CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-351

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:	22-351/0000
Drug Name:	Colchicine 0.6 mg tablets (Colstat™)
Indication(s):	Treatment of gout flares
Applicant:	Mutual Pharmaceutical Company, Inc.
Date(s):	Submitted: September 30, 2008
	PDUFA: July 30, 2009
Review Priority:	**Priority – 6 month**
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Keywords: Clinical trials, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Mutual Pharmaceutical Company, Inc. has proposed Colstat (colchicine) for the treatment of acute gout flares. Based on my review of the data from the controlled clinical trial, Study MPC-004-06-001, I conclude there is statistical evidence to support the efficacy of low-dose (1.8 mg) and standard-dose (4.8 mg) colchicine to treat acute gout attacks as measured by a reduction in pain. The Applicant is also relying on the results of a published trial to support efficacy, Ahern et al., 1987. The review of this article appears to indicate that colchicine is effective in relieving symptoms associated with acute gout flares. However, since detailed study information and data were not available for review, I was not able to **confirm or dispute the author's conclusions.**

1.2 Brief Overview of Clinical Studies

The Applicant is relying on one adequate and well controlled clinical trial and the results of one published clinical trial to support the efficacy of colchicine to treat acute gout flares. These trials are described briefly below.

Study MPC-004-06-001 was a randomized, double-blind, placebo-controlled, multi-center, Phase 3 clinical trial designed to evaluate the efficacy and safety of colchicine in subjects diagnosed with an acute gout flare. The primary objective of this study was to demonstrate the efficacy of colchicine in an acute gout flare based on a 50% reduction of baseline pain at 24 hours. Secondary objectives were to compare the low-dose and standard-dose colchicine groups with respect to pain, time to response and complete pain relief, interference with sleep, and signs and symptoms of inflammation. The primary efficacy comparison was defined as the proportion of responders in the standard-dose colchicine group versus the placebo group. A responder was defined as a patient that achieved at least a 50 % reduction in baseline pain score and did not take rescue medication. A Pearson chi-square test was utilized to assess treatment group differences.

Ahern et al., 1987, randomized 40 men and 3 women with a proven gout attack to either oral colchicine or a matching placebo. Pain was measured using a visual analog scale (VAS). A composite clinical score was also determined using pain, tenderness on palpation, swelling, and redness measured on a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). Assessments **occurred every 6 hours for 48 hours. Data was analyzed using either a student's** *t* test or a chi-square test. Note, this article lacked detailed information regarding the design and conduct of the study, and there were no associated data.

1.3 Statistical Issues and Findings

While the Applicant defined the primary efficacy comparison as the proportion of responders in the standard dose group versus placebo, they have proposed a secondary dose, low-dose colchicine, in the label. Typically any secondary doses that are allowed on the label should incorporate some type of adjustment for multiple comparisons to avoid falsely declaring an ineffective dose effective. The Applicant claims the low-dose is as safe and effective as the standard dose but is better tolerated, i.e. fewer colchicine related adverse events such as vomiting and diarrhea. The statistical comparison of the low-dose group to the standard-dose group was

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The published study, Ahern et al., did not have any data associated with it.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Applicant conducted one pivotal Phase 3 trial to evaluate the efficacy of colchicine in treating patients confirmed to have an acute gout flare. They also are relying on one published trial to support the study. Since there were no data associated with this article, it will be summarized and discussed following my review of the pivotal study in section 3.1.5.

3.1.1 Study Design and Endpoints

While 575 patients were randomized to low-dose or standard-dose colchicine or placebo, only 185 patients had a qualifying gout flare and received treatment. To determine if a flare qualified, patients were to call the Gout Flare Call Center within 12 hours of an attack. Patients confirmed to have an attack were to self-initiate treatment that was dispensed at randomization. To maintain blinding, the medication was dispensed as blister packs containing eight capsules of either 0.6 mg colchicine or placebo. All treatment groups were to take two tablets initially followed by one tablet every hour for six hours. Low-dose colchicine was administered orally as 1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) after 1 hour. The standard-dose was administered as 1.2 mg followed by 0.6 mg every hour for 6 hours. Patients were to record dosing, rescue medication use, pain, and adverse events prior to treatment and at 1, 2, 3, 4, 5, 6, 7, 8, 16, 24, 32, 40, 48, 56, 64, and 72 hours after treatment.

The primary measure of efficacy was defined as response to treatment in the target joint 24 hours after the first dose. Response to treatment was defined as not using rescue medication and at least a 50% reduction from the baseline pain score at 24 hours post-treatment. The target joint was identified prior to unblinding as the joint with the highest baseline pain score. Pain was measured on an 11-point scale with 0 denoting no pain and 10 denoting the worst possible pain. Patients who used rescue medication, discontinued, or did not achieve at least a 50% reduction in pain scores at 24-hours were considered treatment failures. Secondary measures included, but were not limited to, magnitude of pain reduction, time to response, time to complete pain reduction (90% reduction), and time to use of rescue medication.

Based on a 40% response rate in the standard-dose colchicine group and a 10% response rate in the placebo group, the Applicant determined that 141 patients or 47 per treatment arm would be sufficient to detect a significant difference in response rates with 90% power. Estimating that only 50% of randomized patients would have a qualifying gout flare, 390 patients or 130 per treatment were to be randomized.

3.1.2 Patient Disposition and Demographics

The ITT population consisted of 184 patients and was defined as all randomized patients that had a qualifying flare, were instructed to start treatment, and took study drug. One patient randomized to the placebo arm had a qualifying flare but did not contact the Call Center prior to

starting treatment and therefore was not included in the ITT population. Descriptive information regarding demographic characteristics was summarized based on treatment assignment in Table 1.

Table 1. Patient demographics and baseline characteristics

Characteristic	Placebo	Low-dose	Standard-dose	total
Patients	58	74	52	184
Age in years				
Mean (SD)	52 (11)	52 (12)	52 (10)	52 (11)
Median	52	51	52	52
[range]	[24, 78]	[32, 77]	[33, 76]	[24, 78]
Gender (%)				
Male	54 (93)	72 (97)	49 (94)	175 (95)
Female	4 (7)	2 (3)	3 (6)	9 (5)
Race (%)				
Caucasian	46 (79)	66 (89)	40 (77)	152 (83)
Black	11 (19)	4 (6)	10 (19)	25 (13)
Asian	1 (2)	1 (1)	0 (0)	2 (1)
Hispanic	0 (0)	2 (3)	1 (2)	3 (2)
Other	0 (0)	1 (1)	1 (2)	2 (1)
Baseline Pain Score				
Mean (SD)	6.8 (1.4)	6.9 (1.7)	6.9 (1.6)	6.9 (1.6)

Source: Reviewer

Seven patients discontinued either due to lack of efficacy, lost to follow-up, or withdrew consent as shown in Table 2.

Table 2. Patient Disposition

Reason for Discontinuation	Placebo	Low-dose	Standard-dose	total
Lack of efficacy	1	1	0	2
Lost to follow-up	1	1	1	3
Withdrew consent	1	0	1	2

Source: Reviewer

3.1.3 Statistical Methodologies

The primary efficacy comparison was defined as the proportion of responders in the placebo group versus the standard-dose colchicine group and analyzed using an unstratified Pearson chi-square test. The original protocol indicated the analysis would stratify by site. However, there were several sites that only enrolled one patient, so this was not feasible. Since the Applicant defined a single treatment group comparison as the primary efficacy endpoint, no adjustments for multiplicity were incorporated into the analysis. Secondary efficacy analyses included a comparison of the low-dose colchicine versus the placebo group and a cumulative responder's analysis of placebo, low-dose, and standard dose colchicine.

Analyses of secondary endpoints were conducted to provide additional support of efficacy. The endpoints examined in my review are the use of rescue medication prior to 24 hours and absolute difference from baseline pain scores at 24 hours as the Applicant included these endpoints in the label. These endpoints were compared using ANOVA procedures.

Patients that failed to return a diary or record a 24-hour pain score used the 24-hour score recorded by the Gout Flare Call Center. If the 24-hour assessment was not available from the call center or the patient dairy, the next later score within 8 hours was used. If there is not a pain score within 24-32 hours, LOCF was used. For the primary analysis, a patient that discontinued or was lost to follow-up prior to 24-hours was considered a treatment failure.

3.1.4 Results

Primary Efficacy Endpoint

Since response was defined as a 50% reduction from the baseline pain score in the target joint, I examined both baseline pain and the target joint for differences between treatment groups. The overall mean baseline pain scores were 6.8, 6.9, and 6.9 for placebo, 1.8 mg, and 4.8 mg colchicine, respectively. These values were not significantly different using standard ANOVA methods. The distribution of target joints amongst the three treatment groups is shown in Table 3 and the baseline pain score by joint is shown in Table 4. Again, using ANOVA methods, the differences in baseline pain scores were not explained by either treatment assignment or target joint selection.

Table 3. Distribution of selected target joints

Target Joint n (%)	Placebo N=58	Low-dose N=74	Standard-dose N=52	Total N=184
Toe	27 (47)	29 (39)	14 (27)	70 (38)
Wrist	1 (2)	2 (3)	2 (4)	5 (3)
Elbow	0 (0)	4 (5)	2 (4)	6 (3)
Hand	2 (3)	1 (1)	2 (4)	5 (3)
Knee	10 (17)	8 (11)	9 (17)	27 (14)
Ankle	11 (19)	15 (20)	14 (27)	40 (22)
Instep	3 (5)	5 (7)	7 (13)	15 (8)
Other	4 (7)	10 (14)	2 (4)	16 (9)

Source: Reviewer

Table 4. Mean baseline pain score by joint

Target Joint	n	mean	stdev	min	max
Toe	70	6.6	1.7	4.0	10.0
Wrist	5	7.8	1.5	6.0	10.0
Elbow	6	6.5	1.5	4.0	8.0
Hand	5	6.8	0.8	6.0	8.0
Knee	27	7.5	1.7	5.0	10.0
Ankle	40	6.8	1.4	4.0	10.0
Instep	15	7.1	1.2	5.0	9.0
Other	16	6.6	1.7	4.0	10.0

Source: Reviewer

The Applicant's primary analysis used LOCF for missing pain scores in eight patients. Although only two of these patients were classified as responders, one placebo and one standard-dose colchicine patient, for completeness, I examined the impact of LOCF on the primary analysis. I repeated this analysis using BOCF for all missing data. Further, I used BOCF for active treatment patients and LOCF for placebo patients (BOCF/LOCF) as shown in Table 4. Only the BOCF/LOCF method resulted in borderline significance, p-value=0.06. I do not consider this lack of significance sufficient evidence to contradict the Applicant's conclusion regarding the effectiveness of colchicine.

Table 4. Results of primary analysis

Imputation Method	Number of Responders, n (%)		p-value
	Placebo, N=58	Standard-dose, N=52	
LOCF	9 (16)	17 (33)	0.03
BOCF	8 (14)	16 (31)	0.03
BOCF/LOCF*	9 (16)	16 (31)	0.06

* BOCF for colchicine patients with missing data and LOCF for placebo
Source: Reviewer

In the Applicant's primary analysis, some assumptions regarding the use of rescue medication were made for three patients. For these patients, one patient in the placebo arm and two in the standard-dose arm, the use of rescue medication was questionable so the Applicant made the assumption that they used rescue medication and they were considered non-responders. While appropriate, this is not the most conservative analysis. I repeated this analysis by considering the placebo patient a responder and the active treatment patients as non-responders. For exploratory purposes, I also repeated this analysis by simply removing the patients. Results are shown in Table 5.

Table 5. Sensitivity analysis

Analysis	Number of Responders (%)		p-value
	Placebo, N=58	Standard-dose, N=52	
w/assumptions	9 (16%)	17 (33%)	0.03
w/o assumptions	10 (17%)	19 (37%)	0.02
worst case*	10 (17%)	17 (33%)	0.06
Removed (n=57, n=50)	9 (16%)	17 (34%)	0.03

*Colchicine patients used rescue meds, placebo patients did not.
Source: Reviewer

In the most conservative analysis, the result still yielded a numerically higher proportion of responders in the colchicine group; however, the results did not reach statistical significance at the 0.05 level. However, in all other cases the comparisons were significant. Again, I conclude this is not sufficient evidence to change the Applicant's conclusion regarding the effectiveness of colchicine.

Note, there was one placebo patient that the Applicant listed as "not a gout flare (bursitis)". Since this patient was a responder and patient in the placebo arm, I did not make any corrections to the analysis.

Low-dose colchicine. The primary analysis was repeated comparing the low-dose colchicine group to placebo, Table 6. This analysis was also conducted using different imputation methods, as done with the standard-dose. All analyses resulted in a significant difference regardless of the imputation method utilized.

Table 6. Comparison of 1.8 mg colchicine

Imputation Method	Number of Responders (%)		p-value
	Placebo, N=58	Low-dose, N=74	
LOCF	9 (16)	28 (38)	0.005
BOCF	8 (14)	28 (38)	0.002
BOCF/LOCF*	9 (16)	28 (38)	0.005

* BOCF for colchicine patients with missing data and LOCF for placebo
Source: Reviewer

It needs to be noted that while the Applicant listed the primary efficacy comparison as the standard-dose colchicine versus placebo, the proposed label recommends the low-dose. For ease of comparison, the proportions of responders for both comparisons are shown in Table 7.

Table 7. Comparisons for proportion of responders.

Statistic	Placebo	Low-dose	Standard-dose
Number of responders, n (%)	9 (16)	28 (38)	17 (33)
p-value	-	0.005	0.03

Source: Reviewer

Claims derived from secondary endpoints are generally not included in the label, but when they are, some type of multicity adjustment is required. In this case, the multiplicity adjustment is to avoid falsely declaring an ineffective dose effective. Post-hoc, I examined three multiple comparison methods; Bonferroni adjustment, the Hochberg test, and the Intersection-Union test. The Bonferroni adjustment is a single step procedure where the overall alpha is divided by the number of comparisons made. The Hochberg test is stepwise procedure where the first dose is tested and if significant, the second dose is tested. The Intersection-Union test requires both comparisons to be significant. As shown in Table 8, each method resulted in a significant treatment effect for the low dose group. The Bonferroni method did not yield a statistically significant treatment effect for the standard-dose group.

Table 8. Post-hoc multiplicity adjustments

		Significant Treatment Effect, yes/no Adjustment Method (alpha)		
Comparison	p-value	Bonferoni (0.025)	Hochberg (0.05)	Intersection-Union (0.05)
Low-dose	0.005	yes	yes	yes
Standard-dose	0.03	no	yes	yes

Source: Reviewer

Note, there was one placebo patient that the Applicant listed as "not a gout flare (bursitis)". Since this patient was a responder and patient in the placebo arm, I did not make any corrections to the analysis.

Secondary Efficacy Endpoints

Change in pain scores at 24 hours: As further supportive evidence, the change in pain scores at 24 hours was compared using ANOVA procedures. Change was determined by subtracting the pain score at 24 hours from the baseline pain score for each patient. Results are shown in Table 9. The change in pain scores was significantly different from the placebo group for both doses of colchicine.

Table 9. Mean PI scores at baseline, 24 hours, and difference

Mean Pain Score** (SD)	Placebo	Low-dose	Standard-dose
at baseline	6.8 (1.4)	6.9 (1.7)	6.9 (1.6)
at 24 hours	6.2 (2.7)	4.7 (3.2)	4.9 (3.0)
difference	-0.7 (2.8)	-2.2 (3.5)*	-2.0 (2.9)*

*p-value < 0.05
**LOCF used for missing data
Source: Reviewer

Use of rescue medication: The comparison of patients using rescue medication prior to the 24-hour pain assessment is shown in Table 10. Since the Applicant made assumptions regarding the use of rescue medication for three patients (assumed they used rescue medication), this analysis was repeated without these assumptions. Regardless of the assumptions made, the comparison of the low-dose colchicine group to placebo was significantly different while the standard-dose versus placebo was not.

Table 10. Use of rescue medication at 24 hours

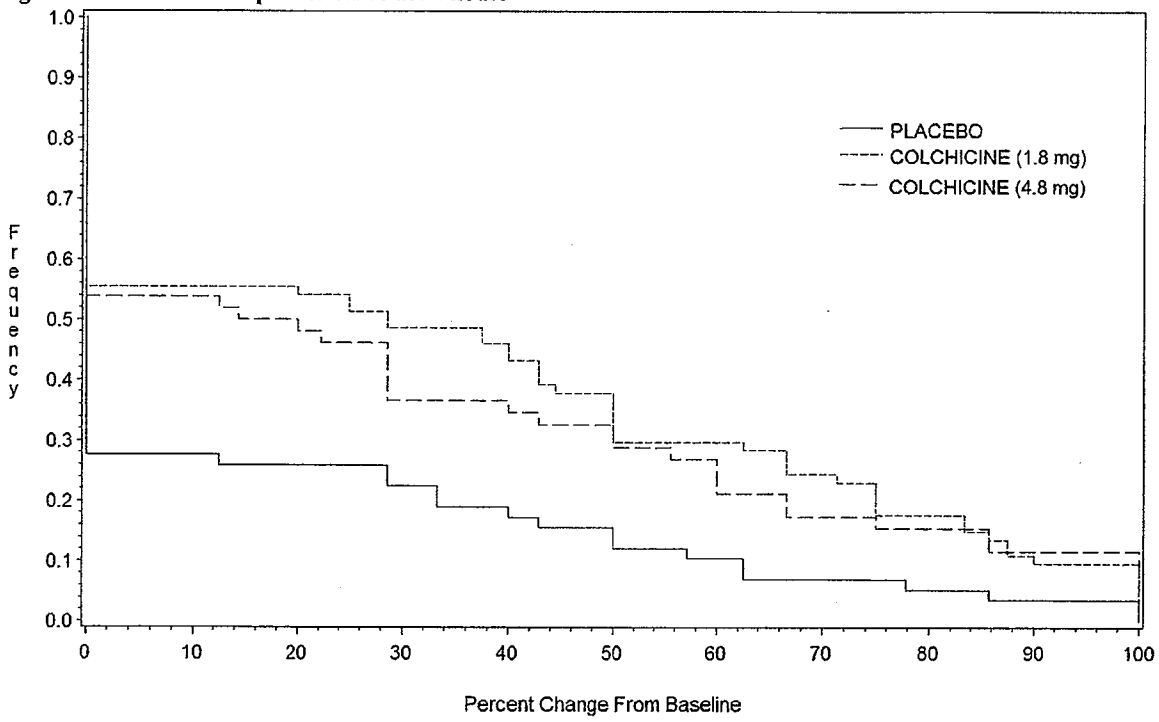
	Treatment		
Use of Rescue Medication, n (%)	Placebo N=58	Low-dose N=74	Standard-dose N=52
Assumptions	29 (50)	23 (31)*	18 (35)
No assumptions	28 (48)	23 (31)*	16 (31)

* p-value < 0.05.
Source: Reviewer

Cumulative Responder Curve: The efficacy of colchicine was further examined by looking at a cumulative responder curve at 24 hours. A cumulative distribution of the proportion of patients obtaining an improvement in baseline scores from 0 to 100% was created and graphed. The Applicant's curve considered 8 placebo patients, 6 low-dose patients, and 4 standard-dose patients that used rescue medication prior to 24 hours as responders since they had an improvement in baseline scores prior to taking rescue medication. In Figure 1, I reconstructed this graph considering these patients as non-responders. Regardless of how these patients were treated, the colchicine treatment groups had more responders than placebo regardless of the

percent improvement. Additionally in most cases, low-dose colchicine appeared to have a higher percentage of responders than standard-dose colchicine.

Figure 1. Cumulative responder curve at 24 hours



Source: Reviewer

3.1.5 Division of Scientific Investigations Report

The Division of Scientific Investigations (DSI) identified discrepancies in the transfer of data from patient diaries to the NDA for three patients regarding their use of rescue medication. Subject 1018-1007 was listed as taking rescue medication at 24 hours in the NDA but the patient diary did not indicate rescue medication use. For subjects 1018-1002 and 1061-1010, the patient's diaries indicated rescue medication use at 24 hours, but the NDA did not reflect this. For these two patients, the dairies indicated rescue medication use at earlier times.

The electronic dataset I used to confirm the Applicant's analyses indicated that these patients used rescue medication before 24 hours, and they were considered treatment failures in my analyses. The electronic dataset submitted by the Applicant indicated subjects 1018-1002, 1018-1007, and 1061-1010 used rescue medication at 6, 18, and 4 hours, respectively.

3.1.6 Supportive Literature

The Applicant identified one randomized, placebo controlled study in the literature, Ahern et al. In a blinded, placebo-controlled trial, 43 in-house patients, 40 men and 3 women, were randomized to either to oral colchicine or a matching placebo. There were no differences noted

in baseline characteristics or demographics. Gout was confirmed by joint aspiration and confirmation of crystallization. The initial dose of colchicine was 1.0 mg followed by 0.5 mg every two hours until complete response or toxicity (vomiting or diarrhea). Clinical endpoints included pain measured on a 100-point visual analog scale and a composite clinical score using pain, tenderness on palpation, swelling, redness measured on a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). These endpoints were assessed every 6 hours for 48 hours. Data was analyzed using either a student's *t* test or a chi-square test. The author concluded that while both groups improved with time, patients treated with colchicine improved sooner than patients in the placebo group.

While the clinical endpoints and analysis seem appropriate, I could not replicate the analysis as there was no data provided. Also, there was not sufficient detail regarding the design and conduct of the study for a thorough review. I did note one concern regarding the ability of the study to maintain blinding. It was reported that all colchicine patients experienced vomiting and/or diarrhea. Since the only sign of toxicity in the placebo group was nausea in five patients, the ability to maintain blinding is questionable. An awareness of treatment assignment could have introduced bias from either the patient or the person performing the clinical assessments.

3.2 Evaluation of Safety

The primary medical officer, Dr. Rosemarie Neuner, reviewed the safety data for this NDA.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The primary efficacy endpoint, proportion of responders, was examined in males and females, patients older than 65 years and those 65 or younger, and in Caucasians and non-Caucasians, Table 10. Since the majority of the patients enrolled were Caucasian males less than 65 years old, these data are simply summarized and reported in Table 10. While there does not appear to be a treatment effect in female and non-Caucasian patients, the sample size is relatively small and no statistical comparisons were conducted. This distribution is consistent with the disease population.

Table 11. Subgroup analysis for gender, age, and race

Subgroup		Proportion of Responders, n/N (%)		
		Placebo	Low-dose	Standard-dose
Gender	Male	7/54 (13)	27/72 (38)	16/49 (33)
	Female	2/4 (50)	1/2 (50)	1/3 (33)
Age	< 65	7/52 (13)	23/61 (38)	13/45 (29)
	≥ 65	2/6 (33)	5/13 (38)	4/7 (57)
Race	Caucasian	6/46 (13)	26/66 (39)	15/40 (38)
	Non-Caucasian	3/12 (25)	2/8 (25)	2/12 (17)

Source: Reviewer

4.2 Other Special/Subgroup Populations

The reviewing medical officer was concerned about the use of certain concomitant medications and if their use could have inflated the observed treatment effect. The total number of patients that used allopurinol, colchicine, paracetamol, prednisone, and NSAIDS during the study is presented overall and by treatment assignment in Table 12.

Table 12. Use of concomitant medication during the study.

Medication	Number of patients (%)			
	Placebo, N=58	Low-dose N=74	Standard-dose, N=52	Total
Allopurinol	14 (24)	29 (39)	10 (19)	53 (29)
Colchicine	3 (5)	8 (11)	3 (6)	14 (8)
Indometacin	21(36)	18 (24)	9 (17)	48 (26)
Ibuprofen	11 (19)	11 (15)	7 (13)	29 (16)
Naproxen	5 (9)	9 (12)	6 (12)	20 (11)
Aspirin	6 (10)	7 (9)	4 (8)	17 (9)
Paracetamol	12 (21)	10 (14)	5 (10)	27 (15)
Corticosteroids	14 (24)	6 (8)	4 (8)	24 (12)

Source: Reviewer

For each of the above medications, I performed an exploratory subgroup analyses on patients using medication and patients not using medication. The results for each medication are shown in Table 13 and discussed following the table.

Table 13. Impact of concomitant medication on response to treatment.

Medication	Used	Proportion of Responders (n/N)		
		Placebo	Low-dose	Standard-dose
Allopurinol	No	5/44	18/45*	13/42*
	Yes	3/14	10/29	3/10
Colchicine	No	8/55	27/66*	16/49*
	Yes	0/3	1/8	0/3
Indometacin	No	7/37	24/56*	15/43
	Yes	1/21	4/18	1/9
Ibuprofen	No	8/47	23/63*	15/44
	Yes	0/11	5/11*	1/8
Naproxen	No	8/53	26/65*	16/46*
	Yes	0/5	2/9	0/6
Aspirin	No	7/52	24/67*	15/48*
	Yes	1/6	4/7	1/4
Paracetamol	No	7/46	28/64*	14/47
	Yes	1/12	0/10	2/5
Corticosteroids	No	8/44	28/68*	16/48
	Yes	0/14	0/6	0/4

*significantly different from placebo, p-value < 0.05.
Source: Reviewer

Allopurinol: The protocol did not restrict the use of allopurinol during the study but the reviewing Medical Officer indicated that if a patient was using allopurinol, they should remain

on allopurinol for the duration of the study. Since there was a significant treatment effect for the subgroup of patients that did not use allopurinol, I conclude that the use of allopurinol by some patients did not have a positive influence on the outcome of the study.

Colchicine: According to the protocol, short term use of colchicine was not a basis for exclusion. However, such use should not have occurred within 30 days prior to the start of the study. Thirty-eight patients reported using colchicine prior to the study but only 14 patients reported taking it during the study. In my opinion, since this was a clinical trial to evaluate colchicine for the treatment of acute gout flares, the use of additional colchicine may have inflated the observed treatment effect. Regardless, those patients that did take additional colchicine did not have a positive impact on the overall treatment effect as there was only one responder in those 14 patients.

NSAIDS: While there were several patients that reported using indometacin, ibuprofen, naproxen, or aspirin, their outcome did not appear to have a positive impact on the treatment effect observed. In most cases, there was a still a significant treatment effect for the subgroup of patients that did not use NSAIDS. However, in the subgroup of patients that did not use indometacin or ibuprofen, there was not a significant treatment effect observed (p-value > 0.05) with the standard-dose comparison, p-value. This result is not unexpected given the overall p-value for the standard dose comparison was 0.03. Also, there were very few patients that used these medications and within those patients were very few, if any, responders.

Paracetamol: Even though the protocol did not specify any restriction on the use of paracetamol during the study, its use did not influence the overall significant treatment effect observed with the low-dose group. However, there was no longer a significant treatment effect for the standard dose comparison in the subgroup of patients that did not use paracetamol. Again, this not unexpected given the overall p-value for the standard dose comparison was 0.03.Further, there were very few patients that used paracetamol and within those patients that did, there were very few, if any, responders.

Corticosteroids: According to the protocol, systemic corticosteroids were not to be used 30 days prior to initiating therapy with the study drug. While 32 patients reported using corticosteroids (15 placebo, 10 low-dose, 7 standard-dose) only 24 patients reported using prednisone, methylprednisolone, or methylprednisolone acetate during the study. Regardless, there was not a positive impact on the study outcome as there were no responders in the patients that used corticosteroids during the study.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I conclude there is sufficient statistical evidence to support the effectiveness of colchicine to treat acute gout flares. This evidence is derived from my review of a single randomized, double-blind, placebo-controlled clinical trial conducted by the Applicant. The primary efficacy endpoint was statistically significant. Regardless of the assumption made regarding use of rescue medication or imputation method, the treatment effect observed did not change in either magnitude or direction. One statistical concern noted was the inclusion of a secondary dose in

the label even though the Applicant did not make any adjustments for multiple comparisons. However, through discussions with the clinical review team and several post-hoc analyses, my concerns were alleviated.

The Applicant is also relying on one published clinical trial to support efficacy. However, there was no data or detailed information regarding the design and conduct of the study for me to conduct a thorough review. I did note one concern regarding the ability of the study to maintain blinding as all colchicine treated patients experienced diarrhea and/or vomiting whereas these events did not occur in the placebo group.

5.2 Conclusions and Recommendations

The Applicant submitted NDA 22-351 to provide evidence of efficacy and safety of colchicine to treat pain associated with acute gout flares. My review of the associated clinical trial supports the Applicant's claim. However, efficacy was also to be supported by a published clinical trial. While the clinical endpoints and statistical analyses seem to indicate that colchicine reduces a patient's pain faster than placebo alone, I was not able to perform as thorough review of this trial. Hence, my conclusion that colchicine is effective in treating pain associated with an acute gout flare is based on the review of one adequate and well controlled trial.

5.3 Label Review

Although the primary efficacy comparison was the proportion of responders in the standard-dose colchicine group versus placebo, the Applicant has proposed low-dose colchicine (1.8 mg) in the label. The comparison of low-dose colchicine to placebo was listed as a secondary comparison in the statistical analysis plan and no multiplicity adjustments were incorporated. However based on discussions with the clinical review team, my post-hoc analyses, and the safety profile, I recommend inclusion of low-dose colchicine in the label.

The following was also reviewed from the Clinical Studies portion of the label. My comments follow the Applicant's wording and are italicized for convenience.

_____ b(4)

_____

_____

The above statements are consistent with the clinical trial.

_____ b(4)

b(4)

This information is consistent with the study report and my review. Note some of this information is included in the table below and need not be repeated.

b(4)

The primary efficacy endpoint was the proportion of responders ——— *therefore, I recommend deletion of the* ——— *Further, all numbers should be* ——— b(4)

b(4)

The inclusion of this figure in addition to the results of primary analysis will need to be discussed amongst the review team.

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

/s/

David Petullo
6/19/2009 04:15:13 PM
BIOMETRICS

Thomas Permutt
6/19/2009 04:28:40 PM
BIOMETRICS
I concur. Dionne Price, team leader, would also have been asked to concur, but she is on leave.