CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-353

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation
CLINICAL STUDIES

NDA:	22-353
Name of drug:	Colchicine 0.6 mg tablets
Indication:	Prophylaxis of gout flares
Applicant:	Mutual Pharmaceutical Company, Inc.
Date(s):	Submitted: November 25, 2008
	PDUFA: September 25, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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	Thomas Permutt, Ph.D.
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Keywords:	NDA review

1 BACKGROUND

Mutual Pharmaceutical Company, Inc. is seeking approval of colchicine 0.6 mg for the prophylaxis of gout flares. Colchicine was approved to treat acute gout flares under NDA 22-351 on July 30, 2009 and familial Mediterranean fever (FMF) under NDA 22-352 on July 29, 2009. The development program for colchicine was discussed at a pre-IND meeting on July 31, 2006 and a pre-NDA meeting on February 4, 2008. Discussions focused on the ability to rely solely on published literature for approval of colchicine. While the Agency agreed that this might be appropriate, it was also suggested that the Applicant conduct at least one controlled trial for acute gout. This trial was conducted by the Applicant and submitted under a separate NDA (22-351) for treatment of acute gout flares. Colchicine for the treatment of FMF was submitted, reviewed, and approved based on published literature. The Applicant also submitted a Citizen's Petition requesting that FDA require any applicant seeking approval of colchicine submit data from clinical, safety, and pharmacokinetic studies in order to satisfy the current standards for approval.

2 REVIEW

The Applicant has identified two published trials to support the approval of colchicine for the prevention of gout flares. These studies are randomized, placebo-controlled studies that evaluate colchicine in preventing gout flares. These studies will be the focus of my review.

2.1 PAULUS ET AL., 1974

In this article, male patients confirmed to have gout were enrolled in a six month randomized, double-blind, placebo-controlled study at sites in Los Angeles, CA and Kansas City, KS. A diagnosis of gout was based on a serum urate level greater than 7.5 mg/100mL and a history of typical acute arthritis that responded promptly to intensive colchicine therapy. Fifty-two patients were randomized to probenecid 500 mg or probenecid 500 mg + colchicine 0.5 mg. Probenecid is a drug that decreases serum urate levels by increasing uric acid excretion in the urine. The two treatments were identical in appearance and were administered orally three times a day. In Los Angeles, all urate lowering agents were discontinued two weeks prior to therapy while in Kansas City patients were stabilized on probenecid two weeks prior to study initiation. A patient was required to visit the study site monthly and report the number of attacks that occurred during the past month. Only attacks judged by the investigator as moderate or severe were included in the analysis. Attacks were rated as moderate or severe by an investigator if the patient's description included definite pain accompanied with swelling and tenderness in the involved joint. If an investigator observed an attack at a patient visit, it was judged based on temperature, tenderness, swelling, and the redness of

involved joint. Nineteen of the 58 attacks reported were actually observed by the investigators.

Prior to unblinding the data, the authors identified patients that clearly showed and maintained a reduction in serum uric acid levels and only included data from these patients in their statistical analyses. Table 1 was duplicated from the publication. There were no reported differences in baseline characteristics

Table 1. Characteristics of Subjects

	Colchicine-Probenecid	Placebo-Probenecid
Number enrolled	29	23
Number analyzed	20	18
Age (years) mean*	53	52
range	34-77	43-73
Number with Tophi*	3	4
Number with crystals in synovial fluid*	6	7
Duration of gout (years) (mean = SE)*	10.5 ± 2.3	10.5 ± 1.8
Attacks of acute gout during 12 months prior to study (by history) mean ± SE*	4.2 ± 1.1†	3.2 ± 0.4
Number treated with uric acid lowering drug for at least 12 months prior to study*	12	12
Months of therapy*	109	94
Serum urate (mg/100 ml ± SE) before study*	8.4 ± 0.4†	9.2 ± 0.6

*Data for patients included in the analysis
†$P > 0.2$ (no significant difference)

Source: Table 1 from Paulus, et al., 1974

In Table 2 of the article, the authors summarized serum urate levels before and after the study, the mean number of attacks per month per patient, and the number of patients with adverse events for each treatment group. The analyses were conducted on 38 patients. The authors indicated that serum urate levels before and after were statistically different within each group. The relevance of this comparison is questionable since the analysis only included patients that showed and maintained a lowered serum urate level. Regardless, on average, for patients that maintained a reduced serum urate level, there were 0.48 flares per patient per month in the probenecid only group and 0.19 in the probenecid + colchicine group. In the table, the authors included two asterisks, one for the mean number of attacks per patient per month for each treatment group. I assumed the authors' intent was to show that the rate of gout attacks in the colchicine + probenecid group was less than the rate of attacks in the probenecid only group. As expected, the authors reported more adverse events in the colchicine + probenecid group compared to probenecid alone, 15/20 versus 8/18. However, these proportions were not significantly different using a chi-square test. Table 2 was duplicated from the article.

Table 2. Effects of Therapy

Treatment Group	Serum Urate mg/100 ml ± SE		Attacks of Gouty Arthritis per Patient per Month ± SE	No. of Patients with (Drug-related) Side Effects
	Before	After		
Colchicine-Probenecid	8.4 ± 0.4	6.3 ± 0.4†	0.19 ± 0.05*	15
Placebo-Probenecid	9.2 ± 0.6	6.2 ± 0.4†	0.48 ± 0.12*	8‡

*$P < 0.05$
†$P < 0.01$
‡$0.1 > P > 0.05$ (chi square analysis)

Source: Table 2 from Paulus, et al., 1974

The authors conclude that treatment with 1.5 mg of colchicine (0.5 mg 3 x daily) decreases the frequency of acute gout attacks in patients whose hyperuricemia has been satisfactorily controlled by probenecid since the analyses excluded patients whose serum uric acid failed. They also state that based on the common occurrence of sides effects attributable to colchicine and its failure to prevent all attacks of gout, physicians should exercise clinical judgment in deciding whom to treat and what dose of colchicine to use.

2.2 BORSTAD ET AL., 2004

The authors described a randomized, placebo-controlled trial in patients confirmed to have gouty arthritis. Prior to colchicine administration all subjects were started on allopurinol 100 mg and were monitored for serum urate levels. Allopurinol is drug used to inhibit the production of uric acid. The dose of allopurinol was increased until a serum urate level less than 6.5 mg/dL was obtained. Subjects were then randomized to receive either placebo or colchicine 0.6 mg orally twice daily. Once daily dosing was utilized for patients with chronic renal insufficiency. Investigators were to maintain a patient on study drug for a minimum of three months. Placebo was not identical in form and treatment compliance was not monitored. Subjects were evaluated at three and six months for evidence of acute gout flares and any evidence of toxicity. Patients were to record length of flares, medications used, and severity of flares using a 100 mm visual analog scale (VAS).

The intent-to-treat population was defined as any patient that was randomized and received treatment. Baseline factors and demographics were compared between treatment groups. To evaluate efficacy, the mean number of flares, proportion of patients with no flares, proportion of patients with more than one flare, mean VAS score per flare, and the average duration of a flare in days were compared between treatment groups using the appropriate statistical methods. Proportions were compared using a Pearson chi-square test, mean number of flares were evaluated using a T-test, and the non-parametric Mann-Whitney test was used to compare mean VAS scores per flare and average length of flares as data was deemed not normally distributed.

While 51 patients were enrolled, only 43 received treatment; 22 in the placebo group and 21 in the colchicine group. The only difference noted between treatment groups for baseline characteristics was the use of diuretics; 57% in the colchicine group versus 27% in the placebo group. However, according to the authors and confirmed by the reviewing medical officer, diuretics are known to elevate serum urate levels and make a patient more prone to gout flares. Table 1 was reproduced from the publication.

Table 1. Baseline demographics and clinical characteristics (n = 43: colchicine = 21, placebo = 22).

Demographic/Characteristic	Colchicine	Placebo	p
Mean age, yrs	63.5	62.5	0.798
Male, %	81	91	0.412
Caucasian race, %	67	73	0.665
Chronic renal insufficiency, %	14	9	0.664
Hypertension, %	90	77	0.412
Hypothyroidism, %	0.05	0.05	1.000
Coronary artery disease, %	29	27	1.000
Tophi, %	62	64	0.907
Alcohol use, %	33	18	0.255
Drugs affecting serum urate levels, %	38	55	0.364
Diuretic use at baseline, %	57	27	0.047
Flares during prior year (mean number)	2.48	2.09	0.343

Source: Table 1 from Borstad, et al., 2004

In this trial, there were 77 acute gouts flares; 12 in the colchicine group and 65 in the placebo group. Flares occurred in 33% of the colchicine subjects and 77% of the placebo subjects. Multiple gout flares occurred in 14% of colchicine subjects and 63% of the placebo subjects. All comparisons resulted in significantly less flares for colchicine treated patients versus placebo. Figured 1 was duplicated from the published article.

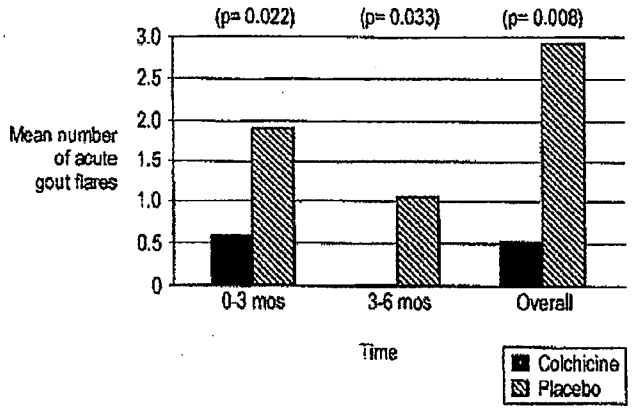

Figure 1. Mean number of acute gout flares at the 0–3 and 3–6 month time periods, and overall (n = 43: colchicine = 21, placebo = 22).

Source: Figure 1 from Borstad, et al., 2004

As with the Paulus et al. study, there were more cases of adverse events (diarrhea) in the colchicine group versus the placebo, 38% and 5%, respectively.

The authors conclude that colchicine in combination with allopurinol reduces the mean number of flares, decreases the likelihood of having one or multiple flares, and decreases the severity of flares. The authors reported that while only three months of treatment was required, there was a benefit for those patients that continued treatment for six months.

3 CONCLUSION

The following were concerns identified in the Paulus et al. publication.

1. I had concerns regarding the use of urate lowering agents in Kansas City versus Los Angeles. At sites in Los Angeles, all urate lowering drugs were removed prior to starting the study while at sites in Kansas City patients were stabilized on probenecid prior to colchicine administration. Since there were no data provided, I was not able to examine the possible effect of this variation.

2. The authors selected only patients that showed and maintained a reduction in serum urate levels but did not specify the criteria used to classify a reduction in serum urate levels. Again since there were no data provided on the excluded patients, it is not clear how the results would have been impacted by an intent-to-treat analysis.

3. A Student's t-test is an appropriate method to compare means. I assumed that the overall mean was calculated from the mean number of flares per patient. The basis for my assumption was the authors' statement that results were calculated from the number of attacks of gout per month of therapy for each patient. However without data, I could not verify the accuracy of my assumption. In addition, it was not clear if the authors' analysis accounted for patients that did not complete the study nor was the cause of withdrawal explained for every patient that withdrew.

4. There could have been discrepancies in patient reported flares versus investigator observed flares since patient described flares and investigator observed flares were evaluated differently. The impact of this on the analyses could not be determined.

The following are concerns identified in the Borstad et al. publication.

1. Blinding may have been compromised as colchicine tablets and placebo tablets looked different. An awareness of treatment assignment could introduce observer bias and possible result in an inflated treatment effect.

2. While the t-test is an appropriate statistical method for comparing group means, it was unclear if the analyses accounted for patients having multiple flares. In addition, the authors provided a table that specified that 14% of patients withdrew in the colchicine arm compared to 18% in the placebo arm. It was not clear if the authors' analysis accounted for patient withdrawal.

In conclusion, while the results from both studies seem to indicate that prophylactic use of colchicine in combination with a serum urate lowering drug reduces the occurrence of acute gout flares, I am unable to confirm the Authors' conclusions. There were shortcomings in the studies which raised concerns regarding the design, conduct, and statistical analyses of the data. Further, these studies appear to have been conducted for research purposes and were not subject to the rigor required for confirmatory studies submitted for regulatory review. With inclusion of the data and/or more details regarding the analysis, my concerns may have been alleviated. However because of the lack of needed information, I am unable to conclude that the articles have provided statistical evidence of efficacy.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22353	ORIG 1		COLCHICINE TABLETS USP 0.6MG

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/s/

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08/11/2009

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STATISTICS FILING CHECKLIST FOR NDA 22-353

NDA Number: 22-353 **Applicant: Mutual Pharmaceutical, Inc.** **Stamp Date: November 25 , 2008**

Drug Name: COLSTAT™ (colchicine tablets) **NDA/BLA Type: Standard**

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			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
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			See comment 1 below

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comments:

1. There were no clinical trials conducted by the Applicant to support the efficacy of colchicine for preventing gout flares. All efficacy data was derived from a comprehensive review of published literature.

2. Safety data from Mutual sponsored Phase 1 studies and NDA 22-351(Study MPC-004-06-001) were submitted in support of this NDA along with an extensive review of published literature, the FDA and World Health Organization post-marketing safety databases, and labeling for foreign colchicine products

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	

STATISTICS FILING CHECKLIST FOR NDA 22-353

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			See comment 2 above
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

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/s/

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2/6/2009 02:15:15 PM
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