

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-301**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

<i>NDA</i>	22-301	<i>Submission Date(s)</i>	December 21, 2007 June 8, 2008 June 13, 2008 July 25, 2008
<i>Brand Name</i>	TRADE NAME (to-be-determined)		
<i>Generic Name</i>	Mesalamine		
<i>PDUFA goal date</i>	October 31, 2008		
<i>Reviewer</i>	Insook Kim, Ph.D.		
<i>Team Leader</i>	Sue-Chih Lee, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology III		
<i>OND Division</i>	Division of Gastroenterology Products and In-Born Errors of Metabolism		
<i>Sponsor</i>	Salix Pharmaceuticals, Inc.		
<i>Relevant IND(s)</i>	IND 62,113		
<i>Submission Type; Code</i>	Original	505(b)(2)	
<i>Formulation; Strengths; Regimen</i>	<ul style="list-style-type: none"> <li>• Oral capsule dosage form contains 0.375 g of mesalamine (5-aminosalicylic acid, 5-ASA)</li> <li>• Four TRADE NAME capsules once daily (1.5 g/day) with or without food</li> </ul>		
<i>Indication</i>	Maintenance of remission of ulcerative colitis in patients 18 years of age and older		

*Optional Intra-divisional briefing was held on September 29, 2008 in presence of Dr. Dennis Bashaw and Dr. Hae-Young Ahn.*

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## **1 Executive Summary**

### **1.1 Recommendations**

The Division of Clinical Pharmacology 3 has reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 22-301 and found it acceptable from clinical pharmacology standpoint provided a mutual agreement regarding the label language can be reached between the sponsor and the Agency.

### **1.2 Phase IV Commitments**

None.

### **1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings**

#### **Overview of Clinical Pharmacology and Biopharmaceutics program**

In support of NDA 22-301, submitted were final study reports of 11 phase 1/2 clinical trials, three phase 3 trials (MPPK 3003, MPPK 3004, MPPK3005) and one in vitro study for drug interaction. Of 11 submitted studies, three of them were most relevant: a relative BA study evaluating mesalamine granules BID and QD and Asacol BID (MPPK 1001), a food effect study (MPPK 1002) and single dose and multiple dose PK study (MPPK1003). All other studies were supportive and conducted using different formulations from the to-be-marketed formulation. Most of the supportive studies were relative BA or food effect study for formulations in development and one PK study were conducted in pediatric patients with inflammatory bowel disease.

In the clinical pharmacology and biopharmaceutics program, the sponsor used mesalamine granules (MG) in different dosage forms, in sachet (sMG) or in capsules (eMG; TRADE NAME). The to-be-marketed product is a capsule containing mesalamine granules which was used in phase 3 clinical trials (MPPK 3003, MPPK 3004, and MPPK3005) and one phase 1 PK study (MPPK1003). The food effect and relative BA studies (MPPK1001 and MPPK1002) were conducted using mesalamine granules (of the same formulation as that in capsule) in sachet. These two products were equivalent based on an in vitro comparative dissolution study (please, also see CMC review by Dr. Gene W. Holbert).

Other than sMG or eMG, several supportive studies including one 12 month phase 3 trial were conducted using FMG (Dr.Falk mesalamine granules in sachet). The FMG was different in formulation from MG and manufactured in Europe while MG was manufactured in the US. The difference in manufacturing site for modified release products is considered the level 3 change in manufacturing site and normally requires a BE study for adequate bridging. Because two products were not compared in an in vivo BE study, we do not consider that two products were sufficiently bridged. Therefore, the studies conducted using FMG product are considered only supportive. The supportive studies pertinent to clinical pharmacology and biopharmaceutics were not reviewed for this NDA. However, one study BIO/SAG-16 conducted with radiolabeled FMG was reviewed because of a labeling claim based on the study.

#### **Pharmacokinetic characteristics**

The pharmacokinetics of mesalamine (5-ASA) and its metabolite, N-Ac-5-ASA, were studied after single dose and multiple oral doses of 1.5 g TRADE NAME (QD, 4 x 375 mg capsules) in 24 healthy

subjects under fasting condition. After a single dose administration of 1.5 g TRADENAME, the peak plasma concentrations of mesalamine were observed at about 4 hours post dose and the half-life was about 9 hours. The mean pharmacokinetic parameters of mesalamine and N-Ac-5-ASA are in Table 1.

**Table 1: Mean ( $\pm$ SD) plasma pharmacokinetic parameters of mesalamine (5-ASA) and N-Ac-5-ASA after a single dose and multiple dose administration of 1.5 g TRADE NAME in Healthy Volunteers**

	Single Dose (%CV) (n=24)	Multiple Doses <sup>b</sup> (%CV) (n=24)
<b>Mesalamine (5-ASA)</b>		
AUC <sub>0-24</sub> ( $\mu$ g*h/mL)	10.96 $\pm$ 4.52 (41.3)	16.90 $\pm$ 5.70 (33.7)
AUC <sub>0-inf</sub> ( $\mu$ g*h/mL)	13.57 $\pm$ 5.44 (39.8)	26.60 $\pm$ 14.82 (55.7)
C <sub>max</sub> ( $\mu$ g/mL)	2.13 $\pm$ 1.10 (51.4)	2.72 $\pm$ 1.14 (41.8)
T <sub>max</sub> (h) <sup>a</sup>	4 (2, 16)	4 (2, 8)
t <sub>1/2</sub> (h)	9.2 $\pm$ 7.1 (59.3)	10.1 $\pm$ 8.1 (68.5)
<b>N-Ac-5-ASA</b>		
AUC <sub>0-24</sub> ( $\mu$ g*h/mL)	25.55 $\pm$ 5.52 (21.6)	37.00 $\pm$ 8.90 (24)
AUC <sub>0-inf</sub> ( $\mu$ g*h/mL)	50.62 $\pm$ 23.06 (45.6)	86.06 $\pm$ 52.48 (61)
C <sub>max</sub> ( $\mu$ g/mL)	2.78 $\pm$ 0.85 (30.5)	3.40 $\pm$ 0.90 (26.3)
T <sub>max</sub> (h) <sup>a</sup>	4 (4, 12)	5 (2, 8)
t <sub>1/2</sub> (h)	12.4 $\pm$ 10.8 (11.6)	13.6 $\pm$ 10.2 (77.8)

<sup>a</sup>: median (min, max)

<sup>b</sup>: 7 days of treatment: Steady-state was achieved on Day 6

In the multiple-dose period, each subject received TRADENAME 1.5 g every 24 hours (QD) for 7 consecutive days. Steady state was achieved on day 6 and mean C<sub>max</sub> was about 22-25% higher for 5-ASA and N-Ac-5-ASA at steady state compared to that after a single dose administration. At steady state, moderate increases (1.5-fold and 1.7-fold) in systemic exposure (AUC<sub>0-24</sub>) to 5-ASA (47.5% CV) and N-Ac-5-ASA (27.4% CV) were observed when compared with a single-dose of TRADE NAME.

In a separate study, after a single-dose of 1.6 g mesalamine granule in sachet (SMG, 2X800mg) under fasting condition about 31.6  $\pm$  10.6% (mean  $\pm$  SD) of the administered dose was systemically absorbed based on the mean combined cumulative urinary excretion of mesalamine and N-Ac-5-ASA. The metabolite, N-Ac-5-ASA was predominant in urine consisting of 30 % of administered dose and approximately 2% was excreted unchanged in urine.

**Food effect**

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Effect of a high fat meal on absorption of mesalamine was studied in 30 healthy subjects receiving 1.6 g of MG in sachet (2 x 0.8 g) (Study MPPK1002). Under fed condition,  $t_{max}$  for mesalamine and N-Ac-5-ASA was prolonged by 4 and 2 hours, respectively. There was a moderate increase in absorption of mesalamine (11-16% increase in AUC) while  $C_{max}$  of mesalamine was similar with or without food. Nevertheless, overall absorption of administered dose was not affected by a high fat meal, based on the combined cumulative urinary excretion of mesalamine and N-Ac-5-ASA. Therefore, sMG can be taken without regard to food. Although the food effect study was conducted using sMG, the food effect study results can be extended to the TRADENAME (eMG) since the release-controlling portion of the products remains the same and the equivalence between sMG and TRADENAME was demonstrated. In addition, the phase 3 trials conducted with eMG, the drug was taken without regard to food intake. Therefore TRADENAME can be taken without regard to food intake.

**Mesalamine (5-ASA) and N-Ac-5-ASA did not inhibit the major CYP enzymes evaluated.**

The final study report of an in vitro drug interaction study (XT0055039) was submitted previously as NDA 20-610, SLR017 dated May 3, 2007 and reviewed by Dr. Abimbola Adelowale of the Division of Clinical Pharmacology 3. The concentration range studied in the in vitro study e.g. 0.1-100  $\mu$ M sufficiently covered the mean  $C_{max}$  for 5-ASA (17  $\mu$ M) and N-Ac-5-ASA (35  $\mu$ M) at steady state with TRADE NAME. There was no significant inhibition of CYP enzymes (Cyp1A2, Cyp2C9, Cyp2C19, Cyp2D6, and Cyp3A4/5) by 5-ASA and its major metabolite N-Ac-5-ASA. Therefore, the study report XT0055039 was not further reviewed this time.

**Relative Bioavailability**

The bioavailability of 5-AS and N-Ac-5-ASA after 4 day administration of sMG by dosage regimen of 0.8 g BID was compared to the dosage regimen of 1.6 g QD. It was also compared to AUC and  $C_{max}$  after administration of Asacol 0.8 g (2 x 400 mg) BID for 4 days in 30 healthy subjects (Study MPPK1001).

The systemic exposure to 5-ASA and N-Ac-5-ASA was higher after sMG 0.8 g BID and 1.6 g QD than Asacol 0.8 g BID. Higher variability (72-128% CV) was observed in PK parameters after Asacol treatment compared to after the sMG treatments (33-55%). The median  $t_{max}$  of 5-ASA and N-Ac-5-ASA after sMG QD was about 3 hours and it was about 16 hours for sMG BID and Asacol BID indicating a carryover effect from the first dose. The mean AUC and  $C_{max}$  of 5-ASA and N-Ac-5-ASA after sMG 0.8g BID and sMG 1.6 QD treatments were higher than those for Asacol 0.8 g BID treatment. The sponsor concluded that PK parameters for Asacol treatment were unreliable because intact or partially intact tablets were recovered from stool samples of 50% of subjects after Asacol treatment. Because the safety and efficacy of 1.5g eMG once daily dosing were evaluated in two placebo-controlled phase 3 clinical trials and one open-label long-term safety trial, the comparison of BA of TRADENAME to Asacol 400 mg tablet is not considered critical to this NDA.

The ratio of mean  $C_{max}$  after sMG 0.8 g BID to after sMG 1.6g QD was 153% for 5-ASA and 118% for N-Ac-5-ASA while the AUC was similar between two treatments. However, attainment of the steady-state is uncertain as sMG was administered once daily or twice daily for 4 days only.

**Table 2\*. Mean (±SD) PK parameters after administration of sMG and ASACOL for 4 days.**

	Treatment BID Asacol 800 mg BID N=28	Treatment B sMG 800 mg BID n=28	Treatment C sMG 1600 mg QD n=28	C/B Ratio (90% CI)
Cmax (µg/mL)				
5-ASA	1.06 ± 1.37	1.82 ± 0.71	3.04 ± 1.67	153 (113, 208)
N-Ac-5-ASA	2.34 ± 1.80	3.61 ± 1.23	4.50 ± 1.82	118 (98, 143)
AUC (µg*h/mL)				
5-ASA	8.43 ± 7.50	14.84 ± 5.50	14.76 ± 6.49	96 (76, 121)
N-Ac-5-ASA	30.72 ± 22.25	46.37 ± 15.43	45.85 ± 19.71	93 (78, 112)
Tmax (h)				
5-ASA	16 (0, 24)	16 (0, 24)	3 (2, 16)	
N-Ac-5-ASA	16 (0, 24)	16 (0, 24)	3 (2, 24)	

\*Modified from the sponsor's table to correct units for Cmax and AUC

**Dose selection rationale for phase 3 program**

The sponsor selected the daily dose of 1.5g for phase 3 trial because the daily dose 1.5 g is close to the approved doses for other mesalamine products for maintenance of remission of Ulcerative colitis e.g. 1.6 g daily dose (0.8 g, BID) for Asacol 400 mg. There was no phase 2 dose-ranging trial conducted. After 4 days of treatment, Cmax was higher for the regimen 1.6 g sMG QD than 0.8g sMG BID regimen while AUC was similar. Because mesalamine is believed to act locally, the higher systemic exposure to 5-ASA and N-Ac-5-ASA is generally not favored from a safety standpoint. Nonetheless, because safety and efficacy of the once daily regimen of 1.5 g mesalamine was evaluated in two placebo-controlled pivotal phase 3 trials, the acceptability of the safety profiles of the proposed dosing regimen will be based on the phase 3 results.

**2 Question-Based Review**

**2.1 General Attributes of the drug**

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

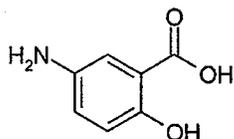
NDA 22-301 was submitted via a 505(b)(2) pathway. The clinical safety and efficacy of the TRADENAME was supported by three phase 3 trials conducted with TRADENAME. The sponsor intended to reference non-clinical findings from the reference product, Asacol 400 mg.

The study report MPPK1003 was submitted at month 5 into the review cycle (June 13, 2008) as an amendment to provide adequate single and multiple dose PK information for TRADE NAME. The deficiency of the study MPPK1003 at the NDA submission was not considered a filing issue. The division agreed to review the study at the filing because the study appeared to be designed better to provide adequate PK information than other studies with weakness in study design e.g. insufficient PK sampling duration (MPPK1002) and uncertainty of attainment of steady-state (MPPK1001).

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2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Each capsule contains 0.375 g of mesalamine USP (5-aminosalicylic acid, 5-ASA), an anti-inflammatory drug. The formulation is presented in Table 3. The structural formula of mesalamine is:



Molecular Weight: 153.135  
Molecular Formula: C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>

**Formulation**

Each eMG capsule is produced by encapsulating, in a hard gelatin size "00" capsule shell, a quantity of mesalamine granules to provide 375 mg of active ingredient (mesalamine) per capsule.

b(4)

The mesalamine granules (MG) in TRADE NAME were modified from the original mesalamine granule formulation (FMG) developed by Dr. Falk Pharma in Germany (Table 3). The sponsor submitted the final reports of studies SAG-16/BIO, SAG-4/BIO, SAG-25/BIO and SAG-19/BIO conducted using FMG. The studies were conducted mostly by different dosage regimens from the except for SAG-25/BIO. Two products were comparable in a comparative in vitro dissolution test and met  $f_2 \geq 50$  criteria (Please, see CMC review by Dr. Gene W. Holbert). However, because of level 3 manufacturing site change for modified release products, an in vivo BE study was required. Therefore, studies conducted using FMG product are considered only supportive.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The mechanism of action of 5-ASA is unknown, but appears to be local to the intestinal mucosa rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that 5-ASA diminishes inflammation by blocking production of arachidonic acid metabolites.

TRADENAME is proposed for the indication of maintenance of remission of ulcerative colitis in patients 18 years of age and older.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

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Each TRADE NAME capsule contains 0.375 g of delayed-release granules for oral administration. The proposed dosage regimen is to take four capsules of TRADENAME (1.5g, 4X0.375g) once daily with or without food.

The single-dose and multiple dose PK study, Study MPPK1003 was conducted using TRADE NAME (eMG) under consistent condition as the proposed dosage regimen. On the other hand, studies MPPK1001 and MPPK 1002 were conducted using mesalamine granules in sachet (sMG) at 1.6 g (2X0.8g). The same mesalamine granules were used for sMG and TRADE NAME and the release of mesalamine from two products were comparable meeting  $f_2 \geq 50$  criteria.

## 2.2 General Clinical Pharmacology

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

**Reviewer's comments:** The bioanalytical assay method used for plasma concentrations of mesalamine and N-Ac-5-ASA in MPPK1001 and MPPK1002 was different from the method used in MPPK1003.

**Study MPPK1001** was a randomized, single center, open-label, crossover trial in 30 healthy subjects that compared the pharmacokinetics, urinary excretion and fecal excretion of mesalamine and N-Ac-5-ASA after oral administration of mesalamine granules (0.8 g BID or 1.6g (2x800mg) QD for 4 days) to that from Asacol (2x 800 mg, QD) tablets.

**Study MPPK1002** was an open-label, randomized, balanced, two-treatment, two-period, two-sequence, cross-over study of a single dose of mesalamine granules (1.6 g, 2 x 800 mg) administered orally following an overnight fast and following ingestion of a high-fat meal (breakfast). Plasma, urine, and feces were collected to assess the effect of a high-fat meal on the pharmacokinetics of mesalamine and N-Ac-5-ASA.

**Study MPPK1003** was open-label, single- and multiple-dose study of the relative bioavailability and pharmacokinetics of eMG in healthy volunteers. A total of 24 subjects were enrolled into this study. Each subject received a single dose of mesalamine administered as 1.5 g eMG (4 x 375 mg) followed by 96 hours of blood sampling for pharmacokinetic analyses. After a 7-day washout period, each subject received multiple doses of mesalamine, administered as 1.5 g eMG (4 x 375 mg) every 24 hours (QD) for 7 consecutive days.

**Study SAG-16/BIO** was a randomized, observer-blind, crossover, single-dose, single-center pharmacoscintigraphy study in 14 healthy male subjects that evaluated the transport, site of release, and absorption of mesalamine from mesalamine granules and the tablet formulation. In this study, healthy male volunteers ingested a single 500-mg mesalamine granules dose containing 2 mg <sup>152</sup>Sm203 (mean 1.4 MBq per dose). (Note: The samarium oxide is not absorbed by the gastrointestinal tract.) Scintigraphy was used to monitor transit and release of drug in the GI tract.

**Studies MPUC3003 and MPUC3004** were similarly designed Phase 3, randomized, double-blind, placebo-controlled, multicenter studies to compare the once daily (QD) dosing of eMG 1.5 g versus placebo after 6 months of treatment in the maintenance of remission of ulcerative colitis (UC), and the safety of eMG at this dose regimen and duration.



2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints and how are they measured in clinical studies?

For studies MPUC3003 and MPUC3004, the primary efficacy endpoint was the proportion of subjects who remained relapse-free at Month 6/EOS. Relapse (or treatment failure) was defined as a rectal bleeding score of 1 or more and a mucosal appearance score of 2 or more as described in the revised Sutherland Disease Activity Index (DAI) in Table 4.

**Table 4. Summary of Revised Sutherland Disease Activity Index for Studies MPUC3003 and MPUC3004**

No.	Indices	Scale Ratings
1	Stool frequency	0 = Normal
		1 = 1 to 2 stools/day more than normal
		2 = 3 to 4 stools/day more than normal
		3 = >4 stools/day more than normal
2	Rectal bleeding	0 = None
		1 = Streaks of blood
		2 = Obvious blood
		3 = Mostly blood
3	Mucosal appearance <sup>a</sup>	0 = Intact mucosa with preserved or distorted vessels
		1 = Erythema, decreased vascular pattern, granularity, no mucosal hemorrhage
		2 = Mucosal hemorrhage without blood in the lumen or gross ulceration, marked erythema, absent vascular pattern, small ulcers
		3 = Blood in lumen, gross ulceration, exudates
4	Physician's rating of disease activity	0 = Normal
		1 = Mild
		2 = Moderate
		3 = Severe
<b>MAXIMUM SCORE</b>		<b>12</b>

Source: Sutherland, et al., 1987

<sup>a</sup> For studies MPUC3003 and MPUC3004, the Sutherland DAI (Sutherland et al. 1987) was revised to remove the term "mild friability" from the mucosal appearance score of 1 and the term "moderate friability" from the mucosal appearance score of 2.

2.2.3 Are the active moieties in the plasma, urine and feces appropriately identified and measured to assess pharmacokinetic parameters?

Mesalamine and a major metabolite, N-Ac-5-ASA were measured in plasma, urine and feces. Because mesalamine is thought to act locally, the systemic exposure of mesalamine and N-Ac-5-ASA is considered most relevant to the safety of the treatment. The measurement of N-Ac-5-ASA has been conducted since AUC of N-Ac-5-ASA was greater than mesalamine e.g. 2 folds higher than mesalamine after multiple doses. In addition, as the absorbed dose is primarily excreted as N-Ac-5-ASA in urine, N-Ac-5-ASA has been considered potentially relevant to kidney toxicity of mesalamine.

The interpretation of fecal samples was complicated due to incapability of differentiate between released and unreleased mesalamine and formation of N-Ac-5-ASA from mesalamine in feces during sample process was not evaluated.

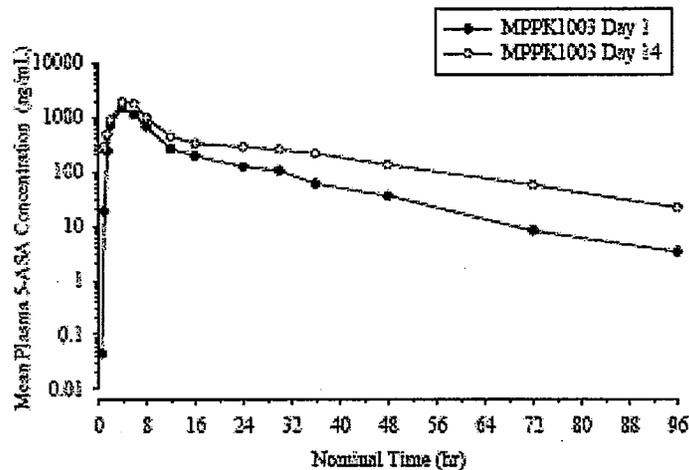
There was no phase 2 dose-ranging study conducted and the systemic exposure of mesalamine and its major metabolite N-Ac-5-ASA was not assessed in patients.

### 2.2.5 Pharmacokinetic Characteristics

The pharmacokinetics of mesalamine (5-ASA) and its metabolite, N-Ac-5-ASA, were studied after a single dose and multiple oral doses of 1.5 g TRADE NAME (QD, 4 x 375 mg capsules) in a crossover study in healthy subjects under fasting. After a single dose administration of 1.5 g TRADENAME, the peak plasma concentrations of mesalamine were observed at about 4 hours post dose and the half-life was about 9 hours (Figure 2). The mean pharmacokinetic parameters of mesalamine and N-Ac-5-ASA are in Table 5.

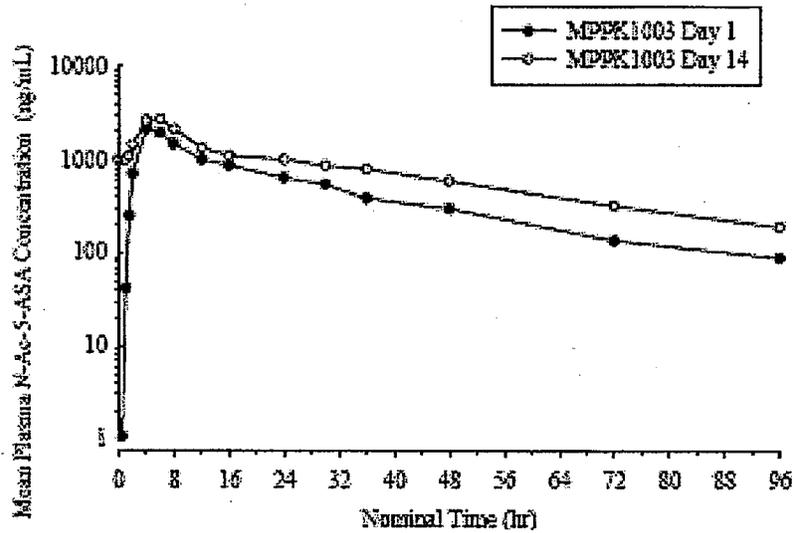
**Figure 2. Mean ( $\pm$ SD) Concentration-Time Profiles of 5-ASA and N-Ac-5-ASA after single dose and multiple doses of 1.5 g TRADE NAME**

(A) 5-ASA



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(B) N-Ac-5-ASA



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Table 5: Mean ( $\pm$ SD) plasma pharmacokinetic parameters of mesalamine (5-ASA) and N-Ac-5-ASA after a single dose and multiple dose administration of 1.5 g TADE NAME in Healthy Volunteers

Mesalamine (5-ASA)	Single Dose (CV%)	Multiple Doses <sup>b</sup> (CV%)
Number of subjects	24	24
AUC <sub>0-24</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	10.96 $\pm$ 4.52 (41.3)	16.90 $\pm$ 5.70 (33.7)
AUC <sub>0-inf</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	13.57 $\pm$ 5.44 (39.8)	26.60 $\pm$ 14.82 (55.7)
C <sub>max</sub> ( $\mu\text{g}/\text{mL}$ )	2.13 $\pm$ 1.10 (51.4)	2.72 $\pm$ 1.14 (41.8)
T <sub>max</sub> (h) <sup>a</sup>	4 (2, 16)	4 (2, 8)
t <sub>1/2</sub> (h)	9.2 $\pm$ 7.1 (59.3)	10.1 $\pm$ 8.1 (68.5)
<b>N-Ac-5-ASA</b>		
AUC <sub>0-24</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	25.55 $\pm$ 5.52 (21.6)	37.00 $\pm$ 8.90 (24)
AUC <sub>0-inf</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	50.62 $\pm$ 23.06 (45.6)	86.06 $\pm$ 52.48 (61)
C <sub>max</sub> ( $\mu\text{g}/\text{mL}$ )	2.78 $\pm$ 0.85 (30.5)	3.40 $\pm$ 0.90 (26.3)
T <sub>max</sub> (h) <sup>a</sup>	4 (4, 12)	5 (2, 8)
t <sub>1/2</sub> (h)	12.4 $\pm$ 10.8 (11.6)	13.6 $\pm$ 10.2 (77.8)

<sup>a</sup>: median (min, max)

<sup>b</sup>: 7 days of treatment: Steady-state was achieved on Day 6

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In the multiple-dose period, each subject received 1.5 g TRADENAME every 24 hours (QD) for 7 consecutive days. Steady state was achieved on day 6 and mean C<sub>max</sub> was about 22-25% higher for 5-ASA and N-Ac-5-ASA at steady state compared to that after a single dose administration. At steady state, moderate increases (1.5-fold and 1.7-fold) in systemic exposure (AUC<sub>0-24</sub>) to 5-ASA and N-Ac-5-ASA were observed when compared with a single-dose of TRADE NAME. The ratio of AUC<sub>24</sub> after multiple doses to AUC<sub>inf</sub> after a single-dose was 1.23 for 5-ASA and 0.78 for N-Ac-5-ASA. While modest variability (40-45 % CV) was associated with AUC<sub>inf</sub> of 5-ASA and N-Ac-5-ASA, it was suggested that it may be a result of slightly lower rate of metabolism to N-Ac-5-ASA following repeated oral administration of TRADENAME.

After a single-dose of 1.6 g mesalamine granule administration (2X800mg) under fasting condition about 31.6 ±10.6% of the administered dose was systemically absorbed based on the combined cumulative urinary excretion of mesalamine and N-Ac-5-ASA collected over 96 hours post-dose (Table 6). Of the administered dose, approximately 2% was excreted unchanged in urine and 29% was excreted as N-Ac-5-ASA.

**Table 6. Percentage of the administered dose (1.6g expressed as mmols of 5-ASA) for cumulative urinary excretion**

	Fasted (N=30) % administered dose	Fed (n=30) % administered dose
5-ASA	1.95± 1.72 (%CV 88.4)	2.47 ± 2.16 (%CV 87.6)
N-Ac-5-ASA	29.62 ± 9.57 (%CV 32.3)	29.48 ± 11.65 (%CV 39.5)
5-ASA plus N-Ac-5-ASA	31.56± 10.55 (%CV 33.4)	31.95± 13.00 (%CV 40.6)

In study BIO/SAC-16, the FMG was compared with another mesalamine tablet for intestinal transit and the extent of absorption while in a target region of intestine e.g. ileo-caecal region based on scintigraphic imaging and partial AUC. The sponsor proposes a labeling claim of "Approximately 80% of an administered oral dose of mesalamine is estimated to be available in the colon, sigmoid, and rectum when dosed as mesalamine granules."

The study was qualitative in nature to compare two products. In addition, the quantitative estimation of local availability of mesalamine in a specific region is limited due to incapability of differentiation of released mesalamine and unreleased mesalamine from the granules or disintegrated versus intact mesalamine granules by scintigraphic analysis. In addition, the absorption while in the region may not be paralleled with the availability of released mesalamine in the target region of intestine due to a limited absorption at the target region of intestine. Therefore, the data provided by this study is considered insufficient to support the quantitative estimation of local availability of administered mesalamine.

In addition, the FMG was manufactured in Europe while TRADENAME was manufactured in the US. The sponsor conducted an in vitro comparative dissolution study and the comparison met the f<sub>2</sub>>50 criteria for equivalence. However, because this manufacturing site change is considered level 3 change, an in vivo BE study is normally required for adequate and sufficient bridging. Therefore, it is unknown how relevant this information to TRADENAME.

#### 2.4 Extrinsic Factors

**2.4.1 Does mesalamine (5-ASA) and N-Ac-5-ASA have in vivo drug interaction potential?**

The in-vitro enzyme inhibition study (Study XT005039) was conducted to evaluate inhibitory effects of 5-ASA and N-Ac-5-ASA, on human cytochrome P450 enzymes. The study report was previously submitted as supplement to NDA 20-610 (SLR 017 dated May 03, 2007) and reviewed by Dr. Abimbola Adebowale of Division of Clinical Pharmacology. The study results are reflected in the current approved Colazal® label. As such the detailed review is referred to the previous review. Below is a brief summary from the original review of Study XT005039 by Dr. Adebowale.

Briefly, to evaluate 5-ASA and N-Ac-5-ASA as direct inhibitors of CYP activity, human liver microsomes (at < 0.1 mg/mL) from a pool of sixteen individuals were incubated with marker substrates, at concentrations approximately equal to their apparent Km, in the presence or absence of 5-ASA, and N-Ac-5-ASA. The target concentrations ranged from 0.1 to 100 µM. In addition, 5-ASA, and N-Ac-5-ASA were evaluated for their ability to function as metabolism-dependent inhibitors at the same concentrations mentioned above, in which case they were pre-incubated with human liver microsomes (at < 0.1 mg/mL) and an NADPH-generating system for 30-minutes to allow for the generation of metabolites or intermediates that might inhibit CYP activity. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls.

Under the experimental conditions examined, there was no evidence of direct inhibition of CYP 1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (as measured by testosterone 6β-hydroxylation and midazolam 1' hydroxylation) by 5-ASA, and N-Ac-5-ASA, as the IC50 values for these enzymes were greater than the highest concentration examined (100 µM). In addition, 5-ASA, and N-Ac-5-ASA did not appear to be metabolism-dependent inhibitors of any of the CYP enzymes that were examined, as an increase in inhibition was not observed upon pre-incubation. The IC50 values for direct and metabolism-dependent inhibition were reported as > 100 µM for all CYP enzymes evaluated.

Below is excerpt from the section 7 drug interactions in the Colazal® label.

***“7 DRUG INTERACTIONS***

*In an in vitro study using human liver microsomes, balsalazide and its metabolites [5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), 4-aminobenzoyl-β-alanine (4-ABA) and N-acetyl-4-aminobenzoyl-β-alanine (N-Ac-4-ABA)] were not shown to inhibit the major CYP enzymes evaluated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5). Therefore, balsalazide and its metabolites are not expected to inhibit the metabolism of other drugs which are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. “*

**2.5 General Biopharmaceutics**

- 2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

**Food effect**

Effect of a high fat meal on absorption of mesalamine granules in sachet (sMG) was studied in 30 healthy subjects received 1.6 g of sMG (2 x 0.8 g). Under fed condition, t<sub>max</sub> for mesalamine and

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N-Ac-5-ASA was prolonged by 4 and 2 hours, respectively and a moderate increase in absorption of mesalamine was observed (16% increase in AUC<sub>last</sub>). But C<sub>max</sub> of mesalamine was similar with or without food. The mean half-lives of mesalamine were estimated to be 5.49 hours with food and 8.42 hours without food; while the mean N-Ac-5-ASA half-life were estimated 10.05 hours with food and 12.56 hours without food, respectively (Table 7, 8).

**Reviewer's comments:** PK sampling duration for 24 hours may have not been sufficient to capture the terminal phase for mesalamine and N-Ac-5-ASA especially under fed condition when the median time to peak plasma concentration was 8 hours. About 30% of individual plasma concentration profile had the last measurable concentration of 5-ASA was  $\geq$  4-folds of LLOQ (0.13  $\mu\text{mol/L}$ ) indicating plasma concentration measurement was not limited by bioanalytical sensitivity. Although the difference between AUC<sub>inf</sub> and AUC<sub>last</sub> for 5-ASA was mostly less than 20%, it is uncertain if AUC<sub>inf</sub> for 5-ASA is reliable because no test for goodness of regression for  $\lambda z$  calculation was provided. On the other hand the difference between AUC<sub>inf</sub> and AUC<sub>last</sub> for N-Ac-5-ASA was mostly greater than 20% suggesting that AUC<sub>inf</sub> for N-Ac-5-ASA may not be reliable.

With a high fat diet, the cumulative urinary excretion over 96 hour post-dose increase about 27% for mesalamine while it was not different for N-Ac-5-ASA compared to under fasting condition. Because the absorbed dose was predominantly excreted as N-Ac-5-ASA in urine, overall cumulative urinary excretion combined for mesalamine and N-Ac-5-ASA was similar under fasting and fed condition. As such overall absorption of administered dose was not affected by a high fat meal.

Although the food effect study was conducted using sMG, the food effect study results can be extended to the TRADE NAME (eMG) since the release-controlling mesalamine granules (MG) remain the same and the equivalence between MG in sachet and MG in capsule (TRADE NAME) was demonstrated in in vitro comparative dissolution study. In addition, the phase 3 trials conducted with eMG, the drug was taken without regard to food intake. Therefore TRADE NAME can be taken without regard to food intake.

**Table 7. Summary of PK parameters of 5-ASA and N-Ac-5-ASA under fasting and under fed condition with a high fat diet.**

	Treatment		Fed/Fasted		
	Fasted N=30	Fed N=30	P value <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>b</sup>
<b>C<sub>max</sub> (<math>\mu\text{mol/L}</math>)</b>					
5-ASA	16.74 $\pm$ 9.46	16.39 $\pm$ 8.30	0.692	104	87, 125
N-Ac-5-ASA	19.09 $\pm$ 9.49	18.59 $\pm$ 7.06	0.734	103	90, 117
<b>AUC<sub>0-last</sub> (<math>\mu\text{mol}\cdot\text{h/L}</math>)</b>					
5-ASA	77.80 $\pm$ 37.56	86.07 $\pm$ 36.20	0.087	116	101, 135
N-Ac-5-ASA	167.21 $\pm$ 68.15	165.08 $\pm$ 54.71	0.801	102	91, 114
<b>AUC<sub>0-inf</sub> (<math>\mu\text{mol}\cdot\text{h/L}</math>)</b>					
5-ASA	84.81 $\pm$ 39.78	89.96 $\pm$ 37.28	0.228	111	96, 128
N-Ac-5-ASA	230.32 $\pm$ 94.73	222.69 $\pm$ 120.83	0.501	95	84, 108
<b>T<sub>max</sub> (h)</b>					
5-ASA	4.00 (3.00, 8.00) <sup>c</sup>	8.00 (3.00, 20.00)	-	-	-
N-Ac-5-ASA	6.00 (2.00, 16.00)	8.00 (3.00, 24.00)	-	-	-

<sup>a</sup> P-values associated with treatment contrast from ANOVA Mixed Effects Model for log-transformed parameters. P-values for T<sub>max</sub> were calculated from the signed rank test.

<sup>b</sup> Calculated from geometric means of log-transformed data.

<sup>c</sup> Median (range).

**Table 8. Cumulative urinary excretion (0-96 h) of 5-ASA and N-Ac-5-ASA with and without a high fat meal**

	Treatment		Fed/Fasted		
	Fasted N=30 (mmol)	Fed N=30 (mmol)	P value <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>b</sup>
5-ASA	0.20 ± 0.18	0.26 ± 0.23	0.165	127	95, 159
N-Ac-5ASA	3.10 ± 1.00	3.08 ± 1.22	0.952	100	87, 112
5-ASA plus N-Ac-5-ASA	3.30 ± 1.10	3.34 ± 1.36	0.879	101	88, 115

<sup>a</sup> P-values associated with treatment contrast from ANOVA Mixed Effects Model for untransformed parameters.

<sup>b</sup> Based on mixed models fit to untransformed data.

## 2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma/urine/feces in the clinical pharmacology and biopharmaceutics studies?

### Bioanalytical methods

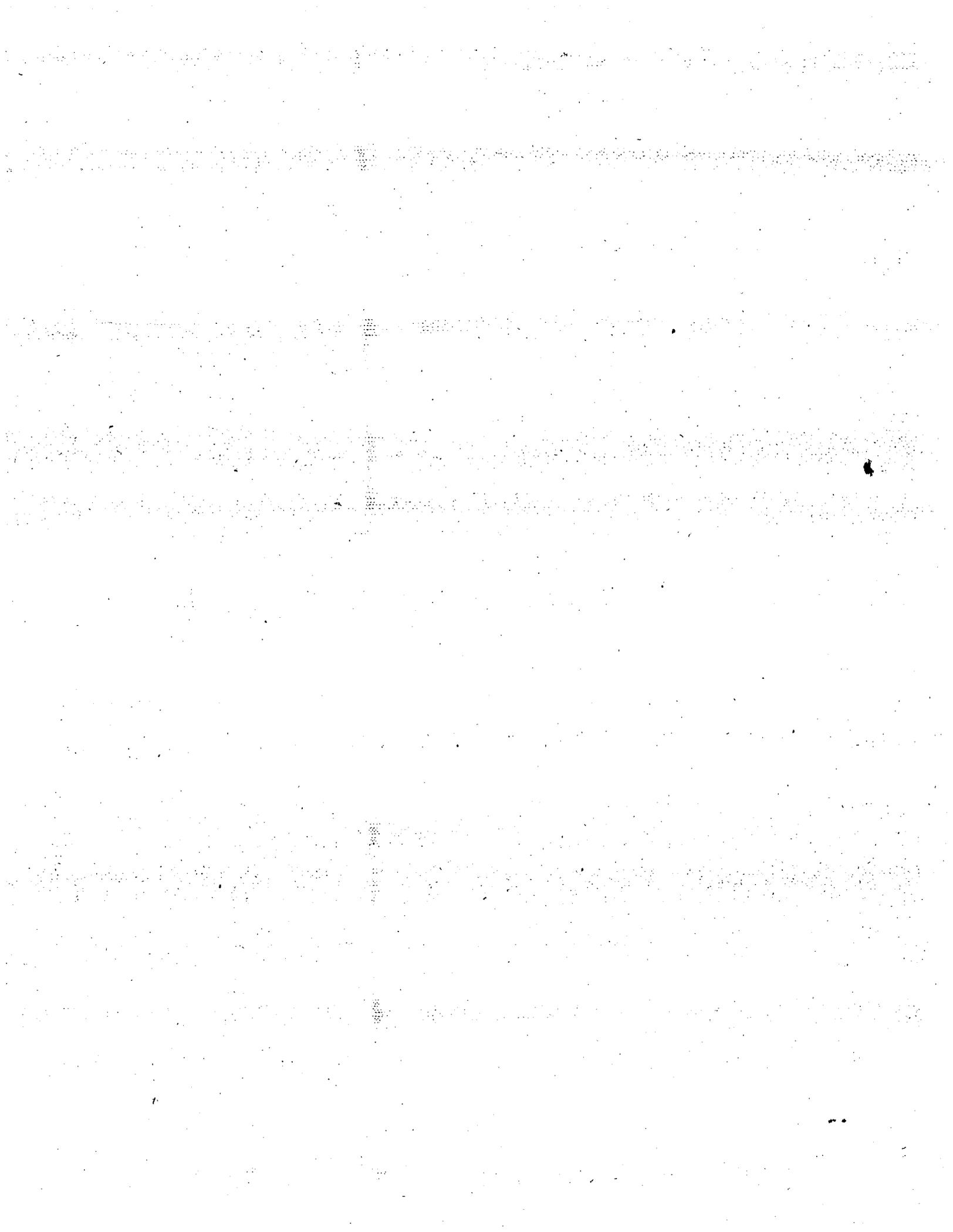
Two different bioanalytical methods were employed to measure the parent drug, 5-ASA (mesalamine) and a major metabolite N-Ac-5-ASA. Two methods were adequately validated with acceptable accuracy, precision and selectivity. The calibration ranges for 5-ASA and N-Ac-5-ASA were different between two methods and assay sensitivity was improved in the method used for study MPPK1003.

A method titled "An LC/MS/MS method for the determination of 5-aminosalicylic acid and N-acetyl-5-aminosalicylic acid" was used for 5-ASA and N-Ac-5-ASA analysis in three biological matrix, sodium heparin plasma (validation report No. 052-03002V), in total or soluble human fecal extract samples (validation report No. 052-04001V), and in urine (validation report No. 052-03003V) in studies MPPK1001 and MPPK1002.

b(4)

Another method, titled "Validation of a method for the determination of N-Acetyl-4-aminobenzoyl-b-alanine, 4-aminobenzoyl-b-alanine, N-acetyl-mesalamine and mesalamine in human plasma using high-performance liquid chromatography with mass spectrometric (MS/MS) detection"(validation report MC06B-0186) was used for sample analysis in study MPPK1003. The bioanalytical method was developed for balsalazide and its metabolites including 5-ASA and N-Ac-5-ASA analysis.

b(4)



2.6.2 Which metabolites have been selected for analysis and why?

A major metabolite N-acetyl 5-ASA identified in plasma, urine and feces was chosen for analysis. The systemic exposure to N-Ac-5-ASA is considered important for safety of mesalamine products and generally required along with the systemic exposure to mesalamine.

2.6.3. What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

**Table 9. Bioanalytical Method Ranges and LLOQ Values for Mesalamine and N-Ac-5-ASA in Plasma, Urine and Feces for studies MPPK1002 and MPPK1001**

Compound	Matrix	Range (ng/mL)	Inter-assay Precision at LLOQ (%)	Inter-assay Accuracy at LLOQ (%)
5-ASA	Plasma	20-1000	7.16	108
	Urine	20-4000	4.34	99.5
	Feces	2000-400000	7.57	91.1
N-Ac-5-ASA	Plasma	20-1000	6.72	97.5
	Urine	100-20000	6.36	91.6
	Feces	1000-200000	13.6	92.7

**Table 10. Bioanalytical Method Ranges and LLOQ Values for Mesalamine and N-Ac-5-ASA in Plasma for study MPPK1003**

	Concentration	5-ASA		N-Ac-5-ASA		
	QC	precision	accuracy	QC	precision	accuracy
Interday	3 ng/ml	5.3 %	99 %	15 ng/ml	2.3 %	100 %
	30 ng/ml	2.4 %	98.7 %	150 ng/ml	2.6%	99.3%
	320 ng/ml	2.4 %	97.9%	1600 ng/ml	2.0%	99.3 %
Intraday	Overall range	1.5-7.2%	96.3-97.7%	Overall range	1.5-3.3%	97.1-99.1%
LLOQ	1 ng/ml	7.9 %	10 %	5 ng/ml	4.6 %	5.1 %
Standard curve range		1-400 ng/ml		5-2000ng/ml		

The above results indicate that the performance of the assay methods is acceptable.

### **3. Detailed Labeling Recommendations**

Reviewer's major labeling revisions are:

- Inclusion of multiple dose PK results.
- PK results in a tabulated format.
- Deletion of fecal excretion results due to the incapability of assay to distinguish released from non-released mesalamine in stool samples which makes the interpretation of the data inconclusive.
- Inclusion of in vitro drug-interaction study results under Pharmacokinetic section.

10 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

4.2. Individual Study Reviews

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Module 5.2. Tabular Listing of All Clinical Studies

Table 5.2-1. Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Healthy Subjects/ Patients Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy	MPUC3003	Module 5.3.5.1.1, Study Report MPUC3003, p. 1	Efficacy and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel group	eMG 1.5 g; QD; Oral	eMG: 209 Placebo: 96	Mild to Moderate UC, Active or in Remission	6 months	Complete; Full
Efficacy	MPUC3004	Module 5.3.5.1.2, Study Report MPUC3004, p. 1	Efficacy and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel group	eMG 1.5 g; QD; Oral	eMG: 164 Placebo: 93	Mild to Moderate UC, Active or in Remission	6 months	Complete; Full
Safety	MPUC3005*	Module 5.3.5.2.1, Interim Study Report MPUC3005, p. 1	Long-term safety and tolerability	Multicenter, open-label	eMG 1.5 g; QD; Oral	eMG: 365 *	Mild to Moderate UC, Active or in Remission	24 months, regulatory approval, or Sponsor or Sponsor termination	Ongoing; Interim
Efficacy	SAG-2/UCA	Module 5.3.5.1.1, Study Report SAG-2/UCA, p. 1	Efficacy and safety	Randomized, double-blind, multicentre, multinational, parallel group	FMG 0.5 g; TID, 1.0 g; TID, 1.5 g; TID; Oral	FMG 1.5 g/d: 104 3.0 g/d: 108 4.5 g/d: 109	Mild to Moderate Active UC	8 weeks	Complete; Full

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Healthy Subjects/ Patients Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy	SAG-15/UCA	Module 5.3.5.1.2, Study Report SAG-15/UCA, p. 1	Efficacy and safety	Randomised, double-blind, double-dummy, multicentre, parallel group	FMG 0.5 g; TID, Mesalamine tablets 0.5 g; TID; Oral	FMG: 115 Mesalamine tablets: 118	Mild to Moderate Active UC	8 weeks	Complete; Full
Efficacy	SAG-26/UCA	Module 5.3.5.1.3, Study Report SAG-26/UCA, p. 1	Efficacy and tolerability	Double-blind, double-dummy, randomised, multicentre, parallel group	FMG 3.0 g; QD, FMG 1.0 g; TID; Oral	3.0 g QD: 191 1.0 g TID: 190	Active UC	8 weeks	Complete; Full
BA/BE	MPPK1001	Module 5.3.1.2.5, Study Report MPPK1001, p. 1	Relative bioavailability of Asacol 800 mg BID versus SMG 1600 mg QD and 800 mg BID	Open-label, randomized, 3-period crossover	SMG 1600 mg; QD and 800 mg; BID; Oral	30	Healthy Subjects	4 days	Complete; Full
BA	MPPK1002	Module 5.3.1.1.2, Study Report MPPK1002, p. 1	Relative bioavailability of single dose administered fasted versus fed	Open-label, randomized, single-dose, 2-period crossover	SMG 1600 mg; Oral	30	Healthy Subjects	Single dose	Complete; Full
BA	SAG-9/BIO	Module 5.3.1.1.1, Study Report SAG-9/BIO, p. 1	Relative bioavailability of single dose administered fasted versus fed	Open-label, randomized, 3-period crossover	Mesalamine granules 1.5 g; Mesalamine tablets 1.5 g; Oral	4 males	Healthy Subjects	Single dose	Complete; Full

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Healthy Subjects/ Patients Diagnosis	Duration of Treatment	Study Status; Type of Report
BA/BE	SAG-1/BIO	Module 5.3.1.2.1, Study Report SAG-1/BIO, p. 1	Relative bioavailability of 3 pH-modified release formulations of mesalamine granules	Non-randomized, single-center, open, 3-period crossover	Mesalamine granules (in 3 pH-modified release formulations) 1.5 g; Oral	4 males	Healthy Subjects	Single dose	Complete; Full
BA	SAG-4/BIO	Module 5.3.1.2.2, Study Report SAG-4/BIO, p. 1	Relative bioavailability and pharmacokinetics of pH-modified release mesalamine granules	Open-label, single-center, randomized, 2-period crossover	Mesalamine granules 0.5 g; TID; Mesalamine tablets 0.5 g; TID; Oral	24 males	Healthy Subjects	4 days	Complete; Full
BA	SAG-7/BIO	Module 5.3.1.2.3, Study Report SAG-7/BIO, p. 1	Relative bioavailability and pharmacokinetics of 5 pH-modified release formulations of mesalamine granules	Non-randomized, single-center, open, 5-period crossover	Mesalamine granules (in 5 pH-modified release formulations) 1.5 g; Oral	4 males	Healthy Subjects	Single dose	Complete; Full
BA	SAG-19/BIO	Module 5.3.1.2.4, Study Report SAG-19/BIO, p. 1	Relative bioavailability of and pharmacokinetics single dose administered fasted versus fed	Single-center, controlled, randomized, crossover	FMG 0.5 g; Oral	24 males	Healthy Subjects	Single dose	Complete; Full

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Healthy Subjects/ Patients Diagnosis	Duration of Treatment	Study Status; Type of Report
PK	SAG-25/BIO	Module 5.3.3.1.1.1, Study Report SAG-25/BIO, p. 1	Pharmacokinetics of single dose administered QD or TID	Open-label, single-center, single and multiple dose randomised, 4-way crossover	FMG 1.5 g; QD, 3.0 g; QD, 0.5 g; TID, 1.0 g; TID; Oral	12 males	Healthy Subjects	Single dose or 3 days	Complete; Full
PK	SAG-18/BIO	Module 5.3.3.1.1, Study Report SAG-18/BIO, p. 1	Pharmacokinetics of single dose in children	Single-center, open, controlled	FMG 20 mg/kg body weight; Oral	13 children	Mild to Moderate Active Crohn's Colitis or Ulcerative Colitis	Single dose	Complete; Full
PK/PD	SAG-16/BIO	Module 5.3.4.1.1.1, Study Report SAG-16/BIO, p. 1	Pharmacodynamics of single dose FMG versus mesalamine tablets	Observer-blind, randomised, single-center, 2-period crossover	FMG 0.5 g; FMG tablets 0.5 g; Oral	14 males	Healthy Subjects	Single dose	Complete; Full

Cross reference: Table 2.7.6-1

Abbreviations: FMG = Dr. Falk Pharma mesalamine granules formulation in an aluminum foil sachet dosage form; SMG = Salix to-be-marketed mesalamine granules formulation in an aluminum foil sachet dosage form; eMG = Salix to-be-marketed mesalamine granules formulation and capsule dosage form; QD = Once daily; BID = 2 times daily; TID = 3 times daily; BA = Bioavailability; BE = Bioequivalence; PK = Pharmacokinetics; PD = Pharmacodynamics; UC = Ulcerative Colitis.

\* The clinical data cutoff for the interim analysis was 09 May 2007; however, data from some subjects were collected through 14 August 2007.

**MPPK1001: The relative absorption and disposition of 5-aminosalicylic acid administered in the fasting state to healthy human subjects: Comparison between 800 mg Asacol twice daily, 800 mg mesalamine pellet formulation twice daily, and 1600 mg mesalamine pellet formulation once daily**

**STUDY OBJECTIVES**

The primary objective of the study was to test the hypothesis that fecal excretion of 5-ASA plus N-Ac-5-ASA with MP 1600 mg administered orally once daily is non-inferior (equivalent) to that with Asacol 800 mg administered orally twice daily.

**Study design**

This was a single-center, phase 1, open-label, randomized, crossover study of 3 treatments in 3 study periods, each separated by a minimum washout of 7 days.

**Treatment**

Treatments were administered orally, and were as follows:

Treatment A: Asacol® 800 mg (2 x 400 mg tablets) BID for 4 days.

Treatment B: MP (Mesalamine pellet = eMG) formulation 800 mg BID for 4 days.

Treatment C: MP (Mesalamine pellet = eMG) formulation 1600 mg (2 x 800 mg) QD for 4 days.

**Selection of Doses in the study**

Mesalamine (1600 mg/day) is a usual and customary dose for the maintenance of remission of UC and is similar to other marketed mesalamine products for that indication (including Asacol tablet 400 mg).

Mesalamine pellets were administered both at 800 mg BID and 1600 mg QD to determine if once daily administration would provide satisfactory colonic exposure. Asacol (1600 mg/day) in two divided doses is the approved US dosage and regimen for maintenance of remission in ulcerative colitis.

**Reviewer's comments:** No phase 2 dose-ranging study was conducted in support of this NDA and the dose of 1500 mg was chosen for phase 3 trials based on customary dose.

**Subject disposition**

Thirty subjects were randomized in the study and 28 completed all 3 treatment periods. One subject discontinued due to AEs and one subject was discontinued due to protocol violation. Subjects were predominantly male (83%) and Caucasian (73%).

Table 4.2.1. Subject disposition

Number of Subjects	Treatment A Asacol® 800 mg BID	Treatment B MP 800 mg BID	Treatment C MP 1600 mg QD
Enrolled	30	30	29
Completed	30 (100%)	30 (100%)	28 (96.5%)
Subjects in safety analysis	30	30	29
PK evaluable population for fecal excretion	27 (90.0%)	27(90.0%)	27 (93.1%)
PK evaluable population for urinary excretion	21 (70.0%)	21(70.0%)	21(72.4%)
PK evaluable population for plasma	28 (93.3%)	28 (93.3%)	28 (96.5%)

**Reviewer's comments**

The steady-state was assumed based on the terminal half-life estimated in study MPPK1002. However, because of uncertainty of the terminal half-life estimation due to a relatively short duration of PK sampling for 24 hours post-dose compared to the estimated half-life of 8-10 hours for 5-ASA and N-Ac-5-ASA. Therefore, the achievement of steady-state in this study was not reliably assumed for both QD and BID dosage regimen. In study MPPK1003 the steady-state was achieved on day 6 which was later than what was estimated based on the terminal half-life.

### **Pharmacokinetic assessment**

#### **Plasma Pharmacokinetic Parameters**

A baseline blood sample for assessment of serum creatinine and predose pharmacokinetic measurements was obtained approximately 15 minutes prior to dosing on the morning of Day 4 for each treatment period. Additional blood samples for pharmacokinetic assessment were taken at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after the morning dose on Day 4.

#### **Fecal Pharmacokinetic Parameters**

All stools were collected during Days 1 to 4 (0 to 96 hours) of each treatment period. Results from analyses were calculated for the following intervals within each treatment period: 0 to 24, 24 to 48, 48 to 72 and 72 to 96 hours. Fecal PK parameters were calculated for total, soluble, and intact (5-ASA plus N-Ac-5-ASA) fecal concentration data collected from all subjects who received study drug and had measurable drug concentration.

#### **Urine Pharmacokinetic Parameters**

Urine samples were collected during the following intervals within each treatment period: 0 to 24, 24 to 48, 48 to 72, and 72 to 96 hours. Urine samples were pooled over each 24-hour collection period.

#### **Safety Assessments**

The safety of the subjects was monitored throughout the study periods. Assessments of safety were based on the following:

- . Adverse events, both reported and observed.
- . Physical examination, including measurement of weight.
- . Vital signs (blood pressure, pulse, and temperature).
- . Clinical laboratory studies (hematology, chemistry, and urinalysis).

### **Results**

#### **Plasma Pharmacokinetics**

The time to maximum drug concentrations was shorter for MPs administered QD than BID for 5-ASA (mean of 3.96 h vs. 11.00 h, respectively) and for N-Ac-5-ASA (mean of 5.21 h vs. 11.68 h, respectively). The mean  $t_{max}$  was similar for 5-ASA and N-Ac-5-ASA for Asacol BID and MP BID administration. The extent of systemic absorption of 5-ASA and N-Ac-5-ASA on day 4 as measured by AUC was similar for both MP regimens. Plasma concentrations of 5-ASA and N-Ac-5-ASA as measured by  $C_{max}$  were higher following MPs administered QD compared to BID on Day 4. Following Asacol dosing, the high variability in systemic exposure to 5-ASA and N-Ac-5-ASA, was observed. In general, the mean  $C_{max}$  and AUC for 5-ASA and N-Ac-5-ASA, was lower after Asacol BID dosing than MP BID and QD dosing.

**Reviewer's comments:** It is unknown if the steady-state was achieved on Day 4 for two different dosage regimens. In a separate study MPPK1003, the steady-state was attained on Day 6 for 5-ASA and N-Ac-5-ASA during 1.5 mg once daily treatment. High variability of systemic

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exposure (72-129%) after Asacol administration may be in part attributed to the recovery of undissolved or partially dissolved Asacol tablet in stool samples as the sponsor noted.

Table 4.2.2. Plasma Pharmacokinetic Parameters for 5-ASA and N-Ac-5-ASA with Different Treatments after 4 days (Mean  $\pm$  SD, in  $\mu\text{mol}$ )

	Treatment A Asacol 800 mg BID n = 28	Treatment B MP 800 mg BID n = 28	Treatment C MP 1600 mg QD n = 28	C/B Ratio (90% CI) p value <sup>a</sup>
<b>C<sub>max</sub> (<math>\mu\text{mol/L}</math>)</b>				
5-ASA	6.93 $\pm$ 8.99 (129.7% CV)	11.92 $\pm$ 4.65 (39.0% CV)	19.87 $\pm$ 10.92 (55.0% CV)	153 (113, 208) p = 0.022
N-Ac-5-ASA	12.01 $\pm$ 9.22 (76.8% CV)	18.53 $\pm$ 6.31 (34.1% CV)	23.06 $\pm$ 9.35 (40.6% CV)	118 (98, 143) p = 0.141
<b>AUC (<math>\mu\text{mol}\cdot\text{h/L}</math>)<sup>b</sup></b>				
5-ASA	54.50 $\pm$ 49.01 (89.9% CV)	97.00 $\pm$ 35.92 (35.9% CV)	96.49 $\pm$ 42.40 (43.9% CV)	96 (76, 121) p = 0.775
N-Ac-5-ASA	157.54 $\pm$ 114.12 (72.4% CV)	237.79 $\pm$ 79.13 (33.3% CV)	235.13 $\pm$ 101.09 (43.0% CV)	93 (78, 112) p = 0.535
<b>T<sub>max</sub> (h)</b>				
5-ASA	16.0 (0, 24.0)	16.0 (0, 24.0)	3.0 (2.0, 16.0)	
N-Ac-5-ASA	16.0 (0, 24.0)	16.0 (0, 24.0)	3.0 (2.0, 24.0)	

<sup>a</sup> ANOVA Mixed Model Effects for log-transformed C<sub>max</sub> and AUC p-values for C<sub>max</sub> and AUC associated with Geometric Mean Ratio treatment contrast.

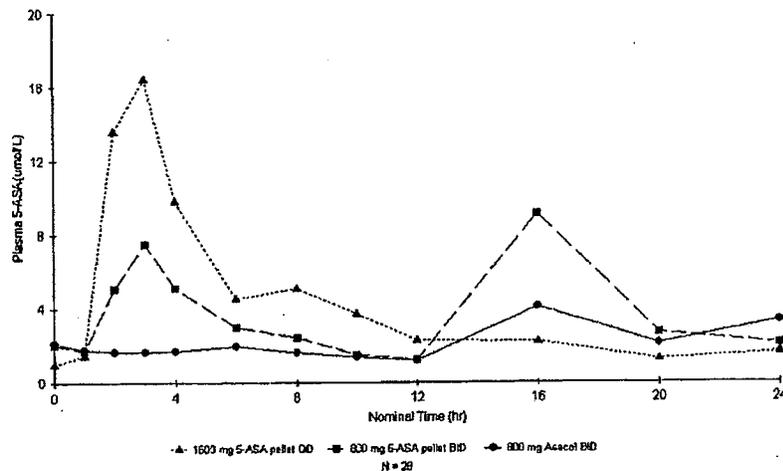
<sup>b</sup> AUC<sub>C</sub> values are listed for Treatments A and B; AUC<sub>0-24</sub> values are listed for Treatment C.

<sup>c</sup> Median difference and lower and upper 90% confidence interval of the median difference for the treatments indicated.

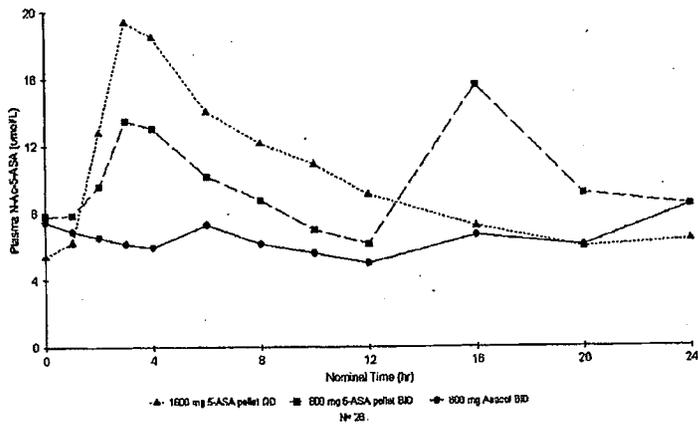
C<sub>max</sub> and AUC values were converted from  $\mu\text{mol/L}$  and  $\mu\text{mol h/L}$  to  $\mu\text{g/mL}$  and  $\mu\text{g}\cdot\text{h/mL}$  by multiplying by 0.153 for 5-ASA and by 0.195 for N-Ac-5-ASA for Table 2 in QBR.

Figure 4.2.1. Plasma concentration-time profile of 5-ASA (A) and N-Ac-5-ASA (B) following 4 days of treatments.

(A) 5-ASA



**(B)N-Ac-5-ASA**



Urinary Excretion

The mean cumulative urinary excretion of 5-ASA plus N-Ac-5-ASA was comparable between MP administered QD and BID. The mean cumulative urinary excretion of 5-ASA plus N-Ac-5-ASA, 5-ASA, and N-Ac-5-ASA was higher for both eMG 800mg BID and 1600 mg QD compared to Asacol.

The cumulative urinary excretion over 24 hour for 5-ASA and N-Ac-5-ASA on Day 4 was 1.99

Table 4.2.3. Mean ( $\pm$  SD) cumulative urinary excretion over 24 hours on Day 4

	Treatment A Asacol 800mg BID (n=21)	Treatment B MP 800 mg BID (n=21)	Treatment C MP 1600 mg QD (n=21)
5-ASA (mmol)	0.08 $\pm$ 0.10	0.25 $\pm$ 0.20	0.30 $\pm$ 0.21
N-Ac-5-ASA(mmol)	1.91 $\pm$ 0.85	3.06 $\pm$ 0.72	2.77 $\pm$ 0.9
5-ASA plus N-Ac-5-ASA (mmol)	1.99 $\pm$ 0.91	3.31 $\pm$ 0.85	3.06 $\pm$ 1.03

Fecal excretion

Table 4.2.4. Mean ( $\pm$  SD) cumulative fecal excretion over 24 hours on Day 4

	Treatment A Asacol 800mg BID (n=25)	Treatment B MP 800 mg BID (n=25)	Treatment C MP 1600 mg QD (n=25)
5-ASA (mmol)	3.13 $\pm$ 1.91	1.91 $\pm$ 0.89	1.81 $\pm$ 0.92
N-Ac-5-ASA(mmol)	1.10 $\pm$ 0.75	1.88 $\pm$ 0.99	1.10 $\pm$ 0.55
5-ASA plus N-Ac-5-ASA (mmol)	4.32 $\pm$ 2.35	3.78 $\pm$ 1.61	2.91 $\pm$ 1.34

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Based on the collection of fecal and urine data up to 24 hours post-dosing on Day 4, the mean cumulative fecal excretion of 5-ASA plus N-Ac-5-ASA was comparable between the once daily (1600 mg QD) and twice daily (800 mg BID) dosing regimens for MP (90% CI: 81, 109). The mean cumulative urinary excretion of 5-ASA plus N-Ac-5-ASA was also comparable between the QD and BID MP regimens (90%: 92, 103). Treatment comparisons between the Asacol and MP regimens were limited because of the number of subjects (~50%) who had intact or partially intact Asacol tablets discovered in their feces following Treatment A and the inability of the analytical extraction method to differentiate between released and total mesalamine. It is not known how the limitations of the extraction method impacted the fecal results for Treatments Band C. However these limitations were equivalent following both treatments allowing for comparison. The cumulative fecal and urinary excretion of 5-ASA and N-Ac-5-ASA were comparable between MP administered once daily (1600 mg QD) and twice daily (800 mg BID) based on collection of data limited to 24 hours post dosing on Day 4.

**Reviewer's comments:** It is unclear if the steady-state was achieved for QD and BID treatments on day 4.

**Safety Assessments**

Table 4.2.5. Summary of Adverse Events Related to Treatment with Asacol 800 mg BID, MP 800 mg BID or 1600 mg QD.

System Organ Class Preferred Term	Treatment A Asacol <sup>®</sup> 800 mg BID n = 30	Treatment B MP 800 mg BID n = 30	Treatment C MP 1600 mg QD n = 29
Subjects with ≥ 1 - treatment-related AEs*	0 (0.0%)	3 (10.0%)	3 (10.3%)
<b>Nervous system disorders</b>			
Headache	0 (0.0%)	1 (3.3%)	3 (10.3%)
<b>Gastrointestinal disorders</b>			
Flatulence	0 (0.0%)	2 (6.7%)	0 (0.0%)
Nausea	0 (0.0%)	0 (0.0%)	1 (3.4%)
<b>General disorders and administration site conditions</b>			
Hunger	0 (0.0%)	0 (0.0%)	1 (3.4%)

\* An AE determined by the Investigator to have a reasonable possibility of being caused by the study drug.  
Source: Summary Table 14.3.4

There was no death or SAEs during the study. One subject withdrew due to an adverse event. Subject 023, a 45-year-old Caucasian female, developed mild oral pain and sinus pain, which was followed two days later by mild swelling on the right side of her face 8 days after completing Treatment B (and during the washout period). On Study Day 29, she received one dose of MP 1600 mg QD but was permanently discontinued from the study on Study Day 30 because of the AEs. All of the AEs were determined by the Investigator to be not related to study drug, mild in severity; all AEs resolved without sequelae within 5 to 7 days of their onset. Mesalamine pellets (MP) were safe and well tolerated in healthy adult volunteers when administered orally once daily (1600 mg QD) or twice daily (800 mg BID) for 4 days.

**Reviewer's comments**

The efficacy and safety of eMG 1500 mg QD regimen was studied in two placebo-controlled phase 3 studies and one open-label long-term safety trial. Therefore, the comparison between Asacol BID regimen and MP regimen is at most supportive information. The comparison between MP QD regimen and MP BID regimen is limited by the weakness in study design, e.g.

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uncertainty of attainment of steady-state and short-duration of the urine sample collection. There is no labeling claim based on this study.

**MPPK1002: The effect of a high-fat meal on the absorption of a single, 100 mg oral dose of mesalamine (5-aminosalicylic acid) administered as a pellet formulation**

Study Design

A phase 1, open-label, randomized, balanced, two-treatment, two-period, two-sequence, crossover study of a single dose mesalamine pellet formulation (1600 mg, 2x800mg) administered orally following an overnight fast and following ingestion of a high-fat meal (breakfast). Study periods (4 days) were separated by a minimum of 7 days. Plasma, urine, and feces were collected to assess the effect of a high-fat meal on the pharmacokinetics of 5-ASA and N-Ac-5-ASA.

Subject disposition

A total of 30 subjects were enrolled and completed the study. Twenty-three subjects were male and 7 subjects were female.

Pharmacokinetic Parameters

Blood samples for PK analysis were collected over 24 hour post-dose. Urine and feces were collected over 96 hours post-dose. The concentrations of 5-ASA and N-Ac-5-ASA measured in plasma, urine, and fecal samples were reported in ng/mL. The reported concentrations of 5-ASA were converted to mmol/mL by dividing the reported concentration by 153.13, the molecular weight of 5-ASA. The reported concentrations of N-Ac-5-ASA were converted to mmol/ by dividing the reported concentration by 195.17, the molecular weight of N-Ac-5-ASA.

**Reviewer's comments:** The PK sampling for 24 hours was insufficient to capture a full PK profile mostly for a metabolite N-Ac-5-ASA and for 5-ASA in some subjects.

Bioanalytical assay

Mesalamine and N-Ac-5-ASA in plasma and urine were analyzed by validated LC/MS/MS method. The bioanalytical assay methods were adequately validated in each matrix with acceptable accuracy and precision. Submitted were the reports for assay validation in human fecal extract samples (No. 052-04001V), in urine (No. 052-03003V) and in plasma (No. 052-03002V). Analytical assay reports for measurement of 5-aminosalicylic acid and N-acetyl-5-aminosalicylic acid in total and soluble human fecal extracts (Analytical report N. 052-04001D), in plasma (No. 052-04002D) and in urine (NO. 052-04003D) were submitted.

Fecal sample process

Soluble 5-ASA and N-Ac-5-ASA

Immediately after defecation, feces were weighed and mixed thoroughly with 2 volumes of 0.1 M phosphate buffer (pH 6.0) at room temperature. Approximately 20 mL of the mixture was added to a 50 mL plastic conical centrifuge tube and centrifuged at 3,000g for 10 minutes at room temperature. Each of three 2-mL aliquots of supernatant was added to 8-mL absolute methanol in a capped test tube and vortexed thoroughly. The test tubes were frozen at -70°C. Samples were assayed for 5-ASA and N-Ac-5-ASA using a validated LC-MS/MS assay.

Total 5-ASA and N-Ac-5-ASA

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An additional 20 mL of feces/phosphate buffer mixture was added to 80 mL absolute methanol, mixed thoroughly and allowed to stand at room temperature for 4 hours. After mixing thoroughly, approximately 40 mL was added to a 50 mL plastic conical centrifuge tube and centrifuged at 3,000g for 10 minutes at room temperature. Three 10-mL aliquots of supernatant were taken, added to capped test tubes and frozen at -70°C. Samples were assayed for 5-ASA and N-Ac-5-ASA using a validated LC-MS/MS assay.

**Results**

**Plasma Pharmacokinetics**

The high-fat meal caused a significant increase in T<sub>max</sub> for both 5-ASA and N-Ac-5-ASA. There were no significant differences between the high-fat meal and fasting with respect to C<sub>max</sub> for 5-ASA or N-Ac-5-ASA. However, there was a modest increase (16%, p = 0.087) in AUC<sub>0-last</sub> for 5-ASA (90% CI: 101, 135). This increase was considered unlikely to be clinically significant.

Table 4.2.6. Plasma Pharmacokinetic Parameters for 5-ASA and N-Ac-5-ASA with Fasting and a High-Fat Meal (Mean ±SD, in μmol)

	Treatment		Fed/Fasted		
	Fasted N=30	Fed N=30	P value <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>c</sup>
<b>C<sub>max</sub> (μmol/L)</b>					
5-ASA	16.74 ± 9.46	16.39 ± 8.30	0.692	104	87, 125
N-Ac-5-ASA	19.09 ± 9.49	18.59 ± 7.06	0.734	103	90, 117
<b>AUC<sub>0-last</sub> (μmol*h/L)</b>					
5-ASA	77.80 ± 37.56	86.07 ± 36.20	0.087	116	101, 135
N-Ac-5-ASA	167.21 ± 68.15	165.08 ± 54.71	0.801	102	91, 114
<b>AUC<sub>0-inf</sub> (μmol*h/L)</b>					
5-ASA	84.81 ± 39.78	89.96 ± 37.28	0.228	111	96, 128
N-Ac-5-ASA	230.32 ± 94.73	222.69 ± 120.83	0.501	95	84, 108
<b>T<sub>max</sub> (h)</b>					
5-ASA	4.00 (3.00, 8.00) <sup>c</sup>	8.00 (3.00, 20.00)	-	-	-
N-Ac-5-ASA	6.00 (2.00, 16.00)	8.00 (3.00, 24.00)	-	-	-

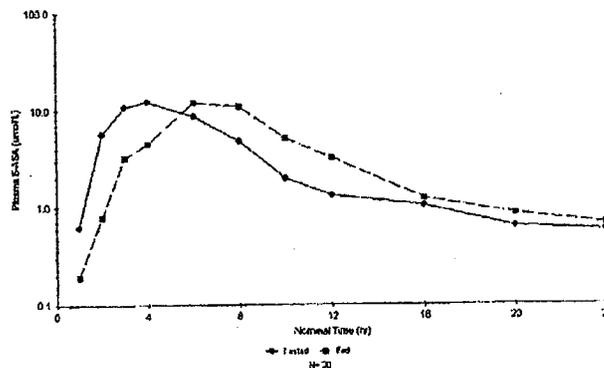
<sup>a</sup> P-values associated with treatment contrast from ANOVA Mixed Effects Model for log-transformed parameters. P-values for T<sub>max</sub> were calculated from the signed rank test.

<sup>b</sup> Calculated from geometric means of log-transformed data.

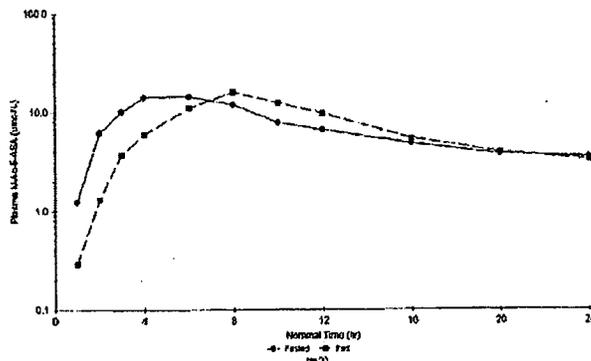
<sup>c</sup> Median (range).

Source: Summary Tables 14.2.7, 14.2.8, 14.2.9, 14.2.10

Figures 4.2.2. Mean plasma concentrations of 5-ASA (A) and N-Ac-5-ASA(B) after a single dose administration of 1.6 g mesalamine granules in sachet  
(A) 5-ASA



(B) N-Ac-5-ASA



The mean half-lives for 5-ASA and N-Ac-5-ASA exhibited fairly large intersubject variability (30% to 60% CV). The apparent terminal half-life of mesalamine was 8.42 (2.92) hours under fasted state and 5.49 (2.3) hours under fed state. The apparent terminal half-life of N-Ac-5-ASA was 12.56(4.01) hours under fasted state and 10.05(6.30) under fasting state

The study demonstrated that the high-fat meal significantly increased  $T_{max}$  for both 5-ASA and N-Ac-5-ASA by 4 and 2 hours, respectively. Under fed condition there was a slight increase (11 %) in 5-ASA  $AUC_{0-\infty}$ , but mean  $C_{max}$  did not significantly differ compared to under fasting condition. Although about 27% increase in the cumulative urinary excretion of 5-ASA was observed with a meal, the high-fat meal had no effect overall extent of absorption of administered dose based on the cumulative urinary excretion of 5-ASA plus N-Ac-5-ASA.

**Reviewer's comment:** The PK sampling duration appears insufficient to capture the terminal phase of PK profile especially for N-Ac-5-ASA. Because the half-life estimation was not detailed in the original study report, the information regarding the method of half-life estimation was requested. The sponsor submitted an amendment dated 7/25/2008 including tables of individual  $\lambda_z$  (Table below). However, the adequacy of  $\lambda_z$  could not be judged based on the provided information because the test of goodness of regression was not provided. In addition, the duration of PK sampling was for 24 hours and may have not been sufficient to adequately estimate the half-life for some subjects given the median  $t_{max}$  under fed condition was 8 hours for 5-ASA and N-Ac-5-ASA. As such, the adequacy of estimation of  $AUC_{inf}$  for 5-ASA and N-Ac-5-ASA is unknown.

Information request by the reviewer

You mentioned that the mean half-lives for 5-ASA and N-Ac-5-ASA were not affected by food. The mean 5-ASA half-lives were 5.79 and 8.42 hours with and without food, respectively; while the mean N-Ac-5-ASA half-lives were 10.05 and 12.56 hours, respectively. Please provide details regarding the half-life estimation, including linear regression plots, for individual subjects. In addition, please provide tabulated PK parameters for individual subjects for studies MPPK 1002 and MPPK 1001. If such information was already submitted, please guide the reviewer to the location (volume # and page).

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Table 4.2.7. Excerpt from the sponsor's response.

Subject ID	Treatment <sup>a</sup>	$t_{1/2}$ <sup>b</sup> (hr)	$\lambda_z$ <sup>c</sup> (1/hr)	$\lambda_z$ Start (hr)	$\lambda_z$ End (hr)
1	Fasted	6.9044	0.1004	6	24
1	Fed	7.2277	0.0959	12	24
2	Fasted	4.7946	0.1446	10	24
2	Fed	8.4443	0.0821	16	24
3	Fasted	7.3429	0.0944	12	24
3	Fed	3.3836	0.2049	16	24
4	Fasted	10.3448	0.067	16	24
4	Fed	1.6917	0.4097	10	24
5	Fasted	9.4346	0.0735	8	24
5	Fed	2.0971	0.3305	12	24
6	Fasted	3.9111	0.1772	16	24
6	Fed	4.4905	0.1544	12	24
7	Fasted	6.1712	0.1123	12	24
7	Fed	5.3088	0.1306	12	24
8	Fasted	6.6575	0.1041	6	24
8	Fed	7.277	0.0953	16	24
9	Fasted	11.5055	0.0602	8	24
9	Fed	5.7739	0.12	12	24
10	Fasted	7.7328	0.0896	8	24
10	Fed	8.0423	0.0862	12	24
11	Fasted	6.2667	0.1106	10	24
11	Fed	8.6018	0.0806	16	24

Continued

Table 4.2.8. Cumulative Urinary Excretion (0 to 96 Hours) of 5-ASA and N-Ac-5-ASA with Fasting and a High-Fat Meal (Mean± SD)

	Treatment		Fed/Fasted		
	Fasted N=30 (mmol)	Fed N=30 (mmol)	P value <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>b</sup>
5-ASA	0.20 ± 0.18	0.26 ± 0.23	0.165	127	95, 159
N-Ac-5ASA	3.10 ± 1.00	3.08 ± 1.22	0.952	100	87, 112
5-ASA plus N-Ac-5-ASA	3.30 ± 1.10	3.34 ± 1.36	0.879	101	88, 115

<sup>a</sup> P-values associated with treatment contrast from ANOVA Mixed Effects Model for untransformed parameters.

<sup>b</sup> Based on mixed models fit to untransformed data.

Source: Summary Tables 14.2.11 and 14.2.12.2

Table 4.2.9. Percentage of the administered dose (1.6g expressed as mmols of 5-ASA) for cumulative urinary excretion collected over 96 hours post-dose

	Fasted (N=30) % administered dose	Fed (n=30) % administered dose
5-ASA	1.95 ± 1.72 (88.4%CV)	2.47 ± 2.16 (87.6%CV)
N-Ac-5-ASA	29.62 ± 9.57 (32.3%CV)	29.48 ± 11.65 (39.5%CV)
5-ASA plus N-Ac-5-ASA	31.56 ± 10.55 (33.4%CV)	31.95 ± 12.98 (40.6%CV)

Table 4.2.10. Cumulative Fecal Excretion (0 to 96 Hours) of Soluble 5-ASA and N-Ac-5-ASA with Fasting and a High-Fat Meal (Mean± SD)

	Treatment		P value <sup>a</sup>	Fed/Fasted	
	Fasted N=30 (mmol)	Fed N=30 (mmol)		Ratio <sup>b</sup>	90% CI <sup>b</sup>
5-ASA	1.80 ± 1.07	1.27 ± 0.75	0.002	70.5	56, 85
N-Ac-5-ASA	1.60 ± 0.63	1.87 ± 0.97	0.040	116.3	103, 129
5-ASA plus N-Ac-5-ASA	3.40 ± 1.32	3.13 ± 1.34	0.131	92.1	83, 101

<sup>a</sup> P-values associated with treatment contrast from ANOVA Mixed Effects Model for untransformed parameters.

<sup>b</sup> Based on mixed models fit to untransformed data.

Source: Summary Tables 14.2.3 and 14.2.6.2

The high-fat meal had no effect on the cumulative fecal excretion of 5-ASA plus N-Ac-5-ASA. However, with a high-fat meal there was a mean 30% decrease in fecal excretion of 5-ASA, a mean 16% increase in N-Ac-5-ASA fecal excretion. These findings suggest that the delay in GI transit caused by the high-fat meal allowed more 5-ASA to be converted to its N-acetyl metabolite by the GI mucosa.

**Reviewer's comments:** The method was incapable of differentiate between released and unreleased mesalamine. The sponsor tested recovery of intact mesalamine granules and Asacol tablet in blank fecal sample for total (unreleased) and soluble (released) mesalamine in fecal extract. Under the experimental condition, soluble mesalamine was measured when mesalamine granules were added to fecal samples whereas without physically crushing Asacol tablets, total mesalamine could not be measured in fecal extract. Because N-Ac-5-ASA was not measured in the recovery study, it is unknown if N-Ac-5-ASA recovered in fecal samples from clinical trials was converted only in the intestinal lumen or also in fecal samples.

Table 4.2. 11. Summary of All Adverse Events

System Organ Class Preferred Term	Treatment		Total N=30 n (%)
	Fasted N=30 n (%)	Fed N=30 n (%)	
<b>Subjects with ≥ 1 AE</b>	6 (20.0%)	5 (16.7%)	9 (30.0%)
<b>Nervous system disorders</b>			
Headache	3 (10.0%)	3 (10.0%)	5 (16.7%)
<b>Gastrointestinal disorders</b>			
Abdominal pain	1 (3.3%)	1 (3.3%)	2 (6.7%)
Flatulence	1 (3.3%)	0	1 (3.3%)
<b>Respiratory, thoracic, and mediastinal disorders</b>			
Dry throat	1 (3.3%)	0	1 (3.3%)
<b>Vascular disorders</b>			
Pallor	0	1 (3.3%)	1 (3.3%)

Source: Summary Table 14.3.4

Mesalamine pellets administered as a single oral dose (1600 mg, 2 x 800 mg) were well tolerated following an overnight fast or a high-fat meal. No deaths, other serious adverse events, or severe adverse events were reported with either treatment group, and no subjects withdrew from the study. The number of subjects who reported an adverse event was comparable between the treatment groups (6 fasted, 5 fed). Headache was the most commonly reported AE overall (5 subjects) and in both treatment groups (3 fasted, 3 fed). (For details, please see the medical review by Dr. Aisha Peterson)

**Reviewer's comments**

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Although the study design has weakness to capture full plasma PK profile especially for N-Ac-5-ASA, the little effect of a high fat diet on overall absorption of administered mesalamine dose was demonstrated by combined cumulative urinary excretion for 5-ASA and N-Ac-5-ASA over 96 hours post-dose. Therefore, the sponsor's conclusion on no significant food effect on absorption of mesalamine is acceptable. Although this food effect study was conducted using mesalamine granules in sachet, the mesalamine granules are the same as in TRADE NAME and equivalence of two products were demonstrated in in vitro dissolution study. Therefore, the food effect observed for mesalamine granules in sachet can be extended to TRADE NAME, mesalamine granules in capsule. As such TRADE NAME can be taken with or without food.

**MPPK1003: A phase I, single- and multiple-dose, relative bioavailability and pharmacokinetic study of encapsulated mesalamine granules administered orally to healthy volunteers**

**Study design**

A single- and multiple-dose study in healthy volunteers. A total of 24 subjects were enrolled. Each subject received a single dose of mesalamine administered under fasting condition as 1.5 g encapsulated granules (4 x 375 mg) followed by 96 hours of blood sampling for pharmacokinetic analyses. After a 7-day washout period, each subject received multiple doses of mesalamine granules administered as 1.5 g encapsulated granules (4 x 375 mg) every 24 hours (QD) for 7 consecutive days following a pre-dose trough blood sample for Days 8 to 14. On Day 14 of the study, blood samples for pharmacokinetic analyses were collected up to 96 hours post dose.

**Subject disposition**

A total of 24 subjects were enrolled and completed the study (12 male subjects and 12 female subjects)

**Bioanalytical assay**

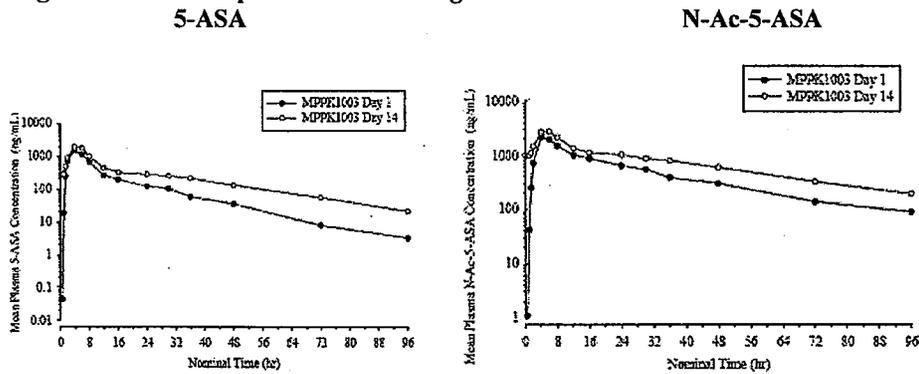
Analytical method report (method number:MN07007): Method for the determination of N-Acetyl-4-aminobenzoic acid, 4-aminobenzoic acid, N-Acetyl-mesalamine, and mesalamine in human plasma using high-performance liquid chromatography with mass spectrometric (MS/MS) detection was submitted.

Method Validation report (report number: MC06B-0186): Validation of a method for the determination of N-Acetyl-4-aminobenzoic acid, 4-aminobenzoic acid, N-acetyl-mesalamine and mesalamine in human plasma using high-performance liquid chromatography with mass spectrometric (MS/MS) detection was submitted.

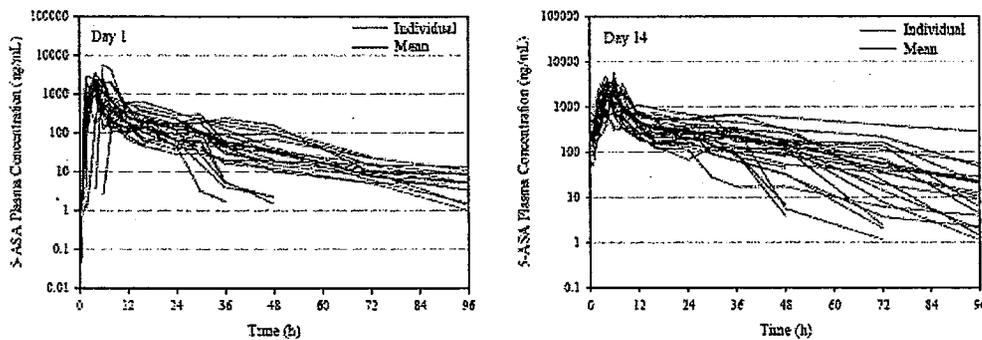
5-ASA and N-Ac-5-ASA in plasma was determined using validated HPLC/MS/MS method and in-run QC was adequately performed for 5-ASA and N-Ac-5-ASA assay (Bioanalytical report No. MC08B-0020).

**Results**

**Figure 4.2.3. Mean ( $\pm$ SD) Concentration-Time Profiles of 5-ASA and N-Ac-5-ASA after single dose and multiple doses of 1500 mg TRADE NAME**



**Figure 4.2.4. Individual and Mean Concentration-Time Profiles of 5-ASA on Day 1 and Day 14**



**Reviewer's comment:** Note that the scale of y-axis is different.

Mean plasma concentrations of 5-ASA and N-Ac-5-ASA peaked at approximately 4 hours post dose and then declined in a multi-exponential manner. Mean plasma concentrations of 5-ASA and N-Ac-5-ASA remained higher than the LOQ of the assay (1.0 and 5.0 ng/mL, respectively) 96 hours after drug administration on Day 1 and 14.

**Table 4.2.12. Steady State Analysis for 5-ASA and N-Ac-5-ASA**

Analytes	Trough Values	P-Values
	Geometric Mean (CV%)	
<b>5-ASA</b>		
Day 9 (2 <sup>nd</sup> dose)	64.49 (82.2)	<.0001
Day 10 (3 <sup>rd</sup> dose)	101.59 (64.6)	<.0001
Day 11 (4 <sup>th</sup> dose)	156.48 (52.5)	<.0001
Day 12 (5 <sup>th</sup> dose)	160.71 (55.3)	0.0001
Day 13 (6 <sup>th</sup> dose)	226.98 (58.9)	<b>0.6849</b>
Day 14 (7 <sup>th</sup> dose)	236.63 (53.1)	NA
<b>N-Ac-5-ASA</b>		
Day 9 (2 <sup>nd</sup> dose)	476.29 (51.5)	<.0001
Day 10 (3 <sup>rd</sup> dose)	645.86 (33.9)	<.0001
Day 11 (4 <sup>th</sup> dose)	807.28 (34.3)	<.0001
Day 12 (5 <sup>th</sup> dose)	780.66 (43.8)	0.0010
Day 13 (6 <sup>th</sup> dose)	983.07 (37.3)	<b>0.6863</b>
Day 14 (7 <sup>th</sup> dose)	959.50 (33.0)	NA

The steady state was achieved by day 6 of the multiple doses based on trough concentrations. The time to steady state assessed using the Helmert contrast approach was slightly longer than expected, assuming that steady state was expected to be observed after approximately 7 terminal half-life values of 5-ASA and N-Ac-5-ASA (corresponding to 99.2% of steady state).

**Table 4.2.13. Mean ( $\pm$ SD) PK parameters of 5-ASA and N-Ac-5-ASA following single dose and multiple doses of 1.5 g TRADENAME**

Parameters	Day 1 (Single Dose)	Day 14 (Multiple Dose)
<b>5-ASA</b>		
AUC <sub>0-24</sub> (ng <sup>*</sup> h/mL)	10963.5 $\pm$ 4523.49	16901.9 $\pm$ 5699.95
AUC <sub>0-t</sub> (ng <sup>*</sup> h/mL)	13300.8 $\pm$ 5354.28	25120.7 $\pm$ 11491.78
AUC <sub>0-inf</sub> (ng <sup>*</sup> h/mL)	13569.6 $\pm$ 5403.44	26607.5 $\pm$ 14823.45
C <sub>max</sub> (ng/mL)	2130 $\pm$ 1100	2720 $\pm$ 1140
T <sub>max</sub> (h) <sup>a</sup>	4.00 (2.00, 16.00)	4.00 (2.00, 8.00)
$\lambda_z$ (h <sup>-1</sup> )	0.07560 $\pm$ 0.055612	0.06878 $\pm$ 0.052024
t <sub>1/2</sub> (h) <sup>b</sup>	9.169 $\pm$ 7.0791	10.078 $\pm$ 8.1134
AI	NA	1.70 $\pm$ 0.808
<b>N-Ac-5-ASA</b>		
AUC <sub>0-24</sub> (ng <sup>*</sup> h/mL)	25550.2 $\pm$ 5524.49	36998.2 $\pm$ 8893.31
AUC <sub>0-t</sub> (ng <sup>*</sup> h/mL)	43817.6 $\pm$ 14454.17	73241.3 $\pm$ 32805.02
AUC <sub>0-inf</sub> (ng <sup>*</sup> h/mL)	50618.8 $\pm$ 23057.66	86066.9 $\pm$ 52484.18
C <sub>max</sub> (ng/mL)	2780 $\pm$ 847	3400 $\pm$ 895
T <sub>max</sub> (h) <sup>a</sup>	4.00 (4.00, 12.00)	5.00 (2.00, 8.00)
$\lambda_z$ (h <sup>-1</sup> )	0.05590 $\pm$ 0.046165	0.05104 $\pm$ 0.037151
t <sub>1/2</sub> (h) <sup>b</sup>	12.400 $\pm$ 10.8469	13.580 $\pm$ 10.1580
AI	NA	1.495 $\pm$ 0.410

<sup>a</sup> Median (range); <sup>b</sup> Harmonic mean (pseudo SD); NA, not applicable

<sup>a</sup> Median (range); <sup>b</sup> Harmonic mean (pseudo SD); NA, not applicable

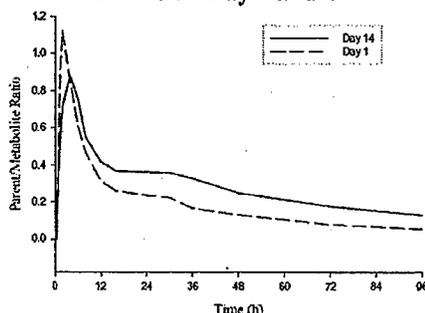
**Table 4.2.14. Pharmacokinetic Linearity Assessment for 5-ASA and N-Ac-5-ASA**

Parameters	Day 14 / Day 1 (AUC <sub>0-24</sub> / AUC <sub>0-168</sub> )	90% CI (Lower-Upper)	p-values
5-ASA	1.23	(1.09, 1.39)	0.0090
N-Ac-5-ASA	0.783	(0.700, 0.878)	0.0015

Source: Appendices 16.1.9.1 and 16.1.9.3

The ratio of AUCs for 5-ASA was 1.23, with confidence intervals slightly above 1. The ratio of AUCs for N-Ac-5-ASA (0.784) was inverse to the ratio of AUCs for 5-ASA, suggesting a lower formation rate or higher elimination rate of N-Ac-5-ASA following repeated oral administrations of TRADENAME. Since the mean t<sub>1/2</sub> values of 5-ASA and N-Ac-5-ASA on Day 1 and Day 14 were within 10% for 5-ASA (9.17 and 10.08 hours, respectively) and for N-Ac-5-ASA (12.40 and 13.58 hours, respectively), the above departure from linearity is likely a result of slightly lower rate of metabolism to N-Ac-5-ASA following repeated oral administrations of TRADENAME, which was not deemed to be clinically relevant.

**Figure 4.2.5. Parent-to-Metabolite Ratios on Day 1 and 14**



The parent-to-metabolite ratio was higher on Day 14 from 12 to 96 hours post dose. These results suggest a higher absorption of 5-ASA and/or a lower formation rate of N-Ac-5-ASA on Day 14 as compared with Day 1.

**Safety**

All reported TEAEs during the study were mild in severity and resolved without sequelae. In total, 3 subjects (13%) experienced TEAEs judged by the investigator as related to study drug. One of these subjects (1024-20) experienced treatment related AEs in both treatment periods. Vomiting was considered a drug-related TEAE in 2 subjects and events of constipation, heartburn, nausea, and somnolence were considered drug related in 1 subject each. Only 1 TEAE, constipation in Subject 1024-01, was treated by the administration of concomitant medications during the study. This event of constipation was treated with prune juice on Day 9 and docusate sodium on Day 10. This concomitant therapy was not expected to affect study results.

**Table 4.2.15. Overview of Treatment-Emergent Adverse Events by Study Phase**

Overview of AE	Single-Dose Period	Multiple-Dose Period
	Days 1-7 N (%)	Days 8-18 N (%)
<b>Subjects with ≥ 1 TEAE</b>	4 (17)	4 (17)
<b>AE Severity<sup>a</sup></b>		
Mild	4 (17)	4 (17)
Moderate	0	0
Severe	0	0
<b>Subjects reporting TEAEs related to study drug</b>	2 (8)	2 (8)
<b>Deaths</b>	0	0
<b>Serious Adverse Events</b>	0	0
<b>Discontinuations due to TEAE</b>	0	0

Source: Data Listing 16.2.7, Appendix 16.2; Abbreviations: TEAE = treatment emergent adverse event.

a If a subject experienced more than one TEAE, the subject is counted only once for the worst severity.

**Cross-study comparison of pharmacokinetic parameters**

The sponsor noted that in cross-study comparison the pharmacokinetic characteristics of mesalamine and N-Ac-5-ASA after administration of TRADE NAME and Dr. Falk Pharma Mesalamine granules (FMG) are largely similar except one notable difference between in the multiple-dose AUC<sub>0-inf</sub>, which was higher in the current study (26607.5 ± 14823.45 ng\*h/mL) than in Dr. Falk study SAG-25 (15942 ± 6815 ng\*h/mL). The sponsor attributed this difference in part to the great variability associated with multiple dose AUC<sub>0-inf</sub>, which was also high when compared to the other pharmacokinetic parameters.

**Reviewer's comments:** The multiple dose PK parameters after FMG administration was evaluated after 4 days of 1.5g FMG once daily administration. Because it is cross-study comparison with different study designs for the treatment duration, 4 days for FMG versus 7 days for TRADENAME, a firm conclusion regarding comparability of two products can not be drawn. In addition, the comparison of any two mesalamine products should be done for both 5-ASA and N-Ac-5-ASA since the systemic exposure to N-Ac-5-ASA is considered of importance from a safety standpoint.

Table 4.2.16. Comparison of 5-ASA Pharmacokinetic Parameters: TRADENAME (MPPK1003) and Dr. Falk Pharma Mesalamine Granules (SAG-25)

Single-dose	MPPK1003 (N = 24)	SAG-25 (N = 12)
AUC <sub>0-24</sub> (ng*h/mL)	10963.5 ± 4523.49	11581 ± 4520
AUC <sub>0-inf</sub> (ng*h/mL)	13569.6 ± 5403.44	13060 ± 4767
C <sub>max</sub> (ng/mL)	2130 ± 1100	3049 ± 1644
T <sub>max</sub> (h) <sup>a</sup>	4.00 (2.00, 16.00)	4.50 (3.00, 6.00)
t <sub>1/2</sub> (h)	9.169 ± 7.0791 <sup>b</sup>	10.57 ± 4.41

Multiple-dose	MPPK1003 (N = 24)	SAG-25 (N = 12)
AUC <sub>0-24</sub> (ng*h/mL)	16901.9 ± 5699.95	13330 ± 5850
AUC <sub>0-inf</sub> (ng*h/mL)	26607.5 ± 14823.45	15942 ± 6815
C <sub>max</sub> (ng/mL)	2720 ± 1140	2833 ± 1581
T <sub>max</sub> (h) <sup>a</sup>	4.00 (2.00, 8.00)	4.21 (3.00, 5.50)
t <sub>1/2</sub> (h)	10.078 ± 8.1134 <sup>b</sup>	Not determined

Source: MPPK1003 Final Clinical Study Report and SAG-25/UCR Final Clinical Study Report (Section 14.2.3 – Pharmacokinetic Parameters – Descriptive Statistics (Mean [arith.] and SD [arith.]) on pages 145 and 146).

Note: Data are presented as arithmetic mean ± SD with the exceptions as indicated in footnotes a and b.

<sup>a</sup> Data for T<sub>max</sub> are presented as median (minimum, maximum).

<sup>b</sup> Data for t<sub>1/2</sub> from MPPK1003 are presented as harmonic mean ± pseudo SD.

**Reviewer's comment:** This study was submitted at month 5 into the review cycle (June 13, 2008) as an amendment to provide adequate single and multiple dose PK information for TRADE NAME. The deficiency of this study at the NDA submission was not considered a filing issue. The division agreed to review the study at the time of NDA filing because the study appeared to be of better design to provide adequate PK information. The study is acceptable to provide adequate PK characteristics of 5-ASA and N-Ac-5-ASA following administration of single dose and multiple doses of TRADE NAME at the dose level proposed for marketing approval.

**SAG-16-/BIO: Observer-blind, single dose, cross-over pharmacoscintigraphic study of the gastrointestinal transit and release of <sup>153</sup>Sm-labelled mesalazine pellets versus <sup>153</sup>Sm-labelled mesalazine tablets in male healthy volunteers**

**Reviewer's note:** In this study report, Dr. Falk mesalamine granules were referred as Salofalk pellets and mesalamine was referred as mesalazine.

The sponsor proposed a labeling claim based on this study for the distribution section under 12.2. Pharmacokinetics as follows: T

b(4)

Objectives

**Primary objective:** To demonstrate in healthy volunteers, by pharmaco-scintigraphy, that Salofalk pellets released the active ingredient 5-ASA in the same target region (Le. terminal ileum-caecal region) like Salofalk tablets.

**Secondary objective:** To compare in healthy volunteers transit behavior and absorption rate and extent along the GI tract of the two radiolabelled formulations

Study rationale

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By the addition of a non-radioactive tracer such as samarium-152 oxide to the finished product, gamma scintigraphy provides information on the transit, disintegration and release of the formulation. The combination of this technique with pharmacokinetics allows to relate the absorption with the derived information provided by scintigraphy (location, transit, initial and complete disintegration etc.). In the present study the gastric and intestinal transit and the absorption of a mesalazine pellet formulation as was compared to a tablet formulation. 80th formulations were added with cold  $^{152}\text{Sm}$ , which was activated to radioactive  $^{153}\text{Sm}$  before use.

Subjects

Fourteen (14) healthy male subjects

Study design

Phase 1, comparative, single center, randomized, observer-blind, cross-over clinical study. Subjects were treated with either mesalazine pellets or mesalazine tablets in a randomized fashion. All volunteers received the alternative preparation after a wash out period of at least 1 week.

Treatment

Test and reference formulations were administered following overnight fasting. Breakfast was given two hours after drug administration. Standardized lunch and dinner were given at the pre-determined time.

Test Formulation

Formulation A: Pellets containing 500 mg of mesalazine and 2 mg of  $^{152}\text{Sm}$

Composition: Each vial contained mesalazine pellets sufficient for 1 application of 500 mg mesalazine

Manufacturer: Dr. Falk Pharma GmbH, Freiburg - Germany

Mode of administration: Oral, content of the vial was poured in a spoon and the medication was taken with 200 mL of water

Reference Formulation

Formulation B: Tablets containing 500 mg of mesalazine and 2 mg of  $^{152}\text{Sm}$

Composition: Each vial contained one 500 mg mesalazine tablet

Manufacturer: Dr. Falk Pharma GmbH, Freiburg - Germany

Mode of administration: Oral, one tablet was swallowed with 200 mL of water

Plasma PK sampling

Up to 24 hours plasma samples were collected at the pre-specified following times: 0 (pre-dose), 0.5, 1, 1, 5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours

Scintigraphic examination

The transit of the pellets and of the tablets along the G.I. tract was recorded with subjects standing in front of the gamma camera. Abdominal scans were taken using a "large field of view" gamma camera, at approx. 20 min intervals up to 6 h, then at approx. 30 min intervals up to 10 h. Further acquisitions were taken at 12 h, and 24 h post-dose. Location of the labelled dosage forms in the GI tract was established by viewing the images on a monitor. The number of counts for each region was recorded at each time interval. The geometric means of the corresponding anterior and posterior count rates were then calculated corrected for radioactive decay and expressed as percentages of the total radioactivity in the abdomen. The relative amount of radioactivity to establish the appearance and disappearance to and from the target region was

defined as 15% (for appearance) and 85% (for disappearance) of the total radioactivity in the region.

Tablets disintegration

The initial tablet disintegration (ITO) was defined as the time when any sign of consistent release of radioactive tracer from the tablets was detected, whilst complete tablet disintegration (CTD) was defined as the time at which the radioactivity had dispersed within the G.I. lumen and no signs of a distinct tablet 'core' remained. The interpretation of the scintigraphic images in order to define ITO and CTD was difficult. For this reason in many cases precise times could not be provided. A certain degree of approximation can be expected in the data presented. The mean time ITO was  $3.14 \pm 0.86$  h (range 2-5 h). In 10 out of 14 subjects the ITO corresponded to the time during which the tablets were located in the small intestine. In the remaining 4 subjects the disintegration started in the terminal ileum-caecal region. The CTD occurred in the colon in all subjects with a mean value of  $8.83 \pm 1.59$  h.

Absorption in the ileo-caecal region (target region)

The pharmacokinetics of 5-ASA and N-Ac-5-ASA were determined in the present study to evaluate the extent of absorption of these compounds while the test and reference formulations were located in the terminal ileum-caecal region (target region). The study protocol foresaw the evaluation of the extent (AUC) of absorption of 5-ASA and of its main metabolite Ac-5-ASA while the two formulations were located in the target region as determined by scintigraphy. When the times of blood collection were not corresponding to the times at which the scintigraphic images were taken, the plasma levels were obtained by linear interpolation of the concentrations available at the times immediately preceding and following the time of interest.

Mean relative absorption at target region

For test and reference formulations the relative percentage of absorption of 5-ASA, Ac-5-ASA and of the sum 5-ASA plus Ac-5-ASA was calculated from the ratio between the extent of absorption in the target region (AUC<sub>tr</sub>) and the overall extent of absorption up to the time at which the last detectable concentration of the of 5-ASA, Ac-5-ASA or their sum was observed (AUC<sub>t</sub>).

Results

Table 4.2.17. Mean time course parameters of pellets and tablets formulations (h)

	PELLETS			TABLETS			ANOVA
	Mean $\pm$ SD	Min	Max	Mean $\pm$ SD	Min	Max	
Gastric emptying	0.94 $\pm$ 0.70	0.05	2.00	0.56 $\pm$ 0.71	0.05	2.33	NS
Location in SI	0.65 $\pm$ 0.40	0.05	1.67	0.79 $\pm$ 0.71	0.05	2.33	NS
Transit time in SI	3.07 $\pm$ 0.88	2.00	4.33	3.00 $\pm$ 0.84	1.95	4.67	NS
Disappearance from SI	3.71 $\pm$ 1.08	2.33	5.33	3.79 $\pm$ 1.17	2.00	5.67	NS
Ileo-caecal region (target region)	3.31 $\pm$ 1.03 <sup>1</sup>	1.33	5.00	3.83 $\pm$ 0.89 <sup>1</sup>	2.33	5.33	-
	↓ 6.15 $\pm$ 2.48 <sup>2</sup>	↓ 3.33	↓ 12.00	↓ 5.56 $\pm$ 1.57 <sup>2</sup>	↓ 3.67	↓ 8.50	-
Ascending colon region	4.08 $\pm$ 1.39 <sup>1</sup>	2.00	6.50	4.74 $\pm$ 1.15 <sup>1</sup>	2.67	6.50	NS
	↓ 13.57 $\pm$ 4.45 <sup>2</sup>	↓ 10.00	↓ 24.00	↓ 10.88 $\pm$ 1.48 <sup>2</sup>	↓ 8.00	↓ 12.00	-
Overall transit time in colon	19.92 $\pm$ 1.39	17.50	22.00	17.37 $\pm$ 4.80	6.67	21.33	NS

1: Entrance, 2: Exit, NS: non significant

**Reviewer's comments:** The quality of the submitted scintigraphic images was generally too poor to review and description of each image was largely insufficient. Therefore, the scintigraphic images could not be verified for the data. It is not clear if the sponsor attempted to have any reference markers for for consistent positioning of each scintigraphic image.

Table 4.2.18. Mean ( $\pm$  SD) PK parameters 5-ASA and N-Ac-5-ASA after a single-dose administration of mesalamine pellets or tablets

	PELLETS (test)			TABLETS (reference)			Significance
	5-ASA	Ac-5-ASA	5-ASA + Ac-5-ASA	5-ASA	Ac-5-ASA	5-ASA + Ac-5-ASA	
$C_{max}$ (ng/mL)	428.89 $\pm$ 281.93	986.09 $\pm$ 435.68	N.D.	1241.10 $\pm$ 1304.70	1736.60 $\pm$ 1321.00	N.D.	NS
$t_{max}$ (h)	4.11 $\pm$ 0.96	4.36 $\pm$ 1.01	N.D.	5.14 $\pm$ 1.23	5.50 $\pm$ 1.18	N.D.	NS
$t_b$ (h)	N.D.	6.70 $\pm$ 2.11	N.D.	N.D.	5.07 $\pm$ 2.08	N.D.	S
MRT (h)	N.D.	10.78 $\pm$ 2.33	N.D.	N.D.	10.13 $\pm$ 2.28	N.D.	-
$AUC_0-t$ (ng·h/mL)	968.32 $\pm$ 628.84	6407.67 $\pm$ 2026.16	39.17 $\pm$ 13.94 <sup>1</sup>	2205.80 $\pm$ 1766.52	8638.93 $\pm$ 4087.22	58.69 $\pm$ 32.01 <sup>1</sup>	S
$AUC_{\infty}$ (ng·h/mL)	N.D.	6802.02 $\pm$ 2013.04	N.D.	N.D.	8947.73 $\pm$ 4052.11	N.D.	-
$Ae_{0-24}$ (nmol)	19894.78 $\pm$ 16647.93	454502.20 $\pm$ 93284.04	474397.00 $\pm$ 95418.91	46970.12 $\pm$ 52027.91	629442.63 $\pm$ 344189.18	676412.70 $\pm$ 391066.90	NS
% of dose			14.53 $\pm$ 2.92			20.71 $\pm$ 11.97	-

<sup>1</sup>: (nmol·h/mL)

**Reviewer's comments:** The sponsor noted that the estimation of  $AUC_{\infty}$  could not been done due to low plasma concentrations of 5-ASA.

Table 4.2.19. Mean relative absorption % ( $\pm$  SD) of 5-ASA, Ac-5-ASA and 5-ASA+Ac-5-ASA from pellets (test) and tablets (reference) in the ileo-caecal region (target region)

	5-ASA	Ac-5-ASA	5-ASA+Ac-5-ASA
<b>Pellets</b>	52.42 $\pm$ 25.48%	28.32 $\pm$ 18.99%	31.80 $\pm$ 18.85%
<b>Tablets</b>	39.91 $\pm$ 29.41%	19.08 $\pm$ 14.11%	23.98 $\pm$ 18.05%

Table 4.2.20. Mean relative absorption % ( $\pm$  SD) of 5-ASA, Ac-5-ASA and 5-ASA+Ac-5-ASA from pellets (test) and tablets (reference) in the ascending colon region

	5-ASA	Ac-5-ASA	5-ASA+Ac-5-ASA
<b>Pellets</b>	45.85 $\pm$ 30.32%	58.42 $\pm$ 20.83%	56.33 $\pm$ 22.34%
<b>Tablets</b>	54.29 $\pm$ 30.33%	54.23 $\pm$ 16.02%	52.83 $\pm$ 18.14%

**Sponsor's conclusion:** These results together with the data on the relative availability in the target region and the transit times indicate that also the systemic availability of Ac-S-ASA is similar in relative extent, location and  $t_{max}$  for both formulations, but different in absolute extent, being higher from tablets.

**Reviewer's comments:** The primary objective of the study is to compare Dr.Falk pellet (FMG) to another mesalamine tablets. Therefore, the study is qualitative in nature.

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Without substantial formulation effects, when administered by oral suspension under fasting, the oral absorption of 5-ASA was rapid and extensive indicated by tmax of about 1 hour and about cumulative urinary excretion of 78% administered dose over 48 hours. The terminal half-life of 5-ASA after oral suspension was about 1 hour. (Yu et al. (1990) Effect of food coadministration on 5-aminosalicylic acid oral suspension bioavailability, Clin. Pharmacol. Ther. 48:26-33). On the other hand, after TRADENAME administration, tmax of mesalamine was about 4 hours (MPPK1003) indicating that the release characteristics from the formulation significantly influences the absorption profile of 5-ASA. The terminal half-life was also significantly prolonged influenced by prolonged absorption in the intestine.

However, the data provided by this study is not sufficient to support the proposed claim of

Because the quantitative estimation of local availability of mesalamine in a specific region is limited due to incapability of differentiation of released and unreleased mesalamine from the granules in scintigraphic analysis and a limited absorption at the target region of intestine which may not be parallel with the availability of released mesalamine in the target region of intestine.

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**4.4 OCP Filing Form**

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA Number	22-301	Brand Name		
OCPB Division	III	Generic Name	Mesalamine granule	
Medical Division	DGP	Drug Class	Anti-inflammatory	
OCPB Reviewer	Insook Kim, Ph.D.	Indication(s)	Ulcerative Colitis	
OCPB Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Capsule	
		Dosing Regimen	4 X 375 mg capsules QD	
Date of Submission	12/31/2007	Route of Administration		
Estimated Due Date of OCPB Review		Sponsor	Salix Pharmaceuticals, Inc.	
PDUFA Due Date	10/31/2008	Priority Classification	Standard	
Division Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1	1	
multiple dose:	X			
<i>Patients-</i>				
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:				
In-vivo effects of primary drug:				
<b>In-vitro:</b>				
Subpopulation studies -				
ethnicity:				

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gender:				
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
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 -	X			
solution as reference:				
alternate formulation as reference:	X	8	2	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		11		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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/s/

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