The Applicant's analysis population in Study CPI-APF-303 was not appropriate. The efficacy population should not have excluded dosed subjects who vomited with two hours after PO medication. I conducted an analysis including these subjects, and the conclusions remained unchanged.

2. INTRODUCTION

2.1 Overview

Acetaminophen is a widely used analgesic and antipyretic. Oral acetaminophen was approved in the United States in 1951. The intravenous (IV) formulation of acetaminophen was first developed by Bristol-Myers Squibb and has been approved for use in European since 2001. The Applicant attained the commercialization rights to IV APAP in North American from BMS in 2006.

The clinical development program was discussed between the Applicant and the Division under IND 58,362. At the End-of-Phase 2 meeting on August 14, 2006, the requirements of a pediatric development program were discussed. The Division stated the following in the post-meeting note:

> Post meeting note: Multiple-dose safety data in appropriate pediatric populations will be required as long as the relative PK of parenteral acetaminophen and oral acetaminophen are different in these patients. Efficacy may be supported to an extent based on the similarity of the PK characteristics. However, as with adult patients, if the PK curve is shifted to the left in pediatric patients, adequate efficacy and safety in pediatric patients must be supported through clinical trial data rather than by bridging to prior findings of efficacy with the oral product.

In March 2008, the Applicant submitted a clinical development plan designed to support the pain and fever indications. The Applicant proposed a single pivotal Phase 3 study (CPI-APF-302) to support the fever indication. The Applicant also proposed a supportive Phase 3 study using PO acetaminophen as the active control. In the letter sent to the Applicant on July 21, 2008, the Division stated that the clinical development plan was sufficient to support submission of a NDA. In addition, he Division agreed that the basis of approval of IV APAP for pediatric indication of fever could be obtained via bridging adult efficacy data with the pediatric PK and safety data.

The Applicant changed the primary efficacy endpoint of the supportive study prior to the database lock based on the results from Study CPI-APF-302. The original endpoint was time to reduction in temperature of 1.5 °C. I didn't find any communications regarding the change of primary efficacy endpoint.

2.2 Data Sources

The statistical review is based on data submitted for studies CPI-APF-302 and CPI-APF-303.

The submitted data can be found at \\Cdsesub1\evsprod\NDA022450\0000\m5\datasets. The Applicant submitted SDTM and analysis-ready datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study CPI-APF-302

Study Design and Endpoints

This study was designed to evaluate the single-dose efficacy of 1000 mg IV APAP in the treatment of healthy adult males with reference standard endotoxin (RSE) induced fever compared to placebo.

Following an overnight observation period, subjects were administered a RSE test dose to confirm the absence of worrisome responses. Subjects were then given RSE 4ng/kg body weight IV. Subjects who failed to achieve a temperature of 38.6 °C within four hours of the RSE dose were excluded from further study participation. Eligible subjects were randomized in a 1:1 ratio to either IV APAP or placebo.

Temperature was recorded at the following time points relative to T0 (start of IV study medication infusion): T5, T10, T15, T20, T25, T30, T40, T50, T60, T75, T90, T105, T120, T150, T180, T210, T240, T270, T300, T330, and T360 minutes. Subjects were asked to provide a global evaluation of the treatment based on a 4-point categorical scale at the time of study termination.

Subjects had access to rescue medication throughout the study. Temperature was recorded just prior to taking rescue medication.

The primary efficacy endpoint was the time-weighted sum of temperature difference from baseline during the 6 hours post-dose (WSTD6). The secondary endpoints included WSTD3, maximum temperature reduction during the period from T0 to T360 minutes, subject's global assessment, and percentage of subjects with temperature < 38 °C at any time point from T0 to T360 minutes.

Patient Disposition, Demographic and Baseline Characteristics

A total of 60 subjects were randomized and received study medication, 31 subjects to the IV APAP group and 29 subjects to the placebo group. There were four subjects who discontinued early, two subjects from each treatment group. The four subjects discontinued because of the need for rescue medication.

All of the enrolled subjects were males no older than 55 years. The demographic and baseline characteristics were balanced across treatment groups. The majority of the subjects were Caucasian (76% of the placebo group, 74% of the IV APAP group). The mean age was 30. The detailed demographic and baseline characteristics are provided in the appendix.

Statistical Methodologies

The primary efficacy endpoint, WSTD6, was analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline temperature at T0 as the covariate. The primary efficacy population was the modified intent-to-treat (mITT) population, defined as all randomized subjects who received a complete dose of study medication.

For subjects with any missing temperature assessment following study medication administration and prior to receiving rescue medication, the last non-missing measured temperature was carried forward. For subjects who received rescue medication, the worst measured temperature was carried forward from the time the rescue medication was requested.

The Applicant performed the primary efficacy analysis disregarding efficacy evaluations obtained after the time of rescue medication request. The Applicant did additional analyses including data after the rescue medication request.

Continuous secondary endpoints, WSTD3 and maximum temperature reduction from T0 to T360, were analyzed using the same model as the one for the primary endpoint. The subjects' global assessment was analyzed using the Cochran-Mantel-Haenszel (CMH) method. The percentage of subjects with temperature <38 ºC at any time point was analyzed using Pearson's chi-square test.

Results and Conclusions

I replicated the Applicant's primary and secondary efficacy results.

Table 1 shows the summary statistics and analysis results from the primary analysis. The analysis result was statistically in favor of IV APAP. The analyses including data obtained after the request of rescue medication resulted in similar findings. The least square mean difference in the table is the difference between group-means controlling for the baseline temperature.

Table 1: Primary Efficacy Results (Study CPI-APF-302)

Summary Statistics (ºC)	**Placebo N=29**	**IV APAP N=31**
MEAN (SD)	-0.7 (3.3)	-3.7 (3.6)
MEDIAN	-1.2	-3.7
MIN, MAX	-10.0, 8.2	-9.8, 5.5
Analysis Results		
Least Square Mean Difference (SE)	-2.5 (0.6)	
ANCOVA p-value	0.0001	

(Source: Module 5, CPI-APF-302 Study Report, Table 6)

The secondary endpoints WSTD3, maximum temperature reduction from T0 to T360 minutes and percentage of subjects with temperature < 38 °C at any time point from T0 to T360 minutes were all statistically significant favoring IV APAP. There was no multiplicity adjustment for the multiple secondary endpoints.

The subjects' global assessment was not statistically different between the IV APAP group and the placebo group. Table 2 presents the analysis results for the subjects' global assessment. The IV APAP group had a higher percentage of subjects with a "Good" score and a lower percentage of subjects with a "Fair" score.

Table 2: Efficacy Results: Global Assessment (Study CPI-APF-302)

Global Assessment	**Placebo N=29**	**IV APAP N=31**
	n (%)	n (%)
Excellent	8 (28)	9 (29)
Good	10 (35)	16 (52)
Fair	9 (31)	5 (16)
Poor	2 (7)	1 (3)
ANCOVA p-value	0.282	

(Source: Module 5, CPI-APF-302 Study Report, Table 10)

The change in temperature from baseline at each assessment time point from T5 to T360 minutes was analyzed using ANCOVA models similar to the primary efficacy analysis. The corresponding results are shown in Table 3. There were no multiplicity adjustments for the p-values.

Figure 1 shows the observed mean temperature by time point for each treatment group. The red line denotes the curve for the IV APAP group and the blue dotted line represents the placebo group. There is clear separation between the temperature curves after 30 minutes.

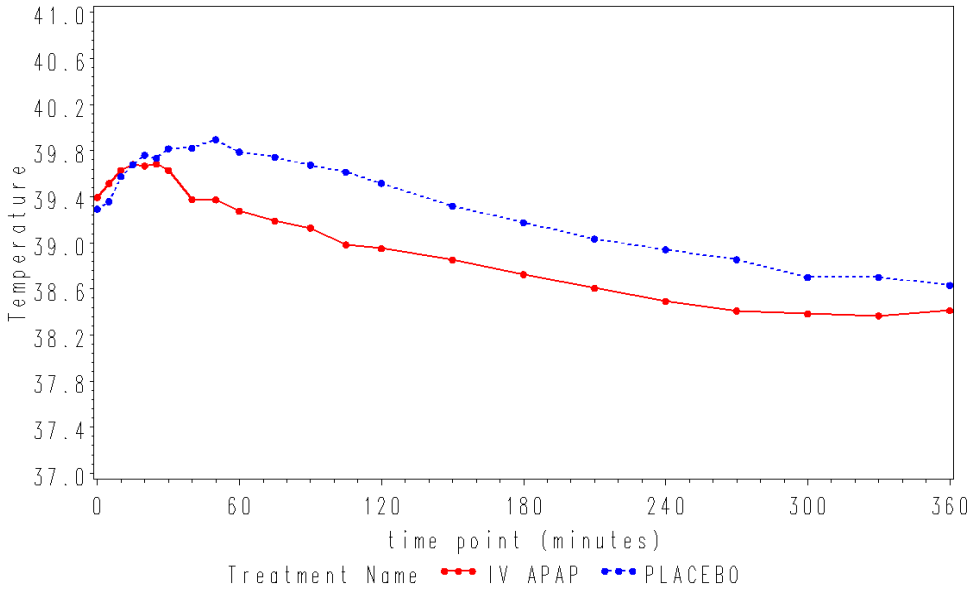
Table 3: Efficacy Results: Change in Temperature from Baseline (Study PI-APF-302)

Time (min)	Mean (SD) Temperature Change (°C) from T0		ANCOVA[1] p-value
	Placebo N = 29	Acetaminophen N = 31	
T5	0.07 (0.66)	0.12 (0.46)	0.6584
T10	0.28 (0.37)	0.24 (0.44)	0.7597
T15	0.39 (0.36)	0.29 (0.40)	0.4186
T20	0.47 (0.37)	0.27 (0.36)	0.0629
T25	0.44 (0.47)	0.29 (0.32)	0.2093
T30	0.52 (0.47)	0.24 (0.33)	0.0085*
T40	0.53 (0.49)	-0.02 (0.48)	<0.0001*
T50	0.60 (0.44)	-0.04 (0.49)	<0.0001*
T60	0.50 (0.59)	-0.14 (0.48)	<0.0001*
T75	0.45 (0.58)	-0.22 (0.49)	<0.0001*
T90	0.38 (0.52)	-0.28 (0.51)	<0.0001*
T105	0.31 (0.51)	-0.43 (0.57)	<0.0001*
T120	0.22 (0.56)	-0.46 (0.55)	<0.0001*
T150	0.02 (0.56)	-0.56 (0.65)	<0.0001*
T180	-0.12 (0.60)	-0.69 (0.64)	<0.0001*
T210	-0.27 (0.59)	-0.81 (0.67)	0.0001*
T240	-0.36 (0.62)	-0.92 (0.71)	0.0002*
T270	-0.44 (0.68)	-1.00 (0.69)	0.0004*
T300	-0.60 (0.73)	-1.03 (0.74)	0.0208*
T330	-0.60 (0.74)	-1.05 (0.77)	0.0176*
T360	-0.67 (0.76)	-1.05 (0.81)	0.0711

* Statistically significant at 0.05 significance level, two-sided

(Source: Module 5, CPI-APF-302 Study Report, Table 12)

Figure 1: Mean Temperature (°C) Curve by Time (Study CPI-APF-302)



3.1.2 Study CPI-APF-303

Study Design and Endpoints

The study design was very similar to that of Study CPI-APF-302. However, this study used a double-dummy design. All subjects received both IV and PO medications. This study used PO acetaminophen 1000 mg as the active control.

Subjects who failed to achieve a temperature of 38.6 °C within four hours of the RSE dose were excluded from further study participation. Eligible subjects were randomized with 1:1 ratio to either IV APAP or PO acetaminophen group.

Temperature was recorded at the following time points relative to T0 (start of IV study medication infusion): T5, T10, T15, T20, T25, T30, T40, T50, T60, T75, T90, T105, T120, T150, T180, T210, T240, T270, T300, T330, and T360 minutes. Subjects were asked to provide a global evaluation of the treatment based on a 4-point categorical scale at the time of study termination.

Subjects had access to rescue medication throughout the study. Temperature was recorded just prior to taking rescue medication.

The primary efficacy endpoint was WSTD2. The original endpoint was time to reduction in temperature of 1.5 °C, but the Applicant elected to modify the primary endpoint to WSTD2 prior to the database lock based on the results of the pivotal study CPI-APF-302, which, the Applicant stated, showed the temperature response was very different from predicted using historically-based modeling.

Patient Disposition, Demographic and Baseline Characteristics

A total of 105 male subjects were randomized and received study medication, 54 subjects to the IV APAP group and 51 subjects to the PO acetaminophen group. There were 24 subjects who vomited within two hours of PO medication, including nine subjects in the IV APAP group and 15 subjects in the PO acetaminophen group. These 24 subjects were not included in the Applicant's efficacy analyses.

The demographic and baseline characteristics were balanced across treatment groups. The majority of the randomized subjects were white or Caucasian (80% of the IV APAP group, 84% of the PO acetaminophen group). The mean ages of the randomized subjects in IV APAP and PO acetaminophen were 33 and 31 years, respectively. There was only one subject older than 58 years. The detailed demographic and baseline characteristics for subjects in the Applicant's efficacy population are provided in the appendix.

Statistical Methodologies

The primary efficacy endpoint, WSTD2, was analyzed using an ANCOVA model with treatment as a factor and baseline temperature at T0 as the covariate. The primary efficacy population was the modified intent-to-treat (mITT) population, defined as all randomized subjects who received one full dose of IV and PO medication and didn't vomit within two hours of PO medication.

Results and Conclusions

I replicated the Applicant's primary efficacy results.

Table 4 shows the summary statistics and analysis result from ANCOVA for WSTD2 using the Applicant's mITT population. The analysis result was statistically in favor of IV APAP.

Table 4: Primary Efficacy Results (Study CPI-APF-303)

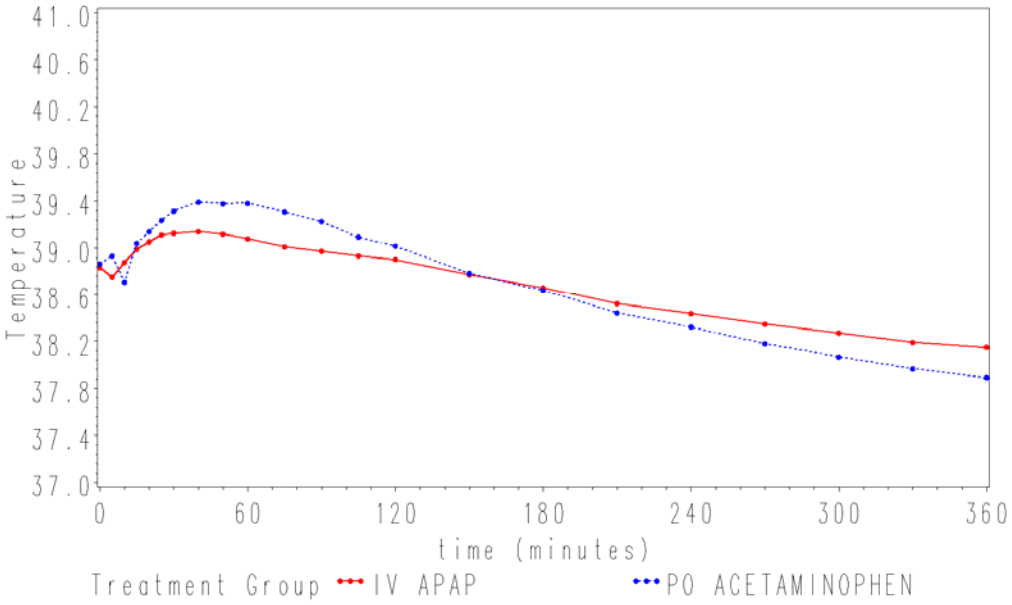
	PO Acetaminophen	**IV APAP**
Summary Statistics (ºC)	**N=36**	**N=45**
MEAN (SD)	0.6 (0.6)	0.3 (0.4)
MEDIAN	0.7	0.3
MIN, MAX	-0.5, 1.6	-0.5, 1.1
Analysis Results		
Least Square Mean Difference (SE)	-0.3 (0.1)	
ANCOVA p-value	0.0039	

(Source: Module 5, CPI-APF-303 Study Report, Table 7)

The Applicant's efficacy population excluded 24 subjects who vomited within 2 hours of PO medication, which was not appropriate. To check the sensitivity of the primary efficacy result to the definition of the efficacy population, I did analyses including all randomized subjects using both last observation carried forward and baseline observation carried forward imputation methods for missing fever assessment. My sensitivity analyses were in favor of IV APAP.

Figure 2 shows the mean temperature by time point for each treatment group for all randomized subjects. The red line denotes the curve for the IV APAP group and the blue dotted line represents the PO acetaminophen group. There is a separation in favor of IV APAP between the temperature curves from T20 to T120 minutes. However, the PO acetaminophen group had a mean lower temperature after T180 minutes.

Figure 2: Mean Temperature Curve (°C) by Time (Study CPI-APF-303)



3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Jacqueline Spaulding. The reader is referred to Dr. Spaulding's review for information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

All subjects enrolled in the two studies were healthy males. All of the subjects in Study CPI-APF-302 study were no older than 55 years. There was only one subject in Study CPI-APF-303 study older than 58 years. Thus, the Applicant did not conduct subgroup analyses for gender and age. The Applicant stated that review of the individual subject data showed that temperature reductions in non-Caucasian subjects were comparable to Caucasian subjects in each study.

I did subgroup analysis by race for the primary endpoint WSTD6 for Study CPI-APF-302. Table 5 presents the summary statistics by race for each treatment group. The results are consistently in favor of IV APAP in each race group.

Table 5: Primary Efficacy Results by Race (Study CPI-APF-302)

	Placebo		IV APA	
Endpoint (WSTD 6)	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Race				
Caucasian	22	-1.1 (2.9)	23	-3.6 (3.9)
Non-Caucasian and Other	7	0.5 (4.3)	8	-4.1 (2.7)

The subgroup analysis by race for the primary endpoint WSTD2 for Study CPI-APF-303 supported IV APAP.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues in the placebo-controlled study. In terms of the primary efficacy endpoint WSTD6, there was a statistically significant difference when comparing IV APAP to placebo. The results demonstrated the efficacy of IV APAP in reducing fever.

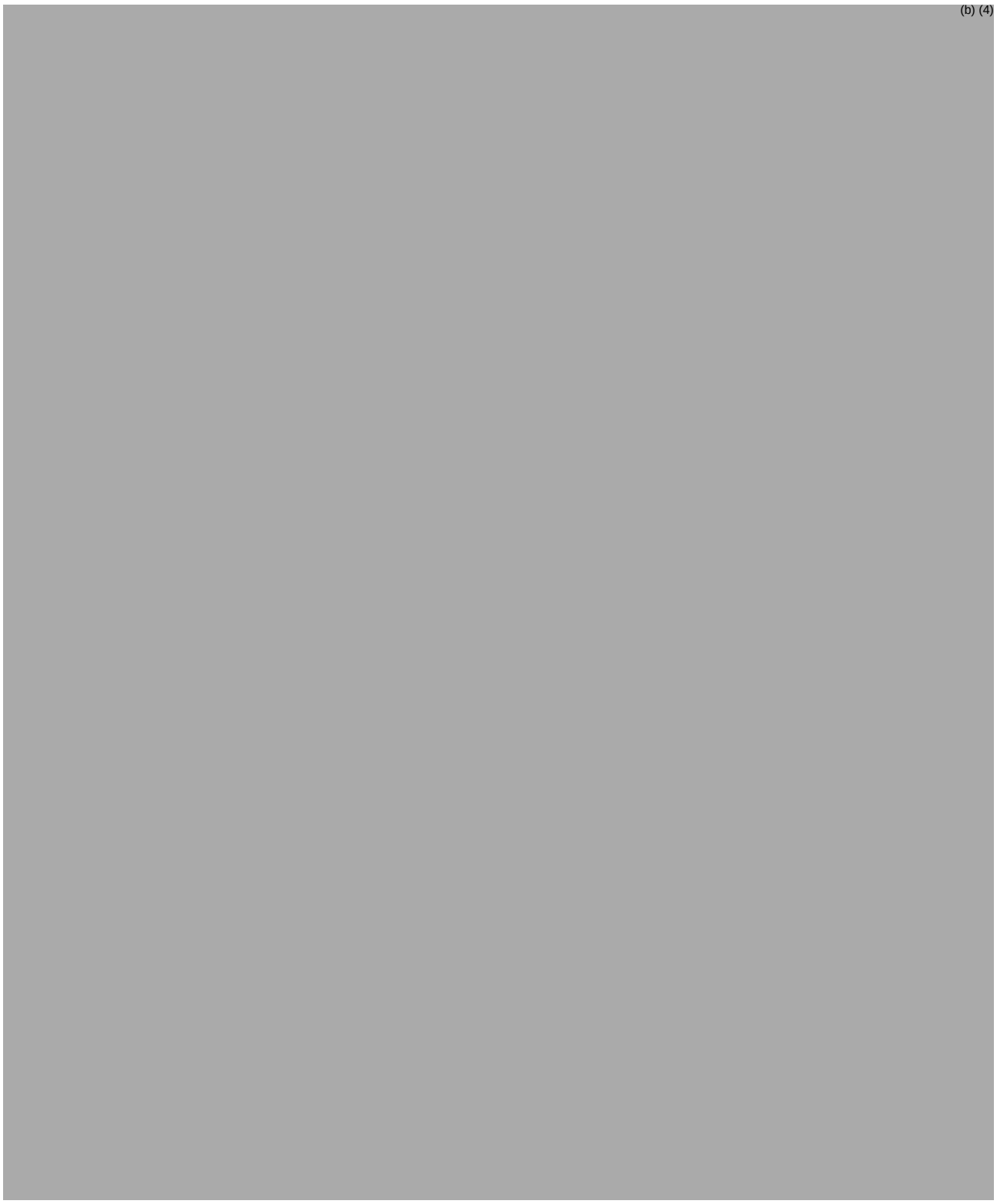
The analysis result in the active-controlled study demonstrated that IV APAP was superior to PO acetaminophen in average temperature reduction through two hours after dose. There was no evidence that IV APAP was better than PO acetaminophen beyond two hours.

5.2 Conclusions and Recommendations

The analysis result in the single placebo-controlled study demonstrated that IV APAP was statistically superior to placebo in the average temperature reduction through 6 hours.

5.2.1 Labeling

The sponsor submitted the following wording for the fever indication in the draft Label:


(b) (4)

APPENDICES

APPEARS THIS WAY ON ORIGINAL

Summary of Demographics and Baseline Characteristics

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Study CPI-APF-302 (Source: Clinical Study Report)

TABLE 3
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS
ANALYSIS POPULATION: MODIFIED INTENT-TO-TREAT POPULATION

	PLACEBO (N=29)	IV APAP (N=31)	TOTAL (N=60)
AGE (YEARS)			
MEAN (SD)	30.0 (10.02)	29.7 (7.35)	29.9 (8.67)
MEDIAN	29.0	28.0	28.0
MIN, MAX	18, 55	18, 49	18, 55
N	29	31	60
SEX [1]			
MALE	29 (100.0%)	31 (100.0%)	60 (100.0%)
ETHNICITY			
HISPANIC OR LATINO	5 (17.2%)	5 (16.1%)	10 (16.7%)
NOT HISPANIC OR LATINO	24 (82.8%)	26 (83.9%)	50 (83.3%)
RACE			
ASIAN	1 (3.4%)	0 (0.0%)	1 (1.7%)
BLACK OR AFRICAN-AMERICAN	6 (20.7%)	7 (22.6%)	13 (21.7%)
WHITE OR CAUCASIAN	22 (75.9%)	23 (74.2%)	45 (75.0%)
OTHER	0 (0.0%)	1 (3.2%)	1 (1.7%)
HEIGHT (IN)			
MEAN (SD)	70.5 (2.21)	69.0 (3.17)	69.8 (2.83)
MEDIAN	70.0	70.0	70.0
MIN, MAX	66, 76	61, 75	61, 76
N	29	31	60
WEIGHT (LBS)			
MEAN (SD)	172.2 (23.69)	179.2 (26.54)	175.8 (25.24)
MEDIAN	169.0	180.0	177.5
MIN, MAX	130, 219	126, 232	126, 232
N	29	31	60
HEART RATE (BPM)			
MEAN (SD)	102.1 (14.80)	103.7 (17.15)	102.9 (15.94)
MEDIAN	103.0	106.0	103.0
MIN, MAX	75, 128	75, 138	75, 138
N	29	31	60
RESPIRATORY RATE (RPM)			
MEAN (SD)	15.8 (1.93)	16.2 (1.59)	16.0 (1.76)
MEDIAN	16.0	16.0	16.0
MIN, MAX	12, 20	11, 18	11, 20
N	29	31	60
SYSTOLIC BLOOD PRESSURE (mmHg)			
MEAN (SD)	131.7 (13.48)	132.8 (21.61)	132.3 (18.00)
MEDIAN	134.0	132.0	132.5
MIN, MAX	101, 152	90, 190	90, 190
N	29	31	60
DIASTOLIC BLOOD PRESSURE (mmHg)			
MEAN (SD)	77.4 (8.01)	77.0 (10.58)	77.2 (9.35)
MEDIAN	77.0	77.0	77.0
MIN, MAX	63, 91	48, 100	48, 100
N	29	31	60
CORE TEMPERATURE PRIOR TO TEST DOSE (°C)			
MEAN (SD)	36.7 (0.23)	36.6 (0.19)	36.7 (0.21)
MEDIAN	36.7	36.6	36.7
MIN, MAX	36.2, 37.1	36.3, 37.1	36.2, 37.1
N	29	31	60
RSE TEST DOSE (ng)			
MEAN (SD)	78.9 (10.95)	82.0 (12.00)	80.5 (11.51)
MEDIAN	77.0	82.0	81.0
MIN, MAX	59.0, 101.0	58.0, 105.0	58.0, 105.0
N	29	31	60
TEMPERATURE PRIOR TO RSE DOSE (°C)			
MEAN (SD)	36.8 (0.25)	36.7 (0.22)	36.7 (0.23)
MEDIAN	36.8	36.7	36.8
MIN, MAX	36.1, 37.2	36.3, 37.1	36.1, 37.2
N	29	31	60

TABLE 3 (Continued)
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS
ANALYSIS POPULATION: MODIFIED INTENT-TO-TREAT POPULATION

	PLACEBO (N=29)	IV APAP (N=31)	TOTAL (N=60)
RSE DOSE (ng)			
MEAN (SD)	309.9 (51.01)	328.1 (48.55)	319.3 (50.18)
MEDIAN	307.0	329.0	324.0
MIN, MAX	170.0, 405.0	231.0, 422.0	170.0, 422.0
N	29	31	60
TEMPERATURE PRIOR TO STUDY DRUG ADMINISTRATION (°C)			
MEAN (SD)	39.3 (0.55)	39.4 (0.49)	39.3 (0.52)
MEDIAN	39.3	39.3	39.3
MIN, MAX	38.2, 41.1	38.6, 40.4	38.2, 41.1
N	29	31	60
MEDICAL HISTORY [2]			
HEENT	4 (13.8%)	4 (12.9%)	8 (13.3%)
CARDIAC	2 (6.9%)	1 (3.2%)	3 (5.0%)
RESPIRATORY	3 (10.3%)	2 (6.5%)	5 (8.3%)
MUSCULOSKELETAL	16 (55.2%)	10 (32.3%)	26 (43.3%)
DERMATOLOGICAL	2 (6.9%)	6 (19.4%)	8 (13.3%)
GASTROINTESTINAL	10 (34.5%)	4 (12.9%)	14 (23.3%)
GENITOURINARY	0 (0.0%)	3 (9.7%)	3 (5.0%)
NEUROLOGICAL	26 (89.7%)	27 (87.1%)	53 (88.3%)
LYMPHATIC	1 (3.4%)	0 (0.0%)	1 (1.7%)
PSYCHIATRIC	1 (3.4%)	0 (0.0%)	1 (1.7%)
ALLERGY HISTORY	11 (37.9%)	8 (25.8%)	19 (31.7%)
OTHER	1 (3.4%)	1 (3.2%)	2 (3.3%)
PHYSICAL EXAMINATION			
VITAL SIGNS AND GENERAL APPEARANCE			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN			
NORMAL	28 (96.6%)	28 (90.3%)	56 (93.3%)
ABNORMAL	1 (3.4%)	3 (9.7%)	4 (6.7%)
HEENT			
NORMAL	29 (100.0%)	29 (93.5%)	58 (96.7%)
ABNORMAL	0 (0.0%)	2 (6.5%)	2 (3.3%)
NECK/THYROID			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
LYMPHATIC			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC			
NORMAL	28 (96.6%)	31 (100.0%)	59 (98.3%)
ABNORMAL	1 (3.4%)	0 (0.0%)	1 (1.7%)
RESPIRATORY			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
PHYSICAL EXAMINATION (CONT.)			
ABDOMEN			
NORMAL	29 (100.0%)	30 (96.8%)	59 (98.3%)
ABNORMAL	0 (0.0%)	1 (3.2%)	1 (1.7%)
GENITOURINARY			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
EXTREMITIES AND VASCULAR			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
OTHER			
NORMAL	29 (100.0%)	31 (100.0%)	60 (100.0%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)

Study CPI-APF-303 (Source: Clinical Study Report)

TABLE 3
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS
ANALYSIS POPULATION: MODIFIED INTENT-TO-TREAT POPULATION

	PO ACETAMINOPHEN (N=36)	IV APAP (N=45)	TOTAL (N=81)
AGE (YEARS)			
MEAN (SD)	32.1 (9.07)	33.8 (11.60)	33.0 (10.52)
MEDIAN	30.0	33.0	32.0
MIN, MAX	19, 50	18, 58	18, 58
N	36	45	81
SEX [1]			
MALE	36 (100.0%)	45 (100.0%)	81 (100.0%)
ETHNICITY			
HISPANIC OR LATINO	0 (0.0%)	0 (0.0%)	0 (0.0%)
NOT HISPANIC OR LATINO	36 (100.0%)	45 (100.0%)	81 (100.0%)
RACE			
AMERICAN-INDIAN OR ALASKA NATIVE	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASIAN	0 (0.0%)	1 (2.2%)	1 (1.2%)
BLACK OR AFRICAN-AMERICAN	7 (19.4%)	10 (22.2%)	17 (21.0%)
NATIVE HAWAIIAN / OTHER PACIFIC ISLANDER	0 (0.0%)	0 (0.0%)	0 (0.0%)
WHITE OR CAUCASIAN	29 (80.6%)	34 (75.6%)	63 (77.8%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)
HEIGHT (IN)			
MEAN (SD)	70.1 (3.03)	70.0 (2.68)	70.0 (2.82)
MEDIAN	70.0	69.0	70.0
MIN, MAX	63, 74	64, 76	63, 76
N	36	45	81
WEIGHT (LBS)			
MEAN (SD)	191.9 (48.96)	192.3 (38.65)	192.1 (43.25)
MEDIAN	183.3	188.8	186.3
MIN, MAX	105.4, 336.6	126.3, 273.0	105.4, 336.6
N	36	45	81
HEART RATE (BPM)			
MEAN (SD)	95.6 (13.27)	95.9 (11.67)	95.8 (12.33)
MEDIAN	95.5	97.0	96.0
MIN, MAX	65, 115	72, 120	65, 120
N	36	45	81
RESPIRATORY RATE (RPM)			
MEAN (SD)	18.2 (2.00)	17.6 (2.84)	17.9 (2.51)
MEDIAN	18.0	18.0	18.0
MIN, MAX	15, 24	10, 22	10, 24
N	36	45	81
SYSTOLIC BLOOD PRESSURE (mmHg)			
MEAN (SD)	119.5 (16.28)	121.1 (16.27)	120.4 (16.19)
MEDIAN	118.5	123.0	122.0
MIN, MAX	78, 148	84, 156	78, 156
N	36	45	81
DIASTOLIC BLOOD PRESSURE (mmHg)			
MEAN (SD)	69.3 (9.89)	70.7 (9.81)	70.1 (9.81)
MEDIAN	68.5	72.0	70.0
MIN, MAX	46, 86	50, 93	46, 93
N	36	45	81
CORE TEMPERATURE PRIOR TO TEST DOSE (°C)			
MEAN (SD)	36.6 (0.31)	36.6 (0.27)	36.6 (0.29)
MEDIAN	36.6	36.6	36.6
MIN, MAX	36.0, 37.3	36.0, 37.1	36.0, 37.3
N	36	45	81
RSE TEST DOSE (ng)			
MEAN (SD)	86.5 (21.40)	87.0 (17.32)	86.8 (19.12)
MEDIAN	83.5	86.0	85.0
MIN, MAX	48, 150	57, 120	48, 150
N	36	45	81
TEMPERATURE PRIOR TO RSE DOSE (°C) [2]			
MEAN (SD)	36.7 (0.28)	36.7 (0.21)	36.7 (0.24)
MEDIAN	36.7	36.7	36.7
MIN, MAX	36.1, 37.3	36.2, 37.1	36.1, 37.3
N	36	45	81
RSE DOSE (ng)			
MEAN (SD)	342.4 (90.51)	345.7 (74.90)	344.2 (81.68)
MEDIAN	330.0	340.0	340.0
MIN, MAX	190, 610	170, 496	170, 610
N	36	45	81
CORE TEMPERATURE BEFORE RANDOMIZATION (°C)			
MEAN (SD)	38.7 (0.08)	38.7 (0.06)	38.7 (0.07)
MEDIAN	38.7	38.7	38.7
MIN, MAX	38.6, 38.9	38.6, 38.8	38.6, 38.9
N	36	44	80

TABLE 3 (Continued)
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS
ANALYSIS POPULATION: MODIFIED INTENT-TO-TREAT POPULATION

	PO ACETAMINOPHEN (N=36)	IV APAP (N=45)	TOTAL (N=81)
TEMPERATURE PRIOR TO STUDY DRUG ADMINISTRATION (°C) [3]			
MEAN (SD)	38.8 (0.14)	38.8 (0.13)	38.8 (0.13)
MEDIAN	38.8	38.8	38.8
MIN, MAX	38.6, 39.2	38.5, 39.1	38.5, 39.2
N	36	45	81
MEDICAL HISTORY [4]			
HEENT	24 (66.7%)	26 (57.8%)	50 (61.7%)
CARDIAC	1 (2.8%)	3 (6.7%)	4 (4.9%)
RESPIRATORY	4 (11.1%)	4 (8.9%)	8 (9.9%)
MUSCULOSKELETAL	11 (30.6%)	26 (57.8%)	37 (45.7%)
DERMATOLOGICAL	5 (13.9%)	2 (4.4%)	7 (8.6%)
GASTROINTESTINAL	7 (19.4%)	9 (20.0%)	16 (19.8%)
GENITOURINARY	2 (5.6%)	0 (0.0%)	2 (2.5%)
NEUROLOGICAL	7 (19.4%)	10 (22.2%)	17 (21.0%)
ENDOCRINE	3 (8.3%)	2 (4.4%)	5 (6.2%)
LYMPHATIC	2 (5.6%)	1 (2.2%)	3 (3.7%)
IMMUNOLOGICAL	1 (2.8%)	1 (2.2%)	2 (2.5%)
PERIPHERAL VASCULAR	1 (2.8%)	0 (0.0%)	1 (1.2%)
PSYCHIATRIC	3 (8.3%)	3 (6.7%)	6 (7.4%)
ALLERGY HISTORY	9 (25.0%)	11 (24.4%)	20 (24.7%)
OTHER	2 (5.6%)	3 (6.7%)	5 (6.2%)
PHYSICAL EXAMINATION			
VITAL SIGNS AND GENERAL APPEARANCE			
NORMAL	26 (72.2%)	42 (93.3%)	68 (84.0%)
ABNORMAL	2 (5.6%)	0 (0.0%)	2 (2.5%)
PHYSICAL EXAMINATION (CONT.)			
SKIN			
NORMAL	4 (11.1%)	3 (6.7%)	7 (8.6%)
ABNORMAL	24 (66.7%)	39 (86.7%)	63 (77.8%)
HEENT			
NORMAL	9 (25.0%)	24 (53.3%)	33 (40.7%)
ABNORMAL	19 (52.8%)	18 (40.0%)	37 (45.7%)
NECK/THYROID			
NORMAL	28 (77.8%)	42 (93.3%)	70 (86.4%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
LYMPHATIC			
NORMAL	28 (77.8%)	42 (93.3%)	70 (86.4%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC			
NORMAL	27 (75.0%)	41 (91.1%)	68 (84.0%)
ABNORMAL	1 (2.8%)	1 (2.2%)	2 (2.5%)
RESPIRATORY			
NORMAL	27 (75.0%)	41 (91.1%)	68 (84.0%)
ABNORMAL	1 (2.8%)	1 (2.2%)	2 (2.5%)
ABDOMEN			
NORMAL	24 (66.7%)	39 (86.7%)	63 (77.8%)
ABNORMAL	4 (11.1%)	3 (6.7%)	7 (8.6%)
PHYSICAL EXAMINATION (CONT.)			
GENITOURINARY			
NORMAL	27 (75.0%)	41 (91.1%)	68 (84.0%)
ABNORMAL	1 (2.8%)	1 (2.2%)	2 (2.5%)
NERVOUS SYSTEM			
NORMAL	28 (77.8%)	42 (93.3%)	70 (86.4%)
ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL			
NORMAL	23 (63.9%)	31 (68.9%)	54 (66.7%)
ABNORMAL	5 (13.9%)	11 (24.4%)	16 (19.8%)
EXTREMITIES AND VASCULAR			
NORMAL	27 (75.0%)	42 (93.3%)	69 (85.2%)
ABNORMAL	1 (2.8%)	0 (0.0%)	1 (1.2%)
OTHER			
NORMAL	27 (75.0%)	41 (91.1%)	68 (84.0%)
ABNORMAL	1 (2.8%)	1 (2.2%)	2 (2.5%)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

FENG LI
10/13/2009

DIONNE L PRICE
10/14/2009
Concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 022450 **Applicant: Cadence Pharmaceuticals, Inc.** **Stamp Date: 05/12/2009**

Drug Name: ACETAVANCE **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			There was only one Phase 3 placebo-controlled efficacy study to support the fever indication. Thus, the applicant did not perform integrated analyses.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			X	For the two fever studies, only male subjects younger than 58 were enrolled. The applicant stated that the temperature reduction in race groups were comparable.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				See clinical review
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Feng Li	June 24, 2009
Reviewing Statistician	Date
Supervisor/Team Leader	Date

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/s/

Feng Li
7/1/2009 10:28:14 AM
BIOMETRICS

Dionne Price
7/1/2009 10:31:08 AM
BIOMETRICS