CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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

PRIMARY REVIEW

NDA:	22-352
Name of drug:	Colchicine
Indication:	——————— in patients with familial Mediterranean disease
Applicant:	Mutual Pharmaceutical Company, Inc
Submission Date:	20 June 2008
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
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b(4)

Keywords: NDA review

1 BACKGROUND

Mutual Pharmaceutical Company, Inc proposes colchicine tablets 0.6 mg for the ——— of familial Mediterranean fever (FMF) as well as ——— ——— to FMF. The development program for colchicine was discussed at a pre-IND meeting (31 July 2006) and a pre-NDA meeting (4 February 2008). Discussions during the meetings focused on the needed information to support an indication of treatment and prevention of acute gout flares as well as the information needed for the currently proposed indication. Specifically, the Applicant proposed to rely on published literature for the FMF indication. In addition, orphan drug designation was granted (25 September 2007) for the FMF indication as the prevalence of this auto-inflammatory disease in the United States is low.

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2 REVIEW

Familial Mediterranean fever is characterized by recurrent attacks of fever, abdominal and joint pain, arthralgia, and rash. A secondary complication of FMF is renal amyloidosis. The Applicant states, "Colchicine is currently the only administered treatment for patients and it has been widely used since first described in 1972."

The Applicant identified three randomized, double-blind, and placebo-controlled studies in the literature. These studies will be the subject of this review. In consultation with the clinical team, this review will not focus on the desired indication of ——— ——— since the referenced literature did not include any randomized, controlled trials.

b(4)

2.1 DINARELLO ET AL., 1974

Dinarello et al. employed a crossover study design and randomly assigned 11 patients to sequences of colchicine 0.6 mg and placebo. The sequences utilized were not provided in the article. The article reads, "Although the initial dose was three tablets daily, most patients were maintained on two tablets of colchicine per day." Patients remained on a 28-day course of treatment (colchicine or placebo) unless a patient experienced an attack. Once an attack was experienced, the course was stopped. After recovery, the next course of treatment was begun. If a patient did not experience an attack during the 28 days, the next course was begun. The duration of the study was 11 months. The study was terminated early based on an interim analysis conducted after the first six patients had completed the study.

Table 1: Effect of Colchicine or Placebo on Frequency of Attacks

Drug	Number of courses	Number of attacks
Placebo	60	38
Colchicine	60	7

Source: Adapted from Table 1, Dinarello, et al., 1974

Table 1 has been reproduced from the publication. Although not explicitly stated in the article, I assumed the table was based on available data from all patients at the time of study termination. The authors used a chi-square test to assess the difference in the number of attacks between colchicine and placebo. They concluded that the number of attacks experienced while on colchicine was statistically significantly different from the number of attacks experienced by patients while on placebo.

2.2 GOLDSTEIN AND SCHWABE, 1974

Goldstein and Schwabe employed a crossover design and randomized 15 patients to one of two sequences. Patients randomized to the first sequence received colchicine 0.6 mg three times daily for the first 90 days followed by placebo for 90 days. Patients randomized to the second sequence received placebo for the first 90 days followed by colchicine for 90 days. During the course of the study, five patients were withdrawn from the study for failure to take the medication or meet follow-up requirements. Table 3 was adapted from the publication.

Table 3: Familial Mediterranean Fever Response to Therapy

Patient	Number of attacks on colchicine	Number of attacks on placebo
1	0	11
2	0	7
3	0	5
4	0	4
5	2	10
6	0	4
7	0	5
8	0	0
9	3	5
10	0	8

Source: Adapted from Table 1 in Goldstein and Schwabe, 1974

The authors did not attribute a response to colchicine to Patient 8 since the patient had no attacks while on colchicine or placebo. The authors analyzed the data using a sign test and concluded that there was a statistically significant decrease in attacks during colchicine treatment.

2.3 ZEMER, ET AL., 1974

Similar to the other studies reviewed, a crossover design was used. Twenty-two patients were randomly assigned to one of two sequences whereby patients received colchicine 0.5 mg twice daily (BID) for two months followed by two months of placebo or patients received placebo for the first two months followed by colchicine 0.5 mg BID. Nine of the 22 patients withdrew during the course of the study. The authors analyzed the data at Month 2 and at Month 4. For the analysis of the Month 2 data, the authors used an unpaired t-test treating the data as originating from two independent samples. The authors additionally analyzed the Month 2 data using a Mann-Whitney test as an alternative to the unpaired t-test. For the Month 4 analysis, the authors used a paired t-test since patients received both colchicine and placebo by the end of the study.

The authors concluded that patients receiving colchicine for the first two months experienced fewer attacks than patients receiving placebo for the first two months. Specifically, the 10 patients receiving colchicine experienced a total of 11.5 attacks, and the 5 patients receiving placebo experienced 25.5 attacks. Apparently, the authors classified patients with "equivocal" attacks as having 0.5 of an attack. When evaluating the data from the completed 4-month study, the authors found that the 8 patients randomized to colchicine followed by placebo experienced 9.5 attacks while on colchicine and 42 attacks while on placebo. Similarly, the authors found that the 5 patients randomized to placebo followed by colchicine experienced 8 attacks while on colchicine and 25.5 attacks while on placebo. The data is displayed in Table 4.

Table 4: Attacks Occurring during Four Months

Patient in Group 1 (colchicine, placebo)	Number of attacks on colchicine	Number of attacks on placebo	Completed the Study
1	2.5	6.5	Yes
2	0	6	Yes
3	1	4	Yes
4	1	4	Yes
5	1	10.5	Yes
6	3	2	Yes
7	1	5	Yes
8	0	4	Yes
9	2	2	No
10	0	0	No
Patient in Group 2 (placebo, colchicine)	**Number of attacks on placebo**	**Number of attacks on colchicine**	**Completed the Study**
11	4	4	Yes
12	9	1.5	Yes
13	5.5	1.0	Yes
14	4.5	1.5	Yes
15	2.5	0	Yes
16	6	0	No
17	2.5	0	No
18	5	0	No
19	3	0	No
20	0	0	No

Source: Adapted from Table 1, Zemer et al., 1974

The authors additionally evaluated the mean number of attacks and concluded that the average number of attacks over two months decreased when patients received colchicine compared to placebo (Table 5).

Table 5: mean Number of Attacks (Two–month data)

Month of Study	Mean Number of Attacks		p-value
	Colchicine	Placebo	
First Month	0.70	2.50	<0.01
Second Month	0.45	2.83	<0.01
Both	1.15	5.25	<0.01

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

3 CONCLUSION

A randomized, blinded, placebo-controlled, crossover design was used in each of the studies reported in the reviewed literature articles. In general, crossover studies require fewer patients than parallel group studies. This can be a particularly attractive feature when investigating the efficacy of a treatment for a rare disorder such as FMF. I initially questioned the ability of the studies to maintain the blind as gastrointestinal side effects are known to result from the use of colchicine. An awareness of the treatment assignment could have introduced bias from perceptions of the outcome. However, my concern was alleviated as the outcome of primary interest was the number of attacks, and according to the clinical team, attacks are unmistakable and cannot easily be misconstrued.

In the Dinarello et al. publication, the data from each patient was not provided. Instead, the authors presented the overall findings in terms of the number of attacks during 60 courses of treatment. The chi-square value presented by the authors could have been achieved by treating the data as originating from a two-by-two table assuming independence. Specifically in this scenario, the chi-square test would assume there were 60 independent observations. However, the 60 courses of treatment did not originate from 60 individuals but represented multiple treatment courses for at most 11 patients. Consequently, the use of the chi-square test assuming independence was incorrect. Without benefit of the data from each patient, I was unable to perform an appropriate analysis.

The statistical methods used by Goldstein and Schwabe and Zemer et al. appeared reasonable. In Goldstein and Schwabe, the authors used a sign test which is a nonparametric alternative to a paired t-test. In the Zemer et al. article, the authors used several analysis methods including an unpaired t-test, a Mann-Whitney test (a nonparametric alternative to an unpaired t-test), and a paired t-test. The statistical test used was mandated by whether the analysis was performed on the two or four month data. In both articles, the authors provided the data for each patient allowing me to replicate their results. I additionally conducted a nonparametric analysis on the Month 4 data in the latter publication. For both articles, I found that there was a statistically

significant difference in the number of attacks experienced by patients while on colchicine compared to the period when they received placebo. My conclusion was in agreement with that of the authors.

In summary, Mutual proposes colchicine for the ———————— of familial Mediterranean fever. Two of the reviewed articles have provided evidence of efficacy. Specifically, a significant reduction in the number of acute attacks was experienced by patients when receiving colchicine compared to placebo.

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/s/

Dionne Price
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