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*APPLICATION NUMBER:*

**22-000**

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

## CLINICAL PHARMACOLOGY REVIEW

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NDA: 22-000	Submission Date(s): 12/21/05, 3/22/06, 5/19/06, 5/31/06, 6/5/06, 7/21/06, 8/8/06, 8/29/06
Brand Name	To be determined
Generic Name	Mesalamine
Reviewer	Sue-Chih Lee, Ph.D.
Acting Team Leader	Abimbola Adebawale, Ph.D.
OCPB Division	Division of Clinical Pharmacology III
OND division	Division of Gastroenterology Products
Sponsor	Shire Development Inc.
Relevant IND(s)	66,193
Submission Type; Code	Standard
Formulation; Strength(s)	Tablets 1.2 g
Proposed Indication	Induction of remission in patients with active, mild to moderate ulcerative colitis (UC)
Proposed Dosing Regimen	2.4-4.8 g QD

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## 1. EXECUTIVE SUMMARY

The brand name for the proposed drug product is still under discussion between the sponsor and the Agency. This review refers to the proposed product as SPD476.

SPD476 is a new formulation of mesalamine (or 5-ASA) intended for the induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC). Currently, there are various approved mesalamine formulations on the market: delayed-release tablets, extended-release capsules, rectal suppositories, and enema. An extended-release capsule formulation, Pentasa®, is marketed by the sponsor. The proposed formulation is designed to release the active ingredient in a delayed and prolonged fashion following oral administration. This formulation has a higher load of mesalamine (1.2 g/tablet) than any of the currently marketed oral mesalamine products. The proposed dosing regimen is 2.4 g to 4.8 g QD while the approved oral products are for TID or QID dosing. The sponsor stated that this high drug load and QD dosing can potentially increase compliance.

This NDA is submitted under the provisions of 505(b)(1). To support this NDA, the sponsor initially submitted five Phase 1, two Phase 2 and three Phase 3 studies. Two additional Phase 1 studies were submitted after the original NDA submission: Study SPD476-105 was submitted on May 31, 2006 and Study SPD476-106 on August 29, 2006.

The seven Phase 1 studies are listed below:

CRO-00-15: scintigraphic and PK study comparing two potential formulations

CRO-PK-00-42: multiple-dose (1.2 g BID) study

SPD476-103: food effect study

SPD476-105: single-dose (2.4 g and 4.8 g) and multiple-dose (2.4 g QD and 4.8 g QD) study

SPD476-106: PK under fasting conditions, food effect, dose proportionality and gender effect.

Studies CRO-00-15 and CRO-PK-00-42 are pilot studies using different formulations or with different dosage regimens while other studies are pivotal Phase 1 studies. During the drug development, the sponsor found that mesalamine was unstable in plasma samples stored at -20°C. This stability issue was initially seriously evaluated as it affected all studies submitted in the original NDA. However, the issue no longer impacts the acceptability of the NDA from the clinical pharmacology standpoint as the sponsor has subsequently provided data from Studies SPD476-105 and SPD476-106, which had samples stored at -80°C.

The PDUFA due date of this NDA was extended for 3 months due to the late submission of Study SPD476-106.

**1.1. RECOMMENDATION**

From the viewpoint of the Office of Clinical Pharmacology, the Clinical Pharmacology and Biopharmaceutics information in the NDA is acceptable provided that a mutual agreement on label language can be reached between the sponsor and the Agency.

**1.2. PHASE IV COMMITMENT**

None

**1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS**

**Stability Issue**

Mesalamine is unstable in plasma samples stored at -20°C due to its reaction with glucose present in the samples<sup>1,2</sup>. All five Phase 1 studies submitted in the original NDA submission had samples stored at -20°C for at least part of the storage time period and, therefore, were affected by the stability issue. The sponsor considered this issue unimportant for Study \_\_\_\_\_ and manageable for ' \_\_\_\_\_ The sponsor also attempted to correct data for Study SPD476-103 by using various equations. Because the sponsor subsequently submitted Studies SPD476-105 and SPD476-106 with valid data, the issue now has little impact on the NDA. However, before the submission of SPD476-106, this issue was critical and was carefully evaluated as described below:

Studies CRO-00-15 and CRO-PK-00-42 had plasma samples stored at -20°C for up to 49 days and 58 days, respectively. The PK data from these studies are deemed unreliable. However, these studies are supportive in nature and, therefore, the stability issue does not have a critical impact on the overall clinical pharmacology information required for the NDA.

Study SPD476-103, a food effect study, had plasma samples stored at -20°C for up to 48 days. Because storage condition and storage time were documented for each sample in this study, the sponsor attempted to correct the affected data by modeling the degradation process using different approaches. However, none of the approaches presented by the sponsor is considered acceptable by this reviewer. As such, this study cannot be used to support the NDA.

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All the biological samples from Study SPD476-105 and the later submitted Study SPD476-106 were stored at -80°C for up to 59 days and, therefore, these studies were not affected by the stability issues discussed above.

**References:**

1. Brendel, E, Meineke, I, Stüwe, E and Osterwald, H. J. Chromatography, Biomedical Applications, 432 (1988) 388-362.
2. Tjørnelund, J and Honeré-Hansen, S. J. Chromatography, Biomedical Applications, 570 (1991) 224-228.

**Pharmacokinetics**

All PK information described in this section is derived from Studies SPD476-105 and SPD476-106.

**Single-Dose PK (5-ASA)**

**Fasting Conditions:**

The plasma 5-ASA concentration-time profiles following single dose administration under fasting conditions were characterized by a median lag-time (Tlag) of 2 hours (Table 1). Some profiles had two peaks, occurring at around 6 hours and 12 hours postdose, respectively, while others had a very late peak (around 30 hours postdose). The absorption process appeared to be prolonged (> 10 hrs) in many subjects and half-life determined in the terminal phase might be affected by the absorption process. The pharmacokinetics parameters following administration of SPD476 were highly variable with a CV ranging from 53% to 93%.

**Table 1: Mean (SD) PK parameters for 5-ASA following single dose administration of SPD476 under fasting conditions (Study SPD476-106)**

Parameter <sup>1</sup> of 5-ASA	SPD476 1.2g (N = 47)	SPD476 2.4g (N = 48)	SPD476 4.8g (N = 48)
AUC <sub>0-t</sub> (ng.h/mL)	9039 <sup>†</sup> (5054)	20538 (12980)	41434 (26640)
AUC <sub>0-∞</sub> (ng.h/mL)	9578 <sup>†</sup> (5214)	21084 <sup>§</sup> (13185)	44775 <sup>#</sup> (30302)

C <sub>max</sub> (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T <sub>max</sub> * (h)	9.0** (4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
T <sub>lag</sub> * (h)	2.0** (0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
t <sub>1/2</sub> (h) (Terminal Phase)	8.56 <sup>†</sup> (6.38)	7.05 <sup>§</sup> (5.54)	7.25 <sup>#</sup> (8.32)

<sup>†</sup>Arithmetic mean of parameter values are presented except for T<sub>max</sub> and T<sub>lag</sub>.

\*Median (min, max); <sup>†</sup>N=43, <sup>‡</sup>N=27, <sup>§</sup>N=33, <sup>#</sup>N=36, \*\*N=46

### ***Dose Proportionality:***

Dose proportionality was studied across the dose range of 1.2 - 4.8 g. Between 1.2 g and 2.4 g doses, both C<sub>max</sub> and AUC<sub>∞</sub> were similar based on the geometric least square means (Table 2). At the dose of 4.8 g, C<sub>max</sub> was less than dose proportional while AUC<sub>0-∞</sub> was slightly more than dose proportional compared to the two lower doses.

**Table 2: Geometric least squares (LS) mean ratios and 90% CIs for 5-ASA bioavailability parameters following doses of 1.2g, 2.4g and 4.8g SPD476 (Study SPD476-106)**

Dose normalised parameter	Ratio of 2.4g:1.2g	Ratio of 4.8g:1.2g	Ratio of 4.8g:2.4g
AUC <sub>0-t</sub>	1.13 (0.953, 1.33)	1.05 (0.889, 1.24)	0.933 (0.794, 1.10)
AUC <sub>0-∞</sub>	1.01 (0.822, 1.24)	1.13 (0.925, 1.39)	1.12 (0.925, 1.36)
C <sub>max</sub>	1.07 (0.823, 1.40)	0.796 (0.610, 1.04)	0.740 (0.569, 0.963)

Geometric LS mean ratio (90% CI) data are presented

### ***Food effect:***

The food effect was studied following administration of single 4.8 g dose of SPD476. High fat meal increased absorption lag time (4 hr vs. 2 hr), and rate of absorption (T<sub>max</sub>: ↓2 hrs; C<sub>max</sub>: ↑91%). Food effect on the extent of absorption is small (AUC<sub>t</sub>: ↑16%; AUC<sub>0-∞</sub>: ↓10%). Because patients were instructed to take SPD476 with food in the pivotal clinical trials, the dosage recommendation will specify that SPD476 be taken with food.

### ***Multiple Dose PK (5-ASA): Fed Conditions***

The sponsor did not conduct a multiple dose study under fasting conditions.

In Study 105, both single dose and steady state PK of mesalamine and its primary metabolite (Ac-5-ASA) were determined. Two doses of SPD476 were studied (2.4 g and 4.8 g for single dose portion of the study and 2.4 g QD and 4.8 g QD for 14 days for the multiple dose portion of the study). All doses were administered 30 minutes after a standard breakfast.

The mean PK parameters following single dose and at steady state are shown in Table 3. A delay of 4 hours in absorption was observed following single dose administration which is consistent with the findings under fed conditions in Study 106. Steady state was achieved by 48 hours. Due to residual plasma concentrations and prolonged absorption process from the previous dose, T<sub>lag</sub> had generally disappeared by Day 14. The AUC<sub>0-24h</sub> at steady state was somewhat greater (↑38% for 2.4 g QD regimen; ↑9% for 4.8

g QD regimen) than would have been expected from the single dose PK assuming linear kinetics. Based on the urinary excretion data, approximately 25% and 27% of the administered dose was absorbed following single dose administration for the 2.4 g and 4.8 g doses, respectively. At steady state, approximately 21-22% of the administered dose was absorbed following administration of SPD476 at 2.4 g QD or 4.8 g QD. Since food has only a small effect on AUC, these values also approximate the extent of absorption under fasting conditions.

**Table 3: Mean PK parameters for 5-ASA following single-dose and multiple-dose administration of SPD476 under fed (standard meal) conditions (Study SPD476-105)**

Parameter <sup>1</sup> of 5-ASA (Single dose)	SPD476 2.4g (N = 28)	SPD476 4.8g (N = 28)
AUC <sub>0-t</sub> (ng.h/mL)	18573 <sup>†</sup> (10969)	47785 (22421)
AUC <sub>0-∞</sub> (ng.h/mL)	19852 <sup>†</sup> (11740)	48141 <sup>#</sup> (25627)
Cmax <sup>2</sup> (ng/mL)	2932 (2957)	4385 (3033)
Tmax (h)	8.04 (4.00-48.0)	8.04 (6.00-32.1)
Tlag (h)	4.00 (1.99-18.0)	4.00 (2.00-16.0)
t <sub>1/2</sub> (h) (Terminal Phase)	7.41 <sup>‡</sup> (4.65)	6.28 <sup>#</sup> (5.31)
Σxu <sup>3</sup> (g)	0.0388 (0.0442)	0.156 <sup>†</sup> (0.121)
% Dose Absorbed <sup>4</sup>	25.2 (10.4)	27.0 <sup>†</sup> (12.6)
Parameter <sup>1</sup> of 5-ASA (Steady State)	SPD476 2.4g QD (N = 28)	SPD476 4.8g QD (N = 24)
AUC <sub>0-24h</sub> (ng.h/mL)	22319 (13697)	49559 (23780)
Cmax (ng/mL)	2918 (2164)	5280 (3146)
Ctrough (ng/mL)	660 (528)	1424 (1261)
Tmax (h)	8.00 (0-22.0)	8.50 (6.00-22.0)
Σxu <sub>0-24h</sub> (g)	0.127 (0.105)	0.364 (0.243)
% Dose Absorbed <sup>4</sup>	22.4 (9.25)	20.8 (11.6)

<sup>1</sup>Median (min, max) data are presented for parameters tmax and Tlag, while arithmetic mean (SD) data are presented for all other parameters.

<sup>2</sup>One subject (#0047) had a Cmax of — .g/mL at 24 hours after receiving SPD476 2.4g, which was approximately 4.5-fold higher than the mean for the other subjects at the same dose level. This exceptionally high Cmax was not observed in this subject following 2.4 g QD dosing of SPD476.

<sup>3</sup>Cumulative amount of 5-ASA excreted in the urine.

<sup>4</sup>Estimated based on the total urinary excretion of 5-ASA and its metabolite, Ac-5-ASA

<sup>†</sup>N = 27; <sup>‡</sup>N = 17; <sup>#</sup>N = 18.

### **Metabolite (Ac-5-ASA):**

**Single-dose PK:** Following single-dose administration of SPD476 under fasted conditions, a lag time of approximately 2 hours for Ac-5-ASA was observed (Table 4), which was similar to that observed with the parent compound, 5-ASA. Systemic exposure and urinary excretion were greater for the metabolite compared to 5-ASA. Plasma AUC for the metabolite was more than 2-fold greater than that of the parent compound at the 1.2 g and 2.4 g doses, but was less than 2-fold at the 4.8-g dose. Like the parent compound, the variability of Ac-5-ASA PK parameters was also high.

**Table 4: Mean ( $\pm$ SD) PK parameters of Ac-5-ASA following single dose of SPD476 1.2g, 2.4g or 4.8g in the fasted state (Study SPD476-106)**

Parameter of Ac-5-ASA	SPD476 1.2g (N = 47)	SPD476 2.4g (N = 48)	SPD476 4.8g (N = 48)
AUC <sub>0-t</sub> (ng.h/mL)	27190 (14577)	52513 (29485)	85126 (45810)
AUC <sub>0-∞</sub> (ng.h/mL)	25695 <sup>†</sup> (11907)	48388 <sup>‡</sup> (31692)	82170 <sup>§</sup> (45380)
Cmax (ng/mL)	1416 (734)	2493 (1540)	3403 (1427)
Tmax* (h)	11.0 (4.0-36.0)	14.0 (4.0-34.1)	15.0 (6.0-34.0)
Tlag* (h)	2.0 (0-4.0)	2.0 (0.0-2.0)	2.0 (0.0-4.0)
t <sub>1/2</sub> (h) (Terminal Phase)	7.85 <sup>†</sup> (4.97)	10.0 <sup>‡</sup> (7.70)	11.6 <sup>§</sup> (8.71)

\* Median (min - max); <sup>†</sup>N=29, <sup>‡</sup>N=32, <sup>§</sup>N=38

### **Gender Effect:**

Across studies, no consistent trend on gender effect was observed. There were differences in study conditions with respect to meal (fasting and high fat meal in Study 106, and standard meal in Study 105). However, the observed discrepancies across studies were likely to be due to the small sample size in view of the high intersubject variability in PK.

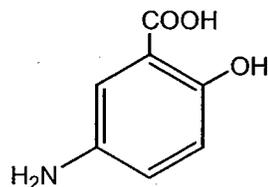
## **2. Question Based Review**

### **2.1 General Attributes**

#### **2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?**

##### **Drug Substance:**

Chemical name: 5-amino-2-hydroxybenzoic acid  
Molecular formula: C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>  
Molecular weight: 153.14



##### **Formulation:**

The goal of therapy with oral mesalamine is to formulate it for optimum drug delivery to the target area (colon and rectum). Currently, there are extended-release (Pentasa® capsules, 250 mg & 500 mg) and delayed release tablet (Asacol® tablets, 400 mg & 800

mg) formulations of mesalamine marketed for the treatment of active UC and/or the maintenance of remission in UC. The SPD476 tablet is a formulation containing 1.2 g of mesalamine per tablet (Table 5). In these tablets,

This is coated with a polymer film that breaks down at pH  $\geq 7$ , at which point the active ingredient, 5-ASA, is gradually released. The high drug loading of 5-ASA per tablet (1.2g) reduces tablet burden and the QD dosing regimen may improve subject compliance.

**Table 5: Components and Composition of SPD476 Tablets**

Ingredient	Amount (mg)	Function	Reference to Standards
<b>Drug substance(s)</b> Mesalazine	1200.0	Active ingredient	EP and USP/NF
<b>Excipient(s)</b>			
Sodium Carboxymethylcellulose			EP + USP/NF
Sodium Carboxymethylcellulose			EP + USP/NF
Carnauba Wax			EP + USP/NF
Stearic Acid			EP + USP/NF
Silica, Colloidal Hydrated			EP + USP/NF
Sodium Starch Glycolate (Type A)			EP + USP/NF
Talc			EP + USP/NF
Magnesium Stearate			EP + USP/NF
Methacrylic Acid Copolymer, Type A <sup>2</sup>			EP + USP/NF
Methacrylic Acid Copolymer, Type B <sup>2</sup>			EP + USP/NF
Triethylcitrate <sup>2</sup>			EP + USP/NF
Titanium Dioxide <sup>2</sup>			EP + USP/NF
Red Ferric Oxide (Ferric Oxide) <sup>2</sup>			USP/NF
Polyethylene glycol 6000 <sup>2</sup>			EP and USP
			EP and USP
			EP and USP
<b>Total</b>	<b>1385.0</b>		

EP: European Pharmacopoeia; NF: United States National Formulary; USP: United States Pharmacopoeia

### **2.1.2 What are the proposed mechanism of action, therapeutic indication and dosage recommendations?**

SPD476 is proposed to be used for the induction of remission in adult patients with active, mild to moderate ulcerative colitis. The proposed dosage is two to four 1.2g tablets to be taken once daily for a total daily dose of 2.4 to 4.8g.

The mechanism of action of mesalamine is not fully understood, but may be largely topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase (i.e., prostaglandins) and lipoxygenase pathways (i.e., leukotrienes and hydroxyeicosatetraenoic acids), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. Recent data also suggest that mesalamine can inhibit the activation of NF $\kappa$ B, a nuclear transcription factor that regulates the transcription of many genes for pro-inflammatory proteins.

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the pivotal clinical trials?**

Two pivotal Phase 3 trials (SPD476-301 and SPD476-302) were conducted, which were randomized, double-blind, parallel group, placebo-controlled studies. Patients with acute mild to moderate UC (total score of 4-10 on the UC Disease Activity Index and with a sigmoidoscopy score of  $\geq 1$  and a physician's global assessment score of  $\leq 2$ ) were enrolled and randomized to receive a treatment for 8 weeks. Doses of study medication were taken with food. No rescue medication was allowed during the study.

Study SPD476-301 included three treatment arms:

- SPD476 1.2g BID (N: 93 randomized; 76 completed),
- SPD 4.8 g QD (N: 94 randomized; 73 completed) and
- placebo (N: 93 randomized; 52 completed).

Study SPD476-302 had four treatment arms:

- SPD476 2.4g QD (N: 86 randomized; 70 completed),
- SPD476 4.8 g QD (N: 85 randomized; 72 completed),
- placebo ((N: 86 randomized; 52 completed) and
- Asacol® 0.8 g TID (N: 86 randomized; 70 completed).

Subjects who were in remission at the end of the 8-week treatment period of this study were given the opportunity to enroll into the open-label Maintenance Phase of extension study SPD476-303. Those who were not in remission (UCDAI score  $> 1$ ) at the End of Study/Early Withdrawal Visit of this study were given the opportunity to enroll into the Acute Phase of extension study SPD476-303.

### **2.2.2 What are the response endpoints and how are they measured in clinical studies?**

The primary endpoint for one Phase 2 trial (Study SPD476-202) and all phase 3 trials (Studies 301, 302 and 303) was induction of remission based on both clinical and endoscopic evaluations rather than clinical (symptomatic) improvement alone. The efficacy is evaluated using the UC Disease Activity Index (UCDAI), which is composed of the following four elements:

- Rectal bleeding
- Stool frequency
- Sigmoidoscopic mucosal appearance, and
- Physician assessment

The scoring system uses a 4-point categorical scale (0 to 3) for each of the four parameters of disease activity. Hence the total score can vary between zero and 12. Remission was defined as a UCDAI score of  $\leq 1$ , with a score of 0 for rectal bleeding and stool frequency and at least a one-point reduction in sigmoidoscopy score from baseline. Given the entry criteria, this definition of remission encompasses an improvement in UCDAI of at least 3 points, with an improvement in sigmoidoscopy.

Note: The pilot efficacy study SPD476-201 used the Rachmilewitz Clinical Activity Index to measure the severity and response to treatment of UC. This is a 7-point scale based on number of stools in the past week, presence of blood in the stools, abdominal pain, investigator's global assessment of disease activity, temperature related to colitis, presence of extraintestinal manifestations and alteration of laboratory findings (erythrocyte sedimentation rate, haemoglobin).

### **2.2.3 How are the dose and dosing regimen determined?**

The first Phase II clinical trial (SPD476-201) investigated the efficacy and safety of SPD476 in 79 subjects with mild to moderate left-sided UC. Dosing of SPD476 1.2g TID was compared with Asacol® rectal suspension 4 g QD. SPD476 appeared to have comparable efficacy to the Asacol® enema in inducing clinical remission and endoscopic remission.

A dose-ranging study (SPD476-202) conducted in 38 subjects with mild to moderate UC compared three different doses of SPD476 (1.2 g/d, 2.4 g/d and 4.8 g/d, all QD). There were no statistically significant differences between the three treatment groups with regards to remission after 8-weeks of treatment; however, SPD476 2.4g and 4.8g appeared to perform better than SPD476 1.2g in improvement of UCDAI total score, rectal bleeding score and PGA score at Week 8. Highest mucosal concentrations of 5-ASA and Ac-5-ASA were observed in the 4.8g QD dose group (48.8 ng/mL) compared to the 2.4 g (7.0 ng/mL) and 1.2 g (11.2 ng/mL) dose groups.

Two pivotal Phase 3 trials (SPD476-301 and 302) in a total of 623 subjects with acute mild to moderate UC compared the percentage of subjects in remission after 8 weeks of

treatment between SPD476 and placebo. Both studies demonstrated that SPD476 was efficacious in the induction of remission when compared to placebo. The response rates for all treatments in the two Phase 3 trials are shown in Table 6.

**Table 6: Response rate for treatment arms in Study SPD476-301**

	Subjects (%) in remission	Odds ratio	CI	p-value
Placebo; N = 85	11 (12.9)			
SPD476 2.4g/day BID; N = 88 versus placebo	30 (34.1)	3.48	(1.44, 8.41)	0.001
SPD476 4.8g/day QD; N = 89 versus placebo	26 (29.2)	2.78	(1.27, 6.06)	0.009

Study SPD476-302:

SPD476 2.4g QD (40.5%; odds ratio: 2.47),  
 SPD476 4.8 g QD (41.2%; odds ratio: 2.40),  
 Placebo: (22.1%;) and  
 Asacol® 0.8 g TID (32.6%).

In either study, there was no statistically significant difference in efficacy between the two dosing regimens studied. Even so, the sponsor is proposing to include both 2.4 g QD and 4.8 g QD regimens in the package insert. These data are currently being evaluated by the clinical division.

**2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?**

*Overall, PK data from Studies SPD476-105 and SPD476-106 are considered reliable. All other studies (CRO-00-15, CRO-PK-00-42, \_\_\_\_\_ and SPD476-103) had questionable PK data as described in Section 1.3. The sponsor's attempt to correct data in Study SPD476-103 was evaluated before the submission of Study SPD476-106 and is described below.*

Study SPD476-103 is a food effect study. The sponsor attempted to correct the affected data from this study by modeling the degradation process using various equations. However, none of the equations used by the sponsor is considered adequate. In addition, in a stability study (YAH/063), degradation rate at -20°C was found to be quite different for samples prepared on different days. Apparently, some unknown factors that were not well controlled in the study can affect the degradation rate. As such, no modeling can correct this problem without further understanding of the degradation process and data correction for Study 103 is impossible. The details are given below.

(1) Correction of data using a polynomial equation:

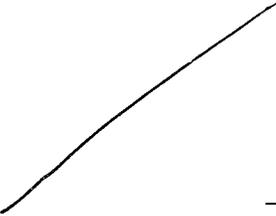
$$y = -1E-05x^3 + 0.0068x^2 - 1.0464x + 101.89$$

The sponsor conducted a stability study at -20°C using spiked samples at three initial concentrations of 5-ASA (5, 800 and 1500 ng/mL; Study YBS-054). The sponsor pooled the stability data from samples of various initial concentrations stored at -20°C for 17, 46 and 68 days and combined them with literature data (Table 7). These data were then fitted to a polynomial equation with the storage time as the sole variable. The data points and the best fit curve are shown in Figure 1. The equation is not suitable for correction purposes because of the following reasons:

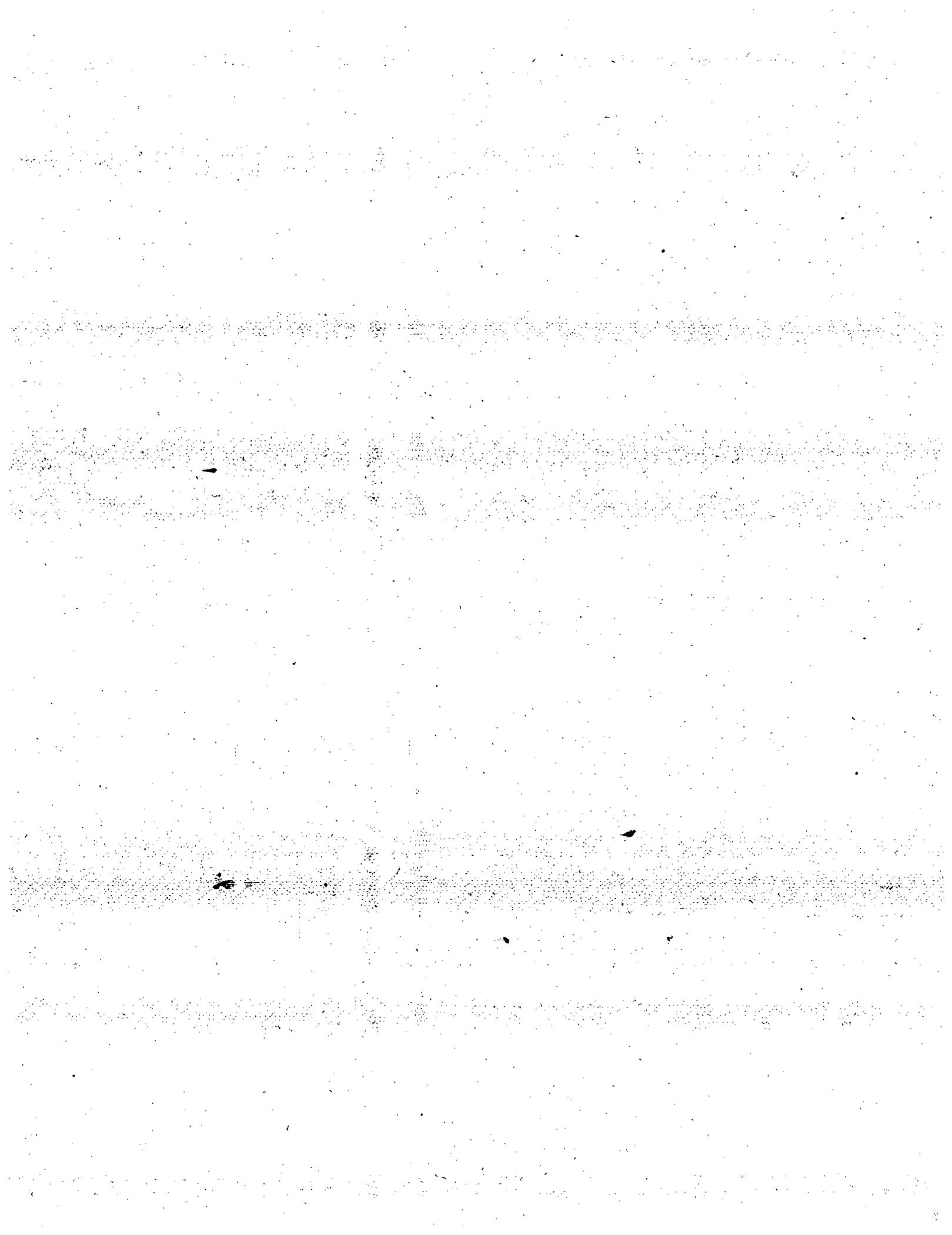
1. Pooling the sponsor's data and literature data for the analysis assumes these data were obtained under similar experimental conditions, which may not be true.
2. The data from Brendel et. al. as shown in the plot do not match those presented in the original article<sup>1</sup>. Even if the data in the plot are correct, these data scatter about the predicted value to a high degree, indicating poor precision of the prediction based on the equation.
3. For the sponsor's data, the equation underpredicts at x=17 days and overpredicts at x= 46 days. In other words, the equation can smooth out the data, thus minimizing the degradation. It is noted that there are no spiked samples with storage times between 17 and 46 days.
4. It is noted that the equation gives a curve that goes upward at x ~120 days after the initial decline and then downward at x > 200 days. This is against conventional scientific belief.

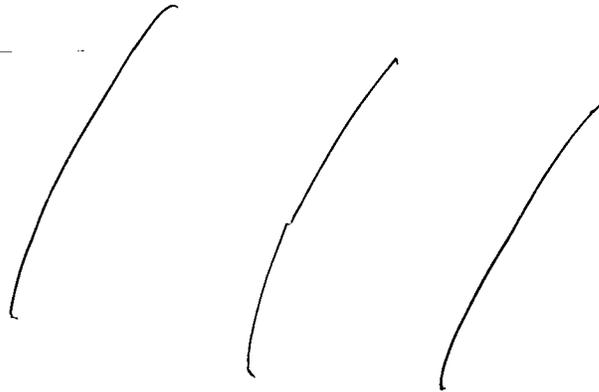
Table 7: Pooled stability data for the polynomial equation

Days Storage	% Degradation	% Remaining	Source	Number of timepoints
0			N/a	N/a
17			YBS/054	12
42			Brendel et al. <sup>1</sup>	3
46			YBS/054	18
68			YBS/054	12
90			Brendel et al. <sup>1</sup>	3
175			Tjornelund & Hansen <sup>2</sup>	1
245			Tjornelund & Hansen <sup>2</sup>	1



**APPEARS THIS WAY  
ON ORIGINAL**

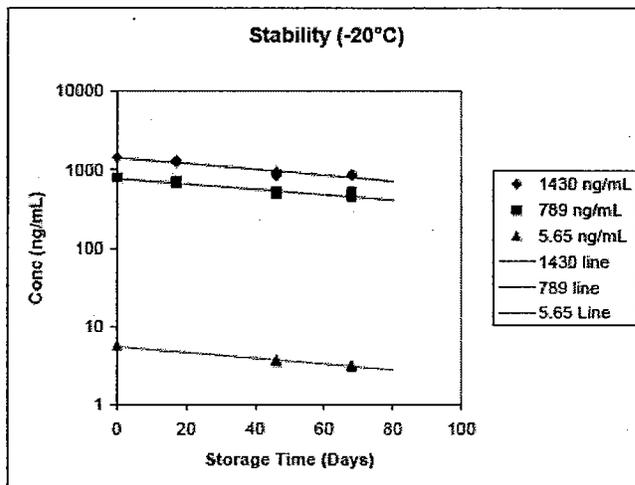




**Figure 1: Decline in 5-ASA in plasma samples stored at nominal -20°C using experimental and published data**

**(2) Correction based on first order degradation kinetics (Arrhenius equation):**

Using data from controls samples of three different initial concentrations (5.65, 789 and 1430 ng/mL) stored at -20C for various time periods up to 72 days (Study YAH/049), the first order degradation rate was determined to be  $-0.00832/\text{day} \pm 0.00045/\text{day}$ . However, the plot did not reveal variability and it is unknown whether the data from other studies would behave the same way.



**Figure 2: First order reaction rates fitted to stability data of 5-ASA in plasma at -20°C.**

(3) **Correction using an equation of constant degradation rate**

$$y=100.000-0.472x\text{Time}$$

$$95\% \text{ CI for the Slope} = (-0.513, -0.432)$$

Spiked plasma samples were prepared at 5, 800 and 1500 ng/mL and stored at nominal -20°C for various periods up to 73 days before being analyzed against freshly prepared calibration standards. In all, some 114 (excluding baseline) data points were derived from this additional analysis and used in this further assessment of depletion of 5-ASA in plasma. Data from the two batches of QC samples, used in the original test sample analysis in study SPD476-103 (YBS study YAH/049) which added a further 200 data points) were also included and the whole data set fitted using a simple linear regression model. The regression line underpredicts when storage times were >40 days. A closer look at the stability data revealed inconsistency in the data from Study 063. Samples prepared on two different days had very different degradation rates. Apparently, some unknown factors that were not controlled in Study 063 can affect the degradation rate. As such, data correction for Study 103 is impossible without further understanding of the degradation process.

Figure 3: Linear regression of stability data from Study YAH063 and QC data from Study 049

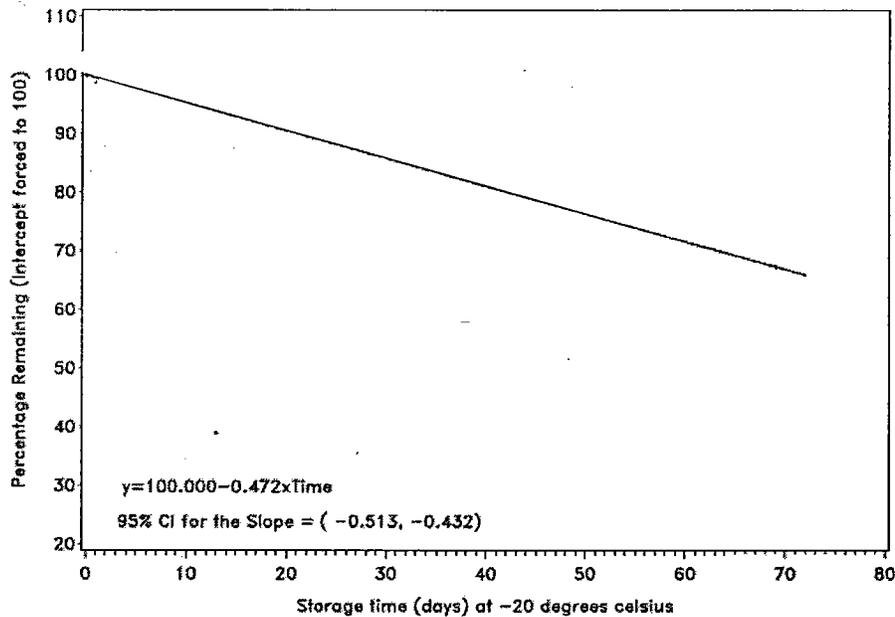
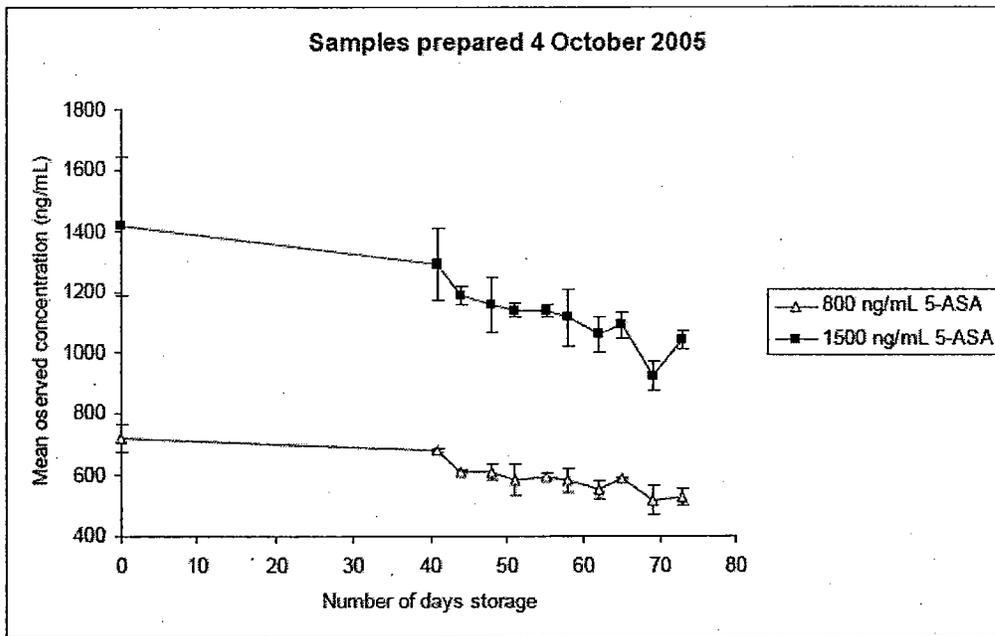
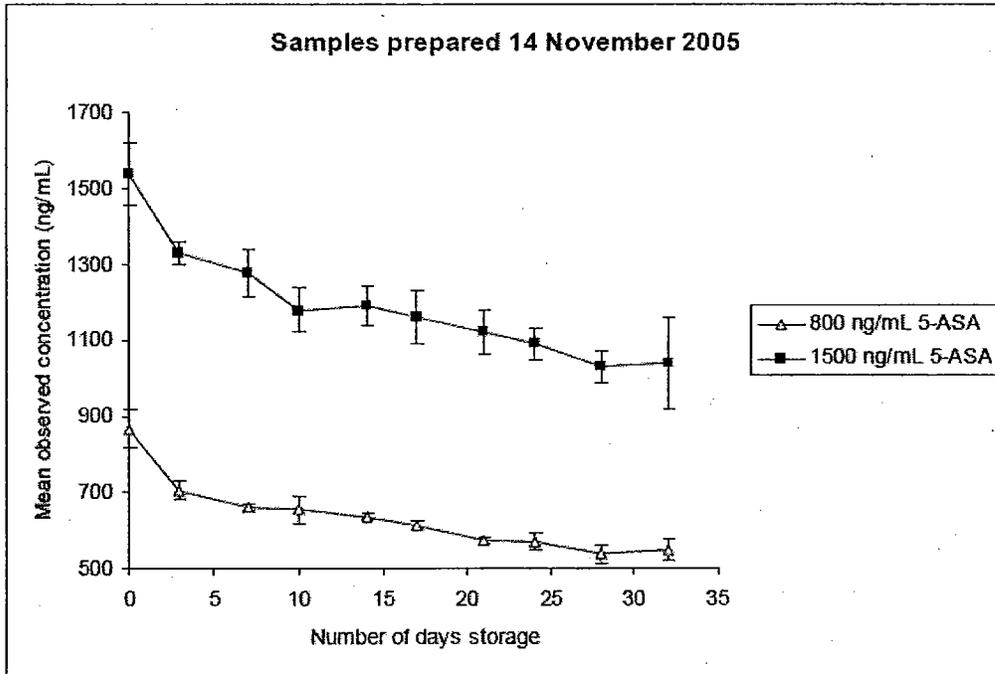


Figure 4. Regression of combined data sets from YAH/049 and YAH/063) at nominal initial concentrations of 800, 1500 and 2500 ng/mL

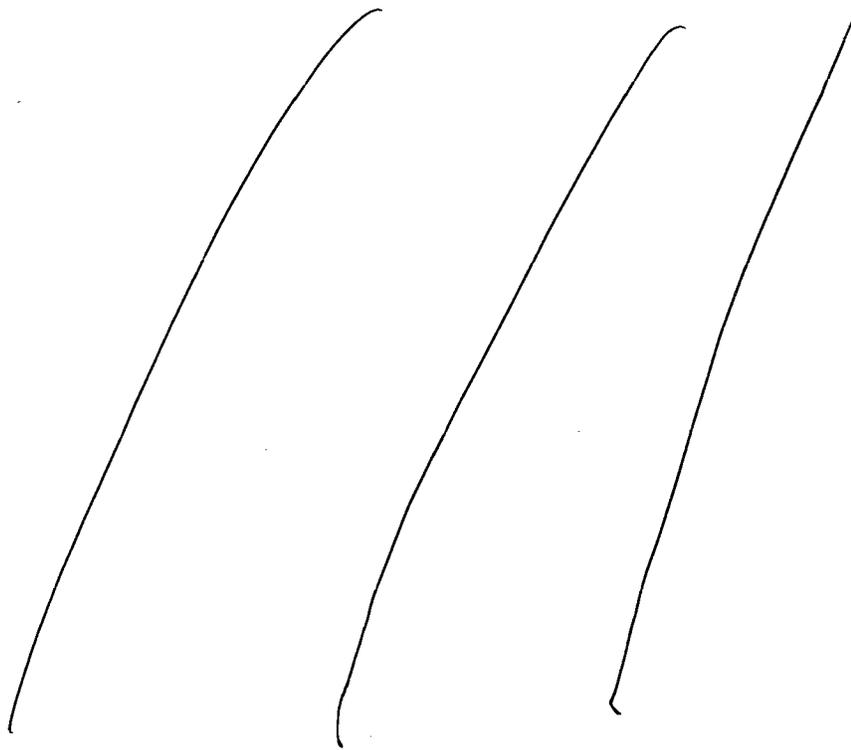


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  ✓   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process



**2.2.6 What are the basic pharmacokinetic parameters for SPD476 following oral administration?**

***Single Dose PK:***

The sponsor conducted a study in which single dose of SPD476 1.2 g, 2.4 g or 4.8 g was administered to healthy subjects under fasting conditions. The plasma 5-ASA concentration-time profiles for these doses were characterized by a median lag-time (T<sub>lag</sub>) of 2 hours. An inspection of individual concentration profiles revealed that some profiles had two peaks, occurring at around 6 hours and 12 hours postdose, respectively. Some subjects had a very late peak (around 30 hours postdose). The absorption process appeared to be prolonged (> 10 hrs) in many subjects and half-life determined in the terminal phase might represent the absorption process rather than the elimination process in some subjects. The pharmacokinetics parameters following administration of SPD476 were *highly variable* with a CV ranging from 53% to 93% (Figure 6; Table 8).

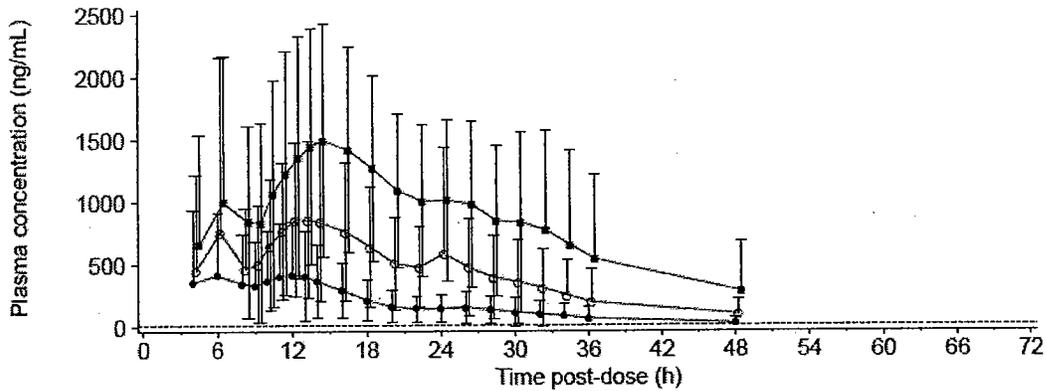


Figure 6: Arithmetic Mean ( $\pm$  SD) Plasma Concentration-Time Profiles of 5-ASA Following a Single Oral Dose of 1.2g, 2.4g and 4.8g SPD476 (Fasted)

Table 8: Mean (SD) PK parameters for 5-ASA following single dose administration of SPD476 under fasting conditions

Parameter <sup>†</sup> of 5-ASA	SPD476 1.2g (N = 47)	SPD476 2.4g (N = 48)	SPD476 4.8g (N = 48)
AUC <sub>0-t</sub> (ng.h/mL)	9039 <sup>†</sup> (5054)	20538 (12980)	41434 (26640)
AUC <sub>0-∞</sub> (ng.h/mL)	9578 <sup>†</sup> (5214)	21084 <sup>§</sup> (13185)	44775 <sup>#</sup> (30302)
C <sub>max</sub> (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T <sub>max</sub> * (h)	9.0** (4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
T <sub>lag</sub> * (h)	2.0** (0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
t <sub>1/2</sub> (h) (Terminal Phase)	8.56 <sup>†</sup> (6.38)	7.05 <sup>§</sup> (5.54)	7.25 <sup>#</sup> (8.32)

<sup>†</sup>Arithmetic mean of parameter values are presented except for T<sub>max</sub> and T<sub>lag</sub>.

\*Median (min, max); <sup>†</sup>N=43, <sup>‡</sup>N=27, <sup>§</sup>N=33, <sup>#</sup>N=36, \*\*N=46

### Dose Proportionality:

Dose proportionality was studied across the dose range of 1.2 - 4.8 g under fasting conditions. Between 1.2 g and 2.4 g doses, both C<sub>max</sub> and AUC<sub>∞</sub> were similar based on the geometric least square means. At the dose of 4.8 g, C<sub>max</sub> was less than dose proportional while AUC<sub>0-∞</sub> was slightly more than dose proportional compared to the two lower doses.

Geometric least squares (LS) mean ratios and 90% CIs for 5-ASA bioavailability parameters following doses of 1.2g, 2.4g and 4.8g SPD476.

Dose normalised parameter	Ratio of 2.4g:1.2g	Ratio of 4.8g:1.2g	Ratio of 4.8g:2.4g
AUC <sub>0-t</sub>	1.13 (0.953, 1.33)	1.05 (0.889, 1.24)	0.933 (0.794, 1.10)
AUC <sub>0-∞</sub>	1.01 (0.822, 1.24)	1.13 (0.925, 1.39)	1.12 (0.925, 1.36)
C <sub>max</sub>	1.07 (0.823, 1.40)	0.796 (0.610, 1.04)	0.740 (0.569, 0.963)

Geometric LS mean ratio (90% CI) data are presented

**Multiple-dose PK:**

Study SPD476-105 was a single- and multiple-dose study. It was an open-label, two-period, randomized, parallel group study in healthy subjects. A total of 52 subjects (26 males and 26 females) completed the study. Subjects were given a single dose of SPD476 2.4g or SPD476 4.8g in Period 1. Period 2 was a multiple-dose treatment period where subjects received the same dose they received in Treatment Period 1, SPD476 2.4g or 4.8g QD for 14 days. All doses were given half an hour after a standard breakfast. Serial blood and urine samples were collected following Day 1 dosing in Period 1 and Day 14 dosing in Period 2. Trough concentrations were determined on various dosing days in Period 2.

Mean plasma concentration-time profiles following single and multiple dosing of SPD476 are presented in Figures 7-a (2.4 g dose) and 7-b (4.8 g dose)

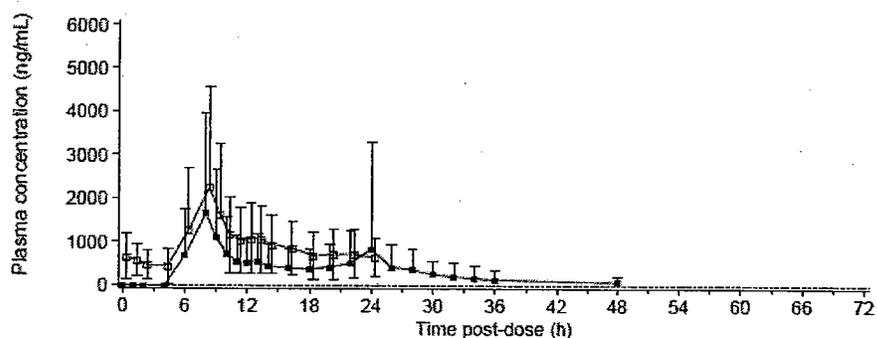


Figure 7-a: Mean (+/-SD) Plasma Concentration Time Profiles for 5-ASA following Administration of Single Dose (2.4 g; Day 1, Period 1; symbol: ■) and Multiple Doses (2.4 g QD; Day 14, Period 2; symbol: □) of SPD476

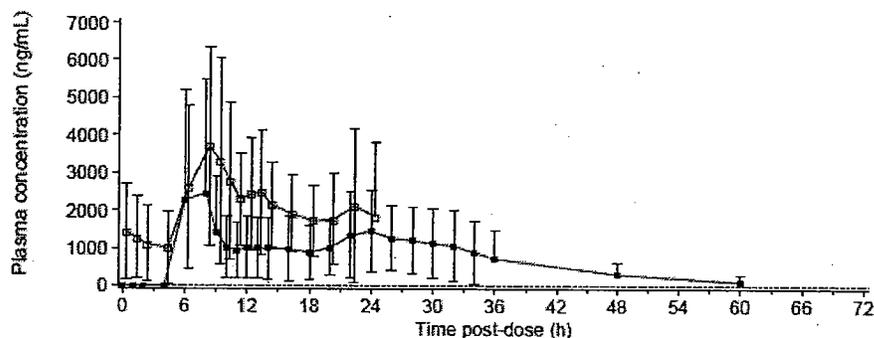


Figure 7-b: Mean (+/-SD) Plasma Concentration Time Profiles for 5-ASA following Administration of Single Dose (4.8 g; Day 1, Period 1; symbol: ■) and Multiple Doses (4.8 g QD; Day 14, Period 2; symbol: □) of SPD476

*Single-dose portion of the study:* As indicated above, plasma concentrations among individuals were highly variable. Following single dose administration under fed conditions, 5-ASA was not detected in the plasma for the first 4 hours (range: 2-18

hours). Peak plasma concentration of 5-ASA occurred at approximately 8 hours postdose. In some subjects, double peaks were observed. Mean PK parameters are presented in Table 9. (It appears that Cmax was less than dose proportional while AUC was more than dose proportional when the dose was increased from 2.4 g to 4.8 g.) Based on urinary recovery of 5-ASA and its metabolite, Ac-5-ASA, it is estimated that 25-27% of the administered dose was absorbed into systemic circulation.

*Multiple-dose portion of the study:* Following 2.4 g QD or 4.8 g QD dosing, steady state was achieved by 48 hours for the majority of subjects based on visual examination of the trough 5-ASA plasma concentrations for individual subjects. Mean steady state PK parameters are presented in Table 9. Due to residual plasma concentrations and prolonged absorption process from the previous dose, Tlag had generally disappeared by Day 14 and steady state Cmax were generally greater than following single dose administration. The AUC<sub>0-24h</sub> at steady state was somewhat (9-38%) greater than would have been expected from the single dose PK if 5-ASA had followed linear kinetics. Based on urinary excretion of 5-ASA and Ac-5-ASA, approximately 21-22% of the administered dose was absorbed into systemic circulation. Based on the urinary excretion data, approximately 21-22% of the administered dose was absorbed following administration of SPD476 at 2.4 g QD or 4.8 g QD. Since food has only a small effect on AUC, these values also approximate the extent of absorption under fasting conditions.

**Table 9: Mean PK parameters for 5-ASA following single-dose and multiple-dose administration of SPD476 under fed (standard meal) conditions**

Parameter <sup>1</sup> of 5-ASA (Single dose)	SPD476 2.4g (N = 28)	SPD476 4.8g (N = 28)
AUC <sub>0-t</sub> (ng.h/mL)	18573 <sup>†</sup> (10969)	47785 (22421)
AUC <sub>0-∞</sub> (ng.h/mL)	19852 <sup>‡</sup> (11740)	48141 <sup>#</sup> (25627)
Cmax <sup>2</sup> (ng/mL)	2932 (2957)	4385 (3033)
Tmax (h)	8.04 (4.00-48.0)	8.04 (6.00-32.1)
Tlag (h)	4.00 (1.99-18.0)	4.00 (2.00-16.0)
t <sub>1/2</sub> (h) (Terminal Phase)	7.41 <sup>‡</sup> (4.65)	6.28 <sup>#</sup> (5.31)
Σxu <sup>3</sup> (g)	0.0388 (0.0442)	0.156 <sup>†</sup> (0.121)
% Dose Absorbed <sup>4</sup>	25.2 (10.4)	27.0 <sup>†</sup> (12.6)
Parameter <sup>1</sup> of 5-ASA (Steady State)	SPD476 2.4g QD (N = 28)	SPD476 4.8g QD (N = 24)
AUC <sub>0-24h</sub> (ng.h/mL)	22319 (13697)	49559 (23780)
Cmax (ng/mL)	2918 (2164)	5280 (3146)
Ctrough (ng/mL)	660 (528)	1424 (1261)
Tmax (h)	8.00 (0-22.0)	8.50 (6.00-22.0)
Σxu <sub>0-24h</sub> (g)	0.127 (0.105)	0.364 (0.243)
% Dose Absorbed <sup>4</sup>	22.4 (9.25)	20.8 (11.6)

<sup>1</sup>Median (min, max) data are presented for parameters tmax and Tlag, while arithmetic mean (SD) data are presented for all other parameters.

<sup>2</sup>One subject (#0047) had a Cmax of — ng/mL at 24 hours after receiving SPD476 2.4g, which was approximately 4.5-fold higher than the mean for the other subjects at the same dose level. This exceptionally high Cmax was not observed in this subject following 2.4 g QD dosing of SPD476.

<sup>3</sup>Cumulative amount of 5-ASA excreted in the urine.

<sup>4</sup>Estimated based on the total urinary excretion of 5-ASA and its metabolite, Ac-5-ASA

<sup>†</sup>N = 27; <sup>‡</sup>N = 17; <sup>#</sup>N = 18.

**Metabolite: Ac-5-ASA**

*Study SPD-106 (single dose, fasting conditions):* The metabolite Ac-5-ASA demonstrated similar disposition to that of the parent compound (5-ASA), with the shapes of the plasma concentration-time profiles mirroring those of 5-ASA. Like the parent compound, the variability of Ac-5-ASA PK parameters was also high. Ac-5-ASA appeared in plasma at the same time as 5-ASA. Following single-dose administration of SPD476 under fasted conditions, a lag time of approximately 2 hours for Ac-5-ASA was observed, which was similar to that observed with the parent compound, 5-ASA. Systemic exposure and urinary excretion were greater for the metabolite compared to 5-ASA. Plasma AUC for the metabolite was more than 2-fold greater than that of the parent compound at the 1.2 g and 2.4 g doses, but was less than 2-fold at the 4.8-g dose.

**Table 10: Mean (±SD) PK parameters of Ac-5-ASA following single dose of SPD476 1.2g, 2.4g or 4.8g (Study SPD-106; fasting conditions)**

Parameter of Ac-5-ASA	SPD476 1.2g (N = 47)	SPD476 2.4g (N = 48)	SPD476 4.8g (N = 48)
AUC <sub>0-t</sub> (ng.h/mL)	27190 (14577)	52513 (29485)	85126 (45810)
AUC <sub>0-∞</sub> (ng.h/mL)	25695 <sup>†</sup> (11907)	48388 <sup>‡</sup> (31692)	82170 <sup>§</sup> (45380)
C <sub>max</sub> (ng/mL)	1416 (734)	2493 (1540)	3403 (1427)
T <sub>max</sub> * (h)	11.0 (4.0-36.0)	14.0 (4.0-34.1)	15.0 (6.0-34.0)
T <sub>lag</sub> * (h)	2.0 (0-4.0)	2.0 (0.0-2.0)	2.0 (0.0-4.0)
t <sub>1/2</sub> (h) (Terminal Phase)	7.85 <sup>†</sup> (4.97)	10.0 <sup>‡</sup> (7.70)	11.6 <sup>§</sup> (8.71)

\* Median (min - max); <sup>†</sup>N=29, <sup>‡</sup>N=32, <sup>§</sup>N=38

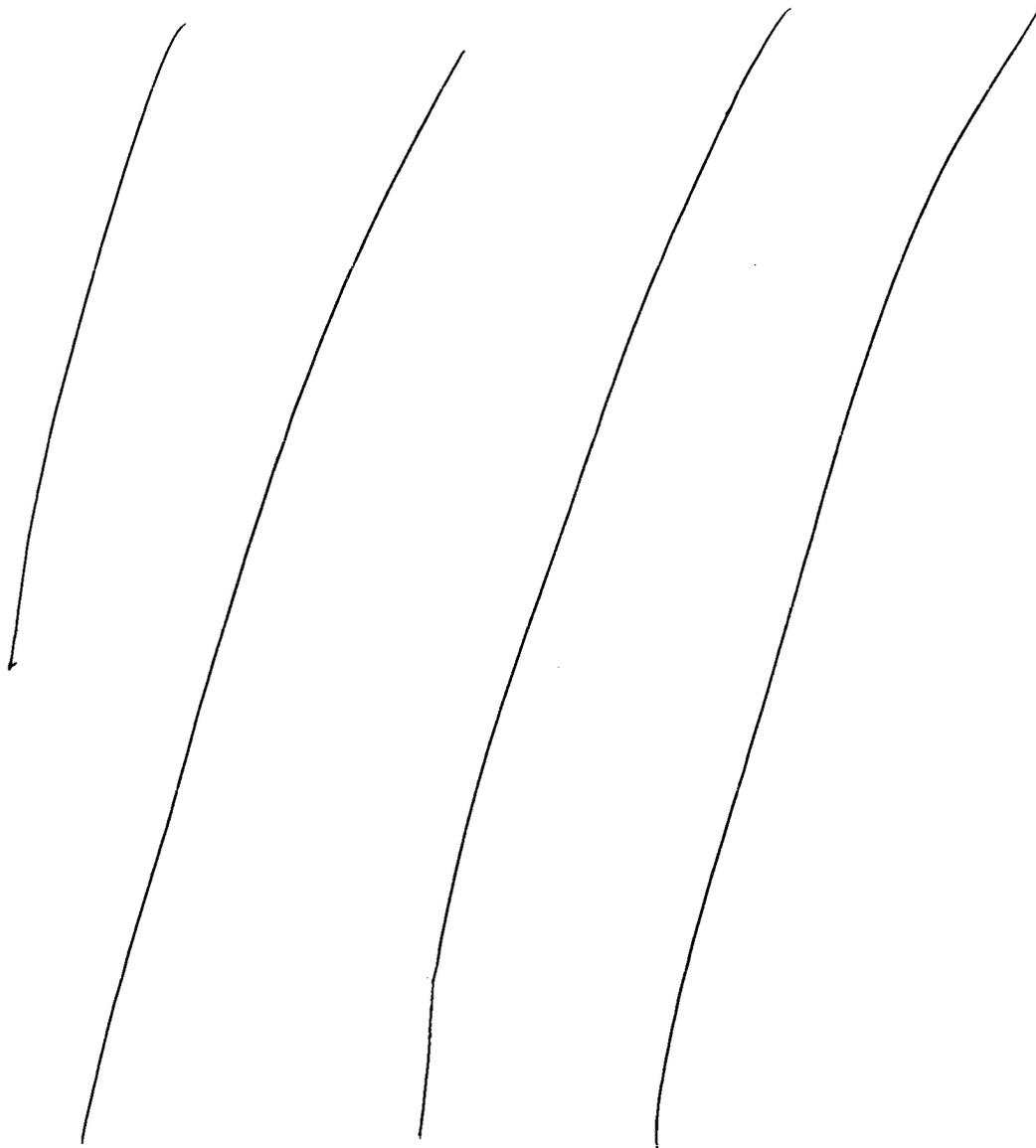
*Study SPD-105 (multiple-dose, fed condition):* Systemic exposure to Ac-5-ASA was greater than that to 5-ASA as noted above, and high variability in the metabolic ratio was observed (0.98 to 9.3) for single and multiple doses of SPD476 2.4g and 4.8g. Compared to that following single dose administration, Ac-5-ASA AUC appeared to decrease while C<sub>max</sub> remained about the same following multiple dosing (Table 10). Renal clearance of Ac-5-ASA exceeded glomerular filtration rate. The amount of Ac-5-ASA excreted in the urine generally accounted for >80% of the absorbed dose following single dose administration.

**Table 11: Mean PK parameters of Ac-5-ASA following single dose administration and at Steady State (Study SPD-105; fed conditions)**

Parameter* of Ac-5-ASA	SPD476 2.4g (N = 28)	SPD476 4.8g (N = 28)
<i>Single Dose</i>		
AUC <sub>0-t</sub> (ng.h/mL)	51401 (23848)	107289 (41266)
AUC <sub>0-∞</sub> (ng.h/mL)	56830 <sup>†</sup> (27732)	109498 <sup>‡</sup> (44838)
C <sub>max</sub> (ng/mL)	3429 (2211)	5535 (2596)
T <sub>max</sub> (h)	9.00 (6.00-48.0)	9.00 (6.00-36.1)
T <sub>lag</sub> (h)	4.00 (1.99-20.0)	4.00 (2.00-14.0)
t <sub>1/2</sub> (h)	9.76 <sup>†</sup> (6.92)	12.6 <sup>‡</sup> (11.3)
Σxu (g)	0.721 (0.294)	1.45 <sup>#</sup> (0.678)

CLR (L/h)	14.8 (3.78)	13.4 <sup>#</sup> (3.81)
<i>Steady State (following QD dosing)</i>		
AUC <sub>0-24h</sub> (ng.h/mL)	41254 (16096)	67845 (28385)
C <sub>max</sub> (ng/mL)	3573 (1912)	5493 (2995)
C <sub>trough</sub> (ng/mL)	1543 (872)	2127 (1342)
T <sub>max</sub> (h)	8.02 (0-22.0)	9.51 (6.00-22.0)
Σx <sub>u</sub> (g)	0.522 (0.160)	0.809 (0.413)
CLR (L/h)	13.5 (3.37)	11.9 (3.13)

<sup>†</sup>N=14, <sup>‡</sup>N=25, <sup>#</sup>N=27



## 2.3 Intrinsic Factors

### Gender effect

Across studies, no consistent trend on gender effect was observed. There were differences in study conditions with respect to meals (fasting and high fat meal in Study 106, and standard meal in Study 105). However, the observed discrepancies across studies were likely to be due to the small sample size in view of the high intersubject variability in PK.

*Study SPD-106 (single dose, fasting & fed conditions):* In this study, 5-ASA AUC<sub>0-inf</sub> tended to be somewhat higher and C<sub>max</sub> somewhat lower in females compared to males (Table 14).

*Note:* There is an error in Table 14. Mean AUC<sub>0-t</sub> for female subjects following administration of SPD476 2.4 g under fasted conditions should be 19735 ng.h/mL, and not 197354 ng.h/mL.

**Table 14: Summary of PK Parameters of 5-ASA in Male and Female Subjects Following Single Doses of SPD476 in the Fed and Fasted States**

Parameter of 5-ASA	SPD476 1.2g (Fasted)		SPD476 2.4g (Fasted)	
	Males (N=24)	Females (N=23)	Males (N=24)	Females (N=24)
AUC <sub>0-4</sub> (ng.h/mL)	8263 <sup>†</sup> (5133)	9931 <sup>†</sup> (4940)	21340 (15199)	197354 (10580)
AUC <sub>0-∞</sub> (ng.h/mL)	8305 <sup>§</sup> (5185)	10760 <sup>*</sup> (5141)	19550 <sup>**</sup> (14979)	22528 <sup>††</sup> (11521)
C <sub>max</sub> (ng/mL)	866 (601)	848 (688)	1964 (1944)	1226 (663)
t <sub>max</sub> <sup>*</sup> (h)	8.51 (4.00-26.0)	10.0 (4.00-32.1)	11.0 (4.00-30.0)	14.0 (4.00-34.1)
t <sub>lag</sub> <sup>*</sup> (h)	2.00 (0-8.00)	2.00 (0-6.03)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
t <sub>1/2</sub> (h)	6.45 <sup>§</sup> (5.24)	10.5 <sup>*</sup> (6.88)	5.83 <sup>**</sup> (3.69)	8.20 <sup>††</sup> (6.76)
Parameter of 5-ASA	SPD476 4.8g (Fasted)		SPD476 4.8g (Fed)	
	Males (N=24)	Females (N=24)	Males (N=24)	Females (N=23)
AUC <sub>0-4</sub> (ng.h/mL)	41435 (28780)	41434 (24940)	53877 (42133)	50191 (41606)
AUC <sub>0-∞</sub> (ng.h/mL)	42564 <sup>‡‡</sup> (34183)	46985 <sup>‡‡</sup> (26676)	55630 <sup>††</sup> (45764)	58448 <sup>§§</sup> (48507)
C <sub>max</sub> (ng/mL)	2213 (1311)	2094 (964)	6452 (5946)	3855 (3109)
t <sub>max</sub> <sup>*</sup> (h)	11.0 (4.00-34.0)	14.0 (4.00-34.0)	8.00 (4.00-26.0)	14.0 (6.00-48.0)
t <sub>lag</sub> <sup>*</sup> (h)	2.00 (1.00-4.00)	2.00 (2.00-4.00)	4.00 (1.00-10.0)	4.00 (1.00-18.0)
t <sub>1/2</sub> (h)	6.30 <sup>‡‡</sup> (10.5)	8.20 <sup>‡‡</sup> (5.49)	9.40 <sup>††</sup> (8.82)	7.15 <sup>§§</sup> (4.59)

Arithmetic mean (SD) data are presented

\* Median (min-max)

† N=23, ‡ N=20, § N=13, #N=14, \*\*N=16, †† N=17, ‡‡ N=18, §§N=15

Source: PK Report (Appendix 3.1), Section 4, Table 10.

*Study SPD-105 (single- & multiple-dose, fed condition):* The PK parameters of 5-ASA following single and multiple doses of SPD476 2.4g and 4.8g in male and female subjects

under fed conditions are presented in Table 15. Systemic exposure of 5-ASA appeared to show some gender differences, with AUC and Cmax generally being 1.1- to 1.9-fold higher in females, regardless of dose level or dosing regimen. Even after normalization for body weight, exposure remained higher in females compared to males (generally being 1.0- to 1.7-fold higher in females for weight-adjusted AUC and Cmax for 5-ASA).

**Table 15: Summary of PK Parameters of 5-ASA in Male and Female Subjects Following Single and Multiple Doses of SPD476 (Study SPD-105)**

Parameter* of 5-ASA	SPD476 2.4g		SPD476 4.8g	
	Males (N = 14)	Females (N = 14)	Males (N = 14)	Females (N = 14)
<b>Single dose:</b>				
AUC <sub>0-4</sub> (ng.h/mL)	13637 <sup>†</sup> (8893)	23156 (10985)	36436 (21744)	59135 (17144)
AUC <sub>0-∞</sub> (ng.h/mL)	14432 <sup>‡</sup> (8306)	24671 <sup>#</sup> (12640)	39391 <sup>**</sup> (24396)	61891 <sup>††</sup> (22536)
C <sub>max</sub> (ng/mL)	1991 (1954)	3874 (3526)	4167 (3139)	4603 (3025)
t <sub>max</sub> (h)	8.00 (4.00-48.0)	8.52 (6.00-34.0)	8.00 (6.00-32.0)	10.0 (6.00-32.1)
T <sub>lag</sub> (h)	4.00 (1.99-9.00)	4.00 (2.00-18.00)	2.00 (2.00-16.0)	4.00 (2.00-16.0)
t <sub>1/2</sub> (h)	7.02 <sup>‡</sup> (4.23)	7.75 <sup>#</sup> (5.22)	5.76 <sup>**</sup> (6.33)	7.10 <sup>††</sup> (3.46)
ΣXu (g)	0.0273 (0.0369)	0.0503 (0.0491)	0.108 <sup>†</sup> (0.120)	0.201 (0.108)
CL <sub>R</sub> (L/h)	1.49 <sup>†</sup> (1.56)	2.00 (1.73)	2.51 <sup>†</sup> (1.69)	3.31 (1.32)
% Dose Absorbed	22.2 (11.5)	28.2 (8.47)	21.9 <sup>†</sup> (10.5)	31.8 (12.8)
<b>Multiple dose:</b>				
AUC <sub>0-∞</sub> (ng.h/mL)	17851 (9545)	26788 (15985)	38784 <sup>###</sup> (24990)	60335 <sup>###</sup> (17452)
C <sub>semax</sub> (ng/mL)	2442 (1671)	3394 (2539)	4000 <sup>###</sup> (3308)	6559 <sup>###</sup> (2486)
C <sub>ssmin</sub> (ng/mL)	449 (277)	870 (638)	978 <sup>###</sup> (912)	1870 <sup>###</sup> (1435)
t <sub>max</sub> (h)	8.00 (1.00-20.0)	8.00 (0-22.0)	9.50 <sup>###</sup> (6.00-16.0)	8.00 <sup>###</sup> (6.00-22.0)
T <sub>lag</sub> (h)	0 (0-0)	0 (0-0)	0 (0-4.0)	0 (0-0)
R <sub>ss</sub>	1.61 <sup>‡</sup> (0.705)	1.17 <sup>#</sup> (0.611)	0.928 <sup>#</sup> (0.717)	1.37 <sup>††</sup> (0.474)
R <sub>obsAUC</sub>	2.28 <sup>‡</sup> (1.45)	2.08 (1.10)	8.35 <sup>###</sup> (22.0)	4.54 <sup>###</sup> (6.14)
R <sub>obsCmax</sub>	3.35 (6.24)	1.06 (0.564)	1.36 <sup>###</sup> (1.01)	2.01 <sup>###</sup> (1.15)
ΣXu (g)	0.0994 (0.0702)	0.155 (0.128)	0.273 <sup>###</sup> (0.253)	0.455 <sup>###</sup> (0.203)
CL <sub>R</sub> (L/h)	5.61 (1.92)	5.40 (2.48)	5.38 <sup>###</sup> (3.52)	7.36 <sup>###</sup> (1.94)
% Dose Absorbed	21.2 (5.01)	23.6 (12.2)	16.6 <sup>###</sup> (12.2)	25.0 <sup>###</sup> (9.75)

Median (min - max) data are presented for parameters t<sub>max</sub> and T<sub>lag</sub>, while arithmetic mean (SD) data are presented for all other parameters.

†N = 13; ‡N = 8; #N = 9; \*\*N = 11; ††N = 7; ###N = 12; .††N = 5

## 2.4 Extrinsic Factors

### 2.4.1 Food effect

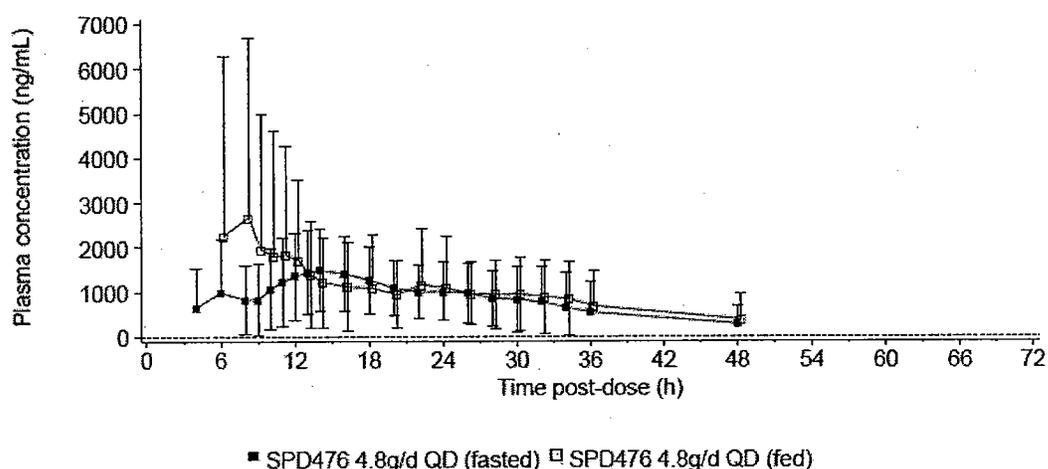
Food effect was observed in Study SPD476-106.

Following administration of 4.8g SPD476 in the fed state (30 minutes after the start of a high fat breakfast) the shape of the absorption profile for 5-ASA was different from that obtained in the fasted state. Although subjects generally showed two or more peaks, the initial sharp peak predominated under fed conditions which occurred slightly later, at 8 hours post-dose. The more protracted peak was also delayed in the fed state, occurring at approximately 24 hours post-dose. In addition, there was a more prolonged lag phase compared to the fasted state (median T<sub>lag</sub>: 4hrs vs. 2 hrs).

Mean AUC differed by less than 20% between the two dietary states, however, mean C<sub>max</sub> was 91% higher in the fed state. Some individuals (nine subjects: seven male, two female) achieved C<sub>max</sub> in excess of 10 μg/mL (range — μg/mL). Of these subjects, four out of nine showed increases in systemic exposure of more than two-fold compared to values in the fasted state. However, the overall range of systemic exposures did not differ substantially in the fed and fasted states.

High fat meal increased median absorption lag time (4 hr vs. 2 hr), decreased median T<sub>max</sub> (10 hr vs. 12 hr) and increased systemic exposure (mean C<sub>max</sub>: ↑91%; mean AUC: ↑16%).

**Figure 8: Mean (± SD) Plasma Concentration-Time Profiles of 5-ASA Following a Single Oral Dose of 4.8g SPD476 in the Fed and Fasted States**



**Table 16: Summary of PK Parameters of 5-ASA Following a Single Dose of 4.8g SPD476 in the Fed and Fasted States for All Subjects**

Parameter of 5-ASA	SPD476 4.8g (fed) (N=47)	SPD476 4.8g (fasted) (N=48)	Ratio of geometric LS means (90% CI) (fed:fasted)
AUC <sub>0-t</sub> (ng.h/mL)	52073 (41460)	41434 (26640)	1.16 (0.909, 1.48)
AUC <sub>0-∞</sub> (ng.h/mL)	56951 <sup>†</sup> (46320)	44775 <sup>‡</sup> (30302)	0.898 (0.673, 1.20)
C <sub>max</sub> (ng/mL)	5181 (4901)	2154 (1140)	1.91 (1.48, 2.47)
AUC <sub>0-med t<sub>max</sub></sub> (ng.h/mL)	15911 (20234)	8296 (6432)	1.19 (0.787, 1.79)
AUC <sub>0-24</sub> (ng.h/mL)	29580 (26398)	23195 (13098)	1.08 (0.821, 1.41)
t <sub>max</sub> <sup>*</sup> (h)	10.0 (4.00-48.0)	12.0 (4.00-34.0)	-0.967 <sup>§</sup> (-3.50, 1.51)
t <sub>lag</sub> <sup>*</sup> (h)	4.00 (1.00-18.0)	2.00 (1.00-4.00)	2.00 <sup>§</sup> (1.50, 3.50)
t <sub>1/2</sub> (h)	8.35 <sup>‡</sup> (7.14)	7.25 <sup>‡</sup> (8.32)	NC

Arithmetic mean (SD) data are presented; N = Number of subjects studied; NC = Not calculated  
<sup>\*</sup> Median (min - max), <sup>†</sup>N=32, <sup>‡</sup>N=36, <sup>§</sup>Median difference



Figure 9: Evaluation of Different Dissolution Conditions for SPD476 Tablets (Batch DR005)

This dissolution method and specification can differentiate SPD476 from Asacol formulation (Figure 10).

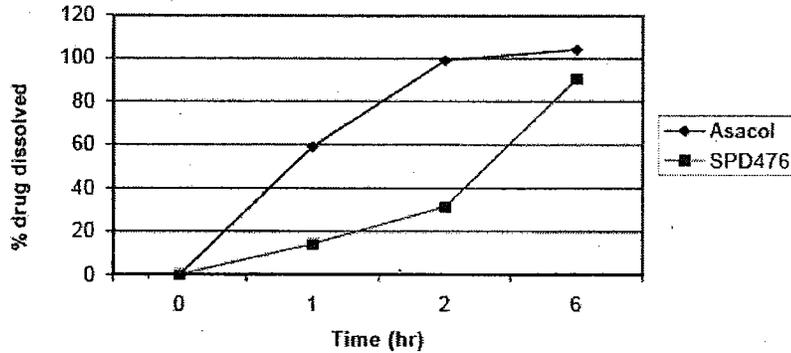


Figure 10: Dissolution Profiles of SPD476 Tablet and Asacol in pH 7.2 Buffer  
(Reviewer's note: The time scale in this plot is not linear.)

**Reviewer's Comment:**

During the stability studies, it was noted that the dissolution results at the pH7.2, 2-hour time point increased with time. Because the clinical batches were used in successful efficacy studies, the age of the batches used in the pivotal clinical studies was therefore noted and the dissolution results at the pH7.2, 2-hour time point noted. The dissolution specification for SPD476 1.2g tablets has therefore been set on the basis of the data from batches used during the pivotal clinical studies and also the stability data. The dissolution points for the clinical batches and the dissolution data from the stability studies for the critical pH 7.2, 2 hr time point are presented in Figures 11 and 12.

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Deliberative Process

## 2.6. Analytical Methods

### 2.6.1 Are the analytical methods used to quantify the active moieties adequately validated?

*The analytical method validation data for Studies SPD476-105 and SPD476-106 are acceptable. It is noted, however, that storage of sample extracts at RT for 48 hours is pushing the stability limit. The sponsor should consider to establish a more appropriate storage time (e.g., 24 hours).*

The analytical method validation as described below refers to samples that were stored on or below  $-80^{\circ}\text{C}$  unless specified otherwise. Plasma and urine samples were analyzed at

Plasma samples:

Human plasma samples were assayed for 5-ASA and Ac-5-ASA using a validated bioanalytical method. The method utilized \_\_\_\_\_ followed by \_\_\_\_\_ and liquid chromatography with tandem mass spectrometric detection in the negative ion mode. \_\_\_\_\_ was the internal standard. The lower limit of quantification (LLOQ) was \_\_\_\_\_/mL with a higher limit of quantification (HLOQ) of \_\_\_\_\_ or a 100 $\mu\text{L}$  plasma aliquot.

**Table 17: Validation results for assay of 5-ASA and Ac-5-ASA in plasma samples**



#### **Reviewer's Comment:**

The analytical method validation data performed at \_\_\_\_\_ for Studies SPD476-105 and SPD476-106 did not include stability of 5-ASA in plasma samples stored at  $-80^{\circ}\text{C}$ . However, we will not request additional data because of the following reasons:

1. The sponsor provided a published article that reported the stability of 5-ASA in plasma samples stored at various temperatures. These authors concluded that 5-ASA was stable for at least 3 months in plasma samples stored at -80°C although it was unstable in samples stored at -20°C.
2. The sponsor had the storage condition validated by another contract laboratory using quality control samples containing 30, 200 and 3200 ng/mL of 5-ASA, respectively. The results indicated that 5-ASA was stable for 7 months in plasma samples stored at -80°C.

The above stability information is useful since the plasma samples from Studies SPD476-105 and SPD476-106 were stored at -80°C for a shorter time period (up to 59 days) compared to the studied sample storage time period.

**Urine samples:**

Human urine samples were assayed for 5-ASA and Ac-5-ASA using a validated bioanalytical method. The method utilized \_\_\_\_\_ followed by liquid chromatography with tandem mass spectrometric detection in the negative ion mode. The LLOQ was \_\_\_\_\_ with a HLOQ of \_\_\_\_\_ µg/mL for a 100 µL urine aliquot.

**Table 18: Validation results for assay of 5-ASA and Ac-5-ASA in urine samples**



**3. Detailed Labeling Recommendations**

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           Trade Secret / Confidential

           Draft Labeling

           Deliberative Process

## 4.2 Appendix 2: OCP Filing and Review Form

<b>Office of Clinical Pharmacology</b>				
<b>New Drug Application Filing and Review Form</b>				
General Information About the Submission				
	Information		Information	
NDA Number	22-000		Brand Name	
OCP Division (I, II, III)	III		Generic Name	
Medical Division	Division of Gastroenterology Products	Drug Class	Not well defined (COX inhibitor)	
OCP Reviewer	Sue-Chih Lee, Ph.D.	Indication(s)	Induction of remission in patients with active, mild to moderate ulcerative colitis (UC)	
OCP Acting Team Leader	Abi Adebowale, Ph.D.	Dosage Form	Tablets	
Date of Submission	12/21/05	Proposed Dosing Regimen	2.4 g QD or 4.8 g QD	
Estimated Due Date of OCP Review	Dec. 15, 2006	Route of Administration	Oral	
Medical Division Due Date	Dec 22, 2006	Sponsor	Shire	
PDUFA Due Date	Jan. 19, 2006	Priority Classification	Standard	
<b>Clin. Pharm. and Biopharm. Information</b>				
	"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.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				References provided
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:	X	2	2	
multiple dose:	x	2	1	
<b>Patients-</b>				
single dose:				
multiple dose:		1	1	Part of a Phase 2 study but was not well conducted
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:	x	2	2	Inconsistent results likely due to small sample size.
pediatrics:				

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 -				
solution as reference:				
alternate formulation as reference:	X	1		Pilot study
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2	2	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	33	6	
Simulations				
Total Number of Studies			11	
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm				
QBR questions (key issues to be considered)	Reliability of bioassay was a major issue. On 5/31/06, the sponsor submitted a fed single- and multiple-dose study. However, there was still other information missing due to the stability issue. On 8/29/06, the sponsor submitted a new study with several components (e.g., fasting PK, food effect and dose proportionality) in response to the stability issue. As such, this problem was resolved. However, the PDUFA due date was extended for 3 months.			
Other comments or information not included above				
Primary reviewer Signature and Date	Sue-Chih Lee, Ph.D. 12/12/06			
Secondary reviewer Signature and Date	Abimbola Adebawale, Ph.D.			

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/s/

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Sue Chih Lee  
12/20/2006 04:44:03 PM  
BIOPHARMACEUTICS

Abi Adebawale  
12/21/2006 10:54:19 AM  
BIOPHARMACEUTICS