CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-351

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-351	Submission Date(s): 9/30/2008, 11/25/2008, 02/03/2009
NDA: 22-352	06/20/2008
Brand Name	Colcrys™
Generic Name	Colchicine Tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Mutual Pharmaceutical Company, Inc.
Relevant IND(s)	72,586
Formulation; Strength(s)	Immediate Release Tablet; 0.6 mg
Indication	Treatment of gout flares (acute gout)
Proposed Dosage Regimen	The recommended dose of Colcrys (colchicine) for treatment of a gout flare is 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later.

Table of Contents

1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Mutual Pharmaceutical Company submitted a 505(b)(2) NDA 22-352 for Colcrys, colchicine tablets on 06/20/2008, for ——————————— familial Mediterranean fever (FMF) ——————————————————————————— b(4)
———————————————The sponsor is relying on literature for clinical pharmacology in special populations, safety and efficacy data in pediatric and adult FMF patients. Because of rare incidence of this disease, its treatment is an orphan indication. As of today, regulatory action on NDA 22-352 by the Agency is pending.

Mutual Pharmaceutical Company also submitted a 505(b)(2) NDA 22-351 for Colcrys, colchicine tablets on 9/30/2008, for the treatment of gout flares (acute gout). Safety and efficacy of Colcrys for treatment of acute gout was evaluated in a single adequate well controlled clinical trial MPC-004-06-001. This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1 week, dose comparison study intended to evaluate the efficacy and safety of colchicine for treatment of gout flares. This study evaluated the safety and efficacy of the currently practiced standard-dose (4.8 mg over 6 hours Ahern et. al. Aust NZ J Med 17:301-304. 1987) and the proposed low-dose colchicine arm (1.8 mg over 1 hour) in comparison with placebo treatment.

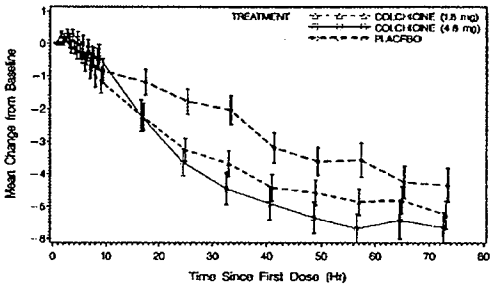
Mutual submitted eight new pharmacokinetic drug interaction studies. Seven studies evaluated the effects of CYP3A4 and P-gp inhibitors on the pharmacokinetics of single-dose colchicine (azithromycin, ketoconazole, ritonavir, verapamil, diltiazem, cyclosporine and grapefruit juice). One study evaluated the clinical drug interaction using a sensitive CYP1A2 substrate, theophylline.

In support of NDA 22-352 (colchicine for familial Mediterranean Fever), Mutual had submitted four clinical 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 11/26/2008.

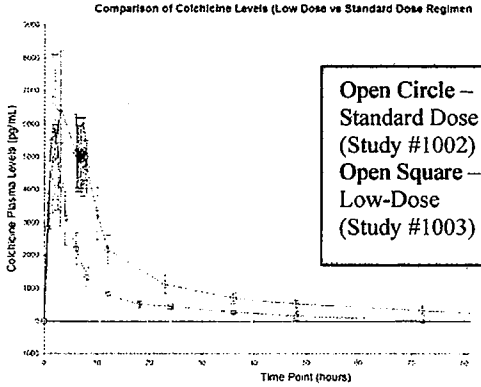
In clinical trial MPC-004-06-001, when compared to placebo treatment, both Low-dose (1.8 mg) and standard-dose (4.8 mg) colchicine regimen provided adequate but similar clinical response with respect to ≥50% pain relief, time to relief and time course of pain relief in patients with acute gout flare. It appears that peak and decrease in plasma colchicine levels occur prior to the time to relief and time course of pain relief noted.

Time Course of Pain Relief: Initially, a similar decrease in target joint pain score was noted in all three treatment groups. A separation in decline of pain scores was noted for the two colchicine treatment groups compared to placebo after approximately 8 hours of first dose. Plasma levels of colchicine peak at around 2 hours, and 8 hours after dosing. Hence, the clinical response appears to be delayed compared to systemic plasma profile of colchicine.

Target Joint Pain Score at Each Assessment Time Point Post First Dose and Corresponding Change from Baseline (Observed Cases Only Without Regard to Rescue) – ITT Population



Comparison of Colchicine Levels (Low Dose vs Standard Dose Regimen



Open Circle – Standard Dose (Study #1002)
Open Square – Low-Dose (Study #1003)

Gastrointestinal disorders such as diarrhea, nausea, vomiting and abdominal discomfort were the most frequent adverse events in colchicine treatment groups. Dose-related increase in number of patients with treatment emergent adverse events of different intensity (mild, moderate and severe) was noted compared to placebo treatment.

Number (%) of Patients with at Least One TEAE with an Incidence of ≥ 2% of Patients in Any Treatment Group

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N = 59)	Colchicine Treatment Group	
		Low Dose (N = 74)	Standard Dose (N = 52)
Number of Patients with at Least One TEAE	16 (27.1)	27 (36.5)	40 (76.9)
Gastrointestinal Disorders	12 (20.3)	19 (25.7)	40 (76.9)
Diarrhea	8 (13.6)	17 (23.0)	40 (76.9)
Nausea	3 (5.1)	3 (4.1)	9 (17.3)
Vomiting	0	0	9 (17.3)
Abdominal Discomfort	2 (3.4)	0	0
General Disorders and Administration Site Conditions	1 (1.7)	1 (1.4)	4 (7.7)
Fatigue	1 (1.7)	1 (1.4)	2 (3.8)
Metabolism and Nutrition Disorders	2 (3.4)	3 (4.1)	0
Gout	1 (1.7)	3 (4.1)	0
Nervous System Disorders	2 (3.4)	1 (1.4)	1 (1.9)
Headache	2 (3.4)	1 (1.4)	1 (1.9)
Respiratory, Thoracic and Mediastinal Disorders	0	2 (2.7)	1 (1.9)
Pharyngolaryngeal Pain	0	2 (2.7)	1 (1.9)

Concentration-response relationship could not be assessed as blood samples were not collected in the clinical trial MPC-004-06-001. However, PK studies from NDA 22-352 submission # 1002 and # 1003 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) (see PK characteristics below).

Drug Interactions

In clinical trial MPC-004-06-001 safety of colchicine has been evaluated between 1.8 mg and 4.8 mg dose for treatment of acute gout. From a clinical pharmacology perspective dosage adjustment in situations due to drug interaction are aimed at maintaining the average Cmax and AUC noted between the Low-dose and Standard-dose.

As noted from the previously reviewed (dated 11/28/2008) clarithromycin-colchicine drug interaction, other strong CYP3A4 inhibitors increase colchicine systemic exposure by 3- to 4-fold. Moderate CYP3A4 inhibitors cause a 2-fold increase in colchicine AUC when coadministered. P-gp inhibition by cyclosporine resulted in 3.5-fold increase in Cmax and AUC of colchicine.

Summary of % Ratio of Cmax or AUC of colchicine when coadministered with interacting drug and compared with colchicine alone.

Study No.	Study Type	% Ratio of C_{max} inhibition/C_{max} without inhibition (90% CI)	% Ratio of AUC_{0-t} inhibition/AUC_{0-t} without inhibition (90% CI)
MPC-004-08-1011 (n=24)	Azithromycin[1] (250 mg for 5 days)	112 (97.5, 130)	147 (127.7, 168.5)
MPC-004-08-1012 (n=24)	Ketoconazole[2] (200 mg bid for 5 days)	195 (179, 214)	299 (270, 332)
MPC-004-08-1013 (n=18)	Low dose Ritonavir[2] (100 mg bid for 5 days)	269 (235, 308)	364 (307, 430)
MPC-004-08-1014 (n=24)	Verapamil ER[3] (240 mg qd for 5 days)	131 (115, 150)	195 (175, 216)
MPC-004-08-1015 (n=24)	Diltiazem ER[3] capsule (240 mg qd for 7 days)	129 (107, 154)	172 (142, 208)
MPC-004-08-1016 (n=24)	Cyclosporine[4] (single 100 mg dose)	338 (288, 395)	337 (295, 385)
MPC-004-08-1017 (n=24)	Grapefruit Juice[3] (240 mL bid for 4 days)	93.25 (83, 105)	94.85 (86.5, 104)

[1] Weak CYP3A4 inhibitor, [2] Strong CYP3A4 inhibitor, [3] Moderate CYP3A4 inhibitor, [4] P-glycoprotein inhibitor in vivo.

Dosage adjustment is needed in patients who are on strong or moderate CYP3A4 inhibitors and P-glycoprotein inhibitors. The following dose adjustment is recommended:

Strong CYP3A4 inhibitors: Sponsor proposed use of a single 0.6 mg colchicine tablet when patients are on strong CYP3A4 inhibitors. This would constitute a 2/3rd decrease in proposed Low-dose regimen of 1.8 mg colchicine. However, pharmacokinetic simulations indicate that patients may be under dosed and hence if the first dose of 0.6 mg in patients on strong CYP3A4 inhibitors is tolerated well, an additional dose of 0.3 mg colchicine may be administered. Simulations of colchicine PK profile indicate that systemic exposure with the 0.9 mg dose is within the noted range for the Low-dose and Standard-dose regimen.

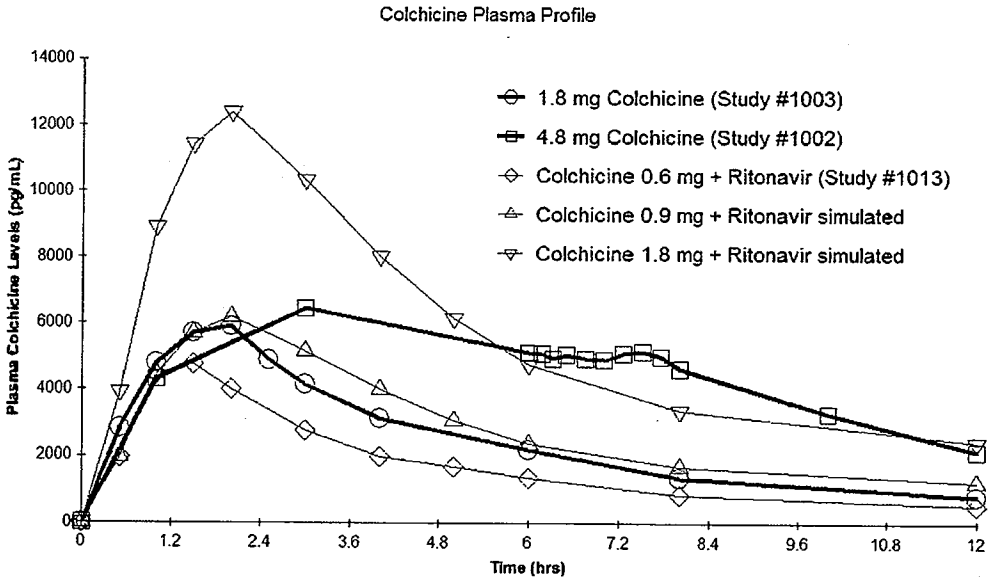
Simulation of strong CYP3A4 inhibition related drug interaction by low dose ritonavir regimen:

The following figure depicts the observed colchicine plasma levels with Low-dose (study #1003), Standard-dose (study #1002) in comparison with either noted (Study#1013) and predicted drug interaction with ritonavir, a strong CYP3A4 inhibitor. Simulations were performed by superposing plasma concentrations from the noted drug interaction following the dosing regimen:

a) Total dose of 0.9 mg: Colchicine tablet 0.6 mg administered at time 0 and half of tablet or 0.3 mg administered at 1 hour. As indicated in the table above, the predicted plasma concentrations are in between those noted for Low-dose and Standard-dose.

b) Total dose of 1.8 mg: Two 0.6 mg colchicine tablets administered at time 0 and 1 hour later. The simulated plasma levels far exceed the colchicine systemic exposure noted following 4.8 mg colchicine dose over 6 hours.

Observed or simulated mean plasma colchicine concentration following administration of colchicine with ritonavir (low dose of 100 mg bid administered over 5 days).



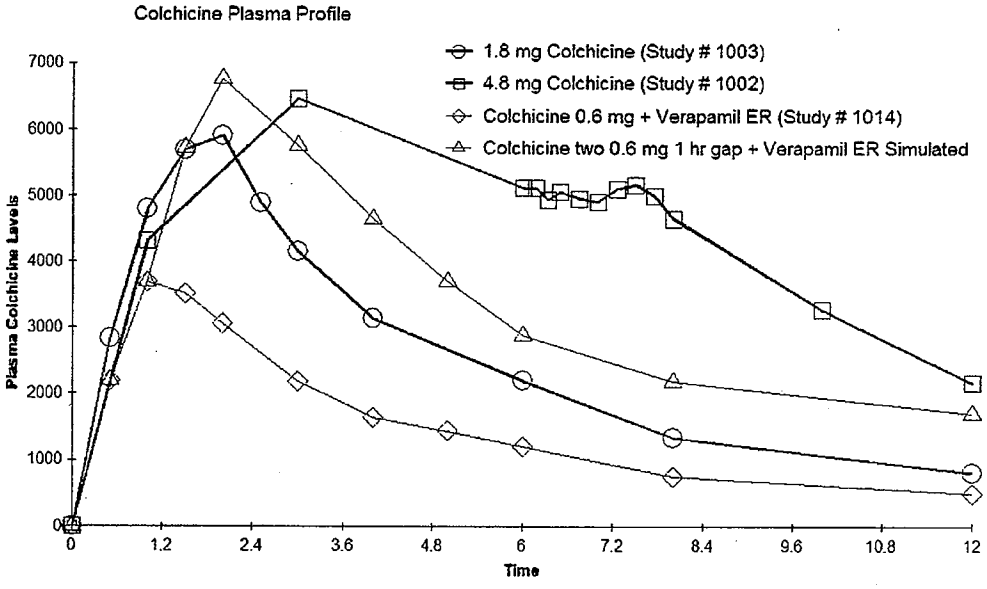
Moderate CYP3A4 inhibitors: Sponsor proposed use of ——— b(4)

——— This would constitute a — decrease in proposed Low-dose regimen of 1.8 mg colchicine. Simulations of colchicine PK profile indicate that systemic exposure with the proposed regimen is within the noted range for the Low-dose and Standard-dose regimen. Hence, the sponsor proposed dose adjustment is acceptable in patients without a history of decreased renal or hepatic function.

Simulation of Moderate CYP3A4 inhibition related drug interaction by verapamil:

The following figure depicts the observed colchicine plasma levels with Low-dose (study #1003), Standard-dose (study #1002) in comparison with either noted or predicted drug interaction with verapamil extended release tablets, a moderate CYP3A4 inhibitor. Simulations were performed by superposing plasma concentrations from the noted drug interaction following total dose of 1.2 mg: one 0.6 mg colchicine tablet administered at time 0 and 1 hour later. The simulated plasma levels are within the range of colchicine systemic exposure noted following colchicine 1.8 mg over 2 hrs and 4.8 mg colchicine dose over 6 hours.

Observed or simulated mean plasma colchicine concentration following administration of colchicine with verapamil extended release tablet (240 mg qd administered over 5 days).



Sponsor is proposing that a ———————————— colchicine may be used in patients with renal or hepatic impairment and receiving moderate CYP3A4 inhibitors. There is no basis for this recommendation and as such it is not acceptable. b(4)

Study # 1017 evaluated effect of grapefruit juice on colchicine pharmacokinetics. Results show that there was no significant drug interaction with the brand of grapefruit juice employed. However, as noted by De Castro et. al. 2006 (J Agri and Food chem. 54: 249-255) there is significant variability of furanocoumarins in different types of grapefruit juices. Hence, caution should be exercised in patients receiving grapefruit juice before they receive colchicine.

Weak CYP3A4 inhibitors: Dosage adjustment is not necessary with weak CYP3A4 inhibitors such as azithromycin. The observed increases in colchicine plasma levels with azithromycin are within the range of exposures noted with the Low-dose and Standard-dose.

P-glycoprotein inhibitors: Sponsor proposed use of a single 0.6 mg colchicine tablet when patients are on P-glycoprotein inhibitors. The proposed dose adjustment is acceptable in patients without a history of decreased renal or hepatic function.

Summary of Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following Colchicine Tablets Administration in Different Regimen

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)
Colchicine 0.6-mg Single Dose (N=13) (study # 1004)	2.45 (28.7)	1.50 (1.0 – 3.0)	10.5 (33.8)	12.3 (36)	4.95 (89.5)
Low Dose or 1.8 mg over 2 hours (Study # 1003) N=13	6.19 (39.30)	1.81 (1.0-2.5)	43.79 (26.12)	52.07 (26.29)	23.63 (39.10)
Standard Dose or 4.8 mg over 6 hours (Study #1002) N=15	6.84 (18.94)	4.47 (3.12-7.50)	104.95 (23.45)	118.20 (22.01)	31.38 (26.65)
Single Dose colchicine 0.6 mg + Azithromycin 250 mg 5-day regimen (Study #1011) N=24	3.05 (40)	1.5 (0.5 -3)	17 (37)	19.6 (39)	6.7 (68)
Single Dose colchicine 0.6 mg + Ketoconazole 200mg bid 5-day regimen (Study #1012) N=24	5.27 (28)	1 (0.5 – 2)	34.3 (27)	43.7 (27)	26 (52)
Single Dose colchicine 0.6 mg + Ritonavir 100 mg bid 5-day regimen (Study #1013) N=18	4.99 (25)	1.5 (1 -1.5)	29 (30)	35 (30)	17.4 (40)
Colchicine 0.6 mg followed by 0.3 mg 1 hour later + Ritonavir 5-day regimen (Simulated) N=18	4.28 (24)	2 (2-3)	46.9 (26)	48.8 (27)	17 (20)
Single Dose colchicine 0.6 mg + Verapamil ER 240 mg qd 5-day regimen (Study #1014) N=24	3.85 (38)	1 (0.5-2)	24.6 (26)	30.6 (27)	17 (35)
Two doses of colchicine 0.6 mg administered with 1 hour gap + Verapamil ER 240 mg qd 5-day regimen (Simulated) N=24	6.8 (35)	2 (1.5 -2)	75 (26)	82 (26)	17 (26)
Single Dose colchicine 0.6 mg + Diltiazem ER capsule 240 mg qd 7-day regimen (Study #1015) N=24	2.8 (44)	1.5 (0.5 – 5)	17.7 (48)	22.5 (49)	12.5 (62)
Single Dose colchicine 0.6 mg + Cyclosporine 100mg single dose (Study #1016) N=23	8.8 (25)	1.5 (0.5 – 2)	39.8 (26)	47.3 (25.6)	20.6 (31)
Single Dose colchicine 0.6 mg + Grapefruit Juice 4-day regimen (Study #1017) N=21	1.97 (20)	1.5 (1 - 3)	8.8 (34)	10.8 (38)	5.6 (63)

Study of colchicine drug interaction with theophylline (Study #1010)

The sponsor noted that incubation of colchicine in hepatocytes resulted in a decreased CYP1A2 activity (see clinical pharmacology review dated 11/28/08). Hence, a drug interaction study #1010 was conducted to evaluate the effect of 14 day colchicine administration on single dose pharmacokinetics of 300 mg theophylline, a sensitive

CYP1A2 substrate. Plasma levels (Cmax and AUC) of theophylline were not significantly different prior to and following colchicine treatment (see table below and the attached synopsis).

Overall, the clinical pharmacology submission is acceptable.

2 QBR

2.1 General Attributes

Mutual Pharmaceutical Company submitted a 505(b)(2) NDA 22-352 for Colcrys, colchicine tablets on 06/20/2008, for ——————————— familial Mediterranean fever (FMF) ——————————————————————— ——————————————. The sponsor is relying on literature for clinical pharmacology in special populations, safety and efficacy data in pediatric and adult FMF patients. Because of rare incidence of this disease, its treatment is an orphan indication. As of today, regulatory action on NDA 22-352 by the Agency is pending.

b(4)

Mutual Pharmaceutical Company also submitted a 505(b)(2) NDA 22-351 for Colcrys, colchicine tablets on 9/30/2008, for the treatment of gout flares (acute gout). Safety and efficacy of Colcrys for treatment of acute gout was evaluated in a single adequate well controlled clinical trial MPC-004-06-001.

Mechanism of action: Several publications suggest that colchicine has anti-inflammatory properties. However, the exact mechanism of the anti-inflammatory actions is unknown and it is an active area of research.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Safety and efficacy of Colcrys was evaluated in a single adequate well controlled clinical trial MPC-004-06-001. This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1 week, dose comparison study intended to evaluate the efficacy and safety of colchicine for treatment of gout flares. This study evaluated the safety and efficacy of the currently practiced standard-dose (4.8 mg over 6 hours Ahern et. al. Aust NZ J Med 17:301-304. 1987) and the proposed low-dose colchicine arm (1.8 mg over 1 hour) in comparison with placebo treatment.

Study No.	N	Study Type
MPC-004-08-1010	30	Drug Interaction Study the Effect of Colchicine on the Pharmacokinetics of Theophylline 0.6 mg Tablet
MPC-004-08-1011	24	Drug Interaction Study the Effect of Azithromycin on the Pharmacokinetics of Colchicine 0.6 mg Tablet
MPC-004-08-1012	24	Drug Interaction Study the Effect of Ketoconazole on the Pharmacokinetics of Colchicine 0.6 mg Tablet
MPC-004-08-1013	24	Drug Interaction Study the Effect of Ritonavir on the Pharmacokinetics of Colchicine 0.6 mg Tablet
MPC-004-08-1014	24	Drug Interaction Study the Effect of Verapamil on the Pharmacokinetics of Colchicine 0.6 mg Tablet
MPC-004-08-1015	24	Drug Interaction Study the Effect of Diltiazem on the Pharmacokinetics of Colchicine 0.6 mg Tablet
MPC-004-08-1016	24	Drug Interaction Study the Effect of Cyclosporine on the Pharmacokinetics of Colchicine 0.6 mg Tablet
MPC-004-08-1017	24	Drug Interaction Study the Effect of Grapefruit Juice on the Pharmacokinetics of Colchicine 0.6 mg Tablet

In the current submission, Mutual submitted eight new clinical 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.

In support of NDA 22-352, Mutual had submitted four clinical 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 11/26/2008.

2. What are the clinical or surrogate endpoints and how were they measured in clinical pharmacology and clinical studies?

MPC-004-06-001 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1 week, dose comparison study intended to evaluate the efficacy and safety of colchicine for treatment of gout flares. This study evaluated the safety and efficacy of the currently practiced standard-dose (4.8 mg over 6 hours Ahern et. al. Aust NZ J Med 17:301-304. 1987) and the proposed low-dose colchicine arm (1.8 mg over 1 hour) in comparison with placebo treatment.

Clinical response: The primary efficacy variable, as defined prospectively in the protocol, was response to treatment in the target joint, based on patient self assessment of pain at 24 hours following the time of first dose as recorded on the Diary. A responder was one who achieved a $\geq$ 50% reduction in pain score relative to the pre-treatment score on the Diary and did not use rescue medication prior to the actual time of 24-hour post-dose assessment. Formal assessment of clinical efficacy can be found in the medical officer review by Dr. Rosemarie Neuner.

Additional endpoints included:

Time to Pain Relief: Time to 50% and 90% reduction in pain in the target joint.

Pain Intensity over Time: Descriptive statistics on change from baseline in pain intensity from 0 to 72 hours were tabulated and the mean pain intensity was plotted by time point for each treatment group. In addition, a total pain relief score over 24 and 32 hours (TOTPAR) was calculated.

All of the clinical pharmacology studies were conducted in healthy human volunteers and as such efficacy of colchicine was not assessed in these studies.

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Exposure-response relationship could not be assessed as blood samples were not collected in the clinical trial MPC-004-06-001. However, PK studies from NDA 22-352 submission # 1002 and # 1003 provide colchicine systemic exposure range for the

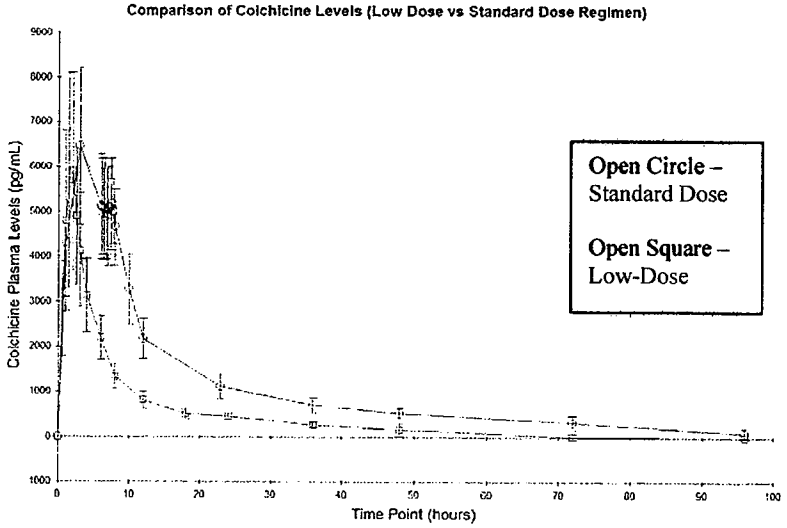
proposed Low-dose regimen (1.8 mg over 2 hours) and Standard-dose (4.8 mg over 6 hours) (see PK characteristics below).

In PK study # 1003, pharmacokinetic profile of a low- dose regimen of colchicine (1.8 mg over 2 hours) was determined in healthy adult male and female volunteers. Subjects received two 0.6 mg colchicine tablets initially, followed by one 0.6 mg colchicine tablet 1 hour later. Peak plasma colchicine concentrations were noted around 1.81 hours after the initial dose. PK parameters are tabulated below.

In study # 1002, pharmacokinetics of oral colchicine tablets at 4.8 mg dose were investigated in healthy adult male and female volunteers. Colchicine tablets were administered as two 0.6 mg over-encapsulated tablets followed by one 0.6 mg over-encapsulated tablet every hour for six additional doses to a total of 4.8 mg. Peak plasma levels of colchicine were noted around 4.5 hours after initial colchicine dose administered. PK parameters are tabulated below. Plasma levels declined thereafter with a "shoulder" or secondary peak in concentrations noted around 7.75 hours following first dose. This secondary peak is probably a result of repeated administration of colchicine tablets every hour (See figure below).

Mean (%CV) Colchicine Pharmacokinetic Parameter Values

Colchicine Dose	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)
Low Dose or 1.8 mg over 2 hours (Study # 1003) N=13	6.19 (39.30)	1.81 (1.0-2.5)	43.79 (26.12)	52.07 (26.29)	23.63 (39.10)
Standard Dose or 4.8 mg over 6 hours (Study #1002) N=15	6.84 (18.94)	4.47 (3.12-7.50)	104.95 (23.45)	118.20 (22.01)	31.38 (26.65)



4. Exposure-response

a) What are the characteristics of dose-response for efficacy? If relevant, indicate the time to the onset and offset of the clinical endpoint.

When compared to placebo treatment, both Low-dose (1.8 mg) and standard-dose (4.8 mg) colchicine regimen provided adequate but similar clinical response with respect to ≥50% pain relief, time to relief and time course of pain relief in patients with acute gout flare. It appears that peak and decrease in plasma colchicine levels occur prior to the time to relief and time course of pain relief noted.

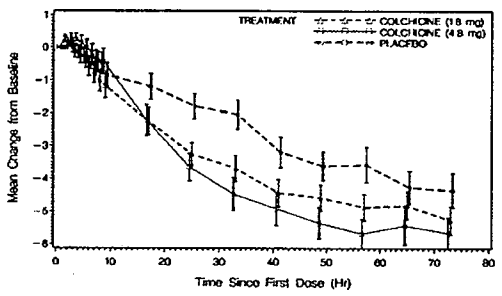
Clinical response: The clinical trial MPC-004-06-001 was planned to study the efficacy of any given dose of colchicine in comparison with placebo. Eight patients (14%) receiving placebo, 28 patients (37.8%) receiving Low-dose colchicine and 17 patients (32.7%) receiving Standard-dose colchicine responded to treatment. The number (or %) of patients did not greatly increase with increasing dose of colchicine. The low-dose colchicine treatment arm has an odds ratio of 3.31 against a 2.64 for the standard (4.8 mg) dose regimen.

Treatment Response Based on Target Joint Pain at 24 Hours Post First Dose (Primary Endpoint) – ITT Population

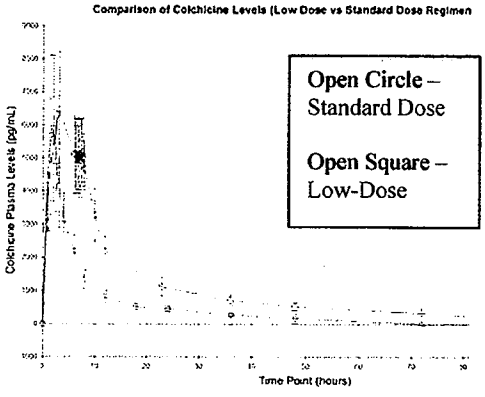
Number (%) of Responders			Treatment Comparisons (Odds Ratio and 95% CI)		
Treatment					
Placebo	Low-Dose	Standard-Dose	Low-Dose vs. Placebo	Standard-Dose vs. Placebo	Standard-Dose vs. Low-Dose
9 (15.5)	28 (37.8)	17 (32.7)	3.31 (1.41, 7.77)	2.64 (1.06, 6.62)	0.8 (0.38, 1.68)

Time Course of Pain Relief: Initially, a similar decrease in target joint pain score was noted in all three treatment groups. A separation in decline of pain scores was noted for the two colchicine treatment groups compared to placebo after approximately 8 hours of first dose. Plasma levels of colchicine peak at around 2 hours, and 8 hours after dosing. Hence, the clinical response appears to be delayed compared to systemic plasma profile of colchicine.

Target Joint Pain Score at Each Assessment Time Point Post First Dose and Corresponding Change from Baseline (Observed Cases Only Without Regard to Res ITT Population



Comparison of Colchicine Levels (Low Dose vs Standard Dose Regimen

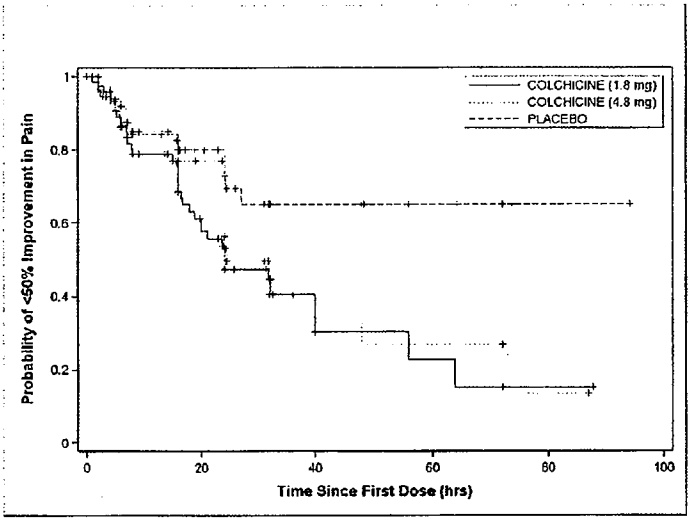


Open Circle – Standard Dose

Open Square – Low-Dose

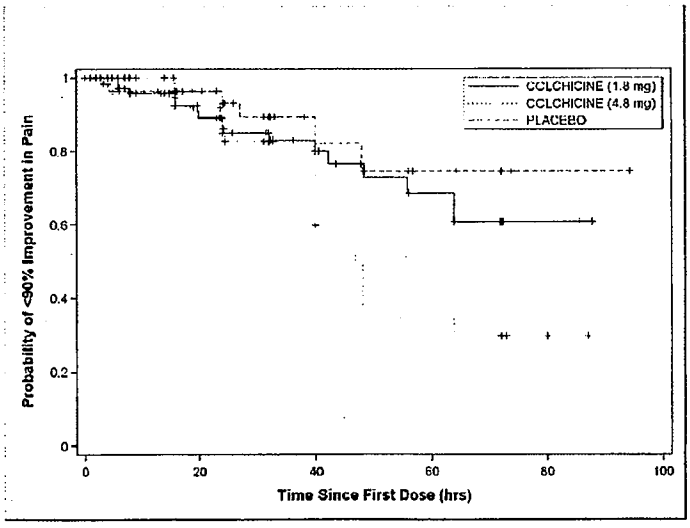
Time to relief: An insufficient number of patients randomized to placebo achieved a 50% reduction and hence the median time to clinical response could not be calculated. The median time to a 50% reduction from baseline for target joint pain score was 24.5 hours for the Low-dose colchicine group and 32.0 hours for the Standard-dose colchicine group. The Kaplan-Maier plot indicating median time to a 50% reduction from baseline for target joint pain score for both doses compared to placebo on the ITT population is in the Figure below.

Median Time to a 50% Reduction from Baseline for Target Joint Pain Score – ITT Population



A total of 17 patients experienced a 90% reduction in target joint pain from baseline within 24 hours of starting treatment; 2 patients in placebo treatment group (3.4%), 9 patients in Low-dose colchicine group (12.2%) and 6 patients in Standard-dose colchicine (11.5%) group. The median time to a 90% reduction from baseline for target joint pain score was 48.0 hours for the Standard-dose group and 64.0 hours for the Low-dose colchicine group (See Kaplan-Maier Plot below).

Median Time to a 90% Reduction from Baseline for Target Joint Pain Score – ITT Population



Total pain relief (TOTPAR) scores at 24 hours were approximately 3 times higher in the Low-dose colchicine group and two times higher in the Standard-dose colchicine group compared to placebo. At the 32 hour time point only Low-dose colchicine group showed significant total pain relief (See table below).

Total Pain Relief (TOTPAR) Based on All Target Joint Pain Scores – ITT Population

Time Point	Statistic	Colchicine Dose		Placebo (N=58)
		Standard (N = 52)	Low (N = 74)	
Hour 24 [1]	n	52	74	58
	Mean (SD)	21.7 (48.35)	29.5 (63.87)	11.8 (51.34)
	Median (Min, Max)	13.8 (-102, 135)	24.3 (-112, 185)	7.3 (-90, 177)
Hour 32 [2]	n	52	74	58
	Mean (SD)	38.5 (69.01)	46.6 (89.81)	17.6 (70.63)
	Median (Min, Max)	28.0 (-102, 185)	42.3 (-151, 257)	7.3 (-114, 241)

Patient 1026-1005 did not have a diary and the 24-hour call to the Call Center was 27 hours after the initial call. As indicated in the SAP (4.7.1.1.3) the Call Center pain score was not eligible for substitution for the missing diary. This patient has been excluded from the 24-hour TOTPAR summary, but not the 32 hour TOTPAR summary; the patient is not considered a responder.

[1] Treatment comparisons: Standard *vs.* placebo (p = 0.3003), Low *vs.* placebo (p = 0.0879), and Standard *vs.* Low (p = 0.4602)

[2] Treatment comparisons: Standard *vs.* placebo (p = 0.1213), Low *vs.* placebo (p = 0.0457), and Standard *vs.* Low (p = 0.5829)

b) What are the characteristics of the dose-response for safety? If relevant, indicate the time to the onset and offset of the undesirable clinical endpoint.

Gastrointestinal disorders such as diarrhea, nausea, vomiting and abdominal discomfort were the most frequent adverse events in colchicine treatment groups. Dose-related increase in number of patients with treatment emergent adverse events of different intensity (mild, moderate and severe) was noted compared to placebo treatment.

Overall Summary of Treatment Emergent Adverse Events

Treatment Emergent Adverse Events #	Placebo	Colchicine Dose	
		Low dose 1.8 mg	Standard dose 4.8 mg
Total Number of TEAEs	27	34	85
Number (%) of Patients with at Least One TEAE	16 (27.1)	27 (36.5)	40 (76.9)
Number (%) of Patients with at Least One Mild TEAE	9 (15.3)	19 (25.7)	15 (28.8)
Number (%) of Patients with at Least One Moderate TEAE	6 (10.2)	8 (10.8)	15 (28.8)
Number (%) of Patients with at Least One Severe TEAE	1 (1.7)	0	10 (19.2)

Number (%) of Patients with at Least One TEAE with an Incidence of ≥ 2% of Patients in Any Treatment Group

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N = 59)	Colchicine Treatment Group	
		Low Dose (N = 74)	Standard Dose (N = 52)
Number of Patients with at Least One TEAE	16 (27.1)	27 (36.5)	40 (76.9)
Gastrointestinal Disorders	12 (20.3)	19 (25.7)	40 (76.9)
Diarrhea	8 (13.6)	17 (23.0)	40 (76.9)
Nausea	3 (5.1)	3 (4.1)	9 (17.3)
Vomiting	0	0	9 (17.3)
Abdominal Discomfort	2 (3.4)	0	0
General Disorders and Administration Site Conditions	1 (1.7)	1 (1.4)	4 (7.7)
Fatigue	1 (1.7)	1 (1.4)	2 (3.8)
Metabolism and Nutrition Disorders	2 (3.4)	3 (4.1)	0
Gout	1 (1.7)	3 (4.1)	0
Nervous System Disorders	2 (3.4)	1 (1.4)	1 (1.9)
Headache	2 (3.4)	1 (1.4)	1 (1.9)
Respiratory, Thoracic and Mediastinal Disorders	0	2 (2.7)	1 (1.9)
Pharyngolaryngeal Pain	0	2 (2.7)	1 (1.9)

2.3 Intrinsic Factors

Pharmacokinetic studies were not conducted by the sponsor to address the influence of age, race, bodyweight, pregnancy and organ dysfunction. However, several publications addressing these intrinsic factors were submitted to the NDA 22-352. These studies were previously reviewed in clinical pharmacology review for NDA 22-352 dated 11/26/2008.

Elderly: *Colchicine should be used with caution in elderly for the treatment of acute gout due to the possibly high systemic exposure.*

Pharmacokinetics of colchicine has not been determined in elderly patients. A published report described the pharmacokinetics of 1 mg oral colchicine tablet in four elderly women compared to six young healthy males (Rochdi et. al. Eur J Clin Pharmacol 1994; 46:351-354). The mean age of the four elderly women was 83 years (range 75 – 93), mean weight was 47 kg (38 – 61 kg) and mean creatinine clearance was 46 mL/min (range 25 – 75 mL/min). Mean peak plasma levels and AUC of colchicine were two times higher in elderly subjects compared to young healthy males. However, it is possible that the higher exposure in the elderly subjects was due to decreased renal function.

2.4 Extrinsic Factors

In vitro studies show that colchicine is a substrate of P-glycoprotein and it is metabolized by CYP3A4. Hence, sponsor evaluated the effect of different strong, moderate, weak CYP3A4 inhibitors and a P-gp inhibitor on the pharmacokinetics of colchicine.

1) Are there any in vivo drug-drug interaction studies that indicate the exposure alone are different when drugs are co-administered? If so, is any dosage adjustment necessary?

As noted from the previously reviewed (dated 11/28/2008) clarithromycin-colchicine drug interaction, other strong CYP3A4 inhibitors increase colchicine systemic exposure by 3- to 4-fold. Moderate CYP3A4 inhibitors cause a 2-fold increase in colchicine AUC when coadministered. P-gp inhibition by cyclosporine resulted in 3.5-fold increase in Cmax and AUC of colchicine.

Dosage adjustment is needed in patients who are on strong or moderate CYP3A4 inhibitors and P-glycoprotein inhibitors. The following dose adjustment is recommended:

Strong CYP3A4 inhibitors: Sponsor proposed use of a single 0.6 mg colchicine tablet when patients are on strong CYP3A4 inhibitors. This would constitute a 2/3rd decrease in proposed Low-dose regimen of 1.8 mg colchicine. However, pharmacokinetic simulations indicate that patients may be under dosed and hence if the first dose of 0.6 mg in patients on strong CYP3A4 inhibitors is tolerated well, an additional dose of 0.3 mg colchicine may be administered. Simulations of colchicine PK profile indicate that systemic exposure with the 0.9 mg dose is within the noted range for the Low-dose and Standard-dose regimen.

Moderate CYP3A4 inhibitors: Sponsor proposed use ——— b(4)

——— *This would constitute a* —— *decrease in proposed Low-dose regimen of 1.8 mg colchicine. Simulations of colchicine PK profile indicate that systemic exposure with the proposed regimen is within the noted range for the Low-dose and Standard-dose regimen. Hence, the sponsor proposed dose adjustment is acceptable in patients without a history of decreased renal or hepatic function.*

Sponsor is proposing that ——— *colchicine may be used in patients with renal or hepatic impairment and receiving moderate CYP3A4 inhibitors. There is no basis for this recommendation and as such it is not acceptable.* b(4)

Weak CYP3A4 inhibitors: Dosage adjustment is not necessary with weak CYP3A4 inhibitors such as azithromycin. The observed increases in colchicine plasma levels with azithromycin are within the range of exposures noted with the Low-dose and Standard-dose.

P-glycoprotein inhibitors: Sponsor proposed use of a single 0.6 mg colchicine tablet when patients are on P-glycoprotein inhibitors. The proposed dose adjustment is acceptable in patients without a history of decreased renal or hepatic function.

Pharmacokinetics of colchicine alone or in presence of various P-gp or CYP3A4 inhibiting drug were evaluated (see attached synopses). Agency recognizes cyclosporine as a P-glycoprotein inhibitor and the drugs evaluated in the studies as CYP3A4 inhibitors as follows:
Strong CYP3A4 inhibitors: clarithromycin, ketoconazole, low dose ritonavir
Moderate CYP3A4 inhibitors: Verapamil, diltiazem, grapefruit juice
Weak CYP3A4 inhibitors: Azithromycin

Taken together, except for grapefruit juice, the ratios of C_{max}, AUC_{0-t}, and for test (colchicine + concomitant treatment) *versus* reference (colchicine alone) treatments are > 125%. This indicates that weak, moderate and strong CYP3A4 inhibitors significantly increase colchicine systemic exposure. P-glycoprotein inhibition by cyclosporine resulted in a 3.5-fold (range 1.6- to 6-fold) increase in colchicine AUC. In clinical trial MPC-004-06-001 safety of colchicine has been evaluated between 1.8 mg and 4.8 mg dose for treatment of acute gout. From a clinical pharmacology perspective dosage adjustment in situations due to drug interaction are aimed to maintain the average Cmax and AUC noted between the Low-dose and Standard-dose.

Summary of % Ratio of Cmax or AUC of colchicine when coadministered with interacting drug and compared with colchicine alone.

Study No.	Study Type	% Ratio of C_{max} inhibition/C_{max} without inhibition (90% CI)	% Ratio of AUC_{0-t} inhibition/AUC_{0-t} without inhibition (90% CI)
MPC-004-08-1011 (n=24)	Azithromycin[1] (250 mg for 5 days)	112 (97.5, 130)	147 (127.7, 168.5)
MPC-004-08-1012 (n=24)	Ketoconazole[2] (200 mg bid for 5 days)	195 (179, 214)	299 (270, 332)
MPC-004-08-1013 (n=18)	Low dose Ritonavir[2] (100 mg bid for 5 days)	269 (235, 308)	364 (307, 430)
MPC-004-08-1014 (n=24)	Verapamil ER[3] (240 mg qd for 5 days)	131 (115, 150)	195 (175, 216)
MPC-004-08-1015 (n=24)	Diltiazem ER[3] capsule (240 mg qd for 7 days)	129 (107, 154)	172 (142, 208)
MPC-004-08-1016 (n=24)	Cyclosporine[4] (single 100 mg dose)	338 (288, 395)	337 (295, 385)
MPC-004-08-1017 (n=24)	Grapefruit Juice[3] (240 mL bid for 4 days)	93.25 (83, 105)	94.85 (86.5, 104)

[1] Weak CYP3A4 inhibitor, [2] Strong CYP3A4 inhibitor, [3] Moderate CYP3A4 inhibitor, [4] P-glycoprotein inhibitor in vivo.

Colchicine pharmacokinetic parameters observed following different dosing regimen and with interacting drugs are summarized in the table below.

Summary of Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following Colchicine Tablets Administration in Different Regimen

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)
Colchicine 0.6-mg Single Dose (N=13) (study # 1004)	2.45 (28.7)	1.50 (1.0 – 3.0)	10.5 (33.8)	12.3 (36)	4.95 (89.5)
Low Dose or 1.8 mg over 2 hours (Study # 1003) N=13	6.19 (39.30)	1.81 (1.0-2.5)	43.79 (26.12)	52.07 (26.29)	23.63 (39.10)
Standard Dose or 4.8 mg over 6 hours (Study #1002) N=15	6.84 (18.94)	4.47 (3.12-7.50)	104.95 (23.45)	118.20 (22.01)	31.38 (26.65)
Single Dose colchicine 0.6 mg + Azithromycin 250 mg 5-day regimen (Study #1011) N=24	3.05 (40)	1.5 (0.5 -3)	17 (37)	19.6 (39)	6.7 (68)
Single Dose colchicine 0.6 mg + Ketoconazole 200mg bid 5-day regimen (Study #1012) N=24	5.27 (28)	1 (0.5 – 2)	34.3 (27)	43.7 (27)	26 (52)
Single Dose colchicine 0.6 mg + Ritonavir 100 mg bid 5-day regimen (Study #1013) N=18	4.99 (25)	1.5 (1 -1.5)	29 (30)	35 (30)	17.4 (40)
Colchicine 0.6 mg followed by 0.3 mg 1 hour later + Ritonavir 5-day regimen (Simulated) N=18	4.28 (24)	2 (2-3)	46.9 (26)	48.8 (27)	17 (20)
Single Dose colchicine 0.6 mg + Verapamil ER 240 mg qd 5-day regimen (Study #1014) N=24	3.85 (38)	1 (0.5-2)	24.6 (26)	30.6 (27)	17 (35)
Two doses of colchicine 0.6 mg administered with 1 hour gap + Verapamil ER 240 mg qd 5-day regimen (Simulated) N=24	6.8 (35)	2 (1.5 -2)	75 (26)	82 (26)	17 (26)
Single Dose colchicine 0.6 mg + Diltiazem ER capsule 240 mg qd 7-day regimen (Study #1015) N=24	2.8 (44)	1.5 (0.5 – 5)	17.7 (48)	22.5 (49)	12.5 (62)
Single Dose colchicine 0.6 mg + Cyclosporine 100mg single dose (Study #1016) N=23	8.8 (25)	1.5 (0.5 – 2)	39.8 (26)	47.3 (25.6)	20.6 (31)
Single Dose colchicine 0.6 mg + Grapefruit Juice 4-day regimen (Study #1017) N=21	1.97 (20)	1.5 (1 - 3)	8.8 (34)	10.8 (38)	5.6 (63)

Simulations of CYP3A4 Inhibition related drug interactions:

Using the method of superposition (Thron CD, Pharmacological Reviews 26(1): 3-31) each individual's plasma concentration data noted following consumption of 0.6 mg colchicine alone or with interacting drug was utilized to predict PK profile of colchicine following different dosing regimen when administered with interacting drug. Pharmacokinetic data analysis and simulations were conducted employing Winonlin version 5.2 software.

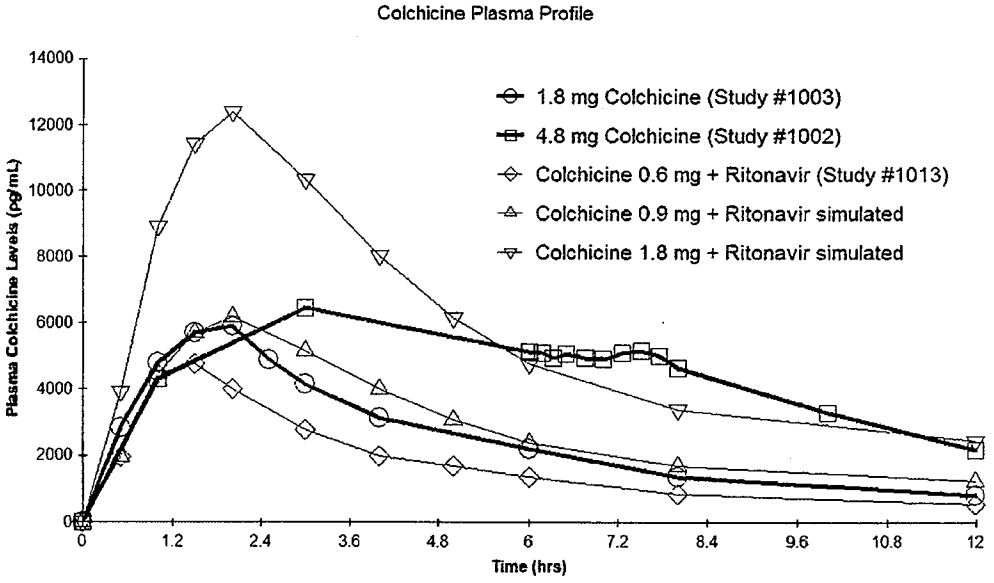
Simulation of strong CYP3A4 inhibition related drug interaction by low dose ritonavir regimen:

The following figure depicts the observed colchicine plasma levels with Low-dose (study #1003), Standard-dose (study #1002) in comparison with either noted (Study#1013) and predicted drug interaction with ritonavir, a strong CYP3A4 inhibitor. Simulations were performed by superposing plasma concentrations from the noted drug interaction following the dosing regimen:

a) Total dose of 0.9 mg: Colchicine tablet 0.6 mg administered at time 0 and half of tablet or 0.3 mg administered at 1 hour. As indicated in the table above, the predicted plasma concentrations are in between those noted for Low-dose and Standard-dose.

b) Total dose of 1.8 mg: Two 0.6 mg colchicine tablets administered at time 0 and 1 hour later. The simulated plasma levels far exceed the colchicine systemic exposure noted following 4.8 mg colchicine dose over 6 hours.

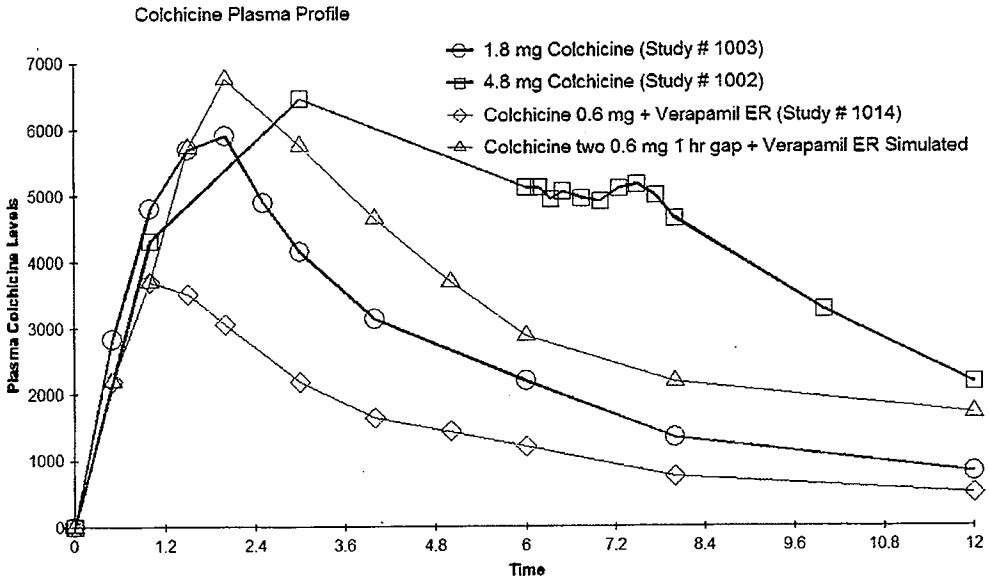
Observed or simulated mean plasma colchicine concentration following administration of colchicine with ritonavir (low dose of 100 mg bid administered over 5 days).



Simulation of Moderate CYP3A4 inhibition related drug interaction by verapamil:

The following figure depicts the observed colchicine plasma levels with Low-dose (study #1003), Standard-dose (study #1002) in comparison with either noted or predicted drug interaction with verapamil extended release tablets, a moderate CYP3A4 inhibitor. Simulations were performed by superposing plasma concentrations from the noted drug interaction following total dose of 1.2 mg: one 0.6 mg colchicine tablet administered at time 0 and 1 hour later. The simulated plasma levels are within the range of colchicine systemic exposure noted following colchicine 1.8 mg over 2 hrs and 4.8 mg colchicine dose over 6 hours.

Observed or simulated mean plasma colchicine concentration following administration of colchicine with verapamil extended release tablet (240 mg qd administered over 5 days).



Study # 1017 evaluated effect of grapefruit juice on colchicine pharmacokinetics. Results show that there was no significant drug interaction with the brand of grapefruit juice employed. However, as noted by De Castro et. al. 2006 (J Agri. and Food Chem. 54: 249-255) there is significant variability of furanocoumarins in different types of grapefruit juices. Hence, caution should be exercised in patients receiving grapefruit juice before they receive colchicine.

Study of colchicine drug interaction with theophylline (Study #1010)

The sponsor noted that incubation of colchicine in hepatocytes resulted in a decreased CYP1A2 activity (see clinical pharmacology review dated 11/28/08). Hence, a drug interaction study #1010 was conducted to evaluate the effect of 14 day colchicine administration on single dose pharmacokinetics of 300 mg theophylline, a sensitive CYP1A2 substrate. Plasma levels (Cmax and AUC) of theophylline were not significantly different prior to and following colchicine treatment (see table below and the attached synopsis).

The following table summarizes the results of the analyses performed on the ln-transformed pharmacokinetic parameters.

Theophylline 300 mg before (Day 1) and after a 14-day Regimen of Colchicine 0.6 mg (Day 19) (N=27)				
Parameter (units)	Colchicine + Theophylline (Test)	Theophylline Alone Reference	% Ratio	90% CI
AUC_{0-t} (µg·hr/mL)	115.50	114.71	100.68	(96.3, 105.27)
$AUC_{0-\infty}$ (µg·hr/mL)	122.75	120.72	101.69	(97.21, 106.37)
C_{max} (µg/mL)	9.62	9.51	101.09	(97.66, 104.63)

2.5 General Biopharmaceutics

Not applicable

2.6 Analytical

An HPLC with tandem mass spectrometry (LC MS/MS) method was developed and validated for the determination of colchicine in human plasma. Colchicine and internal standard ———— are extracted from human plasma matrix (EDTA as the anticoagulant) using a solid phase extraction. The concentrations of quality control (QC) standards are 0.20 ng/mL for the lower level QC, 0.60 ng/mL for the Low QC, 3.20 ng/mL for the Mid-QC, 32.00 ng/mL for the High-QC, and 40.00 ng/mL for the upper level QC (PRACS Bioanalytical method 181.1). The bioanalytical method validation was previously reviewed (see clinical pharmacology review dated 11/26/2008). b(4)

The analysis of blood samples from study #1010 (theophylline colchicine drug interaction study) was performed by an API 3000 LC/MS/MS using ———— as the internal standard (IS). The interface used with the API 3000 LC/MS/MS was a Turbo Ionspray®. The lower limit of quantitation (LLOQ) was 0.2000 µg/mL and the upper limit of quantitation (ULOQ) was 40.00 µg/mL. For standards, the inter-day precision (CV) was 4.4% or better and the accuracy (Bias) ranged from -4.3 to 9.6%. For the QC samples, the inter-day precision (CV) was 4.7% or better and the accuracy (Bias) ranged from -3.6 to 1.7% b(4)

11 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4 Appendix

4.1 Proposed labeling

See Next Page

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4.2 Individual Study Reviews

4.2.1 Study MPC-004-08-1011 synopsis

Study MPC-004-08-1011 synopsis:

Number and Title of Study: MPC-004-08-1011: A One-Direction, Open-Label Drug Interaction Study to Investigate the Effects of Multiple-Dose Azithromycin on Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers
Objectives: The primary objective of this study was to determine the effect of multiple doses of azithromycin on the pharmacokinetics of colchicine administered as a single 0.6-mg dose in healthy adult subjects under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of a single 0.6-mg dose of colchicine administered alone and in combination with multiple-dose azithromycin.
Methodology: This was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study with single-dose colchicine and multiple-dose azithromycin conducted in healthy male and female volunteers. Subjects received a single 0.6-mg colchicine tablet on Day 1 and then completed a 14-day washout period. Beginning on the morning of Day 15, subjects returned to the clinic on a non-confined basis to receive 2 × 250 mg of azithromycin; subjects returned to the clinic each morning on a non-confined basis on Day 16 through Day 18 and received 1 × 250 mg of azithromycin. Following confinement on the afternoon of Day 18, study subjects received 1 × 250 mg of azithromycin and 1 × 0.6 mg of colchicine on Day 19. Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 19 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72 and 96 hours post-dose administration on Days 2-5 and 20-23. Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations. Azithromycin plasma concentrations were not measured.
Number of Subjects **Planned:** 24 **Analyzed:** 21 subjects were analyzed for pharmacokinetics (two subjects withdrew consent due to personal reasons and one subject was removed due to emesis); all 24 subjects were analyzed for safety as all received at least one dose of colchicine. **Diagnosis and Main Criteria for Inclusion:** All subjects were healthy adult, non-smoking, non-obese subjects 18 – 45 years of age inclusive with a BMI of 18 – 32 inclusive who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing, and vital sign measurements.

Test Product:	Dose and Mode of Administration:	Batch Numbers:
Colchicine Tablets USP, (Mutual Pharmaceutical Company, Inc.)	0.6 mg Tablets, Oral	BB 374 0215
Zithromax® 250 mg Tablets USP (Pfizer Labs Division of Pfizer Inc.)	250 mg Tablets, Oral	Lot: 7HP029E Expiration: 1 SEP 10

Duration of Treatment:
The subjects received a single dose of colchicine (1 × 0.6-mg tablet) on Days 1 and 19 and a single dose of azithromycin (2 × 250 mg tablets) once daily on Day 15 and a single dose of azithromycin (1 × 250-mg tablets) once daily on Days 16 - 19. Subject completed a 14-day washout period after the first dose of colchicine on Day 1 and before the first dose of azithromycin on Day 15. Total study participation, exclusive of screening, was 24 days (Period I: 26 July 2008 – 30 July 2008; Period II: 09 August 2008 – 17 August 2008).

Pharmacokinetic:
Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and t½. Parameter values also were separately calculated for men and women. Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with azithromycin (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect, and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference. The above statistical analyses were done using the appropriate SAS® procedure, (SAS® GLM procedure).

The following table summarizes descriptive statistics (mean (%CV)) for colchicine pharmacokinetic parameter values for all 21 subjects with data.

Summary Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following a Single Dose of Colchicine Tablets USP, 0.6 mg before (Day 1) and after a 5-Day Regimen of Azithromycin (Day 19)		
	Arithmetic Mean (%CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Azithromycin (Test) (N=21)	Colchicine Alone (Reference) (N=21)
AUC_{0-t} (ng·hr/mL)	17.16 (37.78)	11.98 (45.81)
$AUC_{0-\infty}$ (ng·hr/mL)	19.61 (39.15)	14.13 (46.73)
C_{max} (ng/mL)	3.05 (39.54)	2.74 (41.52)
T_{max} (hr)	1.5 (0.5 - 3)	1.0 (0.5 - 3)
Kel (1/hr)	0.1426 (47.35)	0.147 (38.53)
$t_{1/2}$ (hr)	6.71 (68.34) [1]	6.07 (66.15) [1]
$V_{ss/F}$ (L)	279.66 (35.34)	361.86 (25.56)
CL/F (L/hr)	35.01 (37.26)	50.24 (40.31)
Weight-Adjusted CL/F (L/hr/kg)	0.46 (27.95)	0.68 (38.6)

When colchicine (0.6-mg single dose) is co-administered with steady-state azithromycin, colchicine concentrations increase to a mean maximum 3.05 ng/mL, which is approximately 12% higher than when administered alone as a single 0.6-mg dose (C_{max} = 2.74 ng/mL). Colchicine AUC_{0-t} and $AUC_{0-\infty}$ concentrations are increased approximately 46% and 40% (17.2 ng·h/mL and 19.6 ng·h/mL) when co-administered with azithromycin as compared to the reported colchicine AUC_{0-t} and $AUC_{0-\infty}$ concentrations when administered alone (12.0 ng·h/mL and 14.1 ng·h/mL), respectively. T_{max} is not affected by the co-administration with azithromycin (1.5 and 1 hours with and without azithromycin co-administration, respectively). Total apparent oral clearance is decreased by 30% when colchicine was co-administered with azithromycin as compared to the reported total apparent oral clearance when colchicine was administered alone (35.0 L/hr *versus* 50.2 L/hr).

The table below provides a statistical summary of the ln-transformed geometric mean colchicine pharmacokinetic parameter values when administered alone *versus* colchicine pharmacokinetic parameter values when administered with azithromycin (Z-Pak® 5-day regimen).

Colchicine Tablets USP, 0.6 mg Before (Day 1) and After a 5-day Regimen of Azithromycin (Day 19) All Subjects (N=21)				
Parameter (units)	Colchicine + Azithromycin (N=21) (Test)	Colchicine Alone (N=21) Reference	% Ratio	90% CI
AUC_{0-t} (ng·hr/mL)	16.09	10.97	146.66	(127.66, 168.48)
$AUC_{0-\infty}$ (ng·hr/mL)	18.31	12.93	141.61	(123.86, 161.91)
C_{max} (ng/mL)	2.86	2.54	112.63	(97.55, 130.04)

The 90% CI around the ratios of the means for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were outside the no interaction pre-specified range, 80%-125%, indicating a statistically significant drug interaction is present when colchicine and azithromycin are co-administered. However, a dosage adjustment may not be necessary considering that safety margin established between the proposed dose (1.8 mg) and the standard dose (4.8 mg) currently practiced.

Safety Results:

Following the administration of colchicine, when given alone, the most common adverse events was headache, reported by 3 subjects (12.5%) and diarrhea and dysmenorrhea each reported by 2 subjects (8.3%). When colchicine was administered with azithromycin the most common adverse event was nausea, reported 2 subjects (9.1%).

4.2.2 Study MPC-004-08-1012 synopsis

Number and Title of Study:
MPC-004-08-1012: A One-Direction, Open-Label Drug Interaction Study to Investigate the Effects of Multiple-Dose Ketoconazole on Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers

Objectives:
The primary objective of this study was to determine the effect of multiple doses of ketoconazole on the pharmacokinetics of colchicine administered as a single 0.6-mg dose in healthy adult subjects under fasted conditions.
The secondary objective of this study was to assess the safety and tolerability of single 0.6-mg dose of colchicine administered alone and in combination with multiple-dose ketoconazole.

Methodology:
This was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study with single-dose colchicine and multiple–dose ketoconazole conducted in healthy male and female volunteers. Subjects received a single 0.6-mg colchicine tablet on Day 1 and then completed a 14-day washout period. Beginning on the morning of Day 15, subjects received 200 mg of ketoconazole b.i.d. (twice daily) for 10 doses (5 days). Dosing was on a non-confined basis (in clinic) for the first 4 days. On Day 19 at 7:15 AM, the subjects received a single 0.6-mg colchicine tablet co-administered with a single 200-mg ketoconazole tablet and in the evening at 7:15 PM, study subjects received the final 200-mg ketoconazole dose.
Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 19 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis and 36, 48, 72, and 96 hours post-dose administration on a non-confined basis.
Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations. Ketoconazole plasma concentrations were not measured.

Diagnosis and Main Criteria for Inclusion:
All subjects were healthy adult, non-smoking, non-obese subjects 18 – 45 years of age with a BMI of 18 – 32 who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing, and vital sign measurements.

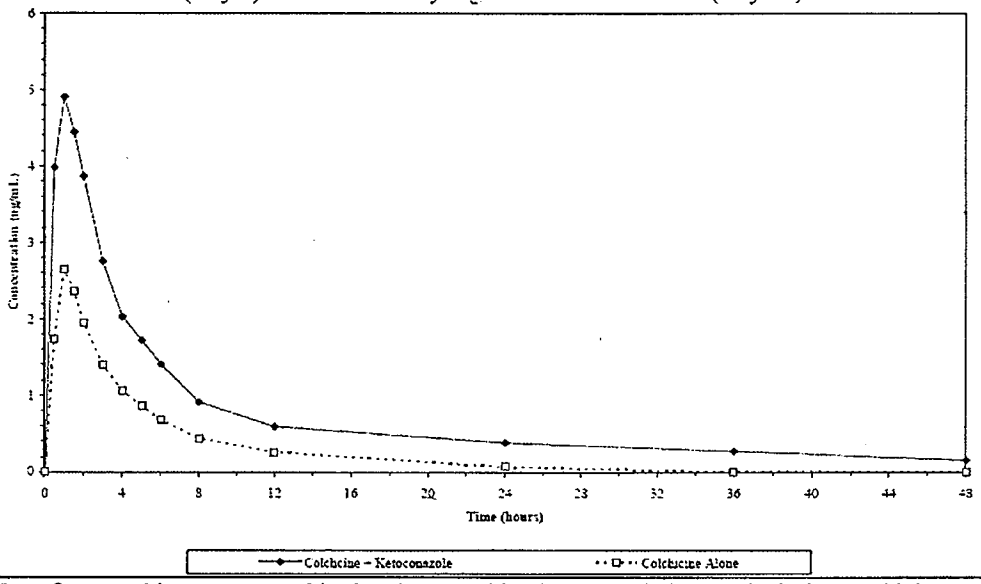
Test Product:	**Dose and Mode of Administration:**	**Batch Numbers:**
Colchicine Tablets USP, (Mutual Pharmaceutical Company, Inc.)	0.6 mg Tablets, Oral	BB 374 0215
Ketoconazole Tablets (Mylan Pharmaceuticals Inc.)	200 mg Tablets, Oral	Lot: 1P4276 Expiration: December 2009

Duration of Treatment:
The subjects received a single dose of colchicine (1 × 0.6-mg tablet) on Days 1 and 19 and a single dose of ketoconazole (1 × 200-mg tablet) twice daily for 5 days (Days 15-19). Subjects completed a 14-day washout period after the first dose of colchicine on Day 1 and before the

first dose of ketoconazole on Day 15. Total study participation, exclusive of screening, was 24 days.

Criteria for Evaluation:
Pharmacokinetic:
Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$. Parameter values also were separately calculated for men and women. Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with ketoconazole (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect, and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

SUMMARY / CONCLUSIONS:
Pharmacokinetic Results:
The following figure illustrates the mean colchicine plasma concentration of single doses of colchicine before (Day 1) and after a 5-day regimen of ketoconazole (Day 19).



Data for 24 subjects were used in the pharmacokinetic and statistical analysis for colchicine. When colchicine (0.6-mg single dose) is co-administered with multiple-dose ketoconazole, colchicine concentrations increase to a mean maximum 5.3 ng/mL, which is approximately 90% higher than the maximum colchicine concentration when colchicine was administered alone as a single 0.6-mg dose (C_{max} = 2.8 ng/mL). T_{max} was not affected by the co-administration with ketoconazole (1.0 hour with and without ketoconazole co-administration). Colchicine AUC_{0-t} and $AUC_{0-\infty}$ are increased approximately 190% (34.4 ng·h/mL) and 205% (43.7 ng·h/mL) when co-administered with ketoconazole as compared to the AUC_{0-t} and $AUC_{0-\infty}$ when administered alone (12.0 ng·h/mL and 14.3 ng·h/mL, respectively). Total

apparent oral clearance is decreased by 70% when colchicine is co-administered with ketoconazole as compared to the total apparent oral clearance when colchicine is administered alone (15 L/hr *versus* 49 L/hr).

The following table summarizes colchicine descriptive statistics (mean (%CV)) for all subjects.

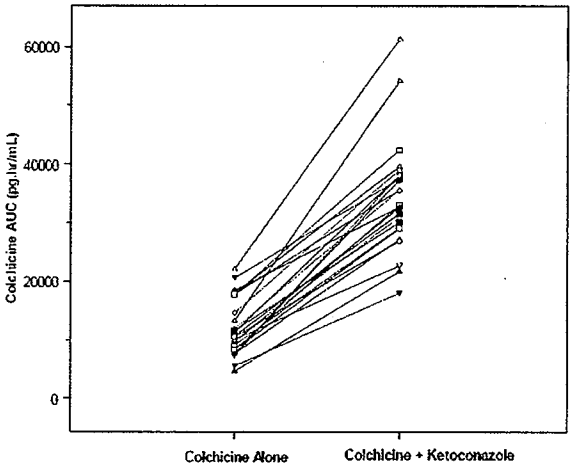
Summary Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following a Single Dose of Colchicine Tablets USP, 0.6 mg before (Day 1) and after a 5-Day Regimen of Ketoconazole (Day 19) (N = 24)

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T_{max}	
	Colchicine + Ketoconazole (Test)	Colchicine Alone (Reference)
AUC_{0-t} (ng·hr/mL)	34.38 (27.47)	11.99 (40.34)
$AUC_{0-\infty}$ (ng·hr/mL)	43.68 (26.72)	14.31 (41.86)
C_{max} (ng/mL)	5.27 (27.75)	2.78 (37.31)
T_{max} (hr)	1 (0.5 - 2.07)	1 (0.5 - 1.5)
Kel (1/hr)	0.0332 (50.21)	0.1491 (43.86)[1]
$t_{1/2}$ (hr)	26.06 (52.84)	6.28 (70.63)[1]
V_{area}/F (L)	502.06 (35.31)	365.70 (34.88)
CL/F (L/hr)	14.80 (29.77)	49.30 (40.74)
Weight-Adjusted CL/F (L/hr/kg)	0.21 (21.96)	0.70 (38.45)

The table below provides a statistical summary of the ln-transformed geometric mean colchicine pharmacokinetic parameter values when administered alone *versus* colchicine pharmacokinetic parameter values when administered with ketoconazole 200-mg tablet twice daily × 5 days.

Colchicine Tablets USP, 0.6 mg before (Day 1) and after a 200 mg Twice Daily 5-Day Regimen of Ketoconazole (Day 19) (N=24)

Parameter (units)	Colchicine + Ketoconazole (Test)	Colchicine Alone (Reference)	% Ratio	90% CI
AUC_{0-t} (ng·hr/mL)	33.22	11.09	299.64	(270.43, 332)
AUC_{0-inf} (ng·hr/mL)	42.14	13.18	319.61	(287.51, 355.28)
C_{max} (ng/mL)	5.08	2.60	195.46	(178.5, 214.02)



N= 11 had <2-fold increase in Cmax, rest all were 2- to 3-fold increase
N=2 had ~ 5-fold increase in AUC, N=20 had 2-to 5-fold increase in AUC

Safety Results:

Following the administration of colchicine, when given alone or in combination with ketoconazole, the most common adverse event was headache occurring in 7 subjects (29.2%); the incidence appeared higher when given in combination (5 subjects or 20.8% *versus* 3 subjects or 12.5%). Dizziness occurred in 2 subjects (8.3%), only after administration of the two drugs together. All AEs were mild to moderate in intensity, and none resulted in any subject being discontinued from the study.

One subject experienced vomiting just prior to Period II. This was felt to be unrelated to the test articles and the subject was able to complete the study.

4.2.3 Study # MPC-004-08-1013 Synopsis

Number and Title of Study: MPC-004-08-1013: A One-Direction, Open-Label Drug Interaction Study to Investigate the Effects of Multiple-Dose Ritonavir on Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers

Objectives: The primary objective of this study was to determine the effect of multiple doses of ritonavir on the pharmacokinetics of colchicine administered as a single 0.6-mg dose in healthy adult subjects under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of single 0.6-mg dose of colchicine administered alone and in combination with multiple-dose ritonavir.

Methodology: This was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study with single-dose colchicine and multiple-dose ritonavir conducted in healthy male and female volunteers. Subjects received a single 0.6-mg colchicine tablet on Day 1 and then completed a 14-day washout period. Beginning on the morning of Day 15, subjects received 100 mg of ritonavir b.i.d. (twice daily) for 10 doses (5 days). Dosing was on a non-confined basis (in clinic) for the first 4 days. On Day 19 at 7:00 AM, the subjects received a single 0.6-mg colchicine tablet co-administered with a single 100-mg ritonavir capsule and in the evening at 7:00 PM, study subjects received the final 100-mg ritonavir dose. Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 19 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis and 36, 48, 72, and 96 hours post-dose administration on a non-confined basis. Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations. Ritonavir plasma concentrations were not measured.

Number of Subjects
Planned: 24
Analyzed: 18 (six subjects discontinued due to abnormal screening laboratory results.)
Diagnosis and Main Criteria for Inclusion:
All subjects were healthy adult, non-smoking, non-obese subjects 18 – 45 years of age with a BMI of 18 – 32 who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing (including a lipid panel), and vital sign measurements.

Test Product:	**Dose and Mode of Administration:**	**Batch Numbers:**
Colchicine Tablets USP, (Mutual Pharmaceutical Company, Inc.)	0.6 mg Tablets,	BB 374 0215
Norvir® Capsules (Abbott Laboratories)	Oral 100 mg Capsules USP, Oral	Lot: 554452E21 Expiration: 1DEC2009

Duration of Treatment:
The subjects received a single dose of colchicine (1 × 0.6-mg tablet) on Days 1 and 19 and a single dose of ritonavir (1 × 100-mg capsule) twice daily for 5 days (Days 15-19). Subjects completed a 14-day washout period after the first dose of colchicine on Day 1 and before the first dose of ritonavir on Day 15. Total study participation, exclusive of screening, was 24 days.

Criteria for Evaluation:

Pharmacokinetic:
Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$. Parameter values also were separately calculated for men and women.
Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with ritonavir (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect, and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference. The above statistical analyses were done using the appropriate SAS® procedure, (SAS® GLM procedure).

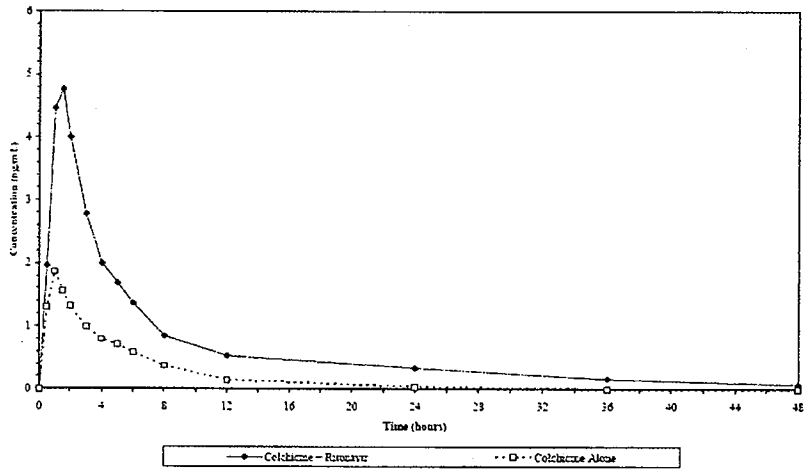
Safety:
All subjects were monitored for adverse events throughout the confinement portion of the study and queried at the out-patient visits. Blood pressure (sitting for at least 5 minutes) and pulse were measured prior to dosing (time 0) and at 1, 2, and 3 hours post dosing on Days 1 and 19, as well as at screening, baseline, and at study exit (Day 23 or early termination). All subjects underwent clinical laboratory testing including hematology, biochemistry (inclusive of lipid panel), urinalysis, and for women of childbearing potential, pregnancy tests at screening, baseline, Period II check-in (Day 18), and prior to discharge from the study (urinalysis was not done at discharge). A urine pregnancy test was also collected on Day 15 prior to the first ritonavir dose administration. A full physical examination was performed at screening with targeted physical examinations being conducted at baseline, Day 18, and study discharge if needed in response to adverse events or changes in medical history. A blood sample was collected on Day 23 for a repeat final fasting lipid panel, if deemed necessary by the Investigator

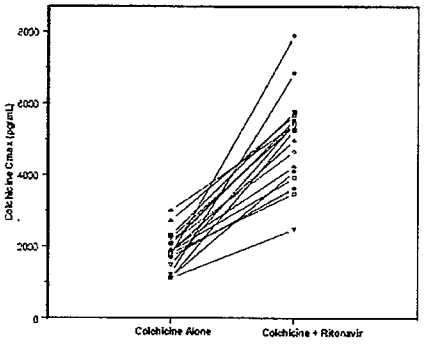
Statistical Methods:

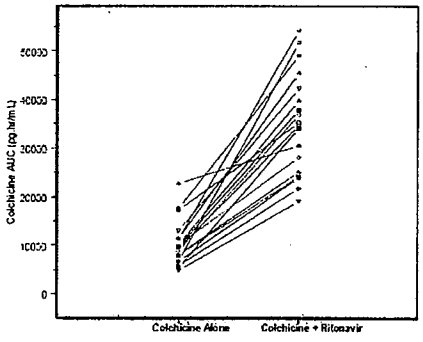
Sample Size:
No formal sample size was performed for the protocol, but it was estimated that 24 subjects completing the study would be sufficient. This sample size was considered adequate based on the sample sizes used in other published colchicine drug interaction studies and in other published colchicine pharmacokinetic studies. Eighteen of the 24 subjects were included in the pharmacokinetic analyses. Although the power of the study is lower than projected due to the smaller sample size, the study conclusion does not change due to the large ratio between colchicine administered with ritonavir and colchicine alone.

SUMMARY / CONCLUSIONS:

Pharmacokinetic Results:
The following figure illustrates the mean colchicine plasma concentration of single doses of colchicine before and after a 5-day regimen of ritonavir.







Summary Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following a Single Dose of Colchicine Tablets USP, 0.6 mg Before (Day 1) and After a 5-day Regimen of Ritonavir (Day 19) - All Subjects

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T_{max}	
	Colchicine + Ritonavir (Test) (N=18)	Colchicine Alone (Reference) (N=18)
AUC_{0-t} (ng·hr/mL)	29.05 (30.76)	8.41 (47.46)
$AUC_{0-\infty}$ (ng·hr/mL)	35.28 (29.79)	10.41 (45.48)
C_{max} (ng/mL)	4.99 (25.18)	1.87 (28.19)
T_{max} (hr)	1.5 (1 - 1.5)	1 (0.5 - 1.5)
Kel (1/hr)	0.0488 (54.26)	0.1666 (44.37)
$t_{1/2}$ (hr)	17.41 (40.15)	5.15 (56.57) [1]
$V_{z/f}/F$	428.5 (30.29)	431.3 (29.34)
CL/F (L/hr)	18.59 (31.58)	67.93 (39.47)
Weight-Adjusted CL/F (L/hr/kg)	0.25 (25.04)	0.95 (41.78)

When colchicine (0.6-mg single-dose) is co-administered with steady-state ritonavir, colchicine concentrations increase to a mean maximum 5 ng/mL, which is approximately

170% higher or 2.7-fold higher than the maximum colchicine concentration when colchicine is administered alone as a single 0.6-mg dose (C_{max} = 1.9 ng/mL). T_{max} is not affected by the co-administration with ritonavir (1.5 and 1.0 hours with and without ritonavir co-administration, respectively). Colchicine AUC_{0-t} is increased approximately 245% (29.1 ng·h/mL) or 3.5-fold when coadministered with ritonavir ER as compared to AUC_{0-t} when administered alone (8.4 ng·h/mL). Total apparent oral clearance is decreased by 70% when colchicine is co-administered with ritonavir as compared to the total apparent oral clearance when colchicine was administered alone (19 L/hr *versus* 68 L/hr).

The following table summarizes the results of the analyses performed on the ln-transformed pharmacokinetic parameters.

Colchicine Tablets USP, 0.6 mg Before (Day 1) and After a 5-day Regimen of Ritonavir (Day 19) All Subjects (N=18)

Parameter (units)	Colchicine + Ritonavir (Test) (N=18)	Colchicine Alone (Reference) (N=18)	% Ratio	90% CI
AUC_{0-t} (ng·hr/mL)	27.79	7.64	363.65	(307.20, 430.48)
AUC_{0-inf} (ng·hr/mL)	33.77	9.55	353.56	(302.02, 413.90)
C_{max} (ng/mL)	4.84	1.80	268.88	(234.83, 307.86)

Safety Results:

Following the administration of colchicine, when given alone or in combination with ritonavir, the most common adverse events were nausea and rhinorrhea, each occuring in 2 subjects (8.3%). There was no apparent difference in adverse events between the two dosing conditions despite the increase in exposure when given with ritonavir. All other treatment-emergent events following administration of colchicine occurred in single subjects (4.2%). These were upper abdominal pain, vomiting, viral gastroenteritis, dysgeusia, headache, and dysmenorrhea.

4.2.4 Study # MPC-004-08-1014 Synopsis

MPC-004-08-1014: A One-Directional, Open-Label Drug Interaction Study to Investigate the Effects of Multiple-Dose Verapamil HCL ER on Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers.
OBJECTIVES: The primary objective of this study was to determine the effect of multiple doses of extended release (ER) verapamil HCl (Mylan Pharmaceuticals, Inc. [verapamil HCl ER]) on the pharmacokinetics of colchicine administered as a single 0.6-mg dose (Mutual) in healthy adult subjects under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of single 0.6-mg dose of colchicine administered alone and in combination with multiple-dose verapamil HCl ER. **METHODOLOGY:** This was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study with single-dose colchicine and multiple-dose verapamil HCl ER conducted in healthy male and female volunteers. Subjects received a single 0.6-mg colchicine tablet on Day 1 and then completed a 14-day washout period. Beginning on the morning of Day 15, subjects returned to the clinic on a non-confined basis to receive 1 × 240 mg of verapamil HCl ER; subjects returned to the clinic each morning on a non-confined basis on Day 16 through Day 18 and received 1 × 240 mg of verapamil HCl ER. Following confinement on the afternoon of Day 18, study subjects received 1 × 240 mg of verapamil HCl ER and 1 × 0.6 mg of colchicine on Day 19. Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 19 at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 and 20-23. Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations. Verapamil plasma concentrations were not measured. **Number of Subjects** **Planned:** 24 **Analyzed:** 24 **Diagnosis and Main Criteria for Inclusion:** All subjects were healthy adult, non-smoking, non-obese subjects between the ages of 18 and 45 years of age, inclusive, with a BMI of 18 – 32, inclusive, who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing, vital sign measurements and 12-lead ECG.

Test Product:	Dose and Mode of Administration:	Batch Numbers:
Colchicine Tablets USP (Mutual Pharmaceutical Company, Inc.)	0.6 mg Tablets, Oral	BB 374 0215
Verapamil Hydrochloride Extended-Release Tablets, USP 240 mg (Mylan Pharmaceuticals Inc.)	240 mg Tablets, Oral	Lot 8C511 Exp. 9/09

DURATION OF TREATMENT:

The subjects received a single dose of colchicine [1 × 0.6-mg tablet on Days 1 and 19] and a single dose of verapamil HCl ER (1 × 240-mg tablet on Days 15 – 18). On Day 19, subjects received a single dose each of colchicine [1 × 0.6-mg tablet] and verapamil HCl ER [1 × 240-mg tablet]. Subjects completed a 14-day washout period after the first dose of colchicine on Day 1 and before the first dose of verapamil HCl ER on Day 15. Total study participation, exclusive of screening, was 23 days.

Criteria for Evaluation:

Pharmacokinetic:

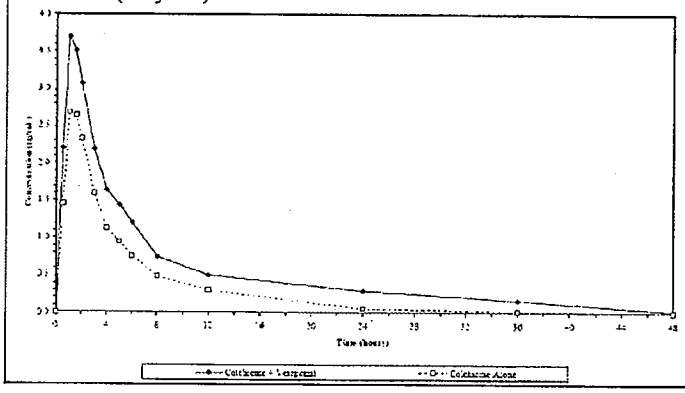
Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$. Parameter values also were separately calculated for men and women.

Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with verapamil HCl ER (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

SUMMARY / CONCLUSIONS:

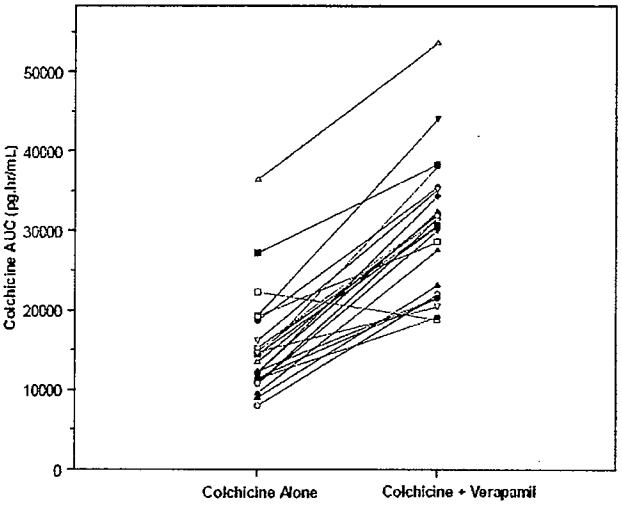
Pharmacokinetic Results:

The following figure illustrates the mean colchicine plasma concentration following single doses of colchicine (0.6 mg) before (Day 1) and after a 5-day regimen of verapamil HCl ER (Day 19).



The following table summarizes descriptive statistics (mean %CV) for colchicine pharmacokinetic parameter values for all 24 subjects with data.

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T_{max}	
	Colchicine + Verapamil HCl ER (N=24) (Test)	Colchicine Alone (N=24) (Reference)
AUC_{0-t} (ng·hr/mL)	24.64 (26.61)	13.09 (40.44)
$AUC_{0-\infty}$ (ng·hr/mL)	30.59 (27.08)	15.37 (41.06)
C_{max} (ng/mL)	3.85 (37.89)	2.97 (42.43)
T_{max} (hr)	1 (0.5 – 2.0)	1.03 (0.5 – 2.0)
K_{el} (1/hr)	0.048 (51.07)[1]	0.1409 (38.47)[1]
$t_{1/2}$ (hr)	17.17 (35.02)	6.24 (65.17)
$V_{ss/F}$ (L)	478.92 (22.69)	342.62 (33.45)
CL/F (L/hr)	21.01 (26.85)	43.93 (31.73)
Weight-Adjusted CL/F (L/hr/kg)	0.3 (27.49)	0.63 (32.49)



Cmax increase was < 2-fold in all subjects. N=15 had ~ 2-fold increase in AUC, N=9 < 2-fold increase Highest AUC increase was ~2.9-fold.

When colchicine (0.6-mg single dose) is co-administered with multiple-dose verapamil HCl ER, colchicine concentrations increase to a mean maximum 3.85 ng/mL, which is approximately 30% higher than when administered alone as a single 0.6-mg dose (C_{max} = 2.97 ng/mL). Colchicine AUC_{0-t} and $AUC_{0-\infty}$ are increased approximately 88% and 99% (24.6 ng·h/mL and 30.6 ng·h/mL), respectively, when co-administered with verapamil HCl ER as compared to AUC_{0-t} and $AUC_{0-\infty}$ when administered alone (13.1 ng·h/mL and 15.4 ng·h/mL, respectively). T_{max} is not affected by the co-administration with verapamil HCl ER (1.00 and 1.03 hours with and without verapamil HCl ER co-administration, respectively). Total apparent oral clearance is decreased by 52% when colchicine is co-administered with verapamil HCl ER as compared to the total apparent oral clearance when colchicine is administered alone (21.0 L/hr *versus* 43.9 L/hr).

The table below provides a statistical summary of the ln-transformed geometric mean colchicine pharmacokinetic parameter values when administered alone *versus* colchicine pharmacokinetic parameter values when administered with verapamil HCl ER.

Colchicine Tablets USP, 0.6 mg Before (Day 1) and After a 5-day Regimen of Verapamil HCl ER (Day 19) All Subjects (N=24)				
Parameter (units)	**Colchicine + Verapamil HCl ER N=24 (Test)**	**Colchicine Alone N=24 (Reference)**	**% Ratio**	**90% CI**
AUC_{0-t} (ng·hr/mL)	23.89	12.26	194.91	(175.20, 216.84)
AUC_{0-inf} (ng·hr/mL)	29.56	14.42	205.03	(184.22, 228.19)
C_{max} (ng/mL)	3.64	2.77	131.45	(115.29, 149.88)

As listed above, the associated 90% CI around the ratios of the means for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were outside the no-interaction pre-specified range, 80%-125%, indicating a statistically significant drug interaction is present when colchicine and verapamil HCl ER are coadministered.

Safety Results:

Following the administration of colchicine, when given alone or in combination with verapamil HCl ER, the most common adverse event was headache occurring in 7 subjects (29.2%). Other AEs reported following administration of colchicine alone were each reported in single subjects, and included upper abdominal pain upper, diarrhea, dizziness, and back pain. All adverse events were mild to moderate in intensity.

4.2.5 Study # MPC-004-08-1015 Synopsis

Number and Title of Study:
MPC-004-08-1015: A One-Directional, Open-Label Drug Interaction Study to Investigate the Effects of Multiple-Dose Diltiazem ER on Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers

Objectives:
The primary objective of this study was to determine the effect of multiple doses of diltiazem ER on the pharmacokinetics of colchicine administered as a single 0.6-mg dose in healthy adult subjects under fasted conditions.
The secondary objective of this study was to assess the safety and tolerability of a single 0.6-mg dose of colchicine administered alone and in combination with multiple-dose diltiazem ER.

Methodology:
This was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study with single-dose colchicine and multiple-dose diltiazem ER conducted in healthy male and female volunteers. During the first confinement period, subjects received a single 0.6-mg colchicine tablet on Day 1 (7:15 AM) under fasted conditions and then completed a 14-day washout period. Beginning on the morning of Day 15, subjects received 240 mg diltiazem ER once daily for 7 doses (7 days). Dosing was on a non-confined basis (in-clinic) for the first 6 days. During the second confinement period on Day 21 (7:15 AM), study subjects received a single 0.6-mg colchicine tablet co-administered with a single 240-mg diltiazem ER capsule under fasted conditions.
Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 21 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis and 36, 48, 72, and 96 hours post-dose administration on a non-confined basis.
Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations. Diltiazem plasma concentrations were not measured.

Number of Subjects
Planned: 24
Analyzed: 24 enrolled and 20 analyzed (1 subject withdrew consent due to schedule conflict, 2 subjects were removed due to missed diltiazem ER doses during the non-confined period, and 1 subject was removed due to an emesis episode)

Diagnosis and Main Criteria for Inclusion:
All subjects were healthy adult, non-smoking, non-obese subjects 18 – 45 years of age inclusive with a BMI of 18 – 32 inclusive who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing, and vital sign measurements.

Test Product:	Dose and Mode of Administration:	Batch Numbers:
Colchicine Tablets USP. (Mutual Pharmaceutical Company. Inc.)	0.6 mg Tablets. Oral	BB 374 0215
Cardizem® CD 240 mg Capsules (Aventis Pharmaceuticals. Inc.)	240 mg Capsules. Oral	Lot: 1107879 Expiration: 04-2010

Duration of Treatment:

The subjects received a single dose of colchicine (1 × 0.6-mg tablet) on Days 1 and 21 and a single dose of diltiazem ER (1 × 240-mg capsules) once daily for 7 days (Days 15 – 21).

Subjects completed a 14-day washout period after the first dose of colchicine on Day 1 and before the first dose of diltiazem ER on Day 15. Total study participation, exclusive of screening, was 25 days.

Criteria for Evaluation:

Pharmacokinetic:

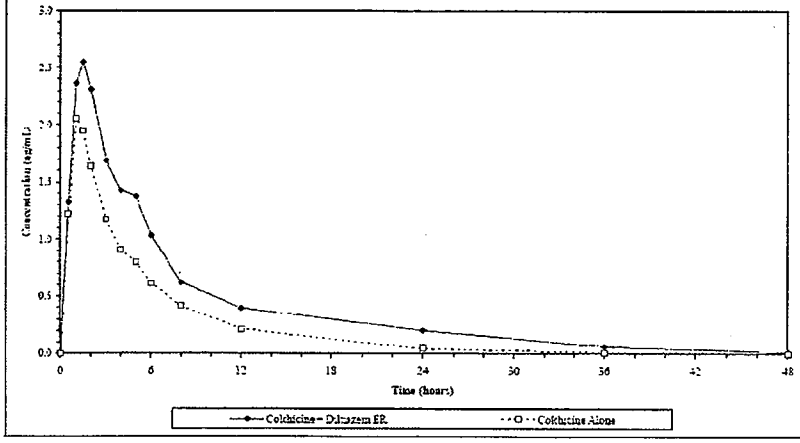
Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$. Parameter values also were separately calculated for men and women.

Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with diltiazem ER (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect, and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

SUMMARY / CONCLUSIONS:

Pharmacokinetic Results:

The following figure illustrates the mean colchicine plasma concentrations following administration of single doses of colchicine 0.6 mg before and after a 7-day regimen of diltiazem ER.

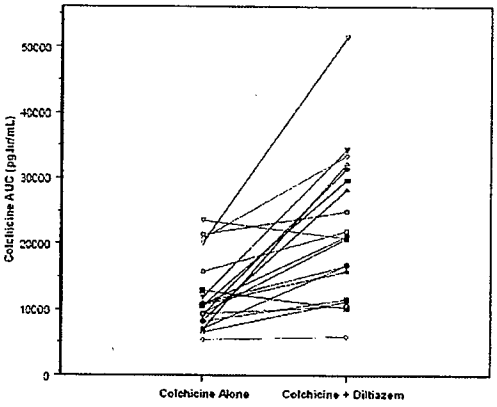


The following table summarizes colchicine pharmacokinetic parameter values descriptive statistics (mean (%CV)).

Summary Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following a Single Dose of Colchicine Tablets USP, 0.6 mg before (Day 1) and after a 7-Day Regimen of Diltiazem ER (Day 21) (N = 20)

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T_{max}	
	Colchicine + Diltiazem ER	Colchicine Alone
AUC_{0-t} (ng·hr/mL)	17.73 (48.75)	10.04 (45.46)
$AUC_{0-\infty}$ (ng·hr/mL)	22.49 (48.89)	12.03 (45.06)
C_{max} (ng/mL)	2.8 (44.42)	2.17 (39.99)
T_{max} (hr)	1.5 (0.5 – 5.0)	1.0 (0.5 – 2.0)
K_{el} (1/hr)	0.0838 (69.14)	0.1589 (40.07)
$t_{1/2}$ (hr)	12.5 (61.8)[1]	5.51 (59.77)[2]
$V_{ss/F}$ (L)	463.49 (28.04)	395.83 (30.33)
CL/F (L/hr)	34.7 (60.42)	58.88 (38.89)
Weight-Adjusted CL/F (L/hr/kg)	0.45 (50.25)	0.78 (40.73)

When colchicine (0.6-mg single-dose) is co-administered with steady-state diltiazem ER, colchicine concentrations increase to a mean maximum 2.80 ng/mL, which is approximately 29% higher than the maximum colchicine concentration when colchicine is administered alone as a single 0.6-mg dose (C_{max} = 2.17 ng/mL). T_{max} is not affected by the co-administration with diltiazem (1.5 and 1.0 hours with and without diltiazem ER co-administration, respectively). Colchicine AUC_{0-t} and $AUC_{0-\infty}$ are increased approximately 77% (17.7 ng·h/mL) and 87% (22.5 ng·h/mL, respectively) when co-administered with diltiazem ER as compared to AUC_{0-t} and $AUC_{0-\infty}$ when administered alone (10.0 ng·h/mL and 12.0 ng·h/mL, respectively). Total apparent oral clearance is decreased by 40% when colchicine is co-administered with diltiazem ER as compared to the total apparent oral clearance when colchicine is administered alone (34.7 L/hr *versus* 58.9 L/hr).



The following table summarizes the results of the analyses performed on the ln-transformed pharmacokinetic parameters.

Colchicine Tablets USP, 0.6 mg Before (Day 1) and After a 7-day Regimen of Diltiazem ER (Day 21) (N=20)

Parameter (units)	Colchicine + Diltiazem ER	Colchicine Alone	% Ratio	90% CI
AUC_{0-t} (ng·hr/mL)	15.74	9.15	171.94	(141.81, 208.48)
$AUC_{0-\infty}$ (ng·hr/mL)	19.90	11.02	180.57	(149.93, 217.48)
C_{max} (ng/mL)	2.58	2.01	128.75	(107.47, 154.24)

Safety Results:

Safety was assessed on the basis of all 24 subjects who received at least one dose of

colchicine.
One subject, Subject 20, was dropped due to an AE (vomiting) while on diltiazem ER. There were no SAEs reported.
Following the administration of colchicine, when given alone or in combination with diltiazem ER, the most common AE was headache, occurring in 5 subjects (20.8%). There was no apparent difference in adverse events between the two dosing conditions despite the increase in colchicine exposure when given with diltiazem ER. All other treatment-emergent events following administration of colchicine occurred in single subjects (4.2 to 5.0%). These were dry eye, eye irritation, nausea, chest pain, musculoskeletal pain, lethargy, pharyngolaryngeal pain, and rhinorrhea.

4.2.6 Study # MPC-004-08-1016 Synopsis

Number and Title of Study:
MPC-004-08-1016: A One-Directional, Open-Label Drug Interaction Study to Investigate the Effects of Single-Dose Cyclosporine on Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers

Objectives:
The primary objective of this study was to determine the effect of single-dose cyclosporine on the pharmacokinetics of colchicine administered as a single 0.6-mg dose in healthy adult subjects under fasted conditions.
The secondary objective of this study was to assess the safety and tolerability of a single 0.6-mg dose of colchicine administered alone and in combination with single-dose cyclosporine.

Methodology:
This was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study with single-dose colchicine and single-dose cyclosporine conducted in healthy male and female volunteers. During the first confinement period, subjects received a single 0.6-mg colchicine tablet on Day 1 (7:15 AM) under fasted conditions, and then completed a 14-day washout period. During the second confinement period on Day 15 (7:15 AM), study subjects received a single 0.6-mg colchicine tablet co-administered with a single 100-mg cyclosporine capsule under fasted conditions.
Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 15 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis and 36, 48, 72, and 96 hours post-dose administration on a non-confined basis.
Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations. Cyclosporine plasma concentrations were not measured.

Number of Subjects
Planned: 24
Analyzed: 23 (one subject was dropped Period II due to out of range laboratory values)

Diagnosis and Main Criteria for Inclusion:
All subjects were healthy adult, non-smoking, non-obese subjects 18 – 45 years of age inclusive with a BMI of 18 – 32 inclusive who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing, and vital sign measurements.

Test Product:	**Dose and Mode of Administration:**	**Batch Numbers:**
Colchicine Tablets USP. (Mutual Pharmaceutical Company, Inc.)	0.6 mg Tablets. Oral	BB 374 0215
Neoral® Soft Gelatin Capsules, USP (R.P. Scherer GmbH)	100 mg Capsules. Oral	Lot: F4116 Expiration: MAY 2009

Duration of Treatment:

The subjects received a single dose of colchicine (1 × 0.6-mg tablet) on Days 1 and 15 and a single dose of cyclosporine (1 × 100-mg capsules) once on Day 15. Subjects completed a 14-day washout period after the first dose of colchicine on Day 1 and before the co-administration of colchicine and cyclosporine on Day 15. Total study participation, exclusive of screening, was 19 days.

Criteria for Evaluation:

Pharmacokinetic:

Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, V_{area}/F, CL/F, and $t_{1/2}$. Parameter values also were separately calculated for men and women.

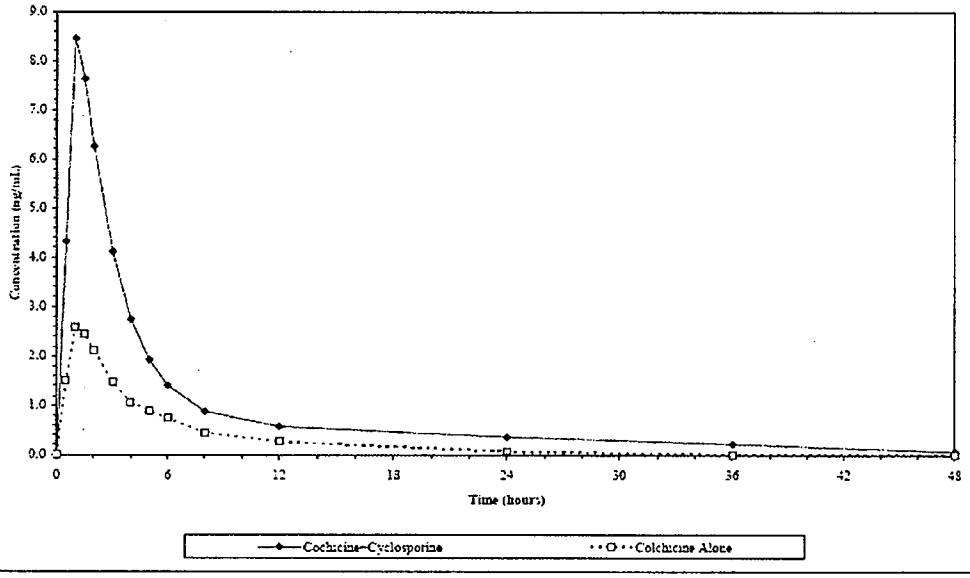
Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with cyclosporine (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect, and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

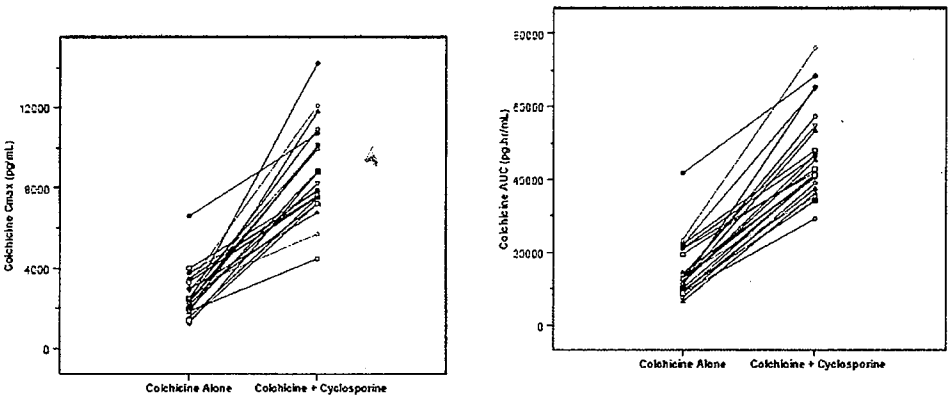
SUMMARY / CONCLUSIONS:

Pharmacokinetic Results:

Data for 23 of 24 subjects were used in the statistical and pharmacokinetic analysis for colchicine.

The following figure illustrates the mean colchicine plasma concentration of single doses of colchicine before and after co-administration with cyclosporine.





Cmax increase was > 5-fold in n=3, 2- to 5-fold in n=16
AUC increase was >5-fold in n=3, 2- to -5-fold in n=19
Highest AUC increase was ~5.9-fold.

The following table summarizes colchicine pharmacokinetic parameter values descriptive statistics (mean (%CV)) for all subjects who completed the study.

Summary Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following a Single Dose of Colchicine Tablets USP, 0.6 mg Alone (Day 1) and with a Single 100-mg Dose of Cyclosporine (Day 15) – N=23

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T_{max}	
	Colchicine + Cyclosporine	Colchicine Alone
AUC_{0-t} (ng·hr/mL)	39.83 (25.89)	12.55 (46.67)
$AUC_{0-\infty}$ (ng·hr/mL)	47.31 (25.65)	15.00 (51.94)
C_{max} (ng/mL)	8.82 (25.22)	2.72 (41.83)
T_{max} (hr)	1 (0.5 – 2.0)	1 (1.0 – 2.0)
K_e (1/hr)	0.0384 (47.43)	0.1471 (50.67)
$t_{1/2}$ (hr)	20.65 (31.18)[1]	6.77 (81.67)[2]
$V_{ss/F}$ (L)	382.89 (27.39)	366.66 (31)
CL/F (L/hr)	13.42 (23.3)	48.24 (39.97)
Weight-Adjusted CL/F (L/hr/kg)	0.18 (21.82)	0.65 (43.56)

When colchicine (0.6-mg single-dose) is co-administered with single-dose cyclosporine, colchicine concentrations increase to a mean maximum 8.82 ng/mL, which is approximately 224% higher than the maximum colchicine concentration when colchicine is administered alone as a single 0.6-mg dose (C_{max} = 2.72 ng/mL). T_{max} is not affected by the co-administration with cyclosporine (both 1.0 hour with and without cyclosporine co-administration, respectively). Colchicine AUC_{0-t} and $AUC_{0-\infty}$ are increased approximately 216% (39.8 ng·h/mL) and 215% (47.3 ng·h/mL) when co-administered with cyclosporine as compared to AUC_{0-t} and $AUC_{0-\infty}$ when administered alone (12.6 ng·h/mL and 15.0 ng·h/mL), respectively. Total apparent oral clearance is decreased by 72% when colchicine is co-administered with cyclosporine as compared to the total apparent oral

clearance when colchicine is administered alone (13.4 L/hr *versus* 48.2 L/hr).
The following table summarizes the results of the analyses performed on the ln-transformed pharmacokinetic parameters.

Colchicine Tablets USP, 0.6 mg Alone (Day 1) and with Cyclosporine (Day 15) (N=23)

Parameter (units)	Colchicine + Cyclosporine	Colchicine Alone	% Ratio	90% CI
AUC_{0-t} (ng·hr/mL)	38.66	11.47	337.14	(295.61, 384.5)
$AUC_{0-\infty}$ (ng·hr/mL)	45.95	13.55	339.12	(299.26, 384.3)
C_{max} (ng/mL)	8.55	2.53	337.57	(288.15, 395.48)

Safety Results:
There were no SAEs reported.
Following the administration of colchicine, when given alone or in combination with cyclosporine, the most common AE was headache, occurring in 4 subjects (16.7%). Three of the subjects had a headache when colchicine was administered together with cyclosporine (13.0%); only 1 subject had a headache when colchicine was administered alone (4.2%). Otherwise, there was no apparent difference in adverse events between the two dosing conditions despite the increase in colchicine exposures when given with cyclosporine. All other treatment-emergent events following administration of colchicine occurred in single subjects (4.2%). These were upper abdominal pain, nausea, bacteriuria, contusion, dizziness, cough, pharyngolaryngeal pain, and throat irritation.

4.2.7 Study # MPC-004-08-1017 Synopsis

Number and Title of Study: MPC-004-08-1017: A One-Direction. Open-Label Drug-Food Interaction Study to Investigate the Effects of Multiple-Daily Consumptions of Grapefruit Juice on the Single-Dose Pharmacokinetics of Colchicine in Healthy Volunteers
Objectives: The primary objective of this study was to determine the effect of multiple daily consumptions of grapefruit juice (240 mL twice daily [*b.i.d.*]) on the pharmacokinetics of colchicine administered to healthy adult subjects as a single 0.6-mg dose under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of single 0.6-mg dose of colchicine administered alone and in combination with multiple daily consumptions of grapefruit juice. **Methodology:** This was an open-label, non-randomized, single-center, one-sequence, two-period drug-food interaction study with single-dose colchicine and multiple daily consumptions of grapefruit juice conducted in healthy male and female volunteers. Subjects received a single 0.6-mg colchicine tablet on Day 1 and then completed a 14-day washout period. Beginning on the morning of Day 15, subjects received a 240-mL serving of grapefruit juice *b.i.d.* (twice daily) for 8 servings (4 days). Dosing was on a non-confined basis (in clinic) for the first 3 days. On Day 18 the subjects received a single 0.6-mg colchicine tablet co-administered with a single 240-mL serving of grapefruit juice and in the evening at 7:15 PM, study subjects received the final 240-mL serving of grapefruit juice. Blood samples were collected for the determination of colchicine plasma concentrations prior to dosing (0) hour and after dose administration on Days 1 and 18 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis and 36, 48, 72, and 96 hours post-dose administration on a non-confined basis. Plasma samples were sent to the bioanalytical laboratory of PRACS Institute, Ltd. – Cetero Research for determination of colchicine plasma concentrations.
Number of Subjects **Planned: 24** **Analyzed: 22 enrolled;** 21 completed (1 subject discontinued due to a missed serving of grapefruit juice on Day 16. Two (2) subjects were not enrolled due to schedule conflicts and did not present to the clinical site for check-in. Therefore, the initial planned enrollment of 24 was not met. **Diagnosis and Main Criteria for Inclusion:** All subjects were healthy adult, non-smoking, non-obese subjects 18 – 45 years of age with a BMI of 18 – 32 who were not using concomitant medications or other products that might interfere with the pharmacokinetic interpretation. Prior to enrollment, all study subjects met the inclusion/exclusion criteria for this study. General health was confirmed by medical history, physical examination, clinical laboratory testing, and vital sign measurements.

Test Product:	Dose and Mode of Administration:	Batch Numbers:
Colchicine Tablets USP. (Mutual Pharmaceutical Company, Inc.)	0.6 mg Tablets, Oral	BB 374 0215
Thirster® 100% Grapefruit Juice (Distributed by Rituals Coffee Company)	240 mL serving, Oral	Lot: L 504 Best by: Feb 06, 09

Duration of Treatment:

The subjects received a single dose of colchicine (1 × 0.6-mg tablet) on Days 1 and 18 and a single serving of grapefruit juice (1 × 240 mL) twice daily for 4 days (Days 15-18). Total study participation, exclusive of screening, was 23 days.

Criteria for Evaluation:

Pharmacokinetic:

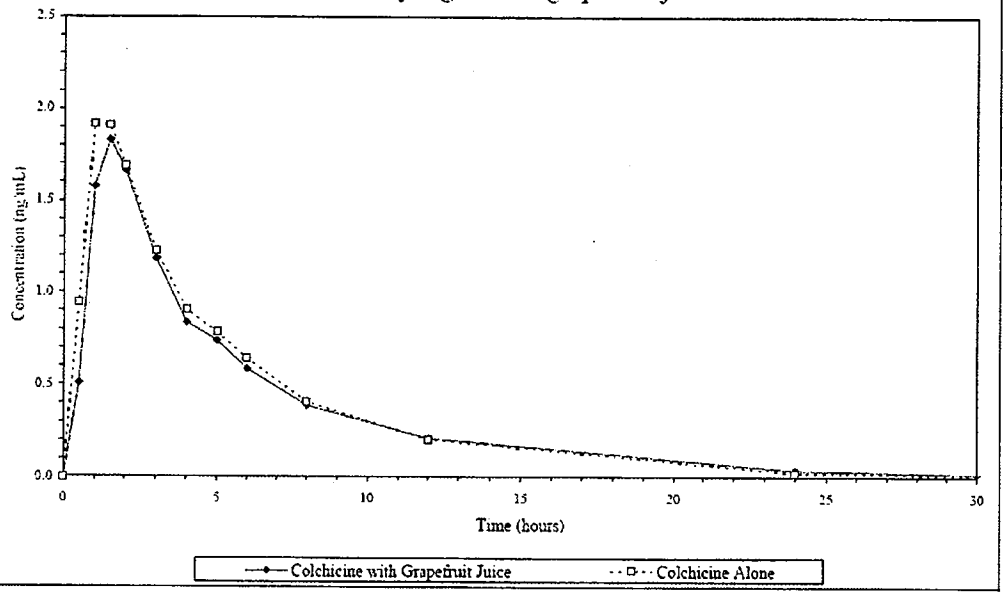
Plasma concentration data from the blood samples collected were used to calculate values for the following colchicine pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, Kel, V_{area}/F, CL/F, and $t_{1/2}$. Parameter values also were separately calculated for men and women.

Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for colchicine with grapefruit juice (Test) *versus* colchicine alone (Reference). The ANOVA model included treatment as a fixed effect and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

SUMMARY / CONCLUSIONS:

Pharmacokinetic Results:

The following figure illustrates the mean colchicine plasma concentration of single doses of colchicine before and after a 4-day regimen of grapefruit juice.



The following table summarizes colchicine pharmacokinetic parameter values descriptive statistics (mean (%CV)) for all subjects. There is little apparent difference in the colchicine pharmacokinetic parameter values for the two dosing conditions.

Summary Mean (%CV) Colchicine Pharmacokinetic Parameter Values Following a Single Dose of Colchicine Tablets USP, 0.6 mg before (Day 1) and after a 4-Day Regimen of Grapefruit Juice (Day 18) (N = 21)

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T_{max} Colchicine + Grapefruit Juice (Test)	Colchicine Alone (Reference)
AUC_{0-t} (ng·hr/mL)	8.82 (34.04)	9.33 (36.1)
$AUC_{0-\infty}$ (ng·hr/mL)	10.85 (38.14)	11.08 (35.64)
C_{max} (ng/mL)	1.97 (20.23)	2.17 (30.05)
T_{max} (hr)	1.5 (1.0 – 3.0)	1 (1.0 – 2.0)
Kel (1/hr)	0.1527 (34.78)	0.1714 (29.22)
$t_{1/2}$ (hr)	5.58 (62.79)[1]	4.64 (54.29)[1]
V_{area}/F (L)	433.06 (27.06)	363.89 (26.75)
CL/F (L/hr)	62.18 (34.45)	60.25 (35.29)
Weight-Adjusted CL/F (L/hr/kg)	0.76 (37.88)	0.74 (40.6)

The following table summarizes the results of the analyses performed on the ln-transformed pharmacokinetic parameters.

Colchicine Tablets USP, 0.6 mg before (Day 1) and after a 4-Day Regimen of Grapefruit Juice (Day 18) (N=21)

Parameter (units)	Colchicine + Grapefruit Juice (Test)	Colchicine Alone (Reference)	% Ratio	90% CI
AUC_{0-t} (ng·hr/mL)	8.35	8.81	94.85	(86.47, 104.04)
AUC_{0-inf} (ng·hr/mL)	10.21	10.50	97.26	(88.08, 107.40)
C_{max} (ng/mL)	1.93	2.07	93.25	(83.07, 104.67)

As listed above, the associated 90% CI around the ratios of the means for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the no interaction pre-specified range, 80%-125%, indicating that no grapefruit juice-drug interaction is present when colchicine and grapefruit juice are co-administered.

Safety Results:

The clinical portion of the study was completed without any significant sequelae attributable to the investigational drug. The safety monitoring was completed to the satisfaction of the clinical investigators; no serious adverse events (SAEs) were reported. No subject discontinued colchicine due to an adverse event nor were there any other significant events.

Three (3) subjects (13.6%) experienced a total of five (5) treatment-emergent adverse events during the course of the study, all mild to moderate in intensity. Diarrhea, occurring in 1 subject (4.5%) was judged treatment related. The other events, headache, cough, chest congestion, and pharyngolaryngeal pain, also occurred in 1 subject each, but were not judged treatment related as the onset of headache was 4 days post dose and the onset of cough, congestion, and pharyngolaryngeal pain was 2 days post dose.

4.2.8 Study MPC-004-06-001 Synopsis

Number and Title of Study: 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 (MPC-004-06-001)
Objectives: • Primary: To demonstrate the efficacy of colchicine in an acute gout attack (gouty flare) based on pain reduction after 24 hours as a measure of response. • Secondary (Efficacy): To compare 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. Assessment of interference with sleep was also a secondary objective, however, due to patient confusion in replying to the Diary question, this was not analyzed. • Secondary (Safety): To determine the safety of colchicine when administered in two different dose regimens. **Methodology:** A multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-comparison study of a Standard-dose of colchicine (4.8 mg) and Low-dose colchicine (1.8 mg). Patients were to be randomized to treatment and study medication dispensed by the Investigator for use in the next gout flare. At Investigator discretion, rescue medication could also be provided; patients were to be encouraged not to use rescue medication within the first 24 hours after starting treatment with study drug. Patients were to self-initiate treatment within 12 hours of a gout flare; determination that the gout flare qualified for treatment was to be made by a Gout Flare Call Center established for the purpose. Patients were to record dosing and rescue medication use, pain, and whether or not gastrointestinal adverse events (nausea, vomiting, diarrhea, and abdominal pain) were present prior to the start of treatment and 1, 2, 3, 4, 5, 6, 7, 8, 16, 24, 32, 40, 48, 56, 64, and 72 hours after the start of dosing. They were to be seen by the Investigator as soon as possible after the gout flare onset and evaluated until resolution of flare and any adverse events (projected to be within 7 days, however, patients were to be followed for longer if necessary). **Number of Subjects (Planned and Analyzed):** 813 patients were screened, 575 patients were randomized (390 planned), and 185 were treated (total 141 planned, 47 per treatment group). Of the 184 patients in the ITT patient population, there were 52 randomized to Standard-dose colchicine, 74 randomized to Low-dose colchicine, and 58 randomized to placebo; there was 1 additional patient in the Safety population (randomized to placebo) for a total of 185 patients. All patients had at least one post-treatment contact and therefore provided efficacy data. **Diagnosis and Main Criteria for Inclusion:** Patients were screened for eligibility by medical and medication use history, physical examination and vital sign measurement, clinical laboratory testing (to be repeated every 3 months until gout flare), and 12-lead electrocardiogram.
Diagnosis Patients with a confirmed diagnosis of gout consistent with the criteria of the American College of Rheumatology (diagnosis based on presence of characteristic urate crystals in the joint fluid and/or a tophus proven to contain urate crystals by chemical or polarized

light microscopic means and/or the presence of at least six of the following clinical, laboratory, and x-ray phenomena: more than 1 prior attack of acute arthritis, maximum inflammation developed within 24 hours, monoarthritis attack, redness observed over joints, first metatarsophalangeal joint painful or swollen, unilateral first metatarsophalangeal 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).

Other key Inclusion Criteria:

- Patients of either gender and of any race ≥18 years of age.
- If female, patients were to be postmenopausal as evidenced by lack of menses for ≥12 consecutive months.
- Patients were to have experienced ≥2 acute gouty arthritic attacks in the 12 months prior to randomization.
- Patients on urate-lowering therapy were to be on a stable dose and schedule with no changes in therapy for 4 weeks prior to randomization and expected to remain on a stable regimen during study participation.
- Patients were to be willing to adhere to the study schedule and the protocol requirements.
- Patients were to be willing and able to give written informed consent. A HIPAA and/or state privacy consent was also to be signed.

Key Exclusion Criteria:

- Patients with acute polyarticular gout (>4 joints).
- Patients who had experienced >2 acute gouty arthritic attacks per month, or >12 attacks overall, in the 6 months prior to randomization.
- Patients with arthritis due to any cause other than gout that may confound any study assessments per Investigator discretion.
- Patients taking colchicine routinely (except for the treatment of an acute gout flare) with such use during the 6 months prior to screening or any prior history of lack of response to or inability to tolerate colchicine.
- Patients with a known hypersensitivity to colchicine or any component of the formulation of study drug.
- Patients with a history of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting within the previous 6 months prior to screening.
- Patients with active myeloid leukemia, obstructive gastrointestinal cancer, or metastatic cancer.
- Patients with chronic renal dysfunction (creatinine clearance <60 mL/min as estimated with the Cockcroft-Gault formula).
- Patients with chronic hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 × the upper limit of normal [ULN], or bilirubin >2.5 mg/dL, or albumin <1.5 gm/dL).
- Patients with a history of alcohol or substance abuse within the 12 months prior to randomization
- Patients with 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.
• Patients using systemic corticosteroid, cyclosporine, adalimumab, etanercept, infliximab, anakinra, abatacept, mycophenolate, azathioprine, anticoagulants (warfarin, heparin, low-molecular weight heparin [LMWH], antithrombin agents, thrombin inhibitors, or selective Factor Xa inhibitors [note, use of aspirin ≤325 mg/day was allowed]), or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and other analgesics such as opiates at screening.
• Use of any investigational drug within 30 days prior to randomization.
• Patients currently participating in another research study or anticipated to enroll in such during participation in this study.
• Patients for whom informed consent could not be obtained.
• Patients who had previously been randomized into this study and begun ingestion of study drug.

Test Product	Dose and Mode of Administration	Batch Number
Colchicine 0.6-mg tablets BB 374 0215	**Standard-dose colchicine (4.8 mg):** 1.2 mg of oral colchicine (2 over-encapsulated 0.6-mg tablets) at onset of confirmed gout flare followed by 0.6 mg of oral colchicine (1 over-encapsulated 0.6-mg tablet) every hour for 6 hours.	35171B0, 38061K0 (kits of over-encapsulated tablets)
	Low-dose colchicine (1.8 mg): 1.2 mg of oral colchicine (2 over-encapsulated 0.6-mg tablets) at onset of confirmed gout flare followed by 0.6 mg of oral colchicine (1 over-encapsulated 0.6-mg tablet) after 1 hour and then 1 oral placebo capsule every hour thereafter for 5 hours.	35171B0 / 35171J0, 38061F0 (kits of over-encapsulated tablets)
Reference Therapy: Placebo (no placebo tablets were manufactured)	Two oral placebo capsules at onset of confirmed gout flare followed by 1 oral placebo capsule every hour for 6 hours	35171A0, 38061H0 (kits of placebo capsules)

Duration of Treatment: 6 hours following confirmed gout flare
Criteria for Evaluation:
Efficacy:
Primary efficacy variable:
• The primary efficacy variable was response to treatment in the target joint, based on patient self assessment of
pain at 24 hours following the time of first dose as recorded on the Diary. A responder was one who achieved a
≥ 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. Patients who used rescue
medication, discontinued prior to the 24-hour post-dose assessment, or did not achieve a ≥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:
• 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:

• Adverse Events (including gastrointestinal tolerability as rated on patient Diary)
• Vital signs (blood pressure and pulse), body weight, and temperature
• Clinical laboratory tests
• Physical examination

Statistical Methods:

Populations:

• The Intent-to-Treat (ITT) population was defined as 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 from the ITT population). The primary efficacy analysis was to be based on an ITT population
• Patients included in the Per Protocol (PP) population were to meet all major inclusion and exclusion criteria and initiated treatment within 12 hours of the onset of the attack; during blinded data review patients whose study participation was not consistent with the intent of the protocol or Good Clinical Practice were excluded.
• The safety population was to consist of all patients who received at least one dose of study medication regardless of whether or not authorized by the Gout Flare Call Center.

Sample Size:

Assuming that 40% of the ITT patients randomized to the Standard-dose colchicine group met response criteria as compared to 10% of the patients randomized to placebo, 47 patients per treatment arm were sufficient to detect a statistically significant treatment group difference with 90% power at a two-tailed alpha of 0.05 (chi-square test corrected for continuity). Estimating that approximately 50% of randomized patients failed to have an acute gout attack during the study and 15% drop out or did not qualify upon contacting the Gout Flare Call Center, at least 390 patients (130 per treatment arm) were to be randomized.

Primary Efficacy Analysis:

The numbers of responders in the Standard-Dose colchicine group and the placebo group, as defined for the primary efficacy variable, were t compared using the unstratified Pearson chi-square test. During blinded study review it was identified that several centers did not enroll at least 1 patient in each treatment arm, therefore, stratification by site was not possible. Instead, centers were pooled together based on a variety of factors and these groupings were used *in lieu* of individual sites; center effects were also separately investigated. Treatment differences were reported as odds ratio with confidence limits on the ratio. Pain scores after rescue use (up through 24 hours) are ignored, essentially a last-observation-carried-forward (LOCF) approach.

Sensitivity analyses were performed by repeating the primary efficacy analysis using alternate methods of defining response: 1) with minimal imputation of information from non-Diary sources for patients with missing or contradictory data (with respect to either

the use of rescue medication or pain score within the 24-hour window), 2) the proportions of responders at the 32- (26- to 36-) hour time point, and 3) proportions of patients in each treatment group with a two-unit reduction from baseline in pain at the 24- and 32-hour time points. In addition, a range of alternate definitions of response, from 0% reduction to 100% reduction relative to baseline, was evaluated; in this analysis, no inferential statistics were generated and results were displayed graphically.

Secondary Efficacy Variables and Analyses:

The Low-Dose colchicine group and placebo and the Standard-Dose and Low-Dose colchicine groups were compared for the primary efficacy variable as a secondary efficacy analysis. In addition, magnitude of pain reduction, a continuous variable, was compared between the three treatment groups using analysis of covariance (ANCOVA) with baseline severity and center type as covariates. Categorical secondary variables (investigator assessment of inflammation and response) were compared between the three treatment using non-parametric statistical methods (unstratified Pearson chi-square test). Secondary efficacy variables that involved time (time to response, pain relief, or rescue medication use) were analyzed using Kaplan-Meier methods. Pain scores after rescue use (up through 24 hours) were ignored.

Subgroup Analyses:

Subgroup analyses were performed to evaluate the effect of age (<45, 45-65, > 65 years), sex, race (white, nonwhite), baseline serum uric acid level (≤ 7 mg/dL or > 7 mg/dL), allopurinol use, diuretic use, admitted alcohol use, time since diagnosis of gout (< 8 years, the median, or ≥ 8 years), number of flares in the past year (≤ 3 or > 3), and renal function (calculated creatinine clearance of < 80 *versus* ≥ 80 mL/min; for obese patients [BMI > 30], ideal body weight was to be used to calculate creatinine clearance instead of actual body weight). Proportions of responders were displayed with patients categorized as noted above; no inferential statistics were performed given the number of exploratory comparisons planned.

Safety Analyses:

Adverse Events

The incidence of treatment-emergent adverse events (coded using the current version of the MedDRA[1] dictionary version 10.0) was tabulated by MedDRA System Organ Class (SOC) and Preferred Term by treatment arm and overall; multiple events within a patient were counted only once and at greatest severity and relationship to study medication. Similar tabulations were prepared by severity (mild, moderate, severe) and by relationship to the study medication not related and related (possible, probable, and definite).

The incidence of GI events captured on the Diary was tabulated separately, together with severity. A composite tabulation of GI events, derived from the Diary and the Concomitant Medications CRF, was also prepared; treatment groups were compared by generating the odds ratio with 95% confidence limits.

SUMMARY / CONCLUSIONS:

Efficacy Results:

Mean pain scores at baseline were 6.8 to 6.9 (on a 0 to 10 scale, with 10 being the worst pain imaginable); median pain score was 7.0. After 24 hours, there were mean 2.0- and 2.2-unit reductions in the Standard-dose colchicine and Low-dose colchicine groups, as compared to a mean 0.7-unit reduction in the placebo group. Seventeen patients (32.7%)

and 28 patients (37.8%) responded to treatment in the Standard-dose colchicine group and Low dose colchicine group, respectively, as compared to 8 patients (13.8%) in the placebo group (p = 0.0343 and 0.0046, respectively).
The conclusion is not altered when only the 169 patients included in the PP population are analyzed. There were statistically significantly more responders in patients randomized to Standard-dose colchicine (16 patients of 48 patients or 33.3%) and Low-dose colchicine (26 of 69 patients or 37.7%) than placebo (8 of 52 patients or 15.4%). The p-values associated with the Odds ratios are 0.0358 and 0.0069, respectively. As with the primary efficacy analysis, there is no difference between the two colchicine dose levels (p = 0.6296).
The median time to a 50% reduction from baseline for target joint pain score was 32.0 hours for the Standard-dose colchicine group and 24.5 hours for the Low-dose colchicine group. An insufficient number of patients randomized to placebo achieved a 50% reduction such that the median time could not be calculated. The survival curves for the two colchicine treatment groups, calculated using Kaplan-Meier methods (with scores after use of rescue medication censored), were statistically significantly different from placebo or nearly so (p = 0.0593 for the Standard-dose group and p = 0.0059 for the Low-dose group); the two colchicine treatment groups do not differ from one another (p = 0.3895). Recognizing that the response to colchicine is not rapid, response at 36 hours was also analyzed. On average, there was little further reduction in mean (2.3-, 2.4-, and 0.7-unit decreases for the Standard-dose colchicine, Low-dose colchicine, and placebo groups, respectively) or median pain scores (2.0 and 2.5 for the Standard-dose and Low-dose colchicine groups, respectively, and 0 for the placebo group). Few additional patients responded between 24 and 32 hours: 2 additional patients randomized to Standard-dose colchicine, 3 patients randomized to Low-dose colchicine, and 1-patient randomized to placebo. Both colchicine treatment groups had statistically significantly greater proportions of responders (36.5% and 41.9% for the Standard-dose and Low-dose colchicine groups, respectively) as compared to placebo (17.2%); p-values for treatment group comparisons relative to placebo were 0.0218 and 0.0024, respectively.
A total of 17 patients experienced a 90% reduction in target joint pain from baseline within 24 hours of starting treatment; 6 patients were randomized to Standard-dose colchicine (11.5%), 9 patients to Low-dose colchicine (12.2%), and 2 patients to placebo (3.4%). The median time for near complete pain relief was 48.0 hours for the Standard-dose group and 64.0 hours for the Low-dose colchicine group; too few placebo patients experienced a 90% reduction to calculate a median time. As with the 50% reduction threshold, the survival curves for the two colchicine treatment groups, calculated using Kaplan-Meier methods, are statistically significantly different from placebo (p = 0.0308) for the Standard-dose group and p = 0.04078) for the Low-dose group); the two colchicine treatment groups do not differ from one another (p = 0.0635).

Safety Results:

Please refer to clinical review for detailed assessment of safety. Briefly, A total of 147 treatment-emergent adverse events (TEAEs) were reported by the Investigators: 85 TEAEs by 40 of 52 patients in the Standard-dose colchicine group (76.9%), 34 TEAEs by 27 of 74 patients in the Low-dose colchicine group (36.5%), and 27 TEAEs by 16 of 59 patients in the placebo group (27.1%). There were approximately twice as many patients randomized to the Standard-dose colchicine group with TEAEs as compared to either the

Low-dose colchicine group or placebo whereas the incidences in the Low-dose colchicine group and placebo were similar. Most events were mild to moderate in intensity, with all but one of the severe events occurring in the Standard-dose colchicine group. There were no treatment-emergent SAEs or discontinuations due to adverse events.
Overall, adverse events related to the gastrointestinal tract were the most commonly reported events and included diarrhea and nausea in both colchicine treatment groups; vomiting occurred only in the Standard-dose colchicine group (17.3%). See question based review for tables.

4.2.9 NDA Filing Memo:

Office of Clinical Pharmacology ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Number	**22-352**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Colchicine Oral Tablets**
Medical Division	**DAARP**	**Drug Class**	**Anti-Inflammatory Agent**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Treatment of Familial Mediterranean Fever**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Tablet**
		Dosing Regimen	**0.6 mg – 2.4 mg**
Date of Submission	**6/20/2008**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Mutual Pharmaceutical Company, Inc.**
PDUFA Due Date		**Priority Classification**	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods		[redacted]	[redacted]	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X			
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3	3	
multiple dose:	X	2	2	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	8	8	DDI studies with CYP3A4 inhibitors and P-gp inhibitor
In-vivo effects of primary drug:	X	1	1	Oral contraceptive study
In-vitro:	X	2	2	CYP induction studies
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	2	2	Publications
hepatic impairment:	X	2	2	Publications
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other Clin Pharm Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**21**	**17**	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**None**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is the dosage adjustment appropriate in situations of drug interactions?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		