CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-351

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-351
Priority or Standard	Standard
Submit Date	September 30, 2008
PDUFA Goal Date	July 30, 2009
Division / Office	Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)/ODEII
Reviewer Name	Rosemarie Neuner, MD, MPH
Review Completion Date	June 25, 2008
Established Name	Colchicine
Trade Name	Colcrys™
Therapeutic Class	Alkaloid
Applicant	Mutual Pharmaceutical Company, Inc.
Formulation	0.6 mg Tablets USP
Dosing Regimen	Total dose: 1.8 mg orally over 1 hour (1.2 mg initially at the first sign of flare with 0.6 mg 1 hour later)
Indication	Treatment of Gout Flares
Intended Population	Adults ≥ 18 years of age with gout

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval for this 505(b)(2) drug application for colchicine for the treatment of gout flares. The data contained in this application is sufficient to support a finding of efficacy and safety for colchicine when administered at a dose of 1.2 mg (2 tablets) at the first sign of gout flare followed by 0.6 mg (1 tablet) one hour later (total dose of 1.8 mg over 1 hour) for the indication of acute gout flare. The overall safety profile of this lower dosing regimen was associated with much less gastrotoxicity than what was has been seen previously with higher dosing regimens of colchicine that have been traditionally used by health care providers to treat this disease.

1.2 Risk Benefit Assessment

The efficacy of colchicine for the treatment of acute gout was demonstrated by a single adequate and well-controlled dose comparison trial in which both a standard-dose (4.8 mg) and low-dose (1.8 mg) regimen of colchicine resulted in similar rates of clinical response as assessed by $\geq$ 50% improvement in target joint pain score at 24 hours post-initiation of colchicine therapy as compared to placebo. Although both dose regimens were comparable in terms of efficacy, the low-dose regimen was better tolerated by subjects. Approximately twice as many patients randomized to the standard dose colchicine treatment group (77%) experienced adverse events as compared to subjects in the low-dose colchicine group (37%) and placebo group (27%) that were mainly gastrointestinal (GI) in nature. Additionally, almost all of the severe adverse events occurred in patients treated with the standard dose regimen of colchicine. These findings are supportive of a dose-response relationship for the GI toxicity and are consistent with the vast amount of historical knowledge of the drug's safety profile. The risk benefit assessment is therefore in favor of the low-dose regimen given colchicine's narrow therapeutic index.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Colchicine has been available in this country for over 70 years as a treatment for acute gout. In view of the extensive experience associated with the use of this drug, its well documented safety profile, and the lack of new safety signals identified during the course of this review of data generated from clinical and pharmacokinetic studies,

postmarketing adverse events, and the worldwide literature, no postmarketing risk management activities should be required for the gout indication.

1.4 Recommendations for Postmarket Requirements and Commitments

Since gout is very rare in children, the Applicant's request for a waiver to conduct studies in children under the Pediatric Equity Act (PREA) (21 USC 355c) was granted. No additional clinical postmarketing requirements and commitments for the gout indication should be required in view of the extensive experience associated with the use of colchicine and its well documented safety profile.

2 Introduction and Regulatory Background

2.1 Product Information

Colchicine, a tricyclic alkaloid, was originally extracted from the autumn crocus (*Colchicum autumnale*). It was originally reported in the first century CE as an effective treatment for gout attacks. Colchicine interacts with beta-tubulin and acts to disrupt microtubules. It is commercially available in this country as 0.5 and 0.6 mg tablets produced by a number of different manufacturers. Mutual Pharmaceuticals wishes to obtain marketing approval for a 0.6 mg tablet of colchicine that will be marketed under the trade name Colcrys™ for the treatment of gout flares in adults $\geq$ 18 years of age when administered as a dose of 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later.

Colchicine's effectiveness as a treatment for gout has been postulated due to its ability to block neutophil-mediated inflammatory responses induced by monosodium urate crystals in synovial fluid by disrupting the function of the neutophils' cytoskeleton and interfering with microtubulin assembly. This results in the prevention of activation, degranulation, and migration of neutrophils to sites of inflammation. New evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex found in neutrophils and monocytes that mediate IL-1β activation.

2.2 Tables of Currently Available Treatments for Proposed Indications

Other treatments currently available for the treatment of acute gout include nonsteroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular injections of corticosteroids, and adrenocorticotropic hormone (ACTH). Although most of the NSAIDs

and systemic and injectable formulations of corticosteroids are approved as treatment for acute gout, ACTH is currently not an approved treatment.

2.3 Availability of Proposed Active Ingredient in the United States

Colchicine has been available for use as a single active ingredient since prior to 1938 in the U.S. It has not been approved by the agency as a single ingredient drug despite its extensive use primarily as both a treatment and prophylactic therapy for gout attacks. Currently, colchicine is marketed by several generic manufacturers as 0.5 mg and 0.6 mg tablets for oral administration as well as in combination with 500 mg of Probenecid for use in the treatment and prevention of gout flares.

2.4 Important Safety Issues With Consideration to Related Drugs

The use of colchicine is limited by its narrow therapeutic window that results in significant gastrointestinal toxicity with acute use. However, gastrointestinal intolerability as well as toxicity in other organ systems can be minimized by using lower doses of colchicine than have been traditionally used in addition to taking renal and hepatic function into consideration when treating patients with gout.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the United States, colchicine has been available for the treatment of gout since prior to 1938. It is classified as a pre-DESI drug since there has never been a new drug application (NDA) approved for its use as a single entity in this country although it was approved for marketing as part of the combination drug product ColBenemid (colchicine 0.5 mg and Probenecid 500 mg) under NDA 12,383 for the treatment of gout in 1961. (Note: This combination product has been withdrawn from the market, however, the Applicant also owns this NDA.) Despite the numerous clinical trials which evaluated colchicine's safety and extensive clinical experience accumulated over the years since it first became available to prescribers, it was subject to being removed from the market as an enforcement issue under the Compliance Policy Guide Section 440.100 Marketed New Drugs without Approved NDAs or ANDAs. Currently approved marketed combination drug products that contain colchicine with Probenecid include Col-Probenecid (NDA 84,279) manufactured by Watson Labs (the reference listed drug) and generic formulations of the latter manufactured by IVAX Pharmaceuticals (ANDA 40,618) and (ANDA 83,734) Concord Labs.

A Pre-IND meeting with the Agency and the Applicant was held on July 31, 2006 to discuss the requirements for the development and approval of colchicine tables USP, 0.6 mg, for the prevention and treatment of acute gout attacks ———— b(4)

———————— . This resulted in the submission of IND 72-586 on February 9, 2007 that was allowed to proceed on March 14, 2007 following feedback comments from the review division regarding modifications to the proposed study protocol. A pre-NDA meeting was requested for February 1, 2008. The Division denied the request, but responded in writing to all of the questions posed in the Applicant's briefing package. The latter included confirmation that one adequate and well-controlled trial in patients with acute gout flares supported by the results from the published placebo-controlled study by Ahern et al[1], the bioavailability and pharmacokinetic drug interaction studies requested during the pre-IND meeting as well as a thorough review of the publicly available safety information would be sufficient to support filing of a new drug application for colchicine. b(4)

On September 30, 2008, Mutual Pharmaceutical Company submitted this NDA for colchicine tablets USP, 0.6 mg (Colcrys™) under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act that permits the use of publically available information supplemented by nonclinical and clinical pharmacology studies conducted by the Applicant to supply safety data not publicly available.

2.6 Other Relevant Background Information

According to information supplied by the Applicant, colchicine is marketed in 50 countries worldwide. In support of the safety profile of this drug, the Applicant submitted the English-translated labeling from the following 9 countries: Argentina, Australia, France, Germany, Great Britain, Mexico, Portugal, Singapore and Uganda.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Mutual Pharmaceutical's submission was appropriately organized to allow information to be reviewed in an acceptable manner. The Applicant's responses to all of FDA's information requests were timely and well organized.

3.2 Compliance with Good Clinical Practices

According to a statement included in the report for MCP-004-06-001, the Applicant certified that this trial was conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology/toxicology data included in this application was reviewed previously by Dr. Lawrence Leshin in support of the Applicant's pending NDA 22-352 (colchicine for Familial Mediterranean Fever). On February 2, 2009, the Applicant agreed to the following post-marketing commitments (PMCs): 1. reduce potentially mutagenic photodegradants in the drug substance/product; and 2. conduct carcinogenicity studies in 2 species. In view of these agreed upon PMCs, Dr. Leshin recommends approval of this current application.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Colchicine's effectiveness as a treatment for gout has been postulated due to its ability to block neutophil-mediated inflammatory responses induced by monosodium urate crystals in synovial fluid by disrupting the function of the neutophils' cytoskeleton and interfering with microtubulin assembly. This results in the prevention of activation, degranulation, and migration of neutrophils to sites of inflammation. New evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex found in neutrophils and monocytes that mediate IL-1β activation.

4.4.2 Pharmacodynamics

No pharmacodynamic studies of colchicine were submitted as part of this application.

4.4.3 Pharmacokinetics

In support of NDA 22-352 (colchicine for familial Mediterranean Fever), Mutual Pharmaceuticals had submitted four clinical pharmacokinetic (PK) studies in healthy volunteers to describe single dose and multiple dose pharmacokinetics of colchicine and its metabolites, two drug interaction studies with clarithromycin and oral contraceptives. In addition, four in vitro metabolism and drug interaction studies were also conducted. These studies were previously reviewed in clinical pharmacology review for NDA 22-352 dated November 26, 2008.

In support of this current application, Mutual Pharmaceuticals submitted eight new pharmacokinetic drug interaction studies. Seven studies evaluated the effects of CYP3A4 and P-gp inhibitors on the pharmacokinetics of single-dose colchicine

(azithromycin, ketoconazole, ritonavir, verapamil, diltiazem, cyclosporine and grapefruit juice). One study evaluated the clinical drug interaction using a sensitive CYP1A2 substrate, theophylline. The results of these studies showed that strong CYP3A4 inhibitors caused an approximate 2 to 3-fold increase in colchicine's C_{max} and 3 to 4-fold increase in its area under the curve (AUC). Moderate CYP3A inhibitors caused a 1.3-fold increase in colchicine's Cmax and a 2-fold increase in its AUC. P-gp inhibitors were associated with approximately a 4-fold increase in colchicine's AUC. From a clinical pharmacology perspective dosage adjustment in patients due to drug interaction should be aimed at maintaining the average C_{max} and AUC noted between the low-dose and standard-dose. [Note: A concentration-response relationship could not be assessed in the clinical trial MPC-004-06-001 since blood samples were not collected. However, PK Studies 1002 and 1003 from the related NDA 22-352 provide colchicine systemic exposure range for the proposed low-dose regimen (1.8 mg over 2 hours) and standard-dose (4.8 mg over 6 hours)].

The results from PK studies in special populations showed that renal impairment (creatinine clearance <15 mL/Min) decreases the plasma clearance of colchicine by 75% while hepatic impairment (i.e., alcoholic cirrhosis) decreases its clearance by approximately 50%.

Based on his review of these data, Dr. Srikanth Nallani is recommending approval of this application provided that an agreement can be reached with the Applicant regarding the following dosing recommendations:

1. Patients with renal or hepatic impairment should not be given colchicine concomitantly with strong P-gp or CYP3A4 inhibitors
2. Colchicine dose should be decreased by a third when co-administered with clarithromycin, ritonavir, ketoconazole, cyclosporine
3. Colchicine dose should be decreased by a half when co-administered with verapamil or diltiazem
4. No dosage adjustment required with azithromycin or grapefruit juice

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A listing of the clinical and single- and multiple-dose pharmacokinetic studies contained in this application in support of the efficacy and safety of colchicine is shown in Table 1:

Table 1 – Tabular Summary of Clinical and Pharmacokinetic Studies

Study/Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Adm.	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 3 Study					
MCP-004-06-001 **Objectives:** 1. Determine the efficacy of colchicine in a gout flare; 2. To compare low and standard dose regimens of colchicine with respect to pain, time to response and complete pain relief and signs and symptoms of inflammation; 3. To determine the safety of colchicine when administered in two different dose regiments	Multicenter, randomized, double-blind, placebo controlled, parallel group, dose comparison study. Study utilized 1:1:1 randomization ratio 89 sites in U.S.	**Standard dose of colchicine (4.8 mg):** 1.2 mg of colchicine orally at onset of gout flare followed by 0.6 mg of oral colchicine every hour for 6 hours; **Low dose of colchicine (1.8 mg):** 1.2 mg of colchicine orally at onset of gout flare followed by 0.6 mg of oral colchicine after 1 hour Placebo orally	N=184 Colchicine groups: Standard dose: 52 subjects Low dose: 74 subjects Placebo: 58 subjects	Adults age ≥ 18 years with confirmed diagnosis of gout via ACR criteria; with ≥ 2 acute gout attacks in the 12 months prior to randomization; if on urate lowering therapy must be on stable dose for 4 weeks prior to randomization	Proportion of subjects who achieved ≥ 50% reduction in pain score at 24 hrs post-dose assessment relative to the pre-treatment score and did not use rescue mediation during the 24 hr. assessment period
Phase 1 PK and Drug-Drug Interaction Studies					
MPC-004-07-1001 **Objective:** Determine the bioequivalence of colchicine tablets USP 0.6 mg when administered under standard fasting conditions and ColProbenecid	Three-way, single dose, crossover with 7 day washouts Bioequivalence study	1 tablet of 0.6 mg colchicine orally	N=28 10 Males; and 18 Females	Healthy Subjects	PK and Safety
MPC-004-07-1002 **Objective:** determine the PK profile of colchicine and its metabolites, 2-, 3-, and 10-demethylocolchicine	Double-blind, double-dummy, single dose PK and Exploratory ECG study	Colchicine 4.8 mg (1.2 mg orally followed by 0.6 mg hourly x 6 doses orally) (standard dose regimen)	N=18 10 Males; 8 Females	Healthy Subjects	PK, Safety and Exploratory ECG
MPC-004-07-1003 **Objective:** Determine the PK profile of colchicine and its metabolites	Open-label, single dose	Colchicine 1.2 mg (1.2 mg orally)	N=13 6 Males; 7 Females	Healthy Subjects	PK and Safety
MPC-004-07-1004 **Objective:** Determine the single and multiple dose PK of colchicine	Open-label, single and multiple dose PK study	Colchicine 1 tablet 0.6 mg orally followed 14 days later by multiple doses (0.6 mg twice daily for 10 days)	N=13 12 Males; 1 Female	Healthy Subjects	PK and Safety
MPC-004-07-1005 **Objectives:** Determine whether steady-state dosing of colchicine tablets USP 0.6 mg influences the steady-state PK profile of ethinyl estradiol or norethindrone	Double-blind, randomized, multiple doses, two sequence drug-drug interaction study	Multiple dose (0.6 mg twice a day for 14 days) with oral contraceptives	N=30 30 Females	Healthy Subjects	PK and Safety
MPC-004-07-1006 **Objectives:** To confirm the extent to which multiple oral doses of clarithromycin influence the single-dose PK profile of colchicine and its metabolites	Open-label, single-dose (0.6 mg colchicine) with and without steady-state clarithromycin PK study	1 tablet colchicine 0.6 mg	N=24 11 Males and 13 Females	Healthy Subjects	PK and Safety

Table 1 – Tabular Summary of Clinical and Pharmacokinetic Studies (cont.)

MPC-004-08-1010 **Objective:** To determine the effect of theophylline on the PK of colchicine under fasted conditions	Multiple dose (0.6 mg colchicine twice a day for 14 days) with theophylline	0.6 mg of colchicine twice a day for 14 days	N=30 16 Males and 14 Females	Healthy Subjects	PK and Safety
MPC-004-08-1011 **Objective:** To determine the effect of azithromycin on the PK of colchicine under fasted conditions	Single dose (0.6 mg of colchicine) drug-interaction study with azithromycin	1 tablet colchicine 0.6 mg	N=24 10 Males; 14 Females	Healthy Subjects	PK and Safety
MPC-004-08-1012 **Objective**: To determine the effect of ketoconazole on the PK of colchicine under fasted conditions	Open-label, one sequence two-period, single dose (0.6 mg colchicine) drug-interaction study with Ketoconazole	1 tablet colchicine 0.6 mg	N=24 7 Males and 17 Females	Healthy Subjects	PK and Safety
MPC-004-08-1013 **Objective:** To determine the effect of ritonavir on the PK of colchicine under fasted conditions	Open-label, single dose (0.6 mg of colchicine) drug-interaction study with ritonavir	1 tablet colchicine 0.6 mg	N=24 14 Males and 10 Females	Healthy Subjects	PK and Safety
MPC-004-08-1014 **Objective**: To determine the effect of multiple doses of extended release verapamil on the PK of colchicine under fasted conditions	Open-label, single dose (0.6 mg of colchicine) drug-interaction study with verapamil	1 tablet colchicine 0.6 mg	N=24 6 Males and 18 Females	Healthy Subjects	PK and Safety
MPC-004-08-1015 **Objective:** To determine the effect of verapamil on the PK of colchicine under fasted conditions	Open-label, single dose (0.6 mg of colchicine) drug-interaction study with diltiazem	1 tablet colchicine 0.6 mg	N=24 15 Males and 9 Females	Healthy Subjects	PK and Safety
MPC-004-08-1016 **Objective:** To determine the effect of cyclosporine on the PK of colchicine under fasted conditions	Open-label, single dose (0.6 mg of colchicine) drug interaction study with cyclosporine	1 tablet colchicine 0.6 mg	N=24 10 Males and 14 Females	Healthy Subjects	PK and Safety
MPC-004-08-1017 **Objective:** 1. To determine the effect of grapefruit juice on the PK of colchicine under fasted conditions; 2. To Assess the safety and tolerability of colchicine administered with grapefruit juice	Open-label, one sequence, two - period, single dose (0.6 mg of colchicine) drug-food interaction study	1 tablet colchicine 0.6 mg	N=22 16 Males and 6 Females	Healthy Subjects	PK and Safety

5.2 Review Strategy

The applicant conducted a single adequate and well-controlled trial, Study MCP-004-06-001, in support of this application. Additionally, the applicant cited the 1987 published results of a randomized controlled trial by Ahern et al[1] as well as the published results of four uncontrolled studies that evaluated the effectiveness of colchicine as a treatment for an acute gout flare. The Division had previously agreed to consider data from a single adequate and well-controlled trial along with the Ahern study as evidence of efficacy of colchicine in acute gout. This medical officer reviewed the results from the **Applicant's pivotal trial (Study MCP-004-06-001) and the study by Ahern et al for efficacy. The other published studies were not reviewed in support of colchicine's** efficacy as a treatment for acute gout for the following reasons: they were all open-label trials, the total dosage of colchicine administered was either not documented or varied in each study, and two of these studies used an intravenous formulation of colchicine that is no longer marketed for safety reasons in this country.

The safety database included all subjects who participated in the pivotal Phase 3 study and in the 14 pharmacokinetic drug interaction trials. Additionally, the Applicant submitted the results of a literature search and postmarketing safety analysis of adverse events associated with the use of colchicine. These data will be discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

In support of efficacy, the applicant submitted a single adequate and well-controlled clinical trial, MCP-004-06-001, and the published results of the single center, double-blind, randomized controlled study by Ahern et al (Aust NZ J Med 17:301-304, 1987) in patients with crystal-proven gout attacks. Both of these studies will be discussed below; however, the discussion of the Ahern et al study will be limited just to data presented in the publication since the original protocol and datasets were not included for review.

Study Number and Title: MCP-004-06-001 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group 1-Week, Dose-Comparison Study to Evaluate the Efficacy, Safety and Tolerability of Colchicine in Subjects with an Acute Gout Flare.

Dates Conducted: This trial was started on April 4, 2007 and completed on December 3, 2007.

Objectives:
Primary Objective:

- To assess the efficacy of colchicine in an acute gout attack (gouty flare) based on pain reduction after 24 hours as a measure of response

Secondary Objectives:

- To evaluate low- and standard- dose regimens of colchicine with respect to pain, time to response and complete pain relief, interference with sleep, and signs and symptoms of inflammation
- To evaluate the safety of colchicine when administered in two different dose regimens

Study Design:
Study MPC-004-06-001 was to have been a 1-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose comparison Phase 3 trial to evaluate the efficacy of standard dose (4.8 mg) versus low dose colchicine (1.8 mg) in treating an acute disease flare in patients with gout. A total enrollment of 390 patients was planned. The overall duration of the trial was to have been 6 months from time of the last patient's enrollment. The duration of participation for each patient was to have been 1 week following confirmation of a gout flare (excluding screening and the time period between randomization and onset of an acute flare). The study was to have been comprised of 3 phases (i.e., the pre-flare, flare and post-flare phases) and the number of study visits were to have varied (i.e., approximately 5 or 6 visits) depending on each patient's gout flare and post-treatment status.

Subjects who had successfully completed the study's screening process were to have been randomized via a 1:1:1 ratio to one of 3 treatment groups: standard-dose colchicine (4.8 mg administered over 6 hours), low-dose colchicine (1.8 mg administered over 1 hour), or placebo. Patients were to have been dispensed a daily diary, trial participation instructions, and a blister pack of study drug to be used at their next gout flare. They were to have been also given rescue medications as per the site investigator's standard practice. The protocol specified that individuals who initially failed to qualify for trial participation could be re-screened for eligibility. Continued study eligibility was to have been re-assessed every 3 months during the time between randomization and disease flare.

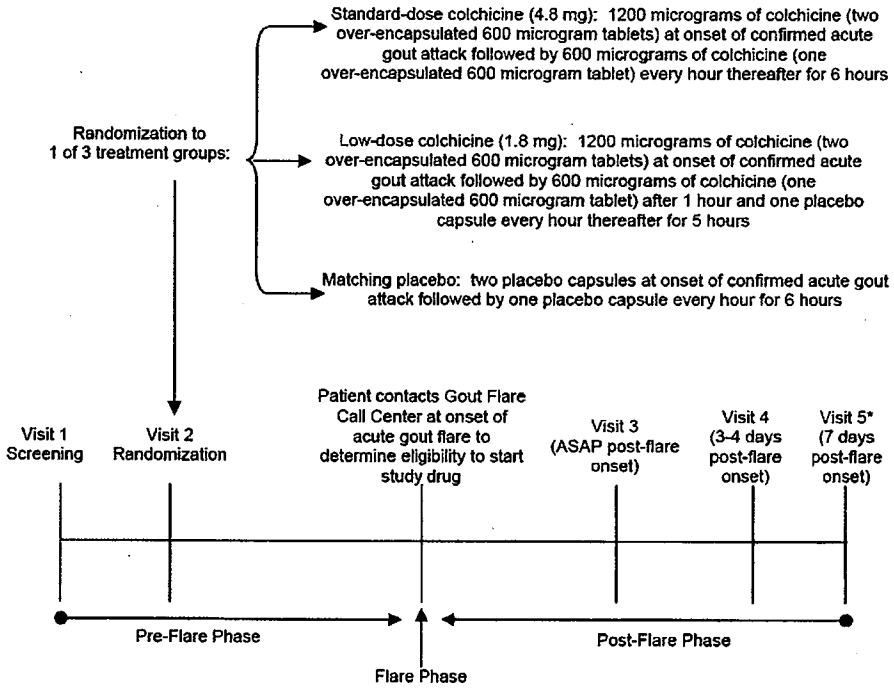
Prior to self-initiation of study medications, patients were to have called trained trial personnel at the gout flare call center to determine if their gout flare qualified for treatment. Eligibility for treatment was to have been established via a standardized questionnaire used by the gout call center to document that the patient had all of the following signs and symptoms of an acute gout flare: swelling, redness, marked tenderness, and pain. Patients whose gout flare had failed to qualify for initiation of study therapy were to have re-contacted the call center in 1 hour for re-assessment. If they continued not to qualify for study treatment, they were to have started alternative therapy without prejudice to future study participation in the event that another gout flare occurred.

Subjects were to have recorded information concerning flare severity, study drug dosing, use of rescue medications and the occurrence of adverse events (AEs) in their diary after being authorized to start study medication. Any patient who had experienced

a severe gastrointestinal AE while taking the study meds was to have discontinued taking them and contacted the investigational site. All patients including those whose attack did not qualify for treatment were to have been evaluated at the study clinic within 48 hours post-flare. Subjects whose flares had not resolved or who had an unresolved AE or clinically significant treatment emergent lab abnormality were to have been followed to resolution or until deemed not clinically significant. Continued eligibility was to have been re-determined by the investigator for non-qualifying patients at this visit.

Figure 1 below is a schema of the study.

Figure 1 –Schema of Study MPC-004-06-001



*Visit 5 will take place 7 days after the onset of the acute gout flare in patients who took at least one dose of study drug whose acute gout flare was still ongoing at Visit 4.

Major Inclusion Criteria:
Subjects were to have been men and women ≥ 18 years of age who met all of the following criteria:

1. Must have had a confirmed diagnosis of gout as per the criteria of the American College of Rheumatology (ACR), based on presence of characteristic urate crystals in the joint fluid and/or tophus proven to contain urate crystals by chemical or polarized light microscopic means and/or the presence of at least 6 of the following clinical, laboratory, and x-ray phenomena: >1 prior attack of acute arthritis, maximum inflammation developed within 24 hours, monoarthritis attack, redness observed over joints, first metatarsophalangeal (MTP) joint painful or swollen, unilateral first MTP joint attack, unilateral tarsal joint attack, proven or suspected tophus, hyperuricemia, asymmetric swelling within a joint on x-ray, subcortical cysts without erosions on x-ray, monosodium urate monohydrate microcrystals in joint fluid during attack, and joint fluid culture negative for organisms during attack
2. Must have experienced $\geq$ 2 acute gouty arthritic attacks in the 12 months prior to randomization
3. If taking a urate lowering therapy must have been on a stable dose and schedule with no changes in therapy for 4 weeks prior to randomization and were expected to remain on a stable regimen during study participation
4. Must have been willing to adhere to study schedule and the protocol requirements
5. Must have been willing and able to give written informed consent and signed a HIPAA and/or privacy consent

Exclusion Criteria:
Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Had acute polyarticular gout (>4 joints)
2. Had experienced > 2 acute gouty arthritis attacks per months, or > 12 attacks overall, in the 6 months prior to randomization
3. Had arthritis due to any cause other than gout that may confound any study assessments per investigator discretion
4. Had any prior history of lack of response to or inability to tolerate colchicine
5. Had a known hypersensitivity to colchicine or any component of the formulation of study drug
6. Had a history of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting within the previous 6 months prior to screening
7. Had active myeloid leukemia, obstructive gastrointestinal cancer, or metastatic cancer
8. Had chronic renal dysfunction (creatinine clearance < 60 mL/min as estimated with the Cockcroft-Gault formula)
9. Had chronic hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 x the upper limit of normal [ULN], gamma glutamyltransferase [GGT] >2 x the ULN, Bilirubin >2.5 mg/dL, prothrombin time (PT) >1.5 x ULN, or albumin < 1.5 gm/dL)

10. Have had a history of alcohol or substance abuse within the 12 months prior to randomization
11. Have had any concomitant illness or other finding that, in the opinion of the investigator, would confound the study data or place the patient at unacceptable risk if the patient were to participate in the study, or that would require frequent adjustments in concomitant medications during the course of the study
12. Have been using systemic corticosteroids, cyclosporine, adalimumab, etanercept, infliximab, anakinra, abatacept, mycophenolate, azathioprine, or chronic use of NSAIDs, acetaminophen, tramadol, and other analgesics such as opiates at screening
13. Had used any investigation drug within 30 days prior to randomization
14. Had been previously randomized into this study and begun ingestion of study drug

Treatment:
Subjects were to have at least 1 joint involvement with a pain assessment of ≥ 4 on a 11-point pain-intensity numeric rating scale (PINRS) at the onset of the acute flare in addition to the signs (i.e., swelling, erythema, and marked tenderness) and symptoms (i.e., rapid onset of maximum pain within the prior 4 to 12 hours, decreased range of motion in the joint, and warmth) of an acute flare before they could be authorized by the gout flare call center to start study treatment. Patients were to have started study treatment within 12 hours of an eligible acute gout flare following consent from the gout flare call center. Subjects were to have taken eight capsules of study medication orally as follows: two capsules orally after receiving authorization by the study call center, followed by one capsule orally every hour over a 6-hour time period. Table 2 below shows the dosing schedule for each treatment group.

Table 2 – Oral Dosing Schedule by Treatment Group

	Prior to First Dose (Hour 0)	Hour 1	Hours 3-7
Standard Dose	Colchicine 0.6 mg x 2	Colchicine 0.6 mg x 1	Colchicine 0.6 mg x 1
Low Dose	Colchicine 0.6 mg x 2	Colchicine 0.6 mg x 1	Placebo x 1
Placebo	Placebo x 1	Placebo x 1	Placebo x 1

Adapted Sponsor's table 9:1; p. 26 of Study MPC-004-06-001 Report.

Removal of Patients from Treatment or Assessment:
Patients were to have been withdrawn from the study if they requested to be discontinued from the trial for any reason, experienced a serious or intolerable adverse event such as a severe gastrointestinal adverse event, had a clinically significant change in a lab parameter, required the use of rescue medication, incurred a protocol violation, or in the event that the study was terminated by either the sponsor or investigator. The protocol also specified that a patient could be deemed no longer eligible to receive study drug by the call center during the flare phase of the trial as a result of changes in either medical history or concomitant medications or by the

investigator during the post-flare phase (Visit 3 or 4) based on whether a patient failed to take at least 1 dose of study drug, as well as responses to a standardized questionnaire and physical exam.

Rescue Medications:
Rescue medication was to have been used by subjects only if intolerable pain associated with the flare continued post use of study drug. Study investigators were to have determined which rescue medication was to have been used by each patient. Subjects were to have been instructed not to use rescue medication until after taking at least the first dose of study drug and in addition to trying to wait until at least 24 hours had past since starting study treatment.

Concomitant Medications:
Use of the following medications by patients was to have been prohibited as follows:
3-days prior to study drug:

- Colchicine
- Azathioprine
- Chronic nonsteroidal anti-inflammatory drugs, acetaminophen, tramadol, and other analgesics such as opiates (Note: Subjects were permitted to have taken these analgesics as needed for musculoskeletal pain under the proviso that such therapy was not taken within 72 hours of the start of study drug to the end of the clinical portion of the study [up to 1 week])

30-days prior to study drug:

- Systemic corticosteroids on a chronic or as needed basis (inhalant, topical and ophthalmic steroids were to have been permitted.)
- Etanercept
- Anakinra
- Mycophenolate
- Cyclosporine
- Macrolide antibiotics (azithromycin, clarithromycin, dirithromycin, erythromycin, or telithromycin)

90-days prior to study drug:

- Adalimumab
- Infliximab
- Abatacept

Efficacy and Safety Assessments:
Efficacy was to have been derived from a variety of information captured by subjects in their diaries, the results of the affected joint examination by the study investigators, and information recorded by the gout flare call center. Patients were to have recorded in their diary dosing and rescue medication use, pain severity (evaluated via 11-point pain-intensity numeric rating scale [PINRS]), sleep interference (evaluated via 11-point

scale), and whether or not gastrointestinal AEs (i.e., nausea, vomiting, diarrhea, and abdominal pain) were present prior to study treatment. This information was to have been captured every hour for the first 8 hours following the initiation of treatment, and then every 8 hours thereafter (while awake) until symptoms disappear or a total of 72 hours of monitoring had passed post initiation of study medications. The gout flare call center was to have documented subjects' pain assessment of each affected joint as reported by each subject at the pre-treatment authorization call, and to have placed a follow-up call to each subject within 24 hours from the onset of the acute flare to determine that the patient had been completing their study diary and the 24-hour pain assessments. Investigators were to have completed clinical assessments of subjects' affected joints consisting of an evaluation of the signs and symptoms of inflammation (i.e., erythema, swelling, and tenderness to touch) utilizing a 3-point rating system for each parameter at Visits 3, 4 and/or 5. A global assessment of response to study treatment using a 5–point rating system (0 = excellent to 4 = none) was to have been completed by the investigator at the final clinic visit (Visit 4 or 5).

Safety was to have been monitored via AE information captured by patients in their diaries as well as on changes noted on physical exam (including blood pressure, pulse, heart rate, respiration, temperature and weight), clinical laboratory tests (serum biochemistry, complete blood count, and urinalysis) that were to have been obtained at Visit 1 (screening) and Visit 4 or 5 (final study visit). EKGs were to have been performed only at screening.

Study Visit Schedule:
The following Tables 3a and 3b are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations:

Table 3a – Schedule of Procedures and Evaluations for Study MPC-004-06-001

Study Phase/Visit Number / Procedure	Pre-Flare Phase		Flare Phase	Post-Flare Phase		
	Visit 1 Screening	Visit 2[1] Randomization (within 2 weeks of Screening)	Acute Gout Flare[2]	Visit 3[3] (ASAP to 48 hours post-flare onset)	Visit 4[4] (>48 to 96 hours post-flare onset)	Visit 5[5] (7 days post-flare onset)/Early Termination
Informed consent/HIPAA Authorization[6]	X					
Inclusion/exclusion criteria	X	X		X[7]	X[7]	
Demographics	X					
Medical history	X	X	X[2]	X[7]	X[7]	
Confirm gout diagnosis[8]	X					
Complete Physical Examination	X				X[4,5]	X[4,5]
Targeted Physical Examination (if needed)		X		X	X[4]	
12-Lead ECG	X					
Laboratory tests[9]	X				X[4,5]	X[4,5]
Vital Signs and body weight[10]	X	X		X	X	X
Randomize patient		X				
Patient contacts Gout Flare Call Center at onset of acute gout flare to confirm eligibility to take study drug[2]			X			
Gout Flare Call Center contacts patients 24 hours post-flare[11]			X			
Gout Flare Call Center contacts non-flared patients on a monthly basis for re-education[12]		←	→			
Patient completes diary for pain assessment[13]			X	X	X	
Patient completes diary for times of meals and sleep interference[14]			X			

Note: Schedule and footnotes are continued on the next page. Arrow designates entire time period.

Sponsor's Table 1; p. 23 of the original study protocol.

Table 3b (cont.) – Schedule of Procedures and Evaluations for Study MPC-004-06-001

Study Phase/Visit Number / Procedure	Pre-Flare Phase		Flare Phase	Post-Flare Phase		
	Visit 1 Screening	Visit 2[1] Randomization (within 2 weeks of Screening)	Acute Gout Flare[2]	Visit 3[3] (ASAP to 48 hours post-flare onset)	Visit 4[4] (>48 to 96 hours post-flare onset)	Visit 5[5] (7 days post-flare onset)/Early Termination
Investigator's examination of affected joint(s)[15]				X	X	X
Investigator's Global Assessment of Response to Treatment					X[4,5]	X[4,5]
AE assessment		X		X	X	X
Concomitant medication assessment	X	X	X[2]	X	X	X
Dispense study drug and diary and counsel patient on the use of rescue medications[16]		X				
Collect study drug blister packs[17] and all diaries				X	X	X

1 Eligible patients will return to the study clinic for confirmation of eligibility and randomization to study drug within 2 weeks of Screening. Patients who are not eligible to participate may be re-screened.
2 When patients develop an acute gout flare they must confirm that their acute gout flare is eligible for treatment with study drug by contacting the Gout Flare Call Center prior to taking any study drug. The patient will be queried regarding any changes in his/her medical health and concomitant medication use since the time of randomization. In order to establish if the patient's acute gout flare will be eligible for treatment with study drug, a standardized questionnaire will be used to document that the patient has all signs/symptoms of an acute gouty arthritic attack.
3 Post-flare, whether eligible for treatment with study drug or not, all patients will return to the clinic for clinical assessments as soon as possible (ASAP) post-flare onset, up to 48 hours post-flare onset. If a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4.
4 To be conducted >48 to 96 hours post-flare onset in patients who took at least one dose of study drug and in patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3. Patients who took at least one dose of study drug and whose acute gout flare is still ongoing at Visit 4 will return to the clinic for a final visit (Visit 5) 7 days post-flare onset; however, if their acute gout flare is resolved at Visit 4, final study assessments will be performed at Visit 4.
5 If a patient who took at least one dose of study drug discontinues from the study prior to completion of the post-flare phase, every effort should be made to complete the assessments scheduled on Visit 5. Visit 5 will take place 7 days after the onset of the acute gout flare in patients who took at least one dose of study drug whose acute gout flare was still ongoing at Visit 4.
6 Patients must sign an Informed Consent Form and HIPAA Authorization prior to any study-related procedures being completed.
7 Post-flare, patients who did not take at least one dose of study drug will have their eligibility to continue study participation confirmed by the Investigator based on the inclusion and exclusion criteria as well as responses to the standardized questionnaire and examination of the patient.
8 Patients must meet criteria of the ACR for acute arthritis of gout at Screening
9 Includes a CBC and hematology tests (hct, hgb, MCH, MCHC, MCV, platelet count, RBC count, WBC count with differential), serum chemistry (albumin, ALK-P, ALT [SGPT], AST [SGOT], BUN, Ca, CO_2, Cl, creatinine, CK, GGT, glucose, LDH, phosphorus, K, Na, total bilirubin, direct bilirubin, total cholesterol, LDL-C, HDL-C, total protein, and uric acid), urinalysis, and coagulation (PT and PTT).
10 Vital signs include oral body temperature, sitting radial or brachial pulse rate, respiratory rate, and sitting blood pressure. Body weight will be measured in pounds.
11 The Gout Flare Call Center will call the patient in 24 hours from the onset of the acute gout flare to make sure the patient has completed the patient diary, including assessments for pain.
12 The Gout Flare Call Center will contact patients on a monthly basis beginning 1 month after randomization to study drug. These contacts will continue until the patient has an acute gout flare or study completion, whichever occurs first. The purpose of these contacts is to re-educate patients about study participation.
13 Patients are to record pain severity for each joint affected by the acute gout flare on a study diary using a PI-NRS before each dose of study drug, the first 8 hours following the start of treatment, and every 8 hours thereafter (while awake) until symptoms disappear or 72 hours have passed since the first dose of study drug was taken, whichever occurs first.
14 Patients are to record times of meals on the day of study drug use. Patients will also record sleep interference on a study diary using an 11-point scale the morning after the acute gout flare.
15 Investigators will examine each joint of the patient affected by the acute gout flare and will rate signs and symptoms of inflammation (erythema [absent, present, or not assessable], swelling [0, "none" to 3, "severe"], and tenderness to touch [0, "none" to 3, "severe"]).
16 Patients who have been dispensed study drug may also be given rescue medication per the clinical site's standard practice. Rescue medication is to be used only if intolerable pain continues after use of study drug. The use of specific rescue medication for intolerable pain associated with an acute gout flare will be at the investigator's discretion. Patients will be instructed not to take rescue medication until after taking at least the first dose of study drug and are encouraged to wait until at least 24 hours after initiating study drug.
17 Sites will be diligent in collecting study drug blister packs from all randomized patients by phoning the patient up to 2 times and finally by sending a certified letter with a postage paid package for return of study drug blister packs.

Sponsor's Table 1 (cont.); p. 23 of the original study protocol.

Outcome Measures:

Primary efficacy variable -

The primary efficacy variable was to have been the response to treatment in the target joint, based on subject self-assessment of pain at 24 hours after taking the first dose of study medication. (Note: The target joint was to have been identified during data analysis as the joint affected by the acute flare with the highest baseline pain score noted in the patient diary. Ties among maximum joint scores for a subject were to have been resolved by random selection.) The definition of a responder to study therapy was one who achieved a $\geq$ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and did not use rescue medication prior to the actual time of 24-hour post-dose assessment. Subjects who used rescue medication, discontinued prior to the 24-hour post-dose assessment, or did not achieve a $\geq$ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score were deemed non-responders.

Secondary efficacy variables-
The study had a number of secondary efficacy variables as follows:

- Magnitude of pain reduction
- Time to response
- Time to complete pain relief (90%) reduction
- Time to use of rescue medications
- Signs and symptoms of inflammation per Investigator's clinical assessments of the target joint
- Investigator global assessment of response to treatment

Safety variables-
The study had a number of safety variables as follows:

- Analysis of adverse events (SAEs) – the treatment emergent period was defined as the active treatment period up to Visit 5 (7 ± 2 days post-flare onset) or longer in the event of unresolved AEs
- Clinical lab tests
- Vital signs and body weight – as measured at each study visit (Visits 1-4 or 5).
- Physical exam – performed at Visit 1 and the final visit (Visit 4 or 5)

Statistical Design, Definitions of Analyzed Populations and Analysis Plan:
Sample Size Calculations
The sample size calculations for this trial were based on the following two assumptions:

- 40% of the intent-to-treat patients randomized to standard dose colchicine met response criteria
- 10% of the placebo patients met response criteria

Based on the above assumptions, and with 47 patients randomized per treatment arm this trial had 90% power to detect a statistically significant treatment group difference using a two-sided alpha of 0.05 (chi-square test corrected for continuity). A projected total of 300 patients (100 per treatment arm) were needed for randomization based on estimates of 45% of randomized patients failing to have an acute gout attack during the trial in addition to 10% dropping out or not qualifying for initiation of study treatment upon contacting the gout flare call center.

Study Populations
Three populations were to have been used for analysis. They were defined as follows:
1. Intent-to-Treat (ITT) Population: would have consisted of all randomized subjects who contacted the gout flare call center, took at least one dose of study drug, and had one subsequent contact.
2. Per-Protocol (PP) Population: would have consisted of a subset of the ITT population who had been confirmed by the Investigator as continuing to meet all major inclusion and exclusion criteria and initiated treatment within 12 hours of the onset of the flare.

3. Evaluable Population: would have consisted of all subjects included in the PP population who had completed the randomized treatment course.

The statistical analysis plan (SAP) specified an intent-to-treat analysis of the primary efficacy variable. The analysis was to have been performed using the Mantel-Haenszel chi-square test stratified for study site to compare the number of responders in the standard dose colchicine group versus the placebo group (i.e., the primary comparison of interest). No adjustment for multiple comparisons was to have been performed since there was only one pre-specified primary efficacy endpoint (i.e., the single treatment group comparison of standard dose colchicine versus placebo). Missing data was to been handled as follows: subjects lost to follow up before completing treatment were to have been considered treatment failures; the gout flare call center 24-hour pain assessment was to have been used in the event that a subject prematurely discontinued from the trial without returning the diary and did not provide a 24-hour pain assessment; the next later pain assessment was to have been used if the 24-hour pain assessment was unavailable from both the subject or the call center; and if the next later assessment was unavailable the last observation carried forward for pain scores at the 24-hour post dose assessment was to have been used. Sensitivity analyses were to have included alternate definitions of response such as magnitude of reduction from baseline and time to response. (Note: These two variables were to have been analyzed as secondary endpoints.) Additional sensitivity analyses were to have been performed using both the PP and evaluable populations if the sample sizes differed from the overall ITT population by more than 10%.

Other secondary efficacy analyses were to have been conducted using the Mantel-Haenszel chi-square test stratified for study site to compare the number of responders in the low dose colchicine group versus the placebo group as well as to the standard dose colchicine group. No adjustment for multiple comparisons was to have been performed. Change in pain intensity, interference with sleep, time to 50% reduction in pain, and time to complete pain relief were to have been analyzed as continuous variables using analysis of covariance with study site, treatment group, and site by treatment group, and site by treatment interaction as independent variables for change in pain intensity and interference with sleep, with baseline score as covariate. The **comparative analyses of the treatment groups for the investigator's clinical assessment** of inflammation and global assessment of response to treatment were to have been also calculated via the Mantel-Haenszel chi-square test stratified for study site.

Safety analyses were to have been conducted on the ITT population. The protocol specified that adverse events (AEs) were to have been coded via a standardized medical dictionary with the incidence summarized by treatment group, relationship, severity, premature withdrawal and seriousness. Descriptive statistics of clinical laboratory test results and vital signs were to have been used to show the change from baseline for each treatment group. Treatment-emergent abnormalities on physical exam

were to have been tabulated and listed by treatment group. By-patient listings of all safety data and concomitant medication used were to have been also generated.

Study Conduct:

Protocol Amendments

Listed below are the 4 protocol amendments made to Study MPC-004-06-001.

1. Amendment 1 (implemented on February 6, 2007)

Minor changes were made to the protocol prior to the enrollment of patients and prior to agency review which did not affect the safety of the study participants or the conduct of the trial.

2. Amendment 2 (implemented on March 20, 2007)

In addition to some minor editorial changes and corrections of misspellings the following changes to the trial protocol were made at the request of the Agency review team:

- Addition of interim visits every 3 months after randomization until an acute attack of gout has occurred. Clinical lab testing (i.e., complete blood count with differential, renal and liver function) was to be performed on subjects at these visits as well as re-evaluation of their concomitant medications, medical history and current complaints. Subjects were to have been discontinued from the study **during the interim screening visit if they no longer met the trial's entry criteria.** Study staff were to have re-educated patients about trial participation at these visits.
- Addition of one follow-up visit (Visit 6) that was to have been conducted 14 days post-flare onset for those patients who require medical follow-up due to an unresolved gout flare, AE, or clinically significant treatment-emergent lab abnormality noted at Visit 5.
- Clarifications regarding previous and concomitant use of colchicine were added. Patients taking colchicine routinely (i.e., for prophylaxis of an acute gout flare) within the 6 months prior to screening were to have been excluded. Use of colchicine in this manner was not to be permitted and these patients were to have been discontinued from the trial. Additionally, colchicine could not have been used within 30 days prior to the start of the study drug.

3. Amendment 3 (implemented on June 22, 2007)

In addition to the correction of minor grammatical errors, the following modifications were made to the study conduct:

- Clarification of the definition of the ITT population as follows: all patients who were randomized, contacted the gout flare call center, and were instructed to **begin taking study drug. Only a patient's returning of a completely unused study** drug blister pack will result in an otherwise qualified patient being excluded form the ITT population.
- Handling of missing data was amended to define a window of time from the 24-hour time point for the next later pain assessment to be used. Specifically, if no 24-hour pain assessment was available from the patient or the gout flare call

center, the next later pain assessment within 8 hours of the 24-hour time point will be used. Additionally, it was clarified that patients with no pain assessments within the 32-hour window will be considered non-responders.

- Screening period was extended from 2 weeks to 28 days since clinical lab tests were to be repeated every 3 months until double-blind treatment was initiated
- Permitted blood to be collected from non-fasting instead of fasting patients
- Removed from the protocol the necessity to collect blood samples for lipid profile, gamma-glutamyltransferase (GGT), prothrombin time (PT) and activated partial thromboplastin time (PTT)
- Entry criteria amended to exclude patients using anticoagulant medications (i.e., warfarin, low-molecular weight heparin antithrombin agents, thrombin inhibitors, or selective Factor Xa inhibitors) at the time of screening and within 30 days of administration of study drug.
- Sample size estimates were updated to reflect preliminary screening failure data (15% instead of 10% drop out or do not qualify upon calling the gout flare call center) and ineligible gout flare rates (50% fail to have an acute flare instead of the previously projected 45%). As a result, the number of potential patients screened was changed from 300 subjects to 390 subjects in order to achieve at least 47 ITT patients per treatment group (130 randomized patients per treatment group).
- Description of plans for conducting interim monitoring of randomization by an unblinded third party in order to determine that a sufficient number of patients had flared (i.e., after 145 patients had contacted the gout flare call center) so that trial enrollment could be terminated were added.
- Gout flare center was to initiate contact by calling patients back within 1 hour who failed to qualify for initiation of study medication.
- The time windows for Visits 5 and 6 were specified: $\pm$ 2 days for Visit 5 and $\pm$ 5 days for Visit 6.
- The format for the unique patient numbering system used to assign center numbers and patient numbers described in the protocol was updated to match the system actually being used.
- Details regarding blinding, packaging, and labeling of study drug were added to the protocol. A more detailed description of the process to be used by investigators for the unblinding of study medication in the event of a medical emergency was included.

4. Amendment 4 (implemented on August 30, 2007)
The following correction to the plans for interim monitoring of randomization was made that changed the number of randomized subjects who contacted the gout flare call center from 145 to 150 randomized patients:

- Enrollment and randomization was to have continued until at least 47 patients who had been randomized to each treatment group had a qualifying gout flare. When approximately 150 randomized patients had contacted the gout flare call

center and been instructed to begin taking study drug, the sponsor was to have authorized an unblinded third party to review enrollment by group. If the target of at least 47 ITT patients per treatment group had been reached, enrollment and authorization for additional patients to initiate treatment was to have ceased; it was foreseen that after the ITT target had been met, additional patients might have been treated in the interim time between notification and implementation at a given site. If the target of at least 47 ITT patients per treatment group had not been met, monitoring by the unblinded third party was to have been continued until the target number of subjects had been met.

As discussed with David Petullo, staff statistician in OTS/Division of Biostatistics II, none of the above changes to the clinical or statistical methodology of the protocol were thought to have impacted on the trial's final outcome results. However, the prohibition of colchicine for 30 days prior to study entry was instituted after patient randomization had already started. Due to concerns of potential additive effects from concomitant colchicine usage, a post-hoc analysis of the primary endpoint looking specifically at response rates of patients using concomitant colchicine was performed by the statistical reviewer and is discussed in Section 6.

RESULTS:

Disposition of Subjects:
A total of 575 subjects from 72 clinical sites in the United States were randomized to the three treatment groups as follows: 193 patients to the standard dose colchicine group; 193 patients to low dose colchicine group; and 189 patients to the placebo group. Table 4 below, summarizes the disposition of randomized patients in this trial. Of those subjects randomized to a treatment group, 185 had a qualifying flare. One patient who flared in the low dose group (Subject 1010-1011) was not counted in the number of patients treated because he was told not to take his study medication by the gout flare call center due to a ruptured study medication capsule. Overall, the rate of study completion was high with 92% of the subjects who flared completing the trial. The highest rate of study completion was in the low dose group (96%), followed by the placebo group (95%), and the standard dose group (87%). More patients withdrew prematurely for the reason other (4%) as compared to lost to follow-up (2%), withdrew consent (1%) or lack of efficacy (1%). [Note: Review of the data from the 7 patients who discontinued from the trial due to other reasons revealed the following: 4 patients (Subjects 1004-1001, 1012-1005, 1014-1005, and 1068-1013) missed taking doses of study medication for a variety of reasons (i.e., did not hear timer, or capsule was missing from kit), 1 patient (Subject 1007-1002) lost a study capsule and could not find it, and 1 patient (Subject 1009-1008) did have a gout flare (flare of bursitis unrelated to gout).]

Table 4 – Subject Disposition for Study MPC-004-06-001

	Colchicine		Placebo (N=189)	Total (N=575)
	Standard Dose (N=193)	Low Dose (N=193)		
Number of Subjects Randomized	193	193	189	575
Number of Subjects with Qualifying Flare	52 (27%)	75[1] (39%)	58 (31%)	185 (32%)
Number of Subjects with No or Non-Qualifying Flare	141	118	131[2]	390[2]
Number of Subjects Treated (ITT)	52	74	58[2]	184[2]
Number of Subjects who Completed the Study	45 (87%)	71 (96%)	55 (95%)	171 (92%)
Number of Subjects who Withdrew from the Study:	7 (13%)	3 (4%)	4 (7%)	14 (8%)
Lack of Efficacy	0 (0%)	1 (1%)	1 (2%)	2 (1%)
Withdrew Consent	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Lost to Follow-Up	1 (2%)	1 (1%)	1 (2%)	3 (2%)
Other	5 (10%)	1 (1%)	1 (2%)	7 (4%)

[1]Subject 1010-1011 had a qualifying flare but was directed not to take study medication because of a burst capsule. Therefore he is counted in the qualifying flare group but not included in any study population.
[2]Subject 1057-1012 had a flare but never called the Flare Call Center and started study treatment without authorization. This subject is counted in the no flare or non-qualifying flare group and is included in the safety population (but not the intent to treat population).
Adapted from Sponsor's Fig. 10:1; p. 66.

Protocol Deviations/Violations:

A total of 47 patients incurred one or more protocol deviations/violations over the course of this trial. The following table (Table 5) shows that the highest rate of protocol deviations/violations occurred in the placebo group (29%) as compared to the standard dose group (25%) and the low dose group (20%). The most common protocol deviation/violation was due to missed study procedure/inappropriate lab testing (11%), followed by missed or late visits (9%), entry violation (5%), other (1%) and concomitant medications (1%). None of these events resulted in a subject being withdrawn from the trial.

Table 5 – Tabular Summary of Subjects with Protocol Deviations

Protocol Deviation	Colchicine		Placebo (N=59)	Total (N=185)
	Standard Dose (N=52)	Low Dose (N=74)		
Number of Subjects with Protocol Deviations	13 (25%)	15 (20%)	17 (29%)	45 (24%)
Entry Violation	4 (8%)	4 (5%)	2 (3%)	10 (5%)
Missed or Late Visits	4 (8%)	5 (7%)	8 (14%)	17 (9%)
Missed Procedure/Inappropriate Lab Test	7 (13%)	6 (8%)	8 (14%)	21 (11%)
Concomitant Medications	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Other[1]	0 (0%)	1 (1%)	1 (2%)	2 (1%)

Other: Subject 1057-1012 took study drug without permission; Subject 1036-1015 did not sign most current ICF.
Adapted from Sponsor's Listing 16.2.2.3 in appendix of final study report.

Further examination of these protocol deviations revealed that the majority were relatively minor in nature and did not impact on the quality of data collected or the trial outcome. The 10 entry violations were due to subjects either taking prohibited

background medications (i.e., chronic NSAIDs or analgesics) or not on a stable dose of allopurinol for the required 4 weeks prior to randomization and will be explored further in Section 6.

Demographics:
Table 6 summarizes the demographic characteristics of the ITT population who participated in this trial. The subjects who participated in this trial were overwhelmingly Caucasian males and had a mean age of 52 years. These patients were also overweight as evidenced by body mass index (BMI) of 33 which is consistent with the fact that obesity is a risk factor for gout. The majority of subjects (89%) had a normal estimated creatinine clearance based on ideal body weight for BMI since subjects with liver disease or renal impairment were prohibited from study entry. Overall, the study population was representative of the types of patients who would be treated with colchicine for acute gout flares. The baseline demographics were generally well balanced between study arms.

Table 6 - Demographic Characteristics of the ITT Population for Study MPC-004-06-001

Demographic Characteristic	Colchicine		Placebo (N=59)	Total (N=185)
	Standard Dose (N=52)	Low Dose (N=74)		
Age:				
Mean (SD)	52 (10)	51 (12)	51 (11)	52 (11)
Median (Min, Max)	52 (33, 75)	50 (31, 76)	51 (24, 78)	51 (24, 78)
Age Group:				
<45 years	14 (27%)	26 (35%)	12 (20%)	52 (28%)
45-65 years	32 (62%)	35 (47%)	41 (70%)	108 (58%)
>65 years	6 (12%)	13 (18%)	6 (10%)	25 (14%)
Gender:				
Male	49 (94%)	72 (97%)	55 (93%)	176 (95%)
Female	3 (6%)	2 (3%)	4 (7%)	9 (5%)
Race:				
American Indian/Alaska Native	0	1 (1%)	0	1 (1%)
Asian	0	1 (1%)	1 (2%)	2 (1%)
Black/African American	10 (19%)	4 (5%)	11 (19%)	25 (14%)
Native Hawaiian/Pacific Island	0	0	0	0
White/Caucasian	40 (77%)	66 (89%)	47 (80%)	153 (83%)
Other	2 (4%)	2 (3%)	0	4 (2%)
Ethnicity:				
Hispanic/Latino	6 (12%)	6 (8%)	1 (2%)	13 (7%)
Not Hispanic/Latino	46 (89%)	68 (92%)	58 (98%)	172 (93%)
Weight (lb):				
Mean (SD)	228 (38)	228 (42)	228 (42)	228 (41)
Median (Min, Max)	222 (149, 322)	226 (153, 361)	219 (166, 339)	221 (149, 361)
Body Mass Index (lb/in^2):				
Mean (SD)	33 (4.6)	33 (6.3)	33 (5.8)	33 (5.7)
Median (Min, Max)	32 (21, 46)	32 (23, 50)	31 (23, 49)	32 (21, 50)
Estimated Creatinine Clearance (based on actual body weight)[a,b]:				
< 80 mL/min	5 (10%)	8 (11%)	7 (12%)	20 (11%)
≥ 80 mL/min	47 (90%)	66 (89%)	52 (88%)	165 (89%)
Estimated Creatinine Clearance (ideal body weight for BMI >30)[c]:				
< 60 mL/min	5 (10%)	11 (15%)	8 (14%)	24 (13%)
60 – 80 mL/min	18 (35%)	22 (30%)	11 (19%)	51 (28%)
≥ 80 mL/min	29 (56%)	41 (55%)	40 (68%)	110 (59%)

[a]Baseline is the measure taken closest in time to first dose date except in the case of Subject 1069-1015 where an earlier measure of body weight (274 lb) was substituted for the closer in time measure of 177 lb; this latter value was judge to be in error because all other body weights were in the 270 lb range.
[b]Actual body weight was used for all patients.
[c]Actual body weight was used for patients with a BMI ≤ 30 and ideal body weight was used for patients with a BMI > 30.
Adapted from Sponsor's Tables 11:2 and 11:4; p. 70 and 72

The overall mean age of onset of gout was 41 years and the overall number of gout attacks per year was 4.3 for the study population (Table 7). The overall mean time since most recent gout flare prior to screening was 1.6 months. The three groups were balanced in terms of mean serum uric acid (8.8 mg/dL) and the presence of at least one tophus (overall 91%). Overall, the subjects who participated in this trial were typical of

patients with gout flares who could potentially benefit from treatment with colchicine. The gout history characteristics were well balanced between study arms.

Table 7- Tabular Summary of Subjects' Gout History (Safety Population N= 185) for Study MPC-004-06-001

Characteristic	Colchicine		Placebo (N=59)	Total (N=185)
	Standard Dose (N=52)	Low Dose (N=74)		
Age at Onset (yrs):				
Mean (SD)	41 (12)	41 (12)	42 (13)	41 (12)
Median (Min, Max)	38 (19, 67)	38 (21, 75)	42 (14, 68)	39 (14, 75)
Number of Attacks in the Year Prior to Screening:				
Mean (SD)	4.7 (3.3)	4.4 (2.2)	3.8 (2.0)	4.3 (2.5)
Median (Min, Max)	4.0 (2, 20)	4.0 (2, 12)	4.0 (2, 12)	4.0 (2, 20)
Time Since Most Recent Flare Prior to Screening (Months):				
Number of Subjects	38	58	50	146
Mean (SD)	1.4 (1.4)	1.6 (1.4)	1.7 (1.8)	1.6 (1.6)
Median (Min, Max)	0.9 (0, 7)	1.1 (0, 8)	1.0 (0, 8)	1.0 (0, 8)
Serum Uric Acid (mg/dL):				
Mean (SD)	9.2 (1.7)	8.5 (1.8)	8.9 (1.9)	8.8 (1.8)
Median (Min, Max)	9.3 (4.6, 13.7)	8.6 (2.1, 12.1)	8.9 (5.3, 13.8)	8.8 (2.1, 13.8)
Distribution of Serum Uric Acid:				
< 7 mg/dL	5 (10%)	17 (23%)	11 (19%)	33 (18%)
7-9 mg/dL	18 (35%)	33 (45%)	19 (32%)	70 (38%)
> 9 mg/dL	29 (56%)	24 (32%)	29 (49%)	82 (44%)
At Least One Tophus Present:				
Yes	7 (14%)	7 (7%)	5 (9%)	17 (9%)
No	45 (87%)	69 (93%)	54 (92%)	168 (91%)

Adapted from Sponsor's Tables 13:1 and 14.1.3; p. 71 and 248

Besides a high rate of musculoskeletal disorders (67%), the study population reported high rates of co-morbid medical conditions affecting the following systems: cardiovascular (58%), metabolic/endocrine (35%), gastrointestinal (28%), and HEENT (28%). Further review of these data did not reveal any significant differences between the two colchicine treatment groups and the placebo group. Information regarding concomitant non-gout medications used by more than 10% of the study population was also examined. The most commonly reported concomitant non-gout classes of medications were cardiovascular agents (48%), alimentary tract and metabolism agents (34%), and agents that affected the nervous system (12%) and respiratory system (11%). The listed drugs most commonly used included ACE inhibitors (17%), cholesterol lowering agents (17%), angiotensin II antagonists (11%), beta blocking agents (14%), thiazides (10%) and proton pump inhibitors (10%). This information is consistent with what is typically seen in gout patients since this disease is commonly associated with chronic disorders such as hypertension, diabetes mellitus, hyperlipidemia and cardiovascular disease.

Treatment Compliance:
The protocol specified that patients' compliance with study medication was to have been assessed by their diary recordings and capsule counts performed on the returned blister packs of blinded study medication. Subjects were also directly queried by the trial investigators regarding ingestion of study medication. Table 8 below, summarizes the results from these methods used to assess patient compliance with study medication. Overall, 85% of subjects self-reported taking all 7 doses of study medication which was substantiated by the capsule counts on the returned blister packs. Of the 7 patients who returned one or two capsules, 4 subjects (10%) were randomized to the standard dose colchicine treatment group, 2 subjects (3%) were randomized to the low dose colchicine group and 1 subject (2%) was from the placebo group. A total of 20 patients did not return their blister pack of study medications. As per the investigator assessment for treatment compliance, 18 out of these 20 patients had taken all of their study medication and reported doing so in their diary as well. One patient in the standard dose group (Subject 1073-1016) and one patient in the placebo group (Subject 1077-1018) were the only two patients where confirmation of compliance was unavailable.

Table 8 – Tabular Summary of Study Drug Compliance for Subjects Who Participated in Study MPC-004-06-001 (Safety Population)

Source	Colchicine Dose		Placebo (N=59)	Overall (N=185)
	Standard Dose (N=52)	Low Dose (N=74)		
Self-Reported via Diary				
Mean (SD) Number of Capsules	6 (1.5)	7 (1.2)	7 (1.0)	7 (1.2)
Number (%) of Subjects Who Took All 7 Doses	38 (73%)	68 (92%)	52 (88%)	158 (85%)
Number (%) of Subjects Who Took < 7 Doses	14 (27%)	6 (8%)	7 (12%)	27 (15%)
Capsule Count				
No Blister Pack Returned/Missing CRF Capsule Count	10	4	6	20
Number (%) of Subjects with No Capsules Returned	38 (91%)	68 (97%)	52 (98%)	158 (96%)
Number (%) of Subjects with > 0 Capsules Returned	4 (10%)	2 (3%)	1 (2%)	7 (4%)
Investigator Assessment				
Number of Subjects	51	74	59	184
Unknown (%)	1 (2%)	0	0	1 (1%)
Yes (%)	46 (90%)	71 (96%)	58 (98%)	175 (95%)
No (%)	5 (10%)	3 (4%)	1 (2%)	9 (5%)

The diary was missing for 3 patients (Low dose colchicine: Subject 1007-1005; Standard dose colchicine: Subject 1026-1005 and Subject 1082-1001).
Adapted Sponsor's Table 11:9; p. 78.

Efficacy

Primary Efficacy Results

The primary efficacy endpoint was a responder analysis based on subject self-assessment of pain at 24 hours post ingestion of the first dose of study medication that was measured by an 11-point pain-intensity numeric rating scale [PINRS]. Table 9 is a tabular summary of the change from baseline in target joint pain score at 24 hours post first dose of study medication for the ITT population upon which the primary efficacy analysis is based. Baseline mean pain scores were similar for all three treatment groups (range 6.8 to 6.9). Both the standard and low dose colchicine groups had lower mean pain scores (4.9 and 4.7, respectively) at 24 hours post first dose of study medication as compared to the placebo group (6.2) resulting in greater mean reductions in pain (standard dose: -2.0 units; low dose: -2.2 units) as compared to the placebo group (-0.7 units).

Table 9 – Tabular Summary of Change from Baseline Target Joint Pain Score at 24 Hours Post First Dose of Study Medication (ITT Population, LOCF)

Timepoint	Colchicine Dose		Placebo (N=58)
	Standard Dose (N=52)	Standard Dose (N=52)	
Baseline:			
Mean (SD)	6.9 (1.6)	6.9 (1.7)	6.8 (1.4)
Median (Min, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)
24-Hours:			
Mean (SD)	4.9 (3.0)	4.7 (3.2)	6.2 (2.7)
Median (Min, Max)	5.0 (0, 10)	5.0 (0, 10)	6.5 (0, 10)
Change From Baseline to 24 Hours:			
Mean (SD)	-2.0 (2.9)	-2.2 (3.5)	-0.7 (2.8)
Median (Min, Max)	-2.0 (-9, 4)	-2.0 (-9, 5)	0.0 (-8,4)

Note: Pain assessed via 11-point pain intensity numeric rating scale where 0 =no pain and 10 = worst pain imaginable.
Adapted Sponsor's Table 14.2.4.1; p. 336.

For purposes of this trial, the definition of a responder to study therapy was one who achieved a $\geq$ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and did not use rescue medication prior to the actual time of 24-hour post-dose assessment. Subjects who used rescue medication, discontinued prior to the 24-hour post-dose assessment, or did not achieve a $\geq$ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score were deemed non-responders. A total of 17 patients in the standard dose colchicine group, 28 patients in the low dose colchicine group and 9 patients in the placebo group met the prespecified criteria for response to therapy. As shown in Table 10, a greater proportion of patients achieved the primary endpoint for both the standard dose (33%) and low dose (38%) colchicine groups as compared to placebo (16%). The differences between each of the treatment groups and the placebo group were statistically significant

(standard dose versus placebo: p=0.0343; low dose versus placebo: p=0.0046). No difference was noted on comparison of response rates for the standard versus low dose colchicine groups (p =0.5529). However, since none of these analyses adjusted for multiple comparisons post-hoc testing for multiplicity were performed by the statistical reviewer. Additionally, these analyses were calculated using the unstratified Pearson chi-square test instead of the prespecified Mantel-Haenszel chi-square stratified for site as per the trial's SAP since stratification was not possible due to the enrollment of less than 1 patient in each treatment group by a number of study sites. Given these circumstances, the use of another chi square testing method was statistically acceptable.

Table 10 – Tabular Summary of Treatment Response Based on Target Joint Pain at 24 Hours Post First Dose of Study Medication (Primary Endpoint) for the Study MPC-004-06-001 (ITT Population)

Number (%) Responders			Treatment Comparison (Odds Ratio and 95% Confidence Interval)		
Colchicine		Placebo (N=58)	Standard vs Placebo	Low vs Placebo	Standard vs Low
Standard Dose (N=52)	Low Dose (N=74)				
17 (33%)	28 (38%)	9 (16%)	2.64 (1.06, 6.62)	3.31 (1.41, 7.77)	0.80 (0.38, 1.68)
			p = 0.0343[1]	p = 0.0046[1]	p = 0.5529[1]

For the primary endpoint, a responder is defined as a patient who achieved a ≥ 50% reduction in pain score and did not take rescue medication prior to the 24-hour post dose assessment.
[1]P-value is from the unstratified Pearson chi-square test.
Sponsor's Table 11:10; p. 79.

Sensitivity Analyses:

The results from multiple sensitivity analyses which involved looking at alternate definitions of response were supportive of the primary efficacy results. These analyses confirmed that treatment group differences noted in the analysis of the primary endpoint were not dependent on a chosen threshold of response. The cumulative distribution of the proportion of subjects who met increasing thresholds of response (i.e., from 0% reduction from baseline to 100% reduction from baseline) showed that there were more responders in the two colchicine treatment groups than in the placebo group. The results of an analysis of treatment response based on target joint pain at 32 hours to permit late development of response to treatment produced similar findings to the primary analysis at 24 hours as did those based on at least a 2-unit reduction in target joint pain score at 24 and 32 hours post first dose of study medication.

Secondary Efficacy Endpoints

There were multiple secondary endpoints which are summarized in Table 11, below:

Table 11 – Tabular Summary of Secondary Endpoint Analyses

Secondary Efficacy Variable	P-value	Comment
Magnitude of Pain Reduction (at 24 hours)	Standard vs Placebo p = 0.0368 Low vs Placebo p = 0.0015 Standard vs Low p = 0.3298	Higher proportion of responders with at least a 2-unit reduction in both the standard (35%) and low dose (43%) colchicine groups than in the placebo group (17%)
Time to Response (time to 50% reduction in target joint pain)	Standard vs Placebo p = 0.0593 Low vs Placebo p = 0.0059 Standard vs Low p = 0.3895	Median time to a 50% reduction from baseline target joint pain score was 32 hours for the standard dose colchicine group, 24.5 hours for the low dose colchicine group, but could not be calculated for the placebo group due to an insufficient number of patients achieving this endpoint
Time to Complete Pain Relief (90%) Reduction	Standard vs Placebo p = 0.0308 Low vs Placebo p = 0.04078 Standard vs Low p = 0.0635	Median time to a 90% for near complete pain relief was 48 hours for the standard dose colchicine group, 64 hours for the low dose colchicine group, but could not be calculated for the placebo group due to an insufficient number of patients achieving this endpoint
Time to Use of Rescue Medications		The time to use of rescue medication was earlier for the placebo group (24 hours) as compared to the standard dose (70 hours) and low dose (36.5 hours) colchicine treatment groups
Signs and Symptoms of Inflammation per Investigator's Clinical Assessment	Standard vs Placebo p = 0.0154 Low vs Placebo p = 0.0451 Standard vs Low p = 0.5851	More patients in the two colchicine treatment groups had lower target joint inflammation scores than patients in the placebo group, however, the mean time to the first post-flare visit relative to the first dose differed between the 3 treatment groups (ranging from 2.6 to 3.6 days) so that the assessments do not correspond to a timepoint close to treatment or resolution
Investigator Global Assessment of Response to Treatment	Standard vs Placebo p < 0.0001 Low vs Placebo p =0.0134 Standard vs Low p = 0.0084	Response was judged to be significantly better in the two colchicine treatment groups compared to the placebo group, however, some evaluations were performed days after the gout flare and resolution.

For some of the secondary endpoints, the timing of evaluations differed greatly between the three treatment groups (i.e., signs and symptoms of inflammation and the global assessment by study investigators) so that the validity of the results generated from these analyses is questionable. Additionally, the analyses of the secondary endpoints did not control for multiplicity. Therefore, these results should not be included in the product's label.

Efficacy Conclusions:
Both the standard dose (4.8 mg) and low dose (1.8 mg) treatment regimens of colchicine were significantly better than placebo in the treatment of acute gout flares as assessed by the higher proportion of patients who had ≥ 50% improvement in target joint pain at 24 hours post-initiation of treatment. These results were supported by similar outcomes observed in the sensitivity analyses as well as the results from the secondary outcomes. Both the standard and low dose colchicine groups were shown to be significantly better than placebo in the magnitude of pain reduction at 24 hours, time to response (i.e., time to 50% reduction in target joint pain), time to complete pain relief (90%) reduction, time to use of rescue medications, and in the investigator's global assessment and signs/symptoms of inflammation. However, the validity of the results generated from the last two secondary endpoints is questionable due to intergroup variations in the timing of the evaluations upon which these analyses are based. Additionally, no multiplicity correction was planned in the protocol or implemented during the analyses of the secondary endpoints. Thus, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

"*Does Colchicine Work? The Results of the First Controlled Study in Acute Gout*"; Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, and Jones M, Aust NZ J Med, 1987

This was to have been a randomized, double blind, placebo-controlled, hospital based study in 43 patients with crystal proven gout to evaluate the efficacy of colchicine as a treatment for acute flares of this disease. Following microscopic confirmation of the presence of monosodium urate crystals on joint aspiration consistent with an acute gout flare, patients were to have been randomized to one of two treatment groups: oral colchicine or matching placebo. Colchicine was to have been administered initially as a 1 mg dose, followed by an additional 0.5 mg every 2 hours until the development of complete response or toxicity (i.e., nausea, vomiting, or diarrhea) was observed. Patients were to have been prohibited from using concomitant analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) for 48 hours prior to study entry or for the duration of their trial participation. Patients were to have assessed their pain via a visual analogue scale (VAS). Blinded investigator assessments that included pain, tenderness on palpation, swelling and redness graded via 4-point scales (none = 0 to severe = 3) were to have used to generate a compounded clinical score (rated 0 to 12). All study subjects were to have been evaluated every 6 hours over a study time course of 48

hours. The protocol specified that improvement was defined as ≥ 50% decrease from baseline measurements. Study results were to have been analyzed using the student's t-test, the chi-square test, regression analysis and analysis of variance for repeated measures.

The subjects who had participated in this study were predominantly male (40 males and 3 females) which is consistent with the patient population who have gout. Other demographic and disease characteristics for this trial population were similar for both treatment groups with respect to age, weight, number of joints involved serum uric acid levels, and baseline pain and clinical scores (Table 12).

Table 12 – Baseline Demographic and Disease Characteristics of Study Subjects*

Demographic and Disease Characteristic	Colchicine (N=22)	Placebo (N=21)
Number of Joints Involved:	22	22
Large**	8	6
Small**	14	16
Age (years):		
Mean (SD)	69 (8)	70 ±8
Range	55-85	56-91
Duration of Symptoms (hours)	38 ± 51	38 ± 29
Weight (kg)	71 ± 9	74 ± 11
Serum Uric Acid (mmol/l) (normal range:0.12-0.45 mmol/l)	0.55 ± 0.16	0.50 ± 0.15
Serum Creatinine (mmol/l) (normal range: 0.06-0.13)	0.14 ± 0.08	0.12 ± 0.03
Clinical Score	9.5 ± 2.8	10.3 ± 2.4
Pain Score	56 ± 21	68 ± 21

Table reproduced from published article by Ahern et al[1]
*No significant differences between the groups were detected using Student's t-test
**Large = knee, ankle, wrist; small = metatarsophalangeal, metacarpophalangeal, interphalangeal

Results

Primary analyses:
Study drug dosing was to have stopped once toxicity had developed, however, pain and clinical assessments were to have continued until 48 hours had elapsed since initiating study medication. Nine patients reportedly had 50% improvement in their pain scores before colchicine toxicity occurred, one patient was symptomatically toxic concurrently with a 50% improvement in pain score, and 12 patients had 50% improvements in their pain scores post-toxicity. In terms of 50% improvement in clinical scores, two patients achieved this prior to developing colchicine toxicity, while twenty patients reached this level of improvement post-toxicity. Table 13 shows that higher rates of patients treated with colchicine in this study had a 50% reduction in both their pain (73%) and clinical scores (50%) as compared to placebo treated patients (pain scores: 32%; clinical score: 5%) which reached statistical significance at 36 hours post-treatment ($p<0.001$). These

rates of improvement in both the pain (73%) and clinical scores (64%) for colchicine treated patients were maintained at 48 hours post-treatment and were found to be significantly higher as compared to those for placebo treated patients (pain score: 36%; clinical score: 23%) ($p<0.05$).

Table 13 – Tabular Summary of the Percentage of Joint Response to Treatment Defined as a 50% Reduction in Pain and Clinical Scores in 1987 Ahern et al[1] Study

	12 Hrs. Post-Treatment	24 Hrs. Post Treatment	36 Hrs Post-Treatment	48 Hrs. Post Treatment
Clinical Score:				
Colchicine	5%	23%	50%**	64%*
Placebo	0%	0%	5%	23%
Pain Score:				
Colchicine	23%	41%	73%*	73%*
Placebo	9%	9%	32%	36%

*p< 0.05; **p<0.01 via chi-square test

Figures 1 and 2 graphically depict the changes in clinical and pain scores for both treatment groups over the course of study observation and show that a therapeutic response to study drug occurred earlier in the colchicine treatment group as compared to the placebo group.

Figure 1 - Change in the Clinical Score
(Note: Bars denote means ± 95% confidence intervals)

Figure 1 copied directly from published 1987 article by Ahern et al[1]

Fig 2 – Change in Pain Score
(Note: Bars denote means ± 95% confidence intervals)

Figure 2 copied directly from published 1987 article by Ahern et al[1]

Secondary Analyses:
Regression analysis was used to determine if baseline pain and clinical scores had any effect on study outcome as assessed via pain or clinical scores at 48 hours. The results of this analysis reportedly demonstrated that colchicine and baseline scores had a significant effect on study outcome at 48 hours accounting for a 40% variance associated with the final scores at this timepoint. Additional analyses involving other baseline demographic and disease characteristics such as age, weight, duration of symptoms, nature of joint involvement, serum uric acid level, and serum creatinine level failed to identify any effect of these variables on the final outcome results.

Analysis of variance with repeated measures was used to determine if the final outcome results for both the pain and clinical scores were affected by time or drug. A diurnal effect was reportedly not shown to exist, however, the results of this analysis for drug effect suggested that colchicine was better than placebo as a treatment for acute gout flares.

Safety (Toxicity)

Patients were to have been dosed until they developed either a complete response or symptoms of colchicine toxicity (i.e., nausea, vomiting, or diarrhea). All patients in the colchicine group reportedly developed diarrhea and/or vomiting at a median time of 24 hours (range: 12-36 hours) or after ingesting a mean dose of 6.7 mg of colchicine. A total of five placebo treated patients reportedly developed nausea during the trial. These results raise questions regarding maintenance of the blind given that the blinded clinical evaluators may have been aware of patients' clinical manifestations of toxicity since they were acting as rheumatology consultants to an inpatient population cared for by hospital staff.

Efficacy Conclusions:
This study demonstrates that a higher percentage of patients treated with colchicine had a significant improvement as assessed by a 50% improvement over both baseline pain and clinical scores as compared to placebo treated patients with crystal-proven gout flares following the administration of a mean dose of 6.7 mg of colchicine. Improvement in both pain and clinical scores occurred earlier in patients treated with colchicine as compared to placebo treated patients. These findings occurred despite the relatively late initiation of study treatment in relation to the time of flare onset (i.e., approximately 38 hours post-flare). However, interpretation of these findings should take into account possible unblinding as a result of symptomatic drug toxicity occurring in all patients randomized to treatment with colchicine.

6 Review of Efficacy

Efficacy Summary

The clinical data submitted in support of a clinical indication for colchicine as a treatment for acute gout was generated from one Phase 3 trial, MCP-004-06-001, and supported by the results from the published randomized controlled trial in acute gout by Ahern et al. MPC-004-06-001 was a double-blind, multicenter, randomized, placebo-controlled, parallel group dose comparison study in 185 patients with acute gout that evaluated the efficacy of two dosing regimens of colchicine when administered orally as total doses of 4.8 mg over 6 hours (i.e., standard dose colchicine group) and 1.8 mg over 1 hour (i.e., low dose colchicine group) compared to placebo. The clinical efficacy of colchicine was demonstrated in this trial as assessed by the primary endpoint, which was defined as a $\geq$ 50% improvement in target joint pain score at 24 hours post-initiation of treatment without the use of rescue medication. A greater proportion of patients achieved the primary endpoint for the standard dose (33%) and low dose (38%)

colchicine groups as compared to placebo (16%). The differences between each of the colchicine treatment groups and the placebo group were statistically significant (standard dose versus placebo: p=0.0343; low dose versus placebo: p=0.0046). No difference was noted on comparison of response rates for the standard versus low dose colchicine groups (p=0.5529). Although none of these analyses adjusted for multiple comparisons, the results from post hoc multiple adjustment analyses (i.e., Bonferoni, Hochberg, and the intersection union test) of the primary endpoint response data supported the findings of the original analysis with statistical significance observed for all three tests comparing the low dose colchicine treatment group versus placebo, and on two out of the three tests comparing the standard dose colchicine treatment group versus placebo. The latter comparison trended towards significance on the Bonferoni analyses. These results were robust based on a variety of sensitivity analyses that evaluated alternate definitions of response.

Additional support for the effectiveness of colchicine in acute gout came from a number of secondary endpoints. The median time to a 50% reduction from baseline for target joint pain score was 32.0 hours for patients randomized to standard dose colchicine group and 24.5 hours for patients in the low dose colchicine group; however, this parameter could not be calculated for the placebo group due to an insufficient number of patients who achieved this level of response. Significantly more placebo patients (50%) also used rescue medication within 24 hours of initiating study drug therapy as compared to the low dose colchicine group (31%; p=0.0273). However, the results of this analysis comparing the use of rescue medication within 24 hours for the standard dose colchicine group (35%) versus placebo was not significantly different (p=0.1034). No difference was noted either when comparing these rates between the two colchicine treatment groups (p=0.6768). The time to use of rescue medication occurred earlier in the patients randomized to placebo (24.0 hours) as compared to 70.0 hours for the standard dose colchicine group and 37 hours for the low dose colchicine group. Since the SAP for this study did not prespecify a correction for multiplicity regarding the secondary endpoints, declaring statistical significance using unadjusted p-values may be inappropriate. Therefore, the results from the secondary endpoint analyses should not be included in the drug label. The results from subpopulation analyses were also not shown to be significantly differently, however, the small number of patients involved in these analyses raises questions concerning the validity of these findings. Examination of a number of background disease factors (i.e., serum uric acid, duration of gout, flare frequency, alcohol use, and weight adjusted creatinine clearance) did not show any overall effect on response to study treatment. Concomitant use of allopurinol, diuretics, systemic corticosteroids, and NSAIDs did not appear to have any impact on study outcome with the exception of ibuprofen usage. The outcome of this analysis may be related to the lack of placebo responders taking ibuprofen.

The trial by Ahern et al, was a randomized, double blind, placebo-controlled, hospital based study in 43 patients with crystal proven acute gout attacks. This trial evaluated a dosing regimen that involved a 1mg initial dose of the drug followed by an additional 0.5

mg every 2 hours until the development of complete response or toxicity (i.e., nausea, vomiting, or diarrhea) was observed. Colchicine's efficacy as a treatment for acute gout was demonstrated by significantly higher rates of patients treated with colchicine having a 50% reduction in both their pain (73%) and clinical scores (50%) as compared to placebo treated patients (pain score:32%; clinical score: 5%) at 36 hours post-treatment ($p<0.001$). These rates of improvement in both the pain (73%) and clinical scores (64%) for colchicine treated patients were maintained at 48 hours post-treatment and were found to be significantly higher as compared to those for placebo treated patients (pain score: 36%; clinical score:23%) ($p<0.05$). Since both the original protocol and data sets for this study were not available for review, the agency could not independently verity these results. One limitation of the study was the potential for unblinding due to colchicine toxicity occurring before there had been a major improvement in the clinical score in 91% of patients randomized to this treatment group.

6.1 Indication

Treatment of gout flare

6.1.1 Methods

Efficacy data contained in the submission generated from the 1-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose comparison study, MPC-004-06-001, in 185 patients with gout were reviewed to assess the applicant's drug application. Analyses of pertinent subgroups were also conducted. All primary and secondary analyses were confirmed by the FDA's statistical reviewer. The design of this study was discussed in Section 5.3.

Additionally, support for colchicine's effectiveness as a treatment for acute gout flares was generated from the 1987 published randomized, double-blind, placebo controlled trial by Ahern et al in 43 patients with crystal-proven gout attacks. The analyses from this trial were also confirmed by the FDA's statistical reviewer. A brief discussion of this study's design can be found in Section 5.3.

6.1.2 Demographics

The baseline characteristics and gout history for the patient population enrolled in MCP-004-06-001 were similar for all three treatment groups with respect to age, gender, race, BMI, number of gout attacks per year, serum uric acid levels, and presence of tophi. There were no significant differences between the two treatment groups with respect to demographics or baseline disease characteristics in the trial published by Ahern et al. These data are discussed in detail in Section 5.4.

6.1.3 Subject Disposition

As discussed in Section 5.4, a total of 171 (92%) patients who met the flare criteria for initiating study treatment were able to complete study MPC-004-06-001 as follows: 96% in the low dose colchicine group, 95% in the placebo group and 87% in the standard dose colchicine group. The majority of patients who prematurely withdrew from this trial did so due to the reason other (4%), followed by lost to follow up (2%), withdrew consent (1%), and lack of efficacy (1%). Since the trial by Ahern et al was conducted as an inpatient study, all subjects were required to complete the 48 hours of study assessments even if study dosing was discontinued due to toxicity. Thus, all patients reportedly completed this trial.

6.1.4 Analysis of Primary Endpoint

A. Study MPC-004-06-001

Study MPC-004-06-001 is an adequate and well-controlled study by virtue of its double-blind, randomized, controlled design. It was intended to evaluate the safety and efficacy of colchicine as a treatment for acute gout flares in patients who met the American College of Rheumatology criteria for gout. The latter is the standard by which patients are diagnosed with this disease. Thus, the results from this trial would be generally applicable to the population with gout. Gout is a non-lethal, crystal induced arthropathy that can result in extremely painful, intermittent inflammatory flares of arthritis that are self-limited in nature. The use of a placebo-controlled study was appropriate for assessing this drug's efficacy since the study endpoints are subjective in nature (i.e., pain and inflammation) and colchicine provides only symptomatic relief and is not a curative agent. It was appropriate to include the use of rescue medication for intolerable pain since this was a placebo-controlled trial and one of the colchicine doses evaluated (i.e., low dose regimen: 1.8 mg) was lower than what had been traditionally used in the management of acute gout flares. The 1-week duration of therapy with 72-hours of assessments post initiation of study therapy was also appropriate given the self-limited nature of gout flares (i.e., 1-2 weeks).

The primary efficacy endpoint for study MPC-004-06-001 was a responder analysis based on the results from a self-administered, 11-point Likert scale for pain intensity of a target joint over 72 hours post-initiation of study treatment for an acute gout flare. This information was to have been recorded in patients' diaries and used to calculate the primary endpoint. In view of gout's disease presentation and course, this trial was designed to be conducted on an outpatient basis using diary cards to capture subjects' assessments of response to study treatment. Patient diaries have been successfully used in analgesic trials to capture this type of information. The Likert scale is a validated self-administered pain assessment tool that has been accepted by the agency for the evaluation of outcomes in analgesic studies. Since a clinically significant improvement

in pain in analgesic trials is considered to be at a minimum of 30% improvement as measured via a numerical rating scale, the proportion of responders with at least a 50% reduction from baseline in the mean pain score of the target joint in gout was deemed an appropriate endpoint.

For purposes of this trial, a responder to study therapy was predefined as a patient who achieved a $\geq$ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and who did not use rescue medication prior to the time of 24-hour post-dose assessment. Subjects who used rescue medication, discontinued prior to the 24-hour post-dose assessment, or did not achieve a $\geq$ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score were deemed non-responders. Mean baseline pain scores were similar for all three treatment groups (range: 6.8 to 6.9). At 24 hours post first dose of study medication, both the standard and low dose colchicine groups had lower mean pain scores (4.9 and 4.7, respectively) as compared to the placebo group (6.2) corresponding to greater mean reductions in pain (standard dose: -2.0 units; low dose: -2.2 units) as compared to the placebo group (-0.7 units). A total of 17 patients in the standard dose colchicine group, 28 patients in the low dose colchicine group and 9 patients in the placebo group met the prespecified criteria for response to therapy. As shown in Table 14, a greater proportion of patients achieved the primary endpoint for both the standard dose (33%) and low dose (38%) colchicine groups as compared to placebo (16%). The differences between each of the treatment groups and the placebo group were statistically significant (standard dose versus placebo: p=0.0343; low dose versus placebo: p=0.0046). No difference was noted on comparison of response rates for the standard versus low dose colchicine groups (p =0.5529). However, none of these analyses adjusted for multiple comparisons. Additionally, they were calculated using the unstratified Pearson chi-square test instead of the prespecified Mantel-Haenszel chi-square stratified for site as per the trial's SAP since stratification was not possible due to the enrollment of less than 1 patient in each treatment group by a number of study sites. Given these circumstances, the use of another chi square testing method was statistically acceptable, however, concerns regarding multiplicity issues were raised.

Table 14 – Tabular Summary of Treatment Response Based on Target Joint Pain at 24 Hours Post First Dose of Study Medication (Primary Endpoint) for the Study MPC-004-06-001 (ITT Population)

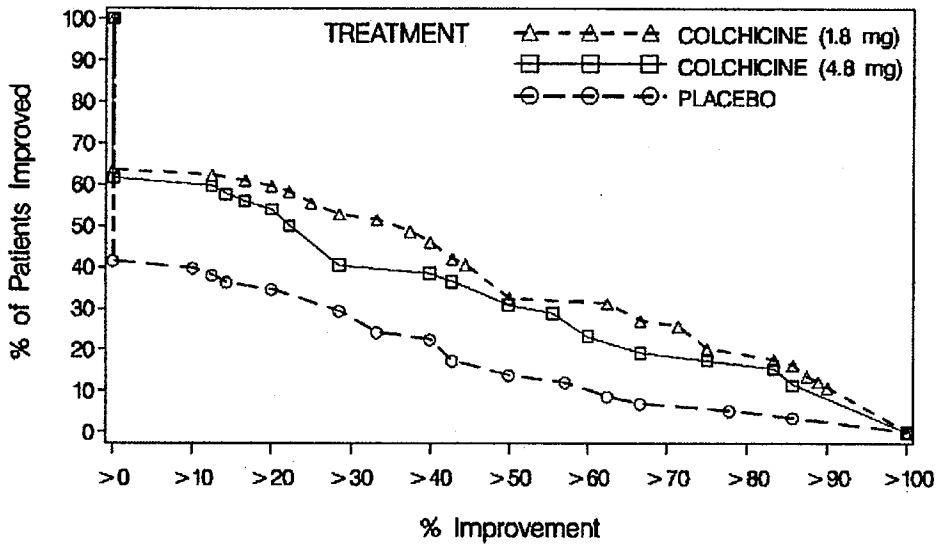
Number (%) Responders			Treatment Comparison (Odds Ratio and 95% Confidence Interval)		
Colchicine		Placebo (N=58)	Standard vs Placebo	Low vs Placebo	Standard vs Low
Standard Dose (N=52)	Low Dose (N=74)				
17 (33%)	28 (38%)	9 (16%)	2.64 (1.06, 6.62)	3.31 (1.41, 7.77)	0.80 (0.38, 1.68)
			p = 0.0343[1]	p = 0.0046[1]	p = 0.5529[1]

For the primary endpoint, a responder is defined as a patient who achieved a ≥ 50% reduction in pain score and did not take rescue medication prior to the 24-hour post dose assessment.
[1]P-value is from the unstratified Pearson chi-square test.
Sponsor's Table 11:10; p. 79.

In view of these multiplicity concerns, the statistical reviewer calculated three different multiple adjustment analyses (i.e., Bonferoni, Hochberg, and the intersection union test) for the results of the primary endpoint post hoc. Overall, these results supported the findings of the original analysis with statistical significance observed for all three tests comparing the low dose colchicine treatment group versus placebo, and on two out of the three tests comparing the standard dose colchicine treatment group versus placebo. The latter comparison trended towards significance on the Bonferoni analyses (alpha=0.025; p-value= 0.03). (Refer to statistician's review of this application for additional information regarding these analyses.)

The results from sensitivity analyses which evaluated alternate definitions of response were supportive of the primary efficacy results. These analyses confirmed that treatment group differences noted in the analysis of the primary endpoint were not dependent on a chosen threshold of response. The cumulative distribution of the proportion of subjects who met increasing thresholds of response (from 0% reduction from baseline to 100% reduction from baseline) that imputed an outcome of no response for patients who used rescue medication showed that there were more responders in the two colchicine treatment groups than in the placebo group. The results of this analysis are graphically depicted in Figure 3.

Figure 3 – Cumulative Distribution of Subjects' Percent Improvement for Target Joint Pain Over 24 Hours Post First Dose of Study Medication for Study MPC-004-06-001 (ITT Population)



Sponsor's Figure 11:1; p. 81.

Two other sensitivity analyses which looked at patients with at least a 2-unit reduction in target joint pain score at 24 and 32 hours (the latter to permit late development of response to treatment) post first dose of study medication produced similar findings to the primary analysis at 24 hours (Table 15). At the 24-hour timepoint, a greater proportion of patients achieved at least a 2-unit reduction in target joint pain score in both the standard dose (35%) and low dose (43%) colchicine groups as compared to placebo (17%). The differences between each of the treatment groups and the placebo group were statistically significant (standard dose versus placebo: p=0.0368; low dose versus placebo: p=0.0015). No difference was noted on comparison of response rates for the standard versus low dose colchicine groups (p =0.3298). At the 32-hour timepoint, a greater proportion of patients again achieved at least a 2-unit reduction in target joint pain score in both the standard dose (39%) and low dose (46%), colchicine groups as compared to placebo (17%). The differences between each of the treatment groups and the placebo group were statistically significant (standard dose versus placebo: p=0.0126; low dose versus placebo: p=0.0005). No difference was noted on comparison of response rates for the standard versus low dose colchicine groups (p =0.4033).

Table 15 – Subjects' Response to Treatment Based on at Least a 2-Unit Reduction in Target Pain Score at 24 hours and 32 Hours Post First Dose in Study MPC-004-06-001 (ITT Population)

Hours Post First Dose	Number (%) Responders			Treatment Comparison (Odds Ratio and 95% Confidence Interval)		
	Colchicine Standard Dose (N=52)	Colchicine Low Dose (N=74)	Placebo (N=58)	Standard vs Placebo	Low vs Placebo	Standard vs Low
24	18 (35%)	32 (43%)	10 (17%)	2.54 (1.04, 6.18)	3.66 (1.61, 8.32)	0.69 (0.33, 1.45)
				p = 0.0368	p = 0.0015	p = 0.3298
32	20 (39%)	34 (46%)	10 (17%)	3.00 (1.24, 7.24)	4.08 (1.80, 9.27)	0.74 (0.36, 1.510
				p = 0.0126	p = 0.0005	p = 0.4033

[1]P-value is from the unstratified Pearson chi-square test.
Sponsor's Table 11:13; p. 82.

B. Published study by Ahern et al

With regards to the trial by Ahern et al, which is an adequate and well controlled study, that evaluated the efficacy of colchicine when given via a traditional dosing method (until complete response or drug toxicity occurs) in patients with crystal-proven acute gout flares. The authors conducted this trial on an inpatient basis in order to ensure that all subjects met entry criteria (i.e., crystal-proven disease) and were compliant with both study therapy and assessments over the 48 hours of study observation. By also controlling access to NSAIDs or analgesics, they were able to create the best case scenario to evaluate colchicine's efficacy in treating acute gout flares. The use of a placebo-controlled study design was appropriate since the trial's endpoints were subjective in nature and susceptible to observer bias (i.e., pain and the clinical signs/symptoms of inflammation) The duration of observation (48 hours) was adequate to capture the necessary data to conclude that the improvement observed was not due to the self-limiting nature of the gout flare.

The primary efficacy endpoints for this trial involved demonstration of 50% improvement over baseline pain and clinical scores. Pain was assessed via a visual analogue scale (VAS) while the clinical score was a composite score generated from assessments by blinded evaluators of the signs and symptoms of inflammation (i.e., pain, tenderness on palpation, swelling and redness). Each of these components were graded using 4-point scales which were added together to generate a final score (score range: 0-12). The authors reportedly validated both of these assessment tools in a previously conducted acute gout study involving indomethacin. Both visual analogue scales and clinical scores have been accepted by the agency for the evaluation of outcomes in analgesic studies and other disease trials. As discussed above, the proportion of responders with at least a 50% reduction from baseline in the mean pain and clinical score of the target joint in gout was deemed an appropriate endpoint given the disease's self-limited inflammatory basis and colchicine's non-curative effects.

Table 16 shows that a higher proportion of patients treated with colchicine in this study had a 50% reduction in both their pain (73%) and clinical scores (50%) as compared to placebo treated patients (pain scores: 32%; clinical score: 5%), which reached statistical significance at 36 hours post-treatment ($p<0.001$). These rates of improvement in both the pain (73%) and clinical scores (64%) for colchicine-treated patients were maintained at 48 hours post-treatment and were found to be significantly higher as compared to those for placebo-treated patients (pain score: 36%; clinical score: 23%) ($p<0.05$). A therapeutic response to study drug appears to occur earlier in the colchicine treatment group as compared to the placebo group in this study as shown in Fig. 1 and 2 in Section 5.3. However, there remains the possibility of bias due to unblinding side effects since colchicine toxicity occurred before there had been a major improvement in the clinical score of 91% of the patients randomized to this treatment group.

Table 16 – Tabular Summary of the Percentage of Joint Response to Treatment Defined as a 50% Reduction in Pain and Clinical Scores in 1987 Ahern et al[1] Study

	12 Hrs. Post-Treatment	24 Hrs. Post Treatment	36 Hrs Post-Treatment	48 Hrs. Post Treatment
Clinical Score:				
Colchicine	5%	23%	50%**	64%*
Placebo	0%	0%	5%	23%
Pain Score:				
Colchicine	23%	41%	73%*	73%*
Placebo	9%	9%	32%	36%

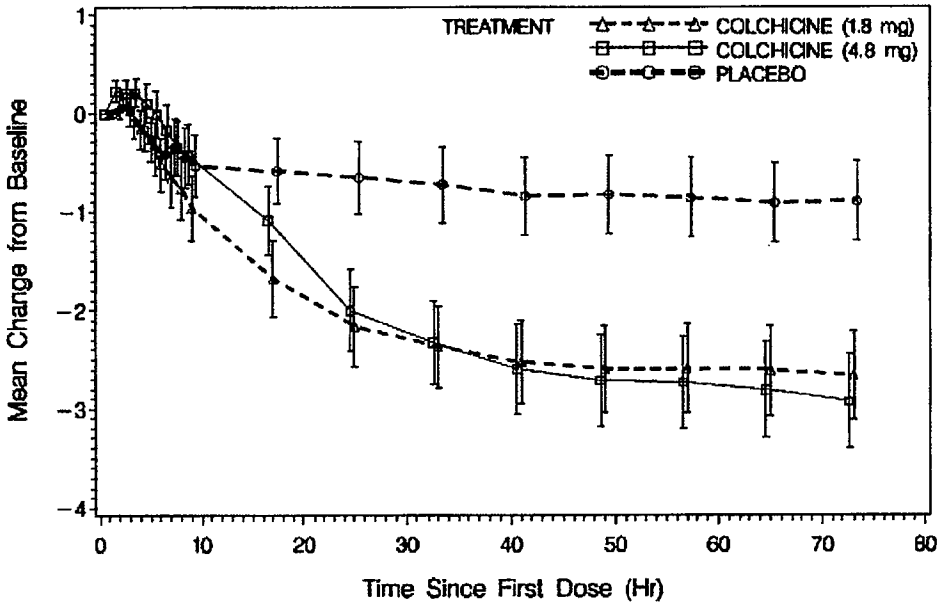
*p< 0.05; **p<0.01 via chi-square test

6.1.5 Analysis of Secondary Endpoints

Time Course of Pain Relief

Figure 4 graphically depicts the time course of pain relief over the 72 hours of target joint pain assessment for each of the 3 treatment groups in study MCP-004-06-001. Over the first 8 hours of reporting there is an initial decrease in the target joint pain score for all 3 treatment groups before the two colchicine groups separate out from the placebo group as they continue to show a steady decline in the mean change over baseline pain score. This is consistent with a therapeutic response to colchicine therapy and is supportive of the primary endpoint results.

Fig. 4 – Target Joint Pain Score at Each Assessment Time Point Post First Dose and Corresponding Change from Baseline (LOCF) (ITT Population)

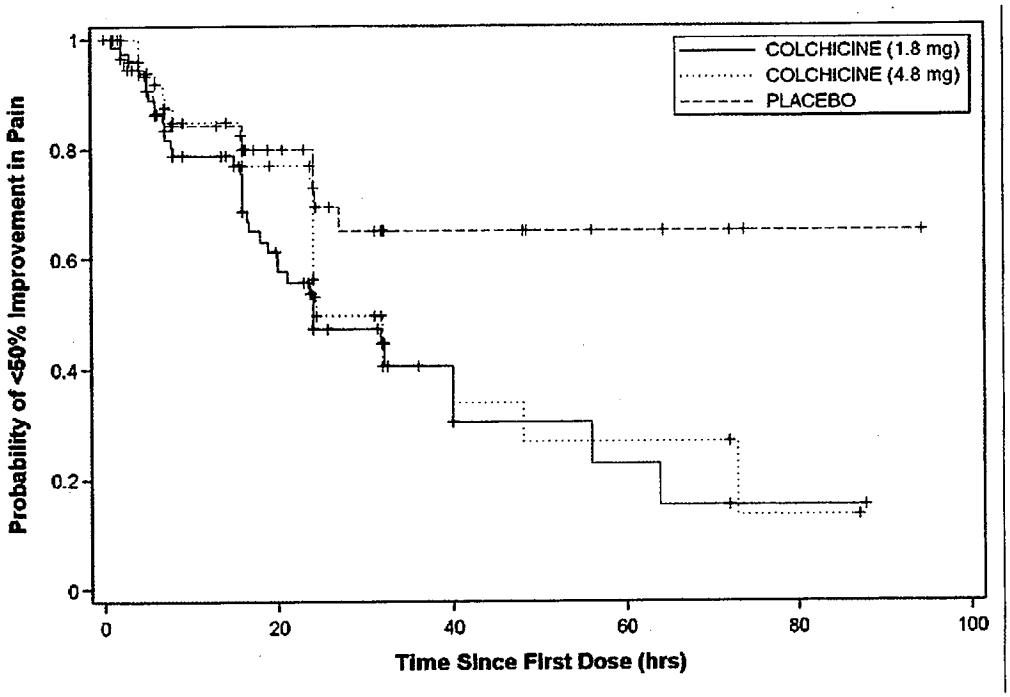


Sponsor's Fig. 2.7.3:3, p. 83.

Time to Response

Since the primary efficacy endpoint was based on subjects demonstrating a ≥ 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score in study MCP-004-06-001, these data were used to plot Kaplan-Meier survival curves for all three treatment groups as shown in Fig. 5. The median time to a 50% reduction from baseline for target joint pain score was calculated to be 32 hours for the standard dose colchicine group and 24.5 hours for the low dose colchicine group, but could not be calculated for the placebo group due to an insufficient number of patients achieving this level of response. These results provide additional support of colchicine's effectiveness as a treatment for acute gout.

Fig. 5 – Median Time to a 50% Reduction from Baseline for Target Joint Pain Score (ITT Population)



Sponsor's Fig. 11:4; p. 85.

Use of Rescue Medication

Acute gout is an extremely painful malady. As per the trial protocol discussed in Section 5.3, patients who participated in this trial were to have been instructed not take rescue medication within the first 12 hours post-ingestion of study drug, and then encouraged not to use them until at least 24 hours had passed since starting study medication. In view of this, the use of rescue medication by trial participants within 24 hours of initiating study therapy was also examined as a secondary endpoint. Table 17 shows that the rate of rescue medication usage within 24 hours of initiating study drug therapy was lower for patients in both the standard dose colchicine group (35%) and in the low dose group (31%) as compared to patients in the placebo group (50%). For this analysis, the difference between the low dose colchicine group and the placebo group was statistically significant (low dose versus placebo: p=0.0273). However, no difference was noted on comparison of the standard dose colchicine group versus placebo (p =0.1034) or on comparison of the standard versus low dose colchicine groups (p =0.6768). **These results provide additional supportive evidence of colchicine's** effectiveness as a treatment for acute gout.

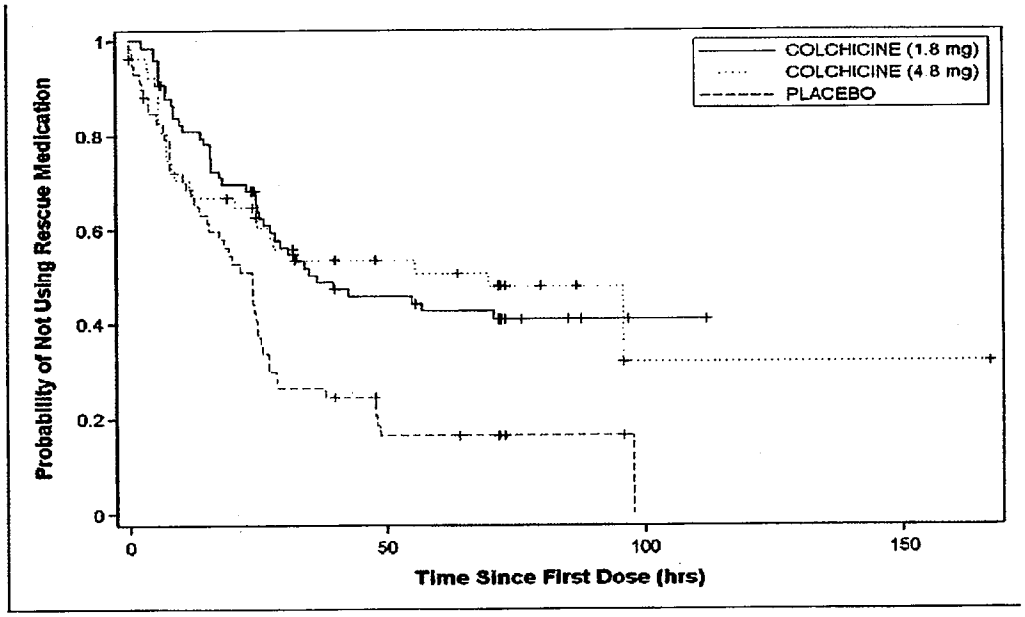
Table 17 – Tabular Summary of the Number of Patients Using Rescue Medication Through the 24-Hour Post-Dose Assessment (ITT Population)

Colchicine Standard Dose (N=52)	Colchicine Low Dose (N= 74)	Placebo (N=58)	Treatment Comparison (Odds Ratio and 95% Confidence Interval)		
			Standard vs Placebo	Low vs Placebo	Standard vs Low
18 (35%)	23 (31%)	29 (50%)	0.53 (0.25, 1.14)	0.45 (0.22, 0.92)	1.17 (0.55, 2.50)
			p = 0.1034	p = 0.0273	p = 0.6768

Sponsor's Table 11:15; p. 88.

The time to use of rescue medication was also calculated for each of the three treatment groups. Not surprisingly, placebo patients used rescue medications earlier (i.e., median 24 hours) as compared to patients in either the standard dose (median of 70 hours) or low dose (median of 37 hours) colchicine treatment groups. The median time to first use of rescue medication is graphically depicted below in Fig. 6 via Kaplan-Meier survival plots for all three treatment groups. These analyses provide supportive evidence in favor of colchicine's efficacy in treating acute gout flares.

Fig. 6 – Median Time to First Use of Rescue Medication: Standard and Low Dose Colchicine Treatment Groups Compared to Placebo (ITT Population)

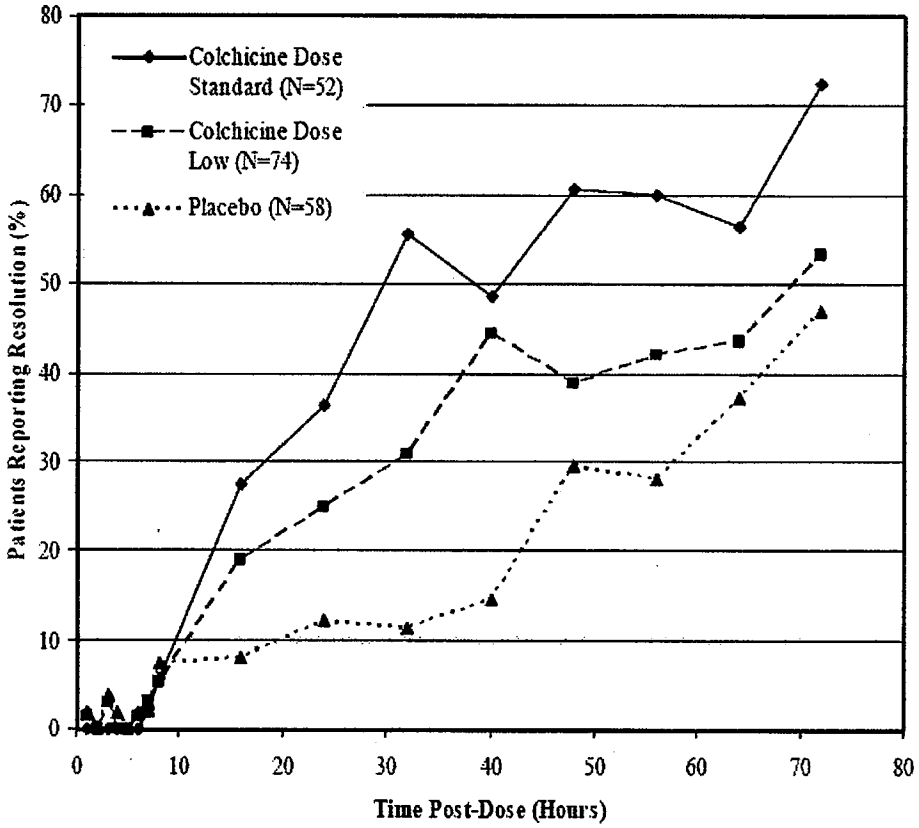


Sponsor's Fig. 11:6; p. 89.

6.1.6 Other Endpoints

As part of the efficacy assessments, subjects were queried if their gout symptoms had resolved at each time point over the 72 hours of study evaluation. A graphic display of these data (Fig. 7) generated from information captured in patients' diaries reveals that at approximately 8 hours post-initiation of study treatment the two colchicine treatment groups separate from the placebo group as the percentage of subjects who reported resolution of their gout flare begins to increase over time for both colchicine treatment groups as compared to the placebo group. These data provide additional supportive evidence of colchicine's effectiveness as a treatment for an acute gout flare.

Fig. 7 – Percentage of Subjects Reporting Resolution of Gout Flare Symptoms at Each Time Assessment Post First Dose of Study Medication (ITT Population)



Sponsor's Fig. 11.7; p. 90.

6.1.7 Subpopulations

In general, the response rates were higher in the colchicine-treated groups than placebo in the various age groups (<45, 45-65, >65 years) (Table 18). In one case, however, patients under 45 years, the response rate in the colchicine standard dose group (14%) was similar to that in the placebo group (9%). This isolated finding is difficult to interpret in view of the small number of patients involved (N=14).

Due to the paucity of female and non-Caucasian patients who participated in this trial, no gender or ethnicity analyses were performed by the applicant. However, the statistical reviewer conducted post hoc analyses for gender and ethnicity effects on treatment. The results of these analyses are difficult to interpret given the small number of subjects involved.

Table 18 – Analysis of Response to Study Therapy by Age by Treatment Group for Study MPC-004-06-001 (ITT Population)

Age Subgroup	Colchicine Standard Dose (N=52)		Colchicine Low Dose (N= 74)		Placebo (N=58)	
	Number	n (%)	Number	n (%)	Number	n (%)
< 45 years	14	2 (14%)	26	11 (42%)	11	1 (9%)
45 – 65 years	32	12 (38%)	35	12 (34%)	41	6 (15%)
> 65 years	6	3 (50%)	13	5 (39%)	6	2 (33%)

Note: A responder is defined as a patient who achieved a ≥ reduction in pain score and did not take rescue medication prior to the 24 hour post dose assessment.
Sponsor's Table 11:27; p. 101.

The sponsor also conducted analyses which evaluated the effects of various background disease risk factors (i.e., serum uric acid level, duration of gout, flare frequency, alcohol use, and weight-adjusted creatinine clearance) on the response to treatment. Table 19 lists the results of these explorations. In general, the response rates in the colchicine-treated groups are higher than with placebo in all subsets examined.

Table 19 – Effect of Various Disease Risk Factors on Response to Study Treatment by Treatment Groups as Assessed via Target Joint Pain Score at 24 hours Post First Dose for Study MPC-004-06-001 (ITT Population)

Subgroup	Colchicine Standard Dose (N=52)		Colchicine Low Dose (N= 74)		Placebo (N=58)	
	Number	n (%)	Number	n (%)	Number	n (%)
Baseline Serum Uric Acid Levels						
≤ 7 mg/dL	4	1 (25%)	17	8 (47%)	11	2 (18%)
> 7 mg/dL	47	16 (34%)	57	20 (35%)	47	7 (15%)
Median Duration of Gout						
< 8 years	26	8 (31%)	37	15 (41%)	28	6 (21%)
≥ 8 years	26	9 (35%)	37	13 (35%)	30	3 (10%)
Flare Frequency 12 Months Prior to Screening						
≤ 3 Flares	22	7 (32%)	32	15 (47%)	26	3 (12%)
> 3 Flares	30	10 (33%)	42	13 (31%)	32	6 (19%)
Admitted Prior Alcohol Use						
Yes	31	9 (29%)	48	18 (38%)	38	6 (16%)
No	21	8 (38%)	26	10 (39%)	20	3 (15%)
Calculated Creatinine Clearance (Weight-Adjusted)						
< 80 mL/min	23	8 (35%)	33	13 (39%)	19	4 (21%)
≥ 80 ml/min	29	9 (31%)	41	15 (37%)	39	5 (13%)

Note: A responder is defined as a patient who achieved a ≥ reduction in pain score and did not take rescue medication prior to the 24 hour post dose assessment.
Sponsor's Table 11:29; p. 103.

Since gout patients commonly take the urate lowering agent allopurinol concomitantly with colchicine in order to manage their gout, the sponsor conducted an analysis involving the subgroup of patients taking this drug during study MCP-004-06-001 as well as patients taking concomitant diuretic therapy which can also cause serum uric acid levels to fluctuate. The results of these analyses are shown in Table 20 below. The numbers of patients taking these drugs were too small to draw any valid conclusions.

Table 20 – Effect of Concomitant Allopurinol or Diuretic Therapy on Response to Study Treatment by Treatment Groups as Assessed via Target Joint Pain Score at 24 hours Post First Dose for Study MPC-004-06-001 (ITT Population)

	Colchicine Standard Dose (N=52)		Colchicine Low Dose (N= 74)		Placebo (N=58)	
	Number	n (%)	Number	n (%)	Number	n (%)
Concomitant Allopurinol Use						
Yes	8	1 (13%)	11	3 (27%)	5	1 (20%)
No	44	16 (36%)	63	25 (40%)	53	8 (15%)
Concomitant Diuretic Use						
Yes	3	1 (33%)	4	2 (50%)	2	1 (50%)
No	49	16 (33%)	70	26 (37%)	56	8 (14%)

Note: A responder is defined as a patient who achieved a ≥ reduction in pain score and did not take rescue medication prior to the 24 hour post dose assessment.
Sponsor's Table 11:28; p. 102.

Before the protocol for MCP-004-06-001 could be amended to exclude patients from participating in the trial who were taking stable doses of concomitant colchicine, 14 patients were randomized as follows: 3 patients to the placebo group, 8 patients to the low dose colchicine group, and 3 patients to the standard dose colchicine group. Due to concerns of an additive effect from taking concomitant colchicine the statistical reviewer performed the following subgroup analysis to determine if the use of concomitant colchicine influenced the outcome of this trial. No additional benefit was derived from taking concomitant colchicine as shown in Table 21.

Table 21 – Analysis of Patients Who Reported Taking Concomitant Colchicine While Participating in Study MPC-004-06-001

Concomitant Colchicine	Proportion of Responders		
	Placebo	Colchicine Low Dose	Colchicine Standard Dose
No	8/55	27/66*	16/49*
Yes	0/3	1/8	0/3
Combined	8/58	28/74*	16/52*

*Significantly different from placebo, p-value <0.005
Courtesy of Dr. Petullo

Although the protocol prohibited the use of chronic NSAIDs or analgesics such as acetaminophen or opiates within 72 hours of study entry in addition to the use of systemic corticosteroids within 30 days of entry and for 1 week after, patients were permitted to use these drugs for short-term therapy during the pre-flare phase. Due to concerns of additive effect from taking these drugs which are commonly used to treat acute gout flares, the statistical reviewer performed post hoc subgroup analyses of patients randomized to study treatment who reported taking these medications during the trial. With the exception of concomitant ibuprofen, none of the other medications influenced the outcome of the study. The results of the concomitant ibuprofen analyses showed lack of responders in placebo group (0/11) taking this NSAID (Table 22). However, there were more responders in the colchicine-treatment groups then in the placebo group for patients taking and patients not taking concomitant ibuprofen.

Table 22 – Analysis of Patients Who Reported Taking Concomitant Ibuprofen While Participating in Study MPC-004-06-001

Concomitant Ibuprofen	Proportion of Responders		
	Placebo	Colchicine Low Dose	Colchicine Standard Dose
No	8/39	23/40*	15/44*
Yes	0/11	5/11*	1/7
Combined	8/58	28/74*	16/52*

*Significantly different from placebo, p-value <0.005
Courtesy of Dr. Petullo

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Colchicine has been used as a treatment for gout in this country since 1938, however, the optimal dose has never been established. Traditionally, dosing of colchicine for acute flares of gout involved continuous administration of the drug orally every hour until either 50% improvement in pain and swelling of the affected joint or signs of gastrointestinal toxicity were observed. Recently, consensus guidelines published by the European League against Rheumatism (EULAR) (Zhang et al[2]) recommended using a lower dose of colchicine (i.e., 0.5 mg three times a day) for the treatment of acute attacks of this disease. In view of this, a dose-response trial primary endpoint of the proportion of subjects with 50% improvement in pain at a specified timepoint was discussed in the pre-IND meetings held with the Applicant as a potential proposed design of the pivotal trial, MPC-004-06-001. Based on the primary endpoint results generated from this study that are shown in Table 13 above, no difference was observed on comparison of response rates for the standard versus low dose colchicine groups (p=0.5529). Comparability between the standard and low dose colchicine treatment groups was also supported by the results of the various secondary endpoint analyses discussed above. In addition to not demonstrating a higher degree of efficacy, the higher dose of colchicine (4.8 mg) was also associated with higher rates of gastrotoxicity and decreased tolerability that will be discussed in Section 7. These results favor the low-dose colchicine regimen as the optimal regimen.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance effects are not relevant to this application because this application assesses only short-term use of colchicine.

6.1.10 Additional Efficacy Issues/Analyses

No correction for multiplicity issues was prespecified by the SAP for study MPC-004-06-001 to be used in conducting the analyses of the trial's primary and secondary endpoints. This may be due to the fact that the applicant did not anticipate a positive result for the low dose colchicine group. The results from post hoc multiple adjustment analyses (i.e., Bonferoni, Hochberg, and the intersection union test) conducted by the agency's statistical reviewer support the robustness of the primary efficacy analysis for the comparison of the low dose colchicine group versus the placebo group. In view of these findings when weighed with the decreased incidence of adverse events, particularly those involving the gastrointestinal system, reported by patients in the low dose group as discussed in Section 7, the risk-benefit ratio favors the low dose colchicine dosing regimen. However, declaring statistical significance of the secondary endpoints using unadjusted p-values may be inappropriate. Thus, the results from the secondary endpoint analyses should not be included in the drug label.

As tightly conducted (i.e., inpatient service, mandatory assessments and no access to confounding rescue medication) as was the study by Ahern et al, the possibility exists that the clinical investigators may have became unblinded while completing their assessments of study subjects who developed gastrointestinal toxicity to colchicine as a result of the dosing regimen employed in this study. The dosing regimen evaluated in this trial is consistent with the manner in which colchicine has been traditionally administered by physicians to treat acute gout flares (i.e. administered until toxicity or response is observed). In this trial, the clinical evaluators were acting in the capacity of rheumatology consultants to hospitalized patients cared for by hospital staff and may not have had access to this information. Nonetheless, both the agency's statistical reviewer and I were unable to exclude the possibility that the pattern of adverse events may have contributed some level of bias to the study results.

7 Review of Safety

Safety Summary

The overall safety profile of colchicine generated from the adequate and well controlled Phase 3 trial MPC-004-04-001, which compared a standard high dose regimen (4.8 mg over 6 hours) versus a low dose regimen of the drug (1.8 mg over 1 hour), was consistent with what has been reported in the medical literature for the past 70 years, mainly gastrointestinal toxicity manifested by diarrhea, nausea, and vomiting. Approximately twice as many subjects randomized to the standard dose colchicine treatment group (77%) experienced treatment-emergent adverse events (TEAEs) as compared to subjects in the low-dose colchicine group (37%) or placebo group (27%) that were predominantly gastrointestinal in nature. The majority of these AEs were mild to moderate in nature, however, almost all of the severe AEs occurred in patients treated with the standard dose regimen of colchicine. Both of these findings are consistent with a definitive dose-response relationship for gastrotoxicity and decreasing tolerability with increasing dose of colchicine. There were no serious adverse events or deaths reported in the safety database associated with colchicine therapy that may be related to the limited exposure to the drug (i.e., one treatment of an acute gout flare) during this trial. The short duration of exposure to colchicine in this trial is a limitation, since no information was gathered to assess the time interval necessary for safe retreatment with colchicine of patients who have repeat gout flares.
Overall compliance with study medications was approximately 85% for all participants, with patients randomized to the standard group having the lowest rate of compliance (73%) as compared to the low dose (92%) and placebo groups (88%). Noncompliance with study medications was probably due to the dose-dependent higher rate of gastrointestinal intolerance seen in patients randomized to the standard dose colchicine regimen. Additionally, there was no evidence of colchicine having an adverse effect on clinical lab test parameters or vital signs, but this again may be a result of the short

duration of exposure to the drug which is known to have toxic effects on the hematopoietic, hepatic, and renal systems as well as on muscles. (Note: Although a QTc prolongation study was not required for this application, the Applicant did submit the results of a failed study in which adequate prolongation in the control arm was not achieved.)

Another limitation of the safety data reviewed in support of colchicine as a treatment for acute gout, were the small numbers of patients involved in the demographic subanalyses for gender, age, and race as well as concomitant allopurinol use and creatinine clearance which made it impossible to draw any valid conclusions from these analyses regarding the possibility of increasing risk for gastrotoxicity associated with these factors

Review of the postmarketing data and worldwide literature also failed to identify any new potential safety signals associated with the use of colchicine.

In view of the comparable efficacy data for both dose regimens of colchicine but the higher rates of gastrotoxicity and decreased tolerability associated with the higher dose regimen (i.e., 4.8 mg), the data favor the low-dose colchicine regimen (i.e., 1.8 mg) as the optimal regimen for the treatment of acute gout.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of the safety for this 505(b)(2) application for colchicine as a treatment for acute gout, the Applicant originally submitted safety data from multiple sources (Table 23). In addition to the safety databases generated from the adequate and well-controlled Phase 3 trial MPC-004-06-001 in patients with acute gout and the 6 single- and multiple-dose pharmacokinetic and drug-drug interaction Phase 1 studies conducted by the applicant, the submission contained supportive safety data for the drug identified during a search of the worldwide literature, an analysis of postmarketing adverse event reports for colchicine collected by the FDA and the World Health Organization (WHO), and labeling information for oral colchicine from 8 foreign countries where the drug is currently marketed besides the most recent (2006) U.S. label for the combination drug product Col-Probenecid. These data were updated with new safety information with a data cut-off date of December 16, 2008 contained in the 120-day safety update. The updated safety database contains data generated from the 8 drug-drug interaction Phase 1 studies with colchicine and inhibitors of CYP3A4 and p-gp conducted by the applicant, as well as 2 publications identified on an updated

literature search and 137 adverse event reports obtained from the FDA's postmarketing safety database.

Table 23 – Overview of Safety Data Submitted in Support of the 505(b)(2) Application for Colchicine as a Treatment for Acute Gout

Source	Population	Number	Data Source/ Study Design	
			Original Safety Database	120-Day Safety Update
Applicant's Studies				
MPC-004-06-001	Adults with Gout	185 Subjects (126 randomized to colchicine)	Multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose comparison study in gout flare	Not applicable
Pharmacokinetic Studies	Healthy Adults	126 Subjects	Six single- and multiple-dose pharmacokinetic and drug-drug interaction studies (83 subjects single dose/1-day regimen and 43 subjects 10-to 14-day steady state regimen)	Updated total number: 314 subjects from 14 single- and multiple-dose pharmacokinetic and drug-drug interaction studies (255 subjects single dose/1-day regimen and 59 subjects 10- to 14-day steady state regimen) (Note: 6 of the 14 studies were contained in the original safety submission)
Medical Literature				
Randomized, placebo-controlled Study	Adults with Gout	43 Subjects (22 randomized to colchicine)	Ahern et al[1], 1987	Not applicable
Other Case Reports	--	--	Additional reports of adverse events	2 publications
Postmarketing Safety Data				
U.S. Food and Drug Administration	Primarily U.S. but includes foreign reports	--	751 adverse event reports from 1969 through 30 June 2007	137 additional adverse event reports through 31 March 2008
World Health Organization	79 countries including the U.S.	--	1380 adverse event reports **from 1968 – March 2006**	Not applicable
Labeling				
Col-Probenecid **(Watson – US;** ANDA 84-279)	--	--	FDA approved Probenecid and colchicine combination **product (550 mg – 0.5 mg),** providing for a maximum daily colchicine dose of 2 mg	Not applicable
Other countries	--	--	Labeling from oral colchicine obtained from Argentina, Australia, Britain, Germany, Mexico, France, Singapore, and Uganda	Labeling obtained from Portugal

Adapted from Sponsor's Table 2.7.4:1; p. 5 SCS

The focus of this safety review will be primarily on the safety data generated from the adequate and well controlled Phase 3 trial MPC-004-06-001 in acute gout supported by the information contained in the 120-day safety update. MPC-004-06-001 evaluated both the efficacy and safety of the formulation and dose regimen of colchicine for which the applicant is seeking marketing approval. The remaining safety data contained in the original submission was reviewed previously by the Agency in support of the Applicant's submission for colchicine as a treatment for familial Mediterranean Fever (FMF). (Note: The reader is referred to Dr. Keith Hull's medical officer review of NDA 22,352.)

Safety data from MPC-004-06-001 and from the 14 PK studies were summarized in the individual trial reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs. All safety analyses that were performed on the double-blind safety population and the single- and multiple-dose open label PK studies, as well as the reviews of the two published citations describing colchicine toxicity from the updated literature search, the tabular summaries of all the postmarketing adverse events and summary narratives of postmarketing adverse events of interest that were contained in the 120-day safety update were examined by this medical officer.

7.1.2 Categorization of Adverse Events

Verbatim terms of AEs recorded in the case report forms (CRF) from safety information captured in patients' diaries and by investigators was coded by the Applicant using MedDRA dictionary Preferred Term and System Organ Class (SOC) (version 10.0). A listing of all AEs coded in this manner including the corresponding verbatim terms was included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety population for MPC-004-06-001 was defined as all patients who received at least one dose of study medication regardless of whether or not they had been authorized by the gout flare call center. The AE, clinical lab findings, vital signs, and ECG data generated from this study was presented separately since it was the only adequate and well-controlled study contained in the submission. The safety data generated from the 14 Phase 1 pharmacokinetic and drug-drug interaction studies were presented in pooled format by the applicant due to similarities in the design of these studies, the doses of colchicine evaluated and population studied (i.e., single dose versus multiple dose, fed versus fasted state, and healthy volunteers). Presenting the data in this format is acceptable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

According to IMS data contained in this application, approximately ———— tables of colchicine were reported to have been sold in the U.S. in 2007 primarily for the treatment of gout. Table 24 summarizes the extent of exposure in the Phase 3 trial MPC-004-06-001 in patients with acute gout. A total of 38 patients were exposed to the 4.8 mg standard dose colchicine regimen and 68 patients were exposed to the 1.8 mg low dose colchicine regimen during this trial. b(4)

Table 24 - Summary of Study Drug Exposure in MPC-004-06-001(Safety Population)

	Colchicine		Placebo (N=59)	Total (N=185)
	Standard Dose (4.8 mg) (N=52)	Low Dose (1.8 mg) (N=74)		
Took All 7 doses of Study Medication:	38 (73%)	68 (92%)	52 (88%)	158 (85%)
Missed at Least 1 dose of Study Medication[1]:	14 (27%)	6 (8%)	7 (12%)	27 (15%)
Took at Least the First 2 Doses of Study Medication:	49 (94%)	71 (96%)[2]	56 (95%)	176 (95%)
Did Not Complete the last 6 Doses:	3 (6%)	2 (3%)	0	5 (3%)

[1]The subsequent rows are not mutually exclusive.
[2]Total dose would be 1.8 mg (the low dose regimen).
Adapted from Table 12:1; p. 105.

With the submission of the 120-day safety update, a total of 314 healthy volunteers were exposed to at least 1 dose of colchicine during their participation in the 14 pharmacokinetic studies: 258 subjects received single 0.6 mg doses or single day acute regimens of 1.8 mg or 4.8 mg of colchicine while the remaining 69 subjects received 0.6 mg twice daily for 10 to 14 days (approximating steady state).

Demographically, the subjects who participated in MCP-004-06-001 were overwhelmingly Caucasian males with a mean age of 52 years. (Refer to Table 5.) A total of 58% of the subjects were between the ages of 45-65 years old, 28% were less than 45 years old and 14% were over 65 years old. Overall, the population studied in this trial was representative of patients who would be potentially treated with colchicine for acute gout flares.

In view of the fact that this application is a 505(b)(2) and colchicine has been medically available in this country as a treatment for acute gout for over 70 years, these exposure data appear to be adequate to support the low dose colchicine dosing regimen.

7.2.2 Explorations for Dose Response

Not applicable for this application.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this application.

7.2.4 Routine Clinical Testing

Subjects who participated in MCP-004-06-001 were to have the following lab tests serially performed at Visit 1 (Screening), 3-month intervals between Visit 2 and the gout flare, and the last clinic visit in the Post-Flare Phase (Visit 4 or 5):

- White blood cell (WBC) count with differential and platelet count
- Serum chemistries: BUN, creatinine, ALT, AST, total bilirubin
- Urinalysis: including pH, specific gravity, protein, glucose, ketones, nitrite, occult blood, bilirubin, and urobilinogen

Additionally, subjects were to have the following blood chemistry tests performed at the screening and final study visits: albumin, alkaline phosphatase, calcium, carbon dioxide, chloride, creatine kinase, glucose, lactic dehydrogenase, phosphorus, potassium, sodium, direct bilirubin, total protein, and uric acid. Treatment emergent abnormal lab test results were to be repeated at Visit 6 at the discretion of the study investigators and the sponsor.

ECGs were to have been performed at Visit 1 (Screening) only. Complete physical exams of all subjects were to have been conducted by study investigators at Visit 1 (Screening) and on the last clinic visit in the Post-Flare Phase (Visit 4 or 5). Vital signs including oral temperature, sitting pulse rate, respiratory rate, and blood pressure as well as body weight were to have been measured at all study visits. Height was to have been measured at Visit 1 (Screening) only.

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the population studied in MCP-004-06-001.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4, Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable since colchicine is the only member of its drug class.

7.3 Major Safety Results

Table 25 summarizes AEs reported in the acute gout safety database for MCP-004-06-001 for the safety population. Overall, 53% of the colchicine-treated patients reported an AE as compared to 27% of placebo-treated patients. Further examination of these data reveals that a higher proportion of subjects (77%) randomized to the standard dose colchicine treatment group reported treatment-emergent AEs as compared to 37% in the low dose colchicine group. No deaths or treatment-emergent serious AEs associated with the use of colchicine were reported to have occurred over the course of this trial. No patients reportedly withdrew prematurely from the study due to an AE.

Table 25 – Tabular Summary of Subjects Who Experienced Adverse Events During Study MPC-004-06-001 (Safety Population)

	Colchicine Standard Dose (N=52)	Colchicine Low Dose (N= 74)	Total Colchicine (N= 126)	Placebo (N=58)
Total Number of Treatment Emergent Adverse Events:	85	34	119	27
Number of Subjects with Any Treatment Emergent Adverse Events:	40 (77%)	27 (37%)	67 (53%)	16 (27%)
Number of Subjects with Any Treatment Emergent Serious Adverse Event:	0	0	0	0
Number of Subjects with Any Severe Treatment Emergent Adverse Event:	10 (19%)	0	10 (8%)	1 (2%)
Deaths:	0	0	0	0
Number of Subjects who Discontinued Due to a Treatment Emergent Adverse Event:	0	0	0	0

Adapted Sponsor's Table 12:3; p. 108

7.3.1 Deaths

There were no deaths reported in the clinical safety database generated from study MCP-004-06-001 or in the pharmacokinetic studies conducted by the applicant.

7.3.2 Nonfatal Serious Adverse Events

There were no treatment-emergent serious adverse events (SAEs) associated with the use of colchicine reported during the flare- or post-flare phases of study MCP-004-06-001.

7.3.3 Dropouts and/or Discontinuations

No patients withdrew prematurely from Study MCP-001-06-004 due to an adverse event (AE) associated with the use of study medications. For completeness, the applicant examined the diary cards of patients who missed a dose or stopped taking study drug in order to determine if it was due to a drug-related safety issue. (Note: This analysis does not include the 3 patients [Subjects 1026-1025, 1082-1001, and 1007-1005] who did not return their diary cards after taking the first dose of study medication.) A total of 27 patients from the three treatment groups missed at least 1 dose of study medication. (Refer to preceding Table 24.) Review of these patients' diary cards identified 16 patients listed in Table 26 below who missed study medications due to a possible safety reason. Eleven out of these 16 patients reported having gastrointestinal AEs that occurred within 1-2 days of initiating therapy that potentially caused them to miss doses of study medication. Seven of these 11 patients who missed study medication doses due to gastrointestinal AEs were in the standard dose colchicine group, 1 patient was in the low dose colchicine group and 3 were in the placebo group. These findings are consistent with colchicine's well-documented dose-dependent poor GI tolerability.

Table 26 – Tabular Summary of Subjects Who Missed a Dose of Study Medication Due to an Adverse Event While Participating in MCP-004-06-001

Subject Number	Age/Sex/Race	Doses Not Taken (Hour)	Rescue Prior to Completion of Dosing	Adverse Event (MedDRA Preferred Term)	Onset (Days)
Standard-Dose Colchicine (4.8 mg)					
1001-1013	45yo/Male/White	2 and 6	No	Diarrhea	1
1005-1003	57yo/Male/Other	2, 3, and 6	Yes	None	--
1007-1002	42yo/Male/White	6	Yes	Nausea Diarrhea Vomiting Lower Abdominal Pain	<1 <1 1 4
1018-1011	39yo/Male/White	3	No	Vomiting Diarrhea	<1 <1
1026-1005[1]	52yo/Male/White	1, 2, 3, 4, 5, 6	No	Diarrhea Diarrhea	<1 <1
1028-1003	45yo/Male/Black	1, 2, 3, 4, 5, 6	No	Dyspepsia Nausea Diarrhea Pruritus	<1 <1 <1 2
1068-1013	46yo/Male/White	6	Yes	None	--
1068-1023	65yo/Female/White	4	No	Diarrhea Diarrhea Nausea Vomiting	1 1 1 2
Low-Dose Colchicine (1.8 mg)					
1055-1002[2]	53yo/Male/White	5, 6	No	Diarrhea	<1
Placebo					
1009-1012	50yo/Male/White	1, 2, 3, 4, 5	Yes	None	--
1015-1001	50yo/Male/White	6	No	Abdominal Pain	<1
1058-1006	53yo/Male/Black	4, 5, 6	No	Diarrhea	<1
1061-1027[2]	42yo/Male/Black	2, 6	Yes	Hypertension	7
1073-1008	45yo/Male/White	1, 2, 3, 4	No	None	--
1077-1018	74yo/Male/White	5, 6	Yes	None	--
1100-1002	63yo/Male/Black	1	Yes	Arthropathy Abdominal Discomfort	<1 3

[1]Patient did not have a diary
[2]Patient indicated on diary that study drug was stopped
Adapted Sponsor's Table 2.7.4:22

Two healthy volunteers were prematurely discontinued from participating in one of the PK studies due to AEs. One subjected vomited post-dosing and had to be removed from the trial since this would have affected the serum concentrations of colchicine, while the other subjected was prematurely withdrawn from the trial due to diarrhea and vomiting post-administration of colchicine. These AEs are consistent with colchicine's GI toxicity profile.

7.3.4 Significant Adverse Events

Severity of AEs was assessed as mild, moderate, or severe by study investigators. As shown in Table 27, most of the AEs were mild to moderate in intensity during study MPC-004-001. However, there were a total of 10 patients (19%) treated with standard dose colchicine and 1 patient (2%) in the placebo group who experienced AEs that were classified as severe in nature by study investigators during this controlled trial. There were no severe AEs reported in the low-dose colchicine group. The AEs that were most commonly assessed as being severe in intensity in the standard dose colchicine group were diarrhea (19%), melena (2%), nausea (2%) and pain in extremity (2%) as compared to gout flare (2%) in the placebo group. The higher rate of severe cases of gastrointestinal AEs seen in the standard dose colchicine group is supportive of the well-documented dose-dependent gastrointestinal toxicity profile associated with this drug.

Table 27 – Tabular Summary of Number (%) of Subjects with Severe Adverse Events by MedDRA System Organ Class Preferred Term for Study MPC-004-06-001 (Safety Population)

Adverse Event Via MedDRA SOC Preferred Term	Colchicine Standard Dose (N=52)	Colchicine Low Dose (N= 74)	Total Colchicine (N= 126)	Placebo (N=58)
All TEAEs:				
Mild	**15 (29%)**	**19 (26%)**	**34 (27%)**	**9 (15%)**
Moderate	**15 (29%)**	**8 (11%)**	**23 (18%)**	**6 (10%)**
Severe	**10 (19%)**	**0**	**10 (8%)**	**1 (2%)**
Gastrointestinal Disorders:	**10 (19%)**	**0**	**10 (8%)**	**0**
Diarrhea	10 (19%)	0	10 (8%)	0
Melena	1 (2%)	0	1 (1%)	0
Nausea	1 (2%)	0	1 (1%)	0
Musculoskeletal and Connective Tissue Disorders:	**1 (2%)**	**0**	**1 (1%)**	**0**
Pain in Extremity	1 (2%)	0	1 (1%)	0
Metabolism and Nutrition Disorders:	**0**	**0**	**0**	**1 (2%)**
Gout	0	0	0	1 (2%)

Note: Subjects reporting more than one AE are only counted once for a given event.
Adapted Sponsor's Table 14.3.1.3; p.441-457.

The one case of severe melena occurred in a 41-year old male (Subject 1069-1012) randomized to the standard dose colchicine group. This patient reportedly took 16 mg of methylprednisolone as rescue medication approximately 4 hours after ingesting his first dose of study medication and developed melena 3 days later. The day before the melena started, the patient reported having pyrexia and severe diarrhea. Both the diarrhea and melena resolved after 3-5 days of treatment with a proton pump inhibitor. This subject was reportedly not taking any non-gout medications at the time these AEs

occurred. A subsequent colonoscopy and esophago-gastroduodenoscopy performed 6 weeks later were consistent with small hemorrhoids, irritable bowel syndrome, erosive duodenitis, erosive gastritis, GERD and hiatal hernia. Based on the sequence of events, and endoscopy findings this medical officer concurs with the sponsor that the gastrointestinal bleeding was probably related to the use of systemic corticosteroids.

No severe AEs were observed in the 14 PK studies conducted by the sponsor.

7.3.5 Submission Specific Primary Safety Concerns

There are no specific primary safety concerns for colchicine since this drug has been available for the treatment of gout for over 70 years and its safety profile has been well documented in patients with this disease.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 28 summarizes the number and rates of AEs by randomized colchicine group that occurred in MCP-004-06-001 by MedDRA system organ class. The overall rate (53%) of AEs among colchicine-treated patients was higher than in the placebo group (27%). The incidence of AEs increased with increasing colchicine dose from 37% in the low dose group to 77% in the standard dose group. The system organ classes with the highest number of AE reports were: gastrointestinal disorders (47%), general administration site conditions (4%), investigations (4%), metabolism and nutrition disorders (2%), respiratory, thoracic and mediastinal disorders (2%) and skin and subcutaneous disorders (2%). Additional examination of the data shown in Table 28 revealed that diarrhea (77%), nausea (17%) and vomiting (17%) were reported more frequently in patients treated with standard dose colchicine compared to patients treated with low dose colchicine (diarrhea: 23%, nausea: 4%, and vomiting: 0) and placebo (diarrhea: 14%, nausea: 5%, and vomiting: 0). These data support that diarrhea and vomiting are dose-dependent AEs associated with the use of colchicine. No new safety issues associated with the use of colchicine were identified on review of these data.

Table 28 – Tabular Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term for Study MPC-004-06-001 (Safety Population)

Adverse Event via MEdDRA SOC Preferred Term	Colchicine Standard Dose (N=52)	Colchicine Low Dose (N= 74)	Total Colchicine (N= 126)	Placebo (N=58)
Number (%) of Subjects with TEAEs[1]	40 (77%)	27 (37%)	67 (53%)	16 (27%)
Gastrointestinal Disorders	40 (77%)	19 (26%)	59 (47%)	12 (20%)
Diarrhea	40 (77%)	17 (23%)	57 (45%)	8 (14%)
Nausea	9 (17%)	3 (4%)	12 (10%)	3 (5%)
Vomiting	9 (17%)	0	9 (7%)	0
Abdominal Pain	1 (2%)	0	1 (1%)	1 (2%)
Abdominal Pain Lower	1 (2%)	0	1 (1%)	0
Abdominal Pain Upper	1 (2%)	0	1 (1%)	0
Dsypepsia	1 (2%)	0	1 (1%)	0
Erosive Duodenitis	1 (2%)	0	1 (1%)	0
Gastritis Erosive	1 (2%)	0	1 (1%)	0
Gastroesophageal Reflux Disease	1 (2%)	0	1 (1%)	0
Hemorrhoids	1 (2%)	0	1 (1%)	0
Hiatus Hernia	1 (2%)	0	1 (1%)	0
Irritable Syndrome	1 (2%)	0	1 (1%)	0
Melena	1 (2%)	0	1 (1%)	0
Constipation	0	1 (1%)	1 (1%)	0
Abdominal Discomfort	0	0	0	2 (3%)
General Administration Site Conditions:	4 (8%)	1 (1%)	5 (4%)	1 (2%)
Fatigue	2 (4%)	1 (1%)	3 (2%)	1 (2%)
Lethargy	1 (2%)	0	1 (1%)	0
Pyrexia	1 (2%)	0	1 (1%)	0
Investigations	3 (6%)	2 (3%)	5 (4%)	1 (2%)
Alanine Aminotransferase Inc.	1 (2%)	0	1 (1%)	0
Aspartate Aminotransferase Inc.	1 (2%)	0	1 (1%)	0
Glucose Urine	1 (2%)	0	1 (1%)	0
Liver Function Test Abn.	1 (2%)	0	1 (1%)	0
Protein Urine	1 (2%)	0	1 (1%)	0
Blood Phosphorus Dec.	0	1 (1%)	1 (1%)	0
Urinary Casts	0	1 (1%)	1 (1%)	0
Blood Creatinine Phosphokinase Inc.	0	0	0	1 (2%)
Metabolism and Nutrition Disorders	0	3 (4%)	3 (2%)	2 (3%)
Gout	0	3 (4%)	3 (2%)	1 (2%)
Hypercholesterolemia	0	0	0	1 (2%)
Hypoglycemia	0	0	0	1 (2%)
Respiratory, Thoracic and Mediast. Disord:	1 (2%)	2 (3%)	3 (2%)	0
Pharyngolaryngeal Pain	1 (2%)	2 (3%)	3 (2%)	0
Skin and Subcutaneous Tissue Disorders:	1 (2%)	1 (1%)	2 (2%)	1 (2%)
Pruritus	1 (2%)	0	1 (1%)	0
Rash	0	1 (1%)	1 (1%)	1 (2%)
Musculoskel. And Connective Tissue Disord.:	1 (2%)	0	1 (1%)	2 (3%)
Pain in Extremity	1 (2%)	0	1 (1%)	0
Arthritis	0	0	0	1 (2%)
Arthropathy	0	0	0	1 (2%)
Nervous System Disorders:	1 (2%)	1 (1%)	2 (2%)	2 (3%)
Headache	1 (2%)	1 (1%)	2 (2%)	2 (3%)
Dizziness	0	0	0	1 (2%)

[1]Note: Subjects reporting more than one AE are only counted once for a given event.
Adapted Sponsor's Table 14.3.1.2; p. 432.

Table 28 – Tabular Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term for Study MPC-004-06-001 (Safety Population) (cont.)

Adverse Event via MEdDRA SOC Preferred Term	Colchicine Standard Dose (N=52)	Colchicine Low Dose (N= 74)	Total Colchicine (N= 126)	Placebo (N=58)
Vascular Disorders:	1 (2%)	0	1 (1%)	1 (2%)
Hypertension	1 (2%)	0	1 (1%)	1 (2%)
Infections and Infestations:	0	1 (1%)	1 (1%)	0
Urinary Tract Infection	0	1 (1%)	1 (1%)	0
Injury, Poisoning and Procedural Complicat.:	0	1 (1%)	1 (1%)	0
Fall	0	1 (1%)	1 (1%)	0
Renal and Urinary Disorders:	1 (2%)	0	1 (1%)	0
Chromaturia	1 (2%)	0	1 (1%)	0
Ear and Labyrinth Disorders:	0	0	0	1 (2%)
Vertigo	0	0	0	1 (2%)

[1]Note: Subjects reporting more than one AE are only counted once for a given event.
Adapted Sponsor's Table 14.3.1.2; p. 432.

Review of the AE data collected from the 14 PK studies (Table 29) was similar to that of the AE profile for colchicine observed in MCP-004-06-001. The most commonly reported AEs were as follows: diarrhea (11%), headache (10%), nausea (6%), vomiting (5%), and dizziness (4%). No new safety issues associated with the use of colchicine were identified on review of these data.

Table 29 – Tabular Summary of the Number (%) of Healthy Adult Volunteers with Adverse Events Following Exposure to Colchicine Reported ≥ 2 Subjects in Any Pharmacokinetic (PK) Study, by PK Study and Overall

MedDRA Preferred Term	Single Dose[1]		Low Dose[3]	High Dose[4]	Multiple Dose[5]	All Exposure
	Fasted[2]	Fed				
	N=229	N=27	N=13	N=15	N=66	N=314
General Disorders and Administration Site Conditions						
Cold Sweats	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	2 (0.6%)
Pallor	4 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.3%)
Gastrointestinal Disorders						
Abdominal Pain Upper	1 (0.4%)	0 (0%)	1 (7.7%)	0 (0%)	3 (4.5%)	5 (1.6%)
Diarrhea	4 (1.7%)	0 (0%)	2 (15.4%)	15 (100%)	14 (21.2%)	35 (11.1%)
Dyspepsia	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	1 (1.5%)	2 (0.6%)
Hypoacusis	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)
Nausea	5 (2.2%)	0 (0%)	1 (7.7%)	7 (46.6%)	5 (7.6%)	18 (5.7%)
Stomach Discomfort	2 (0.9%)	1 (3.7%)	0 (0%)	0 (0%)	5 (7.6%)	8 (2.5%)
Vomiting	1 (0.4%)	1 (3.7%)	0 (0%)	9 (60.0%)	3 (4.5%)	14 (4.5%)
Musculoskeletal and Connective Tissue Disorders						
Pain in Extremity	5 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (1.6%)
Nervous System Disorders						
Dizziness	7 (3.1%)	1 (3.7%)	0 (0%)	1 (6.7%)	4 (6.1%)	12 (3.8%)
Headache	23 (10%)	1 (3.7%)	2 (15.4%)	1 (6.7%)	3 (4.5%)	30 (9.6%)
Syncope	4 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.3%)
Respiratory, Thoracic and Mediastinal Disorders						
Nasopharyngitis	2 (0.9%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	3 (1%)
Pharyngolaryngeal Pain	2 (0.9%)	0 (0%)	0 (0%)	1 (6.7%)	1 (1.5%)	4 (1.3%)
Sinus Congestion	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	2 (0.6%)
Eye Disorders						
Vision Blurred	3 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.0%)

[1]Single dose = 0.6 mg
[2]Subjects pooled from 10 studies: MPC-004-07-101 (N=28); MPC-004-07-1004 (N=13); MPC-004-07-1006 (N=24); MPC-004-08-1011 (N=24); MPC-004-08-1012 (N=24) MPC-004-08-1013 (N=24); MPC-004-08-1014 (N=24); MPC-004-08-1015 (N=24); MPC-004-08-1016 (N=24); MPC-004=-08-1017 (N=24).
[3]MPC-004-07-1003, low dose = 2 x 0.6 mg (1.2 mg) followed by 0.6 mg after 1 hour (total: 1.8 mg/2 hours)
[4]MPC-004-07-1002, high dose = 2 x 0.6 mg (1.2 mg) followed by 0.6 mg q 1h for 6 hours (total: 4.8 mg/6 hours)
[5]Multiple dose = 0.6 mg bid x 10 days in MPC-004-07-1006 and x 14 days in MPC-004-07-1005 and MPC-004-08-1010.

7.4.2.1 Laboratory Findings: Controlled Study

According to the protocol for controlled trial MCP-004-06-001, patients were mandated to undergo laboratory evaluations at study Visit 1 (Screening), 3-month intervals between Visit 2 and the acute gout flare, and the last clinic visit in the Post-Flare Phase (Visit 4 or 5). The following tests were performed at these timepoints:

- Hematology: White blood cell (WBC) count with differential, platelet count, red blood cell (RBC) count, hemoglobulin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV)

- Serum Chemistry: Albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, creatine phosphokinase (CPK), glucose, lactic dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid

- Urinalysis: Appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen, microscopic examination (if needed)

Laboratory data from the controlled pivotal study were presented as follows: actual values and change from baseline by parameter, the incidence of treatment-emergent shifts from normal range relative to baseline, and any significant observations (i.e., values meeting pre-specified criteria for possible clinical significance and/or reported as AEs). The Applicant's provided normal range of values for each lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate. Since colchicine is known to cause hematopoietic, renal, hepatic and muscle toxicities, this review will focus on analyses of lab assessments for these organ systems. The findings from these analyses are as follows

a. Hematology –

The majority of patients' WBC and differential counts were within normal range at baseline and post-flare. More patients (9%) in the placebo group experienced shifts in WBC indices to outside normal range than patients in the standard (4%) and low (3%) dose colchicine groups. Six patients randomized to placebo (9%) and 1 standard dose colchicine patient (2%) had WBC test results that met pre-specified criteria for possible clinical significance. Further review of the case report for the patient randomized to standard dose colchicine (Subject 1091-1002) with the possible clinically significant change revealed that he had leukocytosis (WBC 18,300) with lymphopenia (0.5 x $10^3/\mu L$) one day post treatment that was associated with severe diarrhea and chromaturia. His WBC counts returned to normal on repeat testing one week later.

Review of the platelet count data revealed no meaningful trends on change from baseline to post-flare or on shift table analysis.

More patients randomized to the low dose colchicine group had mean decreases in hematocrit that was probably not due to colchicine since decreases in hematocrit in the standard dose colchicine and placebo groups were of similar magnitude. This is supported by the shift analyses shown in Table 30 which shows that there were more

patients (24%) who had shifts to lower hematocrit levels in the low dose colchicine group as compared to the placebo (11%) and the standard dose colchicine group (7%).

Table 30 – Number (%) of Subjects with Treatment-Emergent Shift in Red Blood Cell Indices Study MCP-004-06-001 (Safety Population)

Parameter	Baseline	Post-Flare								
		Standard Dose Colchicine (N=59)			Low Dose Colchicine (N=74)			Placebo (N=59)		
		Low	Normal	High	Low	Normal	High	Low	Normal	High
RBC Count	Low	9(21%)	2(5%)	--	5(7%)	6(9%)	--	14(26%)	3(6%)	--
	Normal	3(7%)	28(65%)	--	11(16%)	48(68%)	--	3(6%)	34(63%)	--
	High	--	--	1(2%)	--	1(1%)	--	--	--	--
Hemoglobulin	Low	4(9%)	2(5%)	--	3(4%)	1(1%)	--	8(15%)	6(11%)	--
	Normal	4(9%)	33(77%)	--	9(13%)	56(79%)	1(1%)	3(6%)	35(65%)	1(2%0
	High	--	--	--	--	1(1%)	--	--	--	1(2%)
Hematocrit	Low	11(26%)	1(2%)	--	2(3%)	4(6%)	--	11(20%)	7(13%)	--
	Normal	3(7%)	27(63%)	--	17(24%)	44(62%)	1(1%)	6(11%)	25(46%)	1(2%)
	High	--	--	1(2%)	--	3(4%)	--	--	2(4%)	2(4%)

Adapted Sponsor's Table 12:21; p.126 of study report.

Review of these data revealed that a total of 5 subjects [2 (4%) subjects from the placebo group, 2 (3%) subjects from the low dose colchicine group, and 1 (2%) subjects from the standard dose colchicine group] had treatment emergent potentially significant low hemoglobulin/hematocrit levels. Further examination of these data showed that only one patient (Subject 1064-1003) who was a 53-year old male randomized to the low dose colchicine group had a decrease in Hematocrit from a baseline value of 43% to 36% and 38% on Days 3 and 7 post study medication. This case was confounded by the concomitant use of ibuprofen which can cause gastrointestinal bleeding and lower hematocrit levels.

Overall, no new safety issues related to hematological lab indices associated with the use of colchicine were identified on review of these data.

b. Liver Function Tests (LFTs):

Approximately 10% of subjects in each treatment group had elevated baseline LFTs. There were increases in both the mean and median values for both AST and ALT observed on post-flare testing. Shift table analyses (Table 31) showed that more subjects randomized to the standard dose group had elevations in ALT (23%), AST (17%), and direct bilirubin (7%) as compared to low dose subjects (ALT: 7%; AST: 0%; direct bilirubin: 1%] and placebo subjects (ALT: 7%; AST: 10%; direct bilirubin: 2%).

Table 31 – Number (%) of Subjects with Treatment-Emergent Shift in Liver Function Parameters Study MCP-004-06-001 (Safety Population)

Parameter	Baseline	Post-Flare								
		Standard Dose Colchicine (N=59)			Low Dose Colchicine (N=74)			Placebo (N=59)		
		Low	Normal	High	Low	Normal	High	Low	Normal	High
ALT	Low	--	--	--	--	--	--	--	--	--
	Normal	--	31(66%)	11(23%)	--	57(78%)	5(7%)	--	44(76%)	4(7%)
	High	--	--	5 (11%)	--	4(6%)	7(10%)	--	3(5%)	7(12%)
AST	Low	--	--	--	--	--	--	--	--	--
	Normal	--	37(79%)	8(17%)	--	68(93%)	4(5%)	--	50(86%)	6(10%)
	High	--	--	2(4%)	--	1(1%)	--	--	2(3%)	--
Alkaline Phosphatase	Low	--	2(4%)	--	16(22%)	5(7%)	--	4(7%)	3(5%)	--
	Normal	--	44(96%)	--	--	50(69%)	1(1%)	1(2%)	49(85%)	--
	High	--	--	--	--	--	1(1%)	--	1(2%)	--
Bilirubin Direct	Low	1(2%)	--	--	--	1(1%)	--	--	--	--
	Normal	--	40(87%)	3(7%)	1(1%)	68(93%)	1(1%)	1(2%)	53(91%)	1(2%)
	High	--	1 2%)	1 (2%)	--	2(3%)	--	--	2(3%)	1(2%)
Bilirubin Total	Low	--	--	--	--	--	--	--	--	--
	Normal	1(2%)	42(89%)	2(4%)	--	72(99%)	--	--	57(98%)	--
	High	--	--	2(4%)	--	1(1%)	--	--	--	1(2%)
LDH	Low	--	--	--	--	--	--	--	--	--
	Normal	--	40(87%)	3(7%)	--	66(90%)	3(4%)	--	45(78%)	7(12%)
	High	--	1 (2%)	2(4%)	--	3(4%)	1(1%)	--	2(3%)	4(7%)

Adapted Sponsor's Table 12:30; p.133 of study report.

Additional review of the cases of LFT abnormalities showed that 2 patients (Subjects 1064-107 and 1054-1003) randomized to the standard dose colchicine group had elevated LFTs (i.e., ALT ranging: 33-98 U/L and AST ranging: 31-84 U/L) that were clinically significant within 4-5 days post-dosing which resolved on repeat testing in one patient and were improving in the other patient. These findings are consistent with colchicine being a hepatotoxic agent.

Review of the lab data for alkaline phosphatase, direct bilirubin, and LDH revealed no meaningful trends on change from baseline to post-flare or on analyses of shift tables.

Overall, no new safety issues related to hepatic lab assessments associated with the use of colchicine were identified on review of these data.

c. Renal Function:

No meaningful trends on change from baseline to post-flare for any of the 3 treatment groups in serum creatinine or BUN or shift in creatinine, however, 22% of placebo patients did have a shift increase in BUN as compared to 11% in the low dose colchicine and 2% in the standard dose colchicine groups. Because the magnitude of the shift in BUN was greater in the placebo group, they should not be attributed to colchicine even though the latter can cause renal toxicity. A total of 3 subjects (2 [3%]

in the placebo group and 1 [1%] in the low dose colchicine group) had low post-treatment creatinine clearances (i.e., <60 mL/minute), however, all 3 subjects had low creatinine clearances at baseline so these findings should not be attributed to colchicine.

Overall, no new safety issues related to renal lab assessments associated with the use of colchicine were identified on review of these data.

d. Creatinine phosphokinase (CPK)

Mean and median changes from baseline CPK values were similar for the two colchicine treatment groups, however, there was a substantial change over baseline value for this parameter in the placebo group due to a single patient. This patient (Subject 1081-1004) had a 4166 U/L change from baseline that will be discussed below. A number of patients from each treatment group (7 [15%] subjects in the standard dose colchicine group; 10 [14%] subjects in the low dose colchicine group and 9 [16%] subjects in the placebo group) in the controlled study had baseline elevations in CPK which increased with study therapy and were thought to be clinically significant. Review of the shift table analysis (Table 32) reveals 5 (10%) patients in the standard dose colchicine group, 6 (8%) patients in the low dose group and 4 (7%) patients in the placebo group who had elevations above normal in CPK assessments over the course of the trial.

Table 32- Number (%) of Subjects with a Treatment-Emergent Shift in CPK –Safety Population

Parameter	Baseline	Post-Flare								
		Standard Dose Colchicine (N=52)			Low Dose Colchicine (N=74)			Placebo (N=59)		
		Low	Normal	High	Low	Normal	High	Low	Normal	High
CPK	Low	--	1(2%)	--	1(1%)	--	--	2(3%)	--	--
	Normal	--	31(67%)	5(11%)	1(1%)	55(75%)	6(8%)	--	41(71%)	4(7%)
	High	--	4(9%)	5(11%)	--	4(6%)	6(8%)	--	3(5%)	8(14%)

Adapted Sponsor's Table 12:306 p.137 of study report.

Further review of these data revealed that many of these elevations in CPK were generally mild to moderate in magnitude and transient in nature. However, 2 patients were identified who had huge increases in CPK on treatment and were deemed clinically significant (i.e., CPK >1000 U/L). The first patient (Subject 1081-1004) was a 41-year old male randomized to placebo who had a baseline CPK of 924 U/L that increased to 4166 U/L on Day 6 post-study treatment. CPK values reportedly returned to within normal limits on repeat testing. Due to the limited amount of information available the etiology of this rise in CPK is unclear. The second patient (Subject 1028-1003) was a 45-year old male randomized to standard dose colchicine who had a baseline CPK of 631 U/L that increased to 1059 U/L Day 4 post study treatment. No

repeat testing or follow-up was performed. These are expected adverse events since colchicine can cause rhadomyolysis.

Overall, review of the CPK data were consistent with colchicine's known safety profile and its ability to cause rhadomyolysis.

e. Serum electrolytes

Review of the lab data for serum albumin, total protein, calcium, carbon dioxide, chloride, glucose, phosphorus, potassium, and sodium revealed no meaningful trends on change from baseline to post-flare or on analyses of shift tables. However, baseline mean and median serum uric acid levels were elevated above the upper end of normal range for this parameter and changed very little on post-flare testing or on shift table analysis. This is not a surprising finding in view of the fact that the patients who participated in this study had gout and elevated serum uric acids are a hallmark of this disease. Although no meaningful trends on mean change from baseline to post-flare were observed in all 3 treatment groups, there were high percentages of patients with elevated glucose on shift analysis in all 3 treatment groups: 20% in the standard dose colchicine, 19% in the placebo group, and 15% in the low dose colchicine group. This is an expected finding since a large percentage of the patients who participated in this trial had diabetes mellitus.

No new safety signals were identified on review of the overall serum electrolyte lab data generated from the controlled study.

f. Urinalysis

Review of the lab data for urinalysis parameters revealed no clinically meaningful trends on change from baseline to post-flare or on shift table analysis.

7.4.2.2 Laboratory Findings: Pharmacokinetic Studies

Lab test results from the 286 healthy subjects who participated in the Phase 1 and 2 pharmacokinetic studies conducted by the Applicant were submitted in the 120-safety update and were also examined for any safety signals. For the majority of lab parameters assessed, no clinically meaningful trends in changes from baseline were noted. However, a higher than expected proportion of subjects (16%) had post-dose neutrophil counts below the normal range for this parameter (i.e., 2.3×10^3 cells/μL). **Additionally, 8% of these subjects had moderately elevated LFT's which were less than** 2x the upper limit of normal for these parameters. Elevations in serum glucose above the upper limit of normal (i.e., 110 mg/dL) were also reported in 7% of subjects post-exposure to colchicine. The majority of these elevated serum glucoses occurred in women who participated in the oral contraceptive PK study. The proportion of subjects

with elevated serum glucose was similar to that observed when the same subjects were administered placebo during the second period of this study. The cases of neutopenia and elevated LFT's are expected AEs associated with the use of colchicine since its capability to cause hematopoietic and liver toxicity are both well documented. The etiology of the elevated serum glucoses may be due to undiagnosed or early glucose intolerance in these subjects. In general, no new safety signals associated with the administration of colchicine were identified on review of the lab data collected from healthy volunteers who participated in the PK studies.

7.4.3 Vital Signs: Controlled and Pharmacokinetic Studies

According to the protocol for controlled trial MCP-004-06-001, patients were mandated to undergo measurements of a variety of vital signs at each study visit (Visit 1-4 and/or 5). The following vital signs were assessed at these timepoints: oral temperature, sitting radial or brachial pulse rate (PR), respiratory rate (RR), sitting blood pressure (BP) and body weight. Patients' height was to have been measured at Visit 1.

Vital sign data from the controlled pivotal study were presented as follows: actual values and change from baseline by parameter, the incidence of treatment-emergent shifts from normal range relative to baseline, and any significant observations (i.e., values meeting pre-specified criteria for possible clinical significance and/or reported as AEs). The Applicant's listing of normal ranges of values for each vital sign parameter was reviewed and the clinically acceptable range for normal appeared appropriate. Examination of the vital sign data revealed no clinically meaningful trends on change from baseline to post-flare or on analyses of shift tables for any of the assessed parameters.

Vital sign data from the 286 healthy subjects who participated in the Phase 1 and 2 pharmacokinetic studies conducted by the Applicant were submitted in the 120-safety update and were also examined for any potential safety signals. No clinically meaningful trends in changes due to exposure to colchicine were noted on review of these data.

In general, no new safety signal associated with the use of colchicine was identified on review of the vital sign data collected during the controlled trial and the 8 PK studies.

7.4.4 Electrocardiograms (ECGs)

The protocol only required a screening ECG be conducted on all subjects who participated in the controlled trial MCP-004-006-001. There were a total of 95 patients who participated in either single- or multiple-dose PK studies who had post-dose triple

ECGs measurements as part of these studies. Although the sponsor was told that they did not have to do a formal QTc prolongation study in support of colchicine's safety profile, they submitted the results of a failed "thorough QT study." MPC-004-07-1006 was a randomized, double-blind, double-dummy PK and exploratory ECG safety study of a standard dose of colchicine (total dose 4.8 mg over 6 hours) versus moxifloxacin as a positive control for QTc prolongation in 18 healthy volunteers. No definitive conclusions can be drawn from this trial since it failed to demonstrate a positive control necessary for data analysis. Of the remaining 5 PK studies conducted in healthy volunteers in which serial ECGs were performed, no meaningful trends in changes from baseline or clinically significant changes were noted regarding QTc interval changes due to exposure to colchicine.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable for this application.

7.4.6 Immunogenicity

Not applicable for this application.

7.5 Other Safety Explorations

In view of colchicine's propensity to cause AEs involving the gastrointestinal system, additional analyses were conducted on safety data generated from the controlled study to determine the existence of potential safety issues related to demographic characteristics such as age, gender and race. These analyses will be discussed below in the appropriate subsections.

7.5.1 Dose Dependency for Adverse Events

Not applicable for this application.

7.5.2 Time Dependency for Adverse Events

Not applicable for this application.

7.5.3 Drug-Demographic Interactions

Table 33 lists gastrointestinal AEs in patients with gout by treatment group for the following subcohort age groups: <45 years, 45-65 years and >65 years. Patients randomized to standard dose colchicine who were <45 years old and >65 years old reported higher rates of both diarrhea (93% and 100%, respectively), nausea (36% and 17%, respectively) and vomiting (36% and 50%, respectively) as compared to patients 45-65 years of age (diarrhea: 66%; nausea: 9% and vomiting: 3%). Due to the small numbers of patients involved in this age based analysis, the validity of any conclusion is highly questionable. In patients randomized to low dose colchicine, the overall rates of diarrhea were comparable for all 3 age groups, however, the numbers of patients were too small to draw any definitive conclusions for the risk of other GI AEs associated with this dose regimen.

Table 33 – Tabular Summary of the Number (%) of Subjects with Gastrointestinal Treatment-Emergent Adverse Events (TEAEs) by Age in Study MPC-004-06-001 (Safety Population)

MedDRA Preferred Term	Standard Dose Colchicine (N = 52)			Low Dose Colchicine (N = 74)			Placebo (N = 59)		
	<45 yrs (n=14)	45-65 yrs (n=32)	>65 yrs (n=6)	<45 yrs (n=26)	45-65 yrs (n=35)	>65 yrs (n=13)	<45 yrs (n=12)	45-65 yrs (n=41)	>65 yrs (n=6)
Overall	13(93%)	21 (66%)	6(100%)	8 (31%)	12 (34%)	7 (54%)	4 (33%)	12 (29%)	0
GI Disorders	13(93%)	21 (66%)	6(100%)	7 (27%)	9 (26%)	3 (23%)	1 (8%)	11(27%)	0
Diarrhea	13(93%)	21 (66%)	6(100%)	5 (19%)	9 (26%)	3 (23%)	1 (8%)	7 (17%)	0
Nausea	5 (36%)	3 (9%)	1 (17%)	3 (12%)	0	0	1 (8%)	2 (5%)	0
Vomiting	5 (36%)	1 (3%)	3 (50%)	0	0	0	0	0	0

Sponsor's Table 2.7.4:76; p. 97 SCS

Table 34 shows the gender based analysis of gastrointestinal AEs by treatment group. Due to the paucity of female patients who participated in this trial, no definitive conclusions regarding the risk for developing gastrointestinal AEs can be made for either colchicine dose regimen.

Table 34 – Tabular Summary of Number (%) of Subjects with Gastrointestinal Treatment-Emergent Adverse Events (TEAEs) by Gender in Study MPC-004-06-001 (Safety Population)

MedDRA Preferred Term	Standard Dose Colchicine (N = 52)		Low Dose Colchicine (N = 74)		Placebo (N = 59)	
	Male (n=49)	Female (n=3)	Male (n=72)	Female (n=2)	Male (n=55)	Female (n=4)
All TEAEs	37 (76%)	3 (100%)	27 (38%)	0	13 (24%)	3 (75%)
GI Disorders	37 (76%)	3 (100%)	19 (26%)	0	10 (18%)	2 (50%)
Diarrhea	37 (76%)	3 (100%)	17 (24%)	0	7 (13%)	1 (25%)
Nausea	9 (18%)	0	3 (45)	0	2 (4%)	1 (25%)
Vomiting	9 (18%)	0	0	0	0	0

Sponsor's Table 2.7.4:77; p.98 SCS

Similarly, no conclusions can be drawn from the analysis by race for risk of gastrointestinal AEs shown in Table 35 due to the small numbers of non-caucasian patients who participated in the controlled study.

Table 35 – Tabular Summary of Number (%) of Subjects with Gastrointestinal Treatment-Emergent Adverse Events (TEAEs) by Race in Study MPC-004-06-001 (Safety Population)

MedDRA Preferred Term	Standard Dose Colchicine (N = 52)		Low Dose Colchicine (N = 74)		Placebo (N = 59)	
	Caucasian (n=40)	Non-Caucasian (n=12)	Caucasian (n=66)	Non-Caucasian (n=8)	Caucasian (n=47)	Non-Caucasian (n=12)
All TEAEs	32 (80%)	8 (67%)	24 (36%)	3 (38%)	12 (26%)	4 (33%)
GI Disorders	32 (80%)	8 (67%)	17 (26%)	2 (25%)	10 (21%)	2 (17%)
Diarrhea	32 (80%)	8 (67%)	15 (23%)	2 (25%)	7 (15%)	1 (8%)
Nausea	5 (13%)	4 (33%)	2 (3%)	1 (13%)	3 (6%)	0
Vomiting	8 (20%)	1 (8%)	0	0	0	0

Sponsor's Table 2.7.4:78; p.98 SCS

7.5.4 Drug-Disease Interactions

Due to concerns regarding renal clearance of colchicine, the Applicant performed an analysis of gastrointestinal AEs based on calculated creatinine clearance in patients by treatment group shown in Table 36. Overall, the risk for gastrointestinal AEs appears to be comparable in each colchicine treatment group by creatinine clearance category, the number of patients in each renal category is too small to support definitive conclusions.

Table 36 -Tabular Summary of the Number (%) of Subjects with Gastrointestinal Treatment-Emergent Adverse Events (TEAEs) by Creatinine Clearance in Study MPC-004-06-001 (Safety Population)

MedDRA Preferred Term	Standard Dose Colchicine (N = 52)			Low Dose Colchicine (N = 74)			Placebo (N = 59)		
	<60 mL/mm (n=5)	60-80 mL/min (n=18)	>80 mL/min (n=6)	<60 mL/mm (n=11)	60-80 mL/min (n=22)	>80 mL/min (n=41)	<60 mL/mm (n=8)	60-80 mL/min (n=13)	>80 mL/min (n=38)
Overall	4 (80%)	14 (78%)	22(76%)	4 (36%)	9 (41%)	14(34%)	4 (50%)	2 (15%)	10(26%)
GI Disorders	4 (80%)	14 (78%)	22(76%)	3 (27%)	6 (27%)	10(24%)	2 (25%)	2 (15%)	8 (21%)
Diarrhea	4 (80%)	14 (78%)	22(76%)	3 (27%)	6 (27%)	8 (20%)	0	1 (8%)	7 (18%)
Nausea	0	3 (17%)	6 (21%)	0	1 (5%)	2 (5%)	1 (13%)	0	2 (5%)
Vomiting	0	4 (22%)	5 (17%)	0	0	0	0	0	0

Sponsor's Table 2.7.4:79; p. 99 SCS

7.5.5 Drug-Drug Interactions

Allopurinol is commonly taken by gout patients as a concomitant medication to lower serum urate levels. A total of 24 patients who participated in the controlled study reported taking allopurinol during their acute gout flare. Table 37 summarizes the results of the Applicant's analysis of gastrointestinal AEs associated with the user of allopurinol by treatment group. Due to the paucity of patients taking allopurinol while participating in this study, no valid conclusions can be reached regarding this analysis.

Table 37 – Tabular Summary of the Number (%) of Subjects with Gastrointestinal Treatment-Emergent Adverse Events (TEAEs) by Allopurinol use in Study MPC-004-06-001 (Safety Population)

MedDRA Preferred Term	Standard Dose Colchicine (N = 52)		Low Dose Colchicine (N = 74)		Placebo (N = 59)	
	Allopurinol Use (n= 8)	None (n =44)	Allopurinol Use (n= 11)	None (n =63)	Allopurinol Use (n= 5)	None (n =54)
All TEAEs	8 (100%)	32 (73%)	4 (36%)	23 (37%)	1 (20%)	15 (28%)
GI Disorders	8 (100%)	32 (73%)	2 (18%)	9 (26%)	1 (20%)	11 (20%)
Diarrhea	8 (100%)	32 (73%)	2 (18%)	9 (26%)	1 (20%)	8 (15%)
Nausea	1 (13%)	8 (18%)	1 (9%)	0	0	3 (6%)
Vomiting	1 (13%)	8 (18%)	0	0	0	0

Sponsor's Table 2.7.4:17; p. 21 SCS

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no reports of malignancy associated with the use of colchicine in the safety database submitted in support of this indication by the applicant.

7.6.2 Human Reproduction and Pregnancy Data

Data submitted describing colchicine's effect on human reproduction and pregnancy were previously reviewed in support of the familial Mediterranean Fever (FMF) application. Based on data from animal reproduction studies which demonstrated colchicine to be teratogenic in mice when administered in doses of up to two times the maximum recommended human dose, colchicine will be labeled as a FDA Pregnancy Category C drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

Data submitted describing colchicine's effect on growth and in the pediatric population were previously reviewed in support of the FMF indication for this drug.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Data submitted describing acute colchicine toxicity associated with overdose situations were previously reviewed in support of the FMF indication for this drug. A published report by Baud et al[3] describing the successful use of goat-derived colchicine-specific FAb fragments in a patient who had ingested 60 mg of colchicine, 900 mg of Phenobarbital, and 750 mg of opium extract was included for completeness by the applicant. The Fab fragments which were administered 40 hours post ingestion increased urinary excretion of colchicine by six-fold and were able to alter the pharmacokinetics of the drug. Although the Fab fragment was demonstrated to be effective, at the time of this review it is commercially unavailable.

It is unlikely that colchicine will be abused since it does not affect the central nervous system and its most common side effects are GI in nature (i.e., diarrhea, nausea, and vomiting). Review of the published literature did not identify any reports of withdrawal or rebound effect associated with the discontinuation of colchicine therapy.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

In support of colchicine's safety profile as a treatment for acute gout, the Applicant submitted the results of a postmarketing review they conducted of AE reports associated with colchicine that had been spontaneously submitted to the FDA's Spontaneous Reporting System (SRS) and its successor, the Adverse Event Reporting System (AERS Database) for the time period from January 1, 1969 through June 30, 2007. A total of 751 AE reports were identified during this search in which colchicine was listed as the primary or secondary suspect drug. (Note: This number of reports may contain duplicate reports of the same AE.) These data were reviewed previously in support of the FMF indication for colchicine but are included here for completeness. However, an additional 137 AEs from the AERS Database from the time period of July 1, 2007 through March 31, 2008 were submitted in this application's 120-day safety update. Table 38 is a tabular summary of the results from the results from these postmarketing reviews. The most common AEs associated with colchicine prior to 1997 were as follows: diarrhea, myopathy, pancytopenia, overdose, and increased creatinine phosphokinase. After 1997, the most common AEs associated with colchicine were: diarrhea, drug interaction, vomiting, acute renal failure, nausea and gout. No new safety signals were identified on review of this data since colchicine's toxicity profile is well documented in the medical literature due to its availability in this country as a treatment for gout since 1938.

Table 38 –Tabular Summary of the Twenty Most Common Postmarketing Adverse Events Associated with Colchicine (Primary or Secondary Suspect Status) Collected by the FDA's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS Database) from January 1, 1969 to March 31, 2008

FDA SRS Database (1969 –Oct. 1997) COSTART term	Number of Reports	FDA AERS Database MedDRA Preferred Term	Number of Reports	
			Nov. 1997 – June 2007 (Original ISS)	Nov. 1997- March 2008 (120-day Update)
Total	241	Total	510	647
Diarrhea	29	Diarrhea	69	81
Myopathy	21	Drug Interaction	69	75
Pancytopenia	19	Vomiting	65	68
Overdose	18	Renal Failure Acute	59	74
Creatinine Phosphokinase Inc	17	Nausea	54	58
Hypotension	17	Gout	50	54
Neuropathy	17	Diarrhea NOS	49	48
Intentional Overdose	15	Blood Creatinine Inc	44	46
Liver Function Tests Abn	12	Abdominal Pain	43	50
Acute Kidney Failure	11	Pyrexia	41	57
Asthenia	11	Rhabdomyolysis	40	51
Leukopenia	10	Completed Suicide	35	37
Sepsis	10	Blood Creatinine Phosphokinase Inc	34	50
Thrombocytopenia	10	Myopathy	32	41
Agranulocytosis	9	Pancytopenia	31	41
Shock	9	Vomiting NOS	31	31
Apnea	8	Dehydration	30	35
Dehydration	8	Asthenia	28	45
Kidney Function Abn	8	Aspartate Aminotransferase Inc	27	31
Marrow Depression	8	Renal Failure NOS	27	24
Myasthenia	8			
Peripheral Neuritis	8			

Sponsor's table 2.7.4.82; p. 120 of SCS

Included in the postmarketing review was an analysis of death reports associated with colchicine. These cases will not be discussed here since they have been reviewed previously in support of the FMF indication for the drug. There were no new postmarketing reports of deaths included in the 120-day safety update for review or discussion.

The Applicant also conducted a postmarketing review of AEs associated with colchicine collected by the World Health Organization (WHO) for the time period from 1968 through March 2006. This postmarketing summary of safety contained 1380 AE reports associated with the use of colchicine that had been collected from 79 countries. The most common AEs associated with colchicine in this safety summary were similar to

those observed in the postmarketing review of cases collected by the FDA's SRS and AERS Database and included diarrhea, vomiting, nausea, rash, pruritus and acute renal failure. Since these data had been previously reviewed in support of the FMF indication they will not be discussed further in this review and are only included for completeness. No new safety information from this source was included in the Applicant's 120-safety update since the WHO safety database is currently being updated.

In addition to postmarketing reports of clinical AEs associated with the use of colchicine collected by the FDA's SRS and AERS Database, the applicant also submitted a review of postmarketing lab test abnormalities collected by the agency for the time period from January 1, 1969 thorough June 30, 2007. The results of this review are summarized in Table 39. The most common hematological lab AEs associated with colchicine use reported by 10 or more patients were: pancytopenia, thrombocytopenia, decreased platelet count, decreased white blood cells, increased white blood cells, neutropenia and decreased hemoglobulin. In terms of common biochemistry AEs associated with this drug reported by 10 or more patients were: increased blood creatinine, increased creatine phosphokinase (CPK), increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), and increased BUN. Review of the 120-day safety update included cumulative data for the period from November 1, 1997 through March 31, 2008 was similar to the information contained in the original safety submission. No new safety signal was identify on examination of these data.

Table 39 – Tabular Summary of Lab Test Abnormalities Reported ≥ 10 Individuals Collected by the FDA's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS Database) from January 1, 1969 to March 31, 2008

Adverse Event Term	Counts		
	Jan. 1, 1969 – Oct. 31, 1997[1]	Nov. 1, 1997 – June 30, 2007[2]	Nov. 1, 1997 – March 31, 2008[2]
	Original ISS		120-day Safety Update
Hematology			
Pancytopenia	19	31	41
Thrombocytopenia	10	18	25
Platelet Count Decreased	--	16	14
White Blood Cell Decreased	--	16	14
White Blood Cell Increased	--	16	19
Neutropenia	--	14	17
Hemoglobulin Decreased	--	13	13
Biochemistry			
Blood Creatinine Increased	--	44	46
Blood Creatine Phosphokinase Inc	--	34	50
Aspartate Aminotransferase Inc	--	27	31
Alanine Aminotransferase Inc	--	26	30
BUN Inc	--	22	22
CRP Inc.	--	17	19
Creatine Phosphokinase Inc	17	--	--
Blood Uric Acid inc.	--	16	18
Liver Function Tests NOS Abn	--	12	12
Liver Function Tests Abn	12	--	4
Lactic Acidosis	--	11	13
Acidosis	--	10	9
LDH Inc	--	10	10
GGTP Inc	--	10	12

[1]Costart Terminology as per the SRS database
[2]MedDRA Terminology as per the AERS database
Sponsor's Table 2.7.4:88; p. 130

9 Appendices

9.1 Literature Review/References

The Applicant conducted a review of the worldwide literature via the search engine Dialog® of the following databases: Biosis Previews® (1969 to 2008), EMBASE® (1974 to 2008), JICST-Eplus (1985 to 2008), MEDLINE® (1951 to 2008) and Toxfile (1965 to 2008). More than 1200 published articles were identified as of May 2008, out of which 123 publications contributed information regarding the safety profile of colchicine that was reviewed in support of the FMF indication. The Applicant updated this literature review for the 120-day safety update of this application. Six new published articles were thus identified out of which only 2 publications were included in the 120-day safety update since they potentially contained information that could affect the colchicine's proposed label. The findings from these 2 publications will be discussed below.

The first article by Al-Daraji et al[3] evaluated the effects of colchicine on the gastrointestinal tract of 43 patients with FMF treated with colchicine and compared biopsies of their stomach and colon collected over 14-years to those of 17 patients without FMF or colchicine exposure for histological signs of colchicine toxicity. Only 3 patients with FMF were found to have histological changes consistent with colchicine toxicity that were confined to biopsies taken from the gastric antrum. These histological findings were similar to those reported in the literature. The second article by Kamath et al[4] described histological changes in the liver of a 54-year old male post renal transplant with a 15-year history of hepatic C and gout treated with colchicine 0.6 mg once daily. This patient presented with loose stools that were attributed to colchicine but without any hematological evidence of colchicine toxicity. Liver biopsy was performed for tracking the progression of his hepatitis C and was consistent with scattered mitotic figures arrested in metaphase in hepatocytes associated with ring mitotic figures which were not present on a liver biopsy from 7 years earlier. The clinical significance of the ring mitoses is unclear, but has been reported in the literature. Colchicine therapy was not discontinued. The information contained in both of these articles has been reported in the literature previously and does not contribute any new information to the colchicine's safety profile that needs to be added to the drug's label.

References:

[1]Ahern MJ, McCredie M, Reid C, et al. Does colchicine work? The results of the first controlled study in acute gout. Aust NZ Med 1987; 17:301-304.
[2]Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P et al. EULAR evidence based recommendations for gout- Part II Management: report of a task force of the EULAR Standing Committed for International Clinical Studies Including Therapies (ESCISIT) Ann Rheum Dis 2006; 65:1312-1324.

[3]Al-Daraji WI, Al-Mahmoud RM. Gastric changes following colchicine therapy in patients with FMF. Dig Dis Sci 2008; 53:2079-82.
[4]Kamath A, Mehal W, Jain D. Colchicine-associated ring mitosis in liver biopsy and their clinical implications. J Clin Gastroenterol 2008; 42:1060-2.

9.2 Labeling Recommendations

Detailed discussions on labeling have not yet begun. I have no specific comments regarding product labeling at this time.

9.3 Advisory Committee Meeting

No advisory committee meeting was conducted for this application.

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

/s/

Rosemarie Neuner
6/26/2009 11:26:08 AM
MEDICAL OFFICER

Jeffrey N Siegel
6/27/2009 01:50:21 PM
MEDICAL OFFICER