

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-000

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: January 16, 2007

FROM: Brian E. Harvey, M.D., Ph.D.
Division Director, DGP/ODE III/OND

SUBJECT: Division Director Concurrence Memo
NDA 22-000

APPLICANT: Shire US Inc.

DRUG: Lialda (mesalamine) Delayed Release Tablets

DATE SUBMITTED: December 21, 2005

DIVISION RECOMMENDATION:

The primary Medical Officer and Medical Team Leader have both recommended that NDA 22-000, Lialda (mesalamine) Tablets be approved for the induction of remission of active, mild to moderate ulcerative colitis (UC) in adults at the proposed dose of 2.4g/day or 4.8g/day given once daily for 8 weeks. The review teams have concluded that the data supported only the use of the term "Delayed Release". Neither the _____, nor _____ is supported by the data submitted by the sponsor. I concur with these recommendations.

I. BACKGROUND:

Lialda (mesalamine) is a new oral formulation of the established non-steroidal anti-inflammatory agent, mesalamine (5-aminosalicylic acid), for the induction of remission of active, mild to moderate UC in adults. The sponsor stated that their product utilizes a novel MMX Multi Matrix System™ (MMX) drug-delivery technology that provides delayed release of mesalamine throughout the colon.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. DSI/DDMAC/DMETS:

The DDMAC and DMETS consultations were obtained for their perspectives on the proposed proprietary name. DMETS did not recommend either of the proposed proprietary names of "Mesavant" or "Mesavance". After rejecting these original trade names, an alternative name "Lialda" has been found to be acceptable by DMETS.

DDMAC found the proprietary names Lialda, Mesavant and Mesavance acceptable from a promotional perspective.

As outlined by the Medical Team leader, three clinical sites were inspected by the Division of Scientific Investigations (DSI). These studies appeared to have been well conducted at all three of the sites. DSI did not recommend any special follow up and the clinical team agreed that routine surveillance should be continued.

B. CHEMISTRY AND MANUFACTURING:

The sponsor proposed that their product be called "delayed release". Superimposed upon this name issue, there were issues regarding storage temperature and product stability. After extensive discussions with the sponsor and the review team, the sponsor decided to call their drug "Delayed Release" and not have the requirement that the drug be refrigerated once it had been dispensed to the patient. The team also stated that the phrase "See USP Controlled Room Temperature" is appropriate for this product's label based upon the current data.

With the sponsor's decision to use only the term "Delayed Release", there are no outstanding chemistry issues based upon their review. The Chemistry Review Team has recommended approval of this product.

C. PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY:

The primary Pharmacology/Toxicology reviewer and team leader concluded that the NDA may be approved with the labeling changes which have now been finalized. The review team did not recommend that additional nonclinical studies

be conducted. The review team did not report any unresolved nonclinical safety issues based upon their review of this data.

D. BIOPHARMACEUTICS:

As outlined by the Medical Team Leader, the Clinical Pharmacology Team concluded that the Clinical Pharmacology and Biopharmaceutics data information in this NDA is acceptable. This team also agreed with the sponsor's decision to use only the term "Delayed Release". There are no outstanding Clinical Pharmacology issues based upon their review. The sponsor agreed to accept the team's proposed changes to the product label. The Clinical Pharmacology Team has recommended approval of this product.

E. CLINICAL AND STATISTICAL:

Both the primary Medical Officer and the Medical Team Leader provided a detailed review and analysis of the clinical data submitted in support of this NDA. The sponsor submitted data from two phase III studies to support the proposed indication for the induction of remission of active, mild to moderate UC in adults.

The clinical team concluded that both submitted studies (Study 301 and Study 302) successfully demonstrated that the sponsor's drug was effective in the induction of remission of active, mild to moderate UC in adults. Both of the studied doses (2.4g/day and 4.8g/day) were superior to placebo for the primary efficacy endpoint. In addition, both doses also provided consistent benefits in secondary efficacy variables. Both doses appeared to have similar efficacy profiles across both studies.

From a safety perspective, the clinical team concluded that the overall safety profile of this new formulation of mesalamine, at both doses studied, was similar to the observed events of other products in the same class. No new safety issues were identified in the reviewed clinical studies. The incidence and type of adverse events were similar among the three treatment groups in each placebo controlled study and did not demonstrate a dose related increase in adverse events across the groups.

The clinical team did not report any unresolved issues based upon their review of this data and has recommended approval of this product. The statistical team has completed their review and have not raised any issues that would prevent the approval of this drug.

E. PEDIATRIC USE:

The sponsor requested a partial waiver of pediatric studies for children < 6 years. The Division denied this request since the sponsor's justification was inadequate. Although this specific tablet may be too large to be used by these younger children, the sponsor was advised to develop age-appropriate formulations or provide a rationale why this cannot be done. Therefore, the Division granted a deferral for pediatric studies required under PREA. The sponsor is required to

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III. RECOMMENDATIONS FOR REGULATORY ACTIONS

The primary Medical Officer and Medical Team Leader both recommend that NDA 22-000, Lialda (mesalamine) Tablets be approved for the induction of remission of active, mild to moderate ulcerative colitis (UC) in adults at the proposed dose of 2.4g/day or 4.8g/day given once daily for 8 weeks. I concur with these recommendations.

I concur with the conclusion that the current data supports only the use of the term "Delayed Release" and that neither _____ are supported by the submitted data.

I concur with the granting of a deferral for pediatric studies required under PREA. The sponsor is required to _____

I concur that additional Phase 4 commitments or a Risk Management Plan are not justified based upon the current data and analysis.

IV. LABELING RECOMMENDATIONS

After discussions with the sponsor and the review team, I concur with the negotiated label as attached to the approval letter dated January 16, 2007 for this NDA 22-000.

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

/s/

Brian Harvey
1/16/2007 02:51:48 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/16/2007

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

TO: Brian Harvey, MD, Ph.D.
Director
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 22-000

APPLICANT: Shire US Inc.

DRUG: Lialda (mesalamine) Delayed Release Tablets

RECOMMENDATION:

I concur with Dr. Fathia Gibril's recommendations that NDA 22-000, Lialda (mesalamine) be approved for the induction of remission of active, mild to moderate ulcerative colitis (UC) in adults. The recommended dose is 2.4g/day or 4.8g/day given once daily for 8 weeks. To get approval, the sponsor should incorporate the Division's labeling recommendations.

The sponsor is requesting a partial waiver of pediatric studies for children < 6 years. I recommend that this request be denied due to the inadequate justification (i.e. large tablet size). The sponsor was advised to develop age-appropriate formulations or provide a rationale why this is not possible (advise letter dated August 3, 2006).

The Division granted deferral for pediatric assessments for the indication until the efficacy and safety data are available in adults. The sponsor is required to

There are no other Phase 4 commitment, request or risk management steps recommended.

I. BACKGROUND:

Lialda (mesalamine) is a new oral formulation of the established non-steroidal anti-inflammatory agent, mesalamine (5-aminosalicylic acid), for the induction of remission of active, mild to moderate UC in adults.

The exact mechanism of action of mesalamine is not fully understood, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways 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.

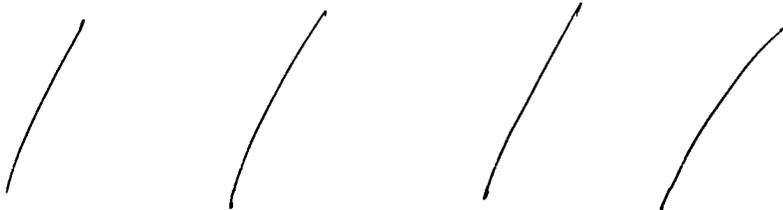
There is an armamentarium of approved mesalamine-containing various oral formulations for the treatment of mildly to moderately active UC, including Sulfasalazine and Colazal® (prodrug formulations), Asacol® (delayed release tablets) and Pentasa® (controlled-release capsules). Mesalamine is also marketed as rectal preparations including Canasa® (rectal suppositories) and Rowasa® (rectal suspension enema) for the treatment of distal active UC.

In this NDA, the sponsor provided 2 phase III studies to support Lialda (mesalamine) for the induction of remission of active, mild to moderate UC in adults. The rationale for the development program was that Lialda (mesalamine) has the highest unit dose of mesalamine (1.2g per tablet), thus it requires fewer tablets per day than available oral mesalamine formulations to deliver a therapeutic dose which is more convenient for patients and may result in better compliance.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

DMETS does not recommend the use of the proprietary names, Mesavant and Mesavance.



DMETS has no objections to the use of the proprietary name, Lialda. This is considered a final decision.

DDMAC finds the proprietary name Lialda, Mesavant and Mesavance acceptable from a promotional perspective.

Three clinical sites were inspected by the Division of Scientific Investigations. The studies appear to have been well conducted at all the sites. No follow up other than routine surveillance is recommended. See Dr. Leslie Ball's review dated August 2, 2006 for details.

B. Chemistry and Manufacturing:

From the CMC perspective, this NDA is recommended for approval. All CMC issues have been satisfactorily resolved and an overall recommendation of Acceptable has been made by the Office of Compliance, according to Dr. George Lunn, CMC reviewer for this NDA. There is no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Based on Dr. Lunn's evaluation, the drug substance meets USP and EP specifications. Satisfactory batch analyses are provided for: — lots from — 3 lots from — and 3 lots from — that have been — Up to — of satisfactory stability data are supplied for batches from each supplier.

The drug product is a formulation that the sponsor claims exhibits delayed — release characteristics. Each tablet contains 1.2 g mesalamine. After an extensive discussion the term "delayed release" was agreed between FDA CMC team and the sponsor.

According to Dr. George Lunn, if in the future

For more detail information, please see Dr. George Lunn's review dated January 3, 2007.

C. Pre-Clinical Pharmacology/Toxicology:

Pharmacology Reviewer, Dr. David Joseph, recommended that the application be approved for the proposed indication and no recommendation for nonclinical studies.

The Sponsor submitted two published reports containing pharmacology studies, in support of a statement in the proposed labeling that provides new information about the mechanism of action. One of these studies demonstrated that treatment of ulcerative colitis patients with mesalamine (1.5-4.5 g/day) produced a decrease in NF- κ B activation in the affected colon segments. The other study showed that mesalamine (20 mM) prevented TNF- α activation of NF- κ B in mouse colon cell cultures.

The toxicity of mesalamine was previously evaluated in repeat-dose studies in mice (13 weeks), rats (13 and 52 weeks), and monkeys (13 and 52 weeks). These studies were presented in the Pharmacology Review of NDA 20,049 dated June 3, 1991. In all species, kidney was the primary target organ of toxicity. Renal toxicity occurred at dose levels of 1200 mg/kg/day and higher in mice, 480 mg/kg/day and higher in rats, and 250 mg/kg/day and higher in monkeys. The severity of the renal lesions was sufficient to produce death in rats at 1200 mg/kg/day and in monkeys at 250 mg/kg/day. However, a NOAEL (no observed adverse effect level) or tolerated dose was established in each of the repeat-dose toxicity studies.

In addition, there are reports of renal toxicity (e.g. interstitial nephritis) in humans given mesalamine therapy. Given the results of the clinical studies with Lialda, and the extensive human experience with approved products containing mesalamine, Dr. Joseph concluded that the renal effects in animals are not considered to be a major safety concern. However, the final labeling should contain information about renal toxicity in animals, similar to that in the approved labeling for Pentasa®.

D. Biopharmaceutics:

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.

The proposed 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.

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 for up to 59 days. These studies were not affected by the stability issues. Please see Dr. Sue-Chih Lee's review in details.

E. Clinical/Statistical:

Efficacy:

The application is primarily supported by data from two placebo controlled phase III studies (Study 301 and Study 302). Both studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in adults with mildly to moderately active UC. While both studies were of similar design, used the same inclusion/exclusion criteria and efficacy endpoints, an additional arm of Asacol 2.4g/day TID (approved formulation) was included in Study 302 as an internal reference. Both studies used Lialda doses of 2.4g/day and 4.8g/day administered once daily (QD) for 8 weeks except for the 2.4g/day group in Study 301, which was given in two divided doses (1.2g BID).

A total of 280 subjects were enrolled in Study 301 and 343 subjects were enrolled in Study 302. Across both studies, the treatment groups were comparable in regard to demographic and baseline characteristics. The study population was primarily Caucasian, had a mean age of 42 years and the proportions of males and females were well balanced. The majority of subjects have never previously smoked and < 10% was current smokers. The disease extent was classified as left-sided disease in the majority of subjects.

In both pivotal studies (Study 301 and Study 302) the primary efficacy endpoint was the proportion of subjects who were in remission at Week 8. Remission was defined as ulcerative colitis disease activity index (UC-DAI) score of ≤ 1 , with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

The efficacy results are summarized in the table below.

Proportion of Subjects in Remission at Week 8

	Mesavance		Placebo n (%)
	2.4g/day n (%)	4.8g/day n (%)	
Study-301	n=88	n=89	n=85
Subjects in Remission	30 (34.1)	26 (29.2)	11 (12.9)
p-value	0.001	0.009	
Study-302	n=84	n=85	n=86
Subjects in Remission	34 (40.5)	35 (41.2)	19 (22.1)
p-value	0.010	0.007	
Pooled Studies	n=172	n=174	n=171
Subjects in Remission	64 (37.2)	61 (35.1)	30 (17.5)
p-value	<0.001	<0.001	

In Study 301, at Week 8 significantly greater proportion of subjects was in remission in

2.4g/day and 4.8g/day groups compared to placebo group (34.1% and 29.2% versus 12.9%), the differences were statistically significant in favor of both active treatment groups ($p=0.001$ and $p=0.009$, respectively).

In Study 302, the primary efficacy analysis showed similar results in which statistically significant differences were seen between each active treatment group (2.4 g/day and 4.8 g/day) and placebo group in favor of active treatments (40.5% and 41.2% vs 22.1%; $p=0.010$ and $p=0.007$, respectively).

Major secondary efficacy endpoints included clinical improvement, defined as a drop in the UC-DAI score of ≥ 3 points from baseline; Clinical remission, defined as subjects who scored 0 for both stool frequency and rectal bleeding (complete resolution of symptoms); Change from baseline in sigmoidoscopy scores and Treatment failure, defined as unchanged, worsened or missing UC-DAI score.

In Study 301, clinical improvement was achieved in 55% (49/88) of subjects in 2.4g/day and 59% (53/89) in 4.8g/day groups compared to 25% (22/85) in placebo group ($p<0.001$ for both doses). Similarly, significantly higher proportion of subjects achieved clinical remission in both active treatment groups compared to placebo group (37.5% and 32.6% vs 18.8%; $p<0.05$). The proportion of subjects with improved sigmoidoscopy scores was significantly greater in the 2.4g/day and 4.8g/day active treatment groups (65%, 57/88 and 72%, 64/89, respectively) compared to the placebo group (37%, 31/85), $p=0.002$ and $p<0.001$, respectively. In regard to treatment failure, significantly higher proportion of subjects was classified as treatment failure in the placebo group (54%, 46/85) compared to 2.4g/day (28%, 25/88) and 4.8g/day groups (24%, 22/89); $p<0.001$.

Similar results were observed in Study 302. Greater proportion of subjects achieved clinical improvement in the 2.4g/day (60%, 51/84) and 4.8g/day groups (64%, 55/85) compared to the placebo group (39%, 34/86), $p=0.006$ and $p<0.001$, respectively. Similarly, significantly higher proportion of subjects achieved clinical remission in both active treatment groups compared to placebo group (41.7% and 41.2% vs 22.1%; $p<0.01$). The proportion of subjects with improved sigmoidoscopy scores was greater in the 2.4g/day (70%, 59/84) and 4.8g/day groups (76%, 65/85) compared to the placebo group (41%, 36/86), $p<0.001$. Significantly higher proportion of subjects was classified as treatment failure in the placebo group (48%, 41/86) compared to the 2.4g/day (21%, 18/84) and 4.8g/day groups (20%, 17/85), $p<0.001$ for both doses.

In conclusion, both studies (Study 301 and Study 302) successfully demonstrated that Lidlda is effective in the induction of remission of active, mild to moderate UC in adults. Both doses (2.4g/day and 4.8g/day) were superior over placebo for the primary efficacy endpoint. Both Lidlda doses also provided consistent benefits in secondary efficacy variables. Both doses appeared to have similar efficacy profiles across both studies as well as pooled studies, suggesting that the high dose would not provide additional clinical benefits.

Safety:

Lialda was evaluated in 655 UC patients in controlled and open-label trials. Of a total of 621 UC patients randomized in controlled studies, 356 received 2.4g/day or 4.8g/day, 179 received placebo and 86 received Asacol (approved formulation).

In pooled analyses of safety data, the percentage of subjects who experienced treatment emergent adverse events (AEs) was similar with placebo and active treatment groups (approximately 35%).

Treatment-related AEs experienced at least by 1% of any Lialda groups (2.4 g/day and 4.8 g/day) and at the rate greater than placebo were headache (5.6%, 3.4% and 0.6%, respectively), flatulence (4%, 2.8%, and 2.8%, respectively), increased alanine aminotransferase (0.6%, 1.1%, 0%, respectively), alopecia (0%, 1.1%, 0%, respectively) and pruritus (0.6%, 1.1% and 0%, respectively). None of alanine aminotransferase changes were deemed to be clinically significant.

The majority of AEs were mild or moderate in severity. The percentage of patients with severe AEs was higher in the placebo group than in 2.4g/day and 4.8g/day active treatment groups (6.2%, 1.1% and 2.2%, respectively). The most common severe AEs were GI disorders which were mainly symptoms associated with UC. Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with Lialda in patients experiencing this event. A lower percentage of Lialda patients discontinued therapy due to AEs compared to placebo (2.2% vs 7.3%). The most frequent AE leading to discontinuation from the therapy was exacerbation of UC (0.8%).

Ten subjects (5 with placebo, 3 with Lialda 2.4g/day and 2 with 4.8g/day) experienced a total of 13 serious adverse events (SAEs). The majority of SAEs (10/13 events) were GI disorders, mostly colitis or UC (7/10). All SAEs were reported to be unrelated to study medication except for two cases of pancreatitis in Lialda group (one with each dose) deemed serious secondary to hospitalization. Both patients recovered from their episodes of pancreatitis. There were no deaths in the Placebo-controlled Pool.

Lialda has not been approved for use in any country. However, the active ingredient of Lialda (i.e. mesalamine) is also the active ingredient in a number of products marketed throughout the world and has a well established safety profile.

In conclusion, the overall safety profile of Lialda was as expected according to the drug class. No new safety issues were identified in the reviewed clinical studies. Both Lialda doses were reasonably safe and tolerated. The incidence and type of adverse events were similar among the three treatment groups in each placebo controlled study and did not indicate dose related increase in adverse events across the groups.

F. Pediatric Use:

The sponsor is requesting a partial waiver of pediatric studies for children < 6 years. I recommend that this request be denied due to the inadequate justification (i.e. large tablet size). The sponsor was advised to develop age-appropriate formulations or provide a rationale why this is not possible (advise letter dated August 3, 2006).

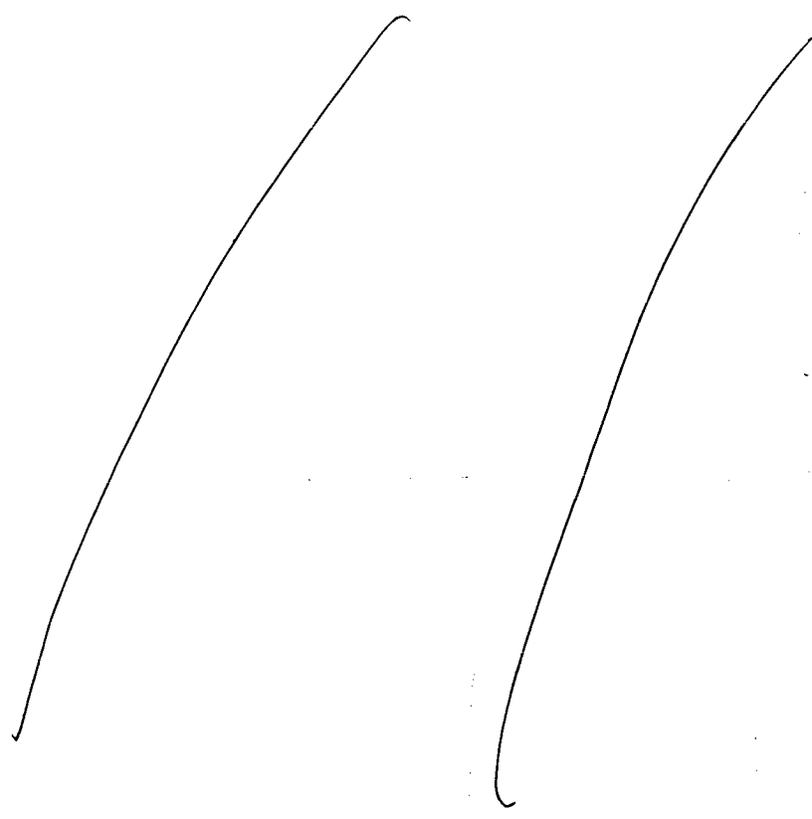
The Division granted deferral for pediatric assessments for the indication until the efficacy and safety data are available in adults. The sponsor is required to

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III. Labeling Recommendations:

I concur with Dr. Fathia Gibril and review team's labeling recommendations listed in her review. The major labeling recommendations are summarized below (Strikethrough represents deletion, while underline represents addition).

- Modify CLINICAL TRIALS section as following:



1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

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/s/

Ruyi He
1/16/2007 12:11:38 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-000
Submission Code 0000

Letter Date 12/21/05
Stamp Date 12/21/05
PDUFA Goal Date 01/19/07

Reviewer Name Fathia Gibril, M.D., M.H.Sc.
Review Completion Date 11/16/06

Established Name Mesalamine
(Proposed) Trade Name Mesavance
Therapeutic Class Anti-inflammatory
Applicant Shire

Priority Designation Standard

Formulation Tablet
Dosing Regimen 2.4g and 4.8g once daily
Indication Induction of remission of active,
mild to moderate ulcerative colitis
Intended Population Adult Males and Females

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation for approval of Mesavance for the induction of remission of active, mild to moderate ulcerative colitis (UC) in adults pending satisfactory labeling negotiations with the sponsor. The recommended dose is 2.4g/day or 4.8g/day given once daily for 8 weeks. The recommendation is based on two similarly designed placebo controlled clinical trials demonstrating clinically meaningful and statistically significant efficacy findings and an acceptable safety profile. Both Mesavance doses were safe and well tolerated. The incidence and type of adverse events were similar among the three treatment groups in each placebo controlled study and did not indicate dose related increase in adverse events across the Mesavance groups.

Note: In this review the proposed Trade Name, Mesavance, has been used. However, it should be pointed out that the final agreement between the sponsor and Agency regarding Trade Name designation for the product has not been reached at the time this review was completed.

1.2 Recommendation on Postmarketing Action

1.2.1 Risk Management Activity

There is no active risk management program requested for this new drug application (NDA).

1.2.2 Required Phase 4 Commitments

No phase 4 requests are required for this approval.

The Division granted deferral for pediatric assessments for the indication until the efficacy and safety data are available in adults. The sponsor is required to

The request for a partial waiver for children < 6 years of age was denied due to the inadequate justification (i.e. large tablet size). The sponsor was advised to develop age-appropriate formulations or provide a rationale why this is not possible (advise letter dated August 3, 2006).

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests for this NDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In the current NDA 22-000 submission, the sponsor (Shire) is seeking approval of Mesavance, a new oral formulation of the established non-steroidal anti-inflammatory agent, mesalamine (5-aminosalicylic acid), for the induction of remission of active, mild to moderate UC in adults. The rationale for the development program was that Mesavance has the highest unit dose of mesalamine (1.2g per tablet), thus it requires fewer tablets per day than available oral mesalamine formulations to deliver a therapeutic dose which is more convenient for patients and may result in better compliance.

The application is primarily supported by data from two placebo controlled phase III studies (Study 301 and Study 302). Both studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies to evaluate the efficacy and safety of Mesavance in adults with mildly to moderately active UC. While both studies were of similar design, used the same inclusion/exclusion criteria and efficacy endpoints, an additional arm of Asacol 2.4g/day TID (approved formulation) was included in Study 302 as an internal reference. However, the comparison of interest was Mesavance versus placebo. Both studies used Mesavance doses of 2.4g/day and 4.8g/day administered once daily (QD) for 8 weeks except for the 2.4g/day group in Study 301, which was given in two divided doses (1.2g BID). The doses and regimen used in the pivotal studies were based on the data from a small phase II dose-ranging study (Study 202).

In Study 301, a total of 280 subjects were enrolled at 52 centers in U.S. and non-U.S. countries (Europe, Australia, India, Costa Rica, and Mexico). Study 302 was conducted entirely outside U.S. (Europe and Israel) at 49 centers and enrolled a total of 343 subjects including 87 subjects in Asacol arm. Across both studies, the treatment groups were comparable in regard to demographic and baseline characteristics. The study population was primarily Caucasian, had a mean age of 42 years and the proportions of males and females were well balanced. The majority of subjects have never previously smoked and < 10% was current smokers. The disease extent was classified as left-sided disease in the majority of subjects.

The safety of Mesavance was evaluated in 655 UC patients in controlled and open-label trials. In the two 8-week placebo-controlled pivotal clinical trials involving 535 UC patients, 356 received Mesavance 2.4g/day (n=177) or 4.8g/day (n=179) and 179 received placebo. A randomized, multi-centre, open-label, 12 to 14 months extension study (Study 303) to evaluate the safety and tolerability of Mesavance for the maintenance of UC in remission is currently ongoing. At the time of this NDA submission, Mesavance has not been approved for use in any country.

1.3.2 Efficacy

- Efficacy Endpoints

In both pivotal studies (Study 301 and Study 302) the primary efficacy endpoint was the proportion of subjects who were in remission at Week 8. Remission was defined as ulcerative colitis disease activity index (UC-DAI) score of ≤ 1 , with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline. For the primary efficacy analysis, two primary treatment comparisons were made including Mesavance 2.4 g/day versus placebo and Mesavance 4.8 g/day versus placebo. The study-wise false positive error rate from performing two primary comparisons was controlled using the Bonferroni-Holm method.

Major Secondary Efficacy Endpoints:

- Clinical improvement, defined as a drop in the UC-DAI score of ≥ 3 points from baseline
- Clinical remission, defined as subjects who scored 0 for both stool frequency and rectal bleeding (complete resolution of symptoms)
- Change from baseline in sigmoidoscopy scores
- Treatment failure, defined as unchanged, worsened or missing UC-DAI score

The UC-DAI score was defined as the sum of four parameters including rectal bleeding, stool frequency, mucosal appearance on sigmoidoscopy and physician global assessment. Each parameter was assessed on scales from 0 to 3, with 3 being the most severe score. It should be pointed out that in both pivotal studies, evidence of mucosal friability on sigmoidoscopy was scored a '2' in the sigmoidoscopy portion of the UC-DAI rather than the usual score of '1', indicating that the presence of mucosal friability defines the subject as a non-responder for the primary endpoint.

Medical Officer (MO) comment: It is worth mentioning that there is no rigorous standard to evaluate the efficacy of therapy for UC. While there are many empiric indices for the assessment of disease activity in UC, none of them have been formally validated, which makes comparisons with the literature difficult.

- Primary Efficacy Analyses

The Agency's statistical reviewer verified the sponsor's data and concurs with the results of efficacy analyses. The primary efficacy analyses were performed on the intention-to-treat (ITT) population.

Proportion of Subjects in Remission at Week 8

	Mesavance		Placebo n (%)
	2.4g/day n (%)	4.8g/day n (%)	
Study-301	n=88	n=89	n=85
Subjects in Remission	30 (34.1)	26 (29.2)	11 (12.9)
p-value	0.001	0.009	
Study-302	n=84	n=85	n=86
Subjects in Remission	34 (40.5)	35 (41.2)	19 (22.1)
p-value	0.010	0.007	
Pooled Studies	n=172	n=174	n=171
Subjects in Remission	64 (37.2)	61 (35.1)	30 (17.5)
p-value	<0.001	<0.001	

In Study 301, at Week 8 significantly greater proportion of subjects was in remission in Mesavance 2.4g/day and 4.8g/day groups compared to placebo group (34.1% and 29.2% versus 12.9%), the differences were statistically significant in favor of both active treatment groups (p=0.001 and p=0.009, respectively). Since 18 ITT subjects were excluded from the aforementioned primary analysis due to non-compliance with Good Clinical Practice, an additional analysis (sensitivity analysis) was performed in which the 18 subjects were treated as non-responders. In this analysis, the superiority of both active treatments (2.4g/day and 4.8g/day) over placebo was confirmed: 33.3% (31/93) and 28.7% (27/94) vs 12.9% (12/93); p=0.001 and 0.008, respectively.

In Study 302, the primary efficacy analysis showed similar results in which statistically significant differences were seen between each active treatment group (2.4 g/day and 4.8 g/day) and placebo group in favor of active treatments (40.5% and 41.2% vs 22.1%; p=0.010 and p=0.007, respectively).

MO comment: in each pivotal study as well as pooled studies, the primary efficacy analysis demonstrated that at Week 8, both Mesavance doses were superior over placebo. The remission rates in Study 302 were notably higher for all three treatment groups compared to the rates seen in Study 301, although the reason for disparity is unclear. Both studies were almost identical in study design and conduct with the exception of dosing schedule in the 2.4g/day group which was administered BID in Study 301 and QD in Study 302. The fact that similar magnitude of increased remission rates were also seen in both placebo and Mesavance 4.8g/day QD treatment arms, both of which can be directly compared between studies would indicate that this was study related rather than anomalous to a particular treatment arm. It worth noting hat the two studies were conducted in different groups of countries. It is possible that multinational clinical studies are liable to be characterized by degree of heterogeneity. However, in the reviewer's opinion, the apparent differences in the remission rates has no impact on the overall interpretation of the efficacy data given the efficacy of both Mesavance doses compared to placebo remained comparable in Study 302, and more importantly, the treatment effect was similar to that in Study 301.

While the pivotal studies were not designed to demonstrate superiority of one Mesavance dose over the other dose (2.4g/day vs 4.8g/day), the two doses appeared to have similar efficacy profiles across both studies as well as pooled studies, suggesting that the high dose would not provide additional clinical benefits. Both regimens (QD and BID) of Mesavance 2.4g/day dose are shown to be effective, thus the sponsor's recommendation to use QD regimen in the labeling is acceptable.

The proposed duration of therapy is consistent with the current clinical practice and approved mesalamine products for the indication.

- Supportive Analysis

In Study 302, an exploratory analysis comparing four treatment arms showed that the proportion of subjects in remission at Week 8 was greater in the Mesavance 4.8g/day and 2.4g/day groups compared to the Asacol 2.4g/day and placebo groups (41.2% and 40.5%, 32.6% and 22.1%, respectively). However, the differences between active treatment groups were not statistically significant.

MO comment: Asacol finding would not provide conclusive comparative efficacy information, as it was tested only in one study. Furthermore, the clinical trials that led to Asacol approval used different efficacy criteria and endpoints, which make comparison across studies difficult.

- Secondary Efficacy Analyses

In Study 301, clinical improvement was achieved in 55% (49/88) of subjects in Mesavance 2.4g/day and 59% (53/89) in 4.8g/day groups compared to 25% (22/85) in placebo group ($p < 0.001$ for both doses). Similarly, significantly higher proportion of subjects achieved clinical remission in both active treatment groups compared to placebo group (37.5% and 32.6% vs 18.8%; $p < 0.05$). The proportion of subjects with improved sigmoidoscopy scores was significantly greater in the 2.4g/day and 4.8g/day active treatment groups (65%, 57/88 and 72%, 64/89, respectively) compared to the placebo group (37%, 31/85), $p = 0.002$ and $p < 0.001$, respectively. In regard to treatment failure, significantly higher proportion of subjects was classified as treatment failure in the placebo group (54%, 46/85) compared to Mesavance 2.4g/day (28%, 25/88) and 4.8g/day groups (24%, 22/89); $p < 0.001$.

Similar results were observed in Study 302. Greater proportion of subjects achieved clinical improvement in the Mesavance 2.4g/day (60%, 51/84) and 4.8g/day groups (64%, 55/85) compared to the placebo group (39%, 34/86), $p = 0.006$ and $p < 0.001$, respectively. Similarly, significantly higher proportion of subjects achieved clinical remission in both active treatment groups compared to placebo group (41.7% and 41.2% vs 22.1%; $p < 0.01$). The proportion of subjects with improved sigmoidoscopy scores was greater in the 2.4g/day (70%, 59/84) and 4.8g/day groups (76%, 65/85) compared to the placebo group (41%, 36/86), $p < 0.001$. Significantly higher proportion of subjects was classified as treatment failure in the placebo group (48%, 41/86) compared to Mesavance 2.4g/day (21%, 18/84) and 4.8g/day groups (20%, 17/85), $p < 0.001$ for both doses. Analyses of secondary efficacy variables showed statistically

significant differences between Asacol and placebo arms for all but one variable (i.e. clinical remission) in favor of Asacol.

MO comment: Although the results of secondary efficacy analyses supported the primary efficacy findings by consistently demonstrating greater response with active treatments over placebo, the reader is cautioned that the numerous p-values presented by the sponsor are not adjusted for multiple comparisons that have been performed.

- Efficacy Analyses by Subgroup (Pooled Pivotal Studies)

In pooled pivotal studies, the subgroup analysis by gender demonstrated that both active treatment groups were superior over placebo in both males and females. In males, the remission rate was 29.4% (25/85) with 2.4g/day and 28.7% (25/87) with 4.8g/day compared to 14.3% (12/84) with placebo ($p=0.016$ and $p=0.019$, respectively). Similar results were seen in females: 44.8% (39/87) with 2.4g/day and 41.4% (36/87) with 4.8 g/day compared to 20.7% (18/87) with placebo ($p<0.001$ and $p=0.004$, respectively).

In a subgroup with moderate disease, both active treatments were superior over placebo for the primary endpoint: 33% (34/104) with 2.4g/day and 35% (36/103) with 4.8g/day compared to 16% (18/112) with placebo ($p=0.004$ and $p=0.001$, respectively). In a subgroup with mild disease, superiority over placebo was achieved with the 2.4g/day group (45%, 30/67 vs 21%, 12/58; $p=0.004$), while there was a tendency for greater efficacy in 4.8g/day group compared to placebo group, the difference did not reach a statistical significance (36%, 25/70 vs 21%, 12/58; $p=0.061$).

Significantly greater proportion of subjects with left-sided disease achieved remission with both 2.4g/day and 4.8g/day groups compared to placebo group (37%, 51/137 and 33%, 46/138 vs 19%, 24/129; $p<0.001$ and $p=0.006$, respectively). Similar results were observed in subjects with proximal disease (37%, 13/35 and 43%, 15/35 vs 14%, 6/42; $p=0.034$ and 0.005, respectively), however, the number of subjects in this group was small.

Analysis by age and race would not provide meaningful information given the small number of patients aged ≥ 65 years (<10%) and a small number of non-Caucasians in the clinical program.

In conclusion, both studies (Study 301 and Study 302) successfully demonstrated that Mesavance is effective in the induction of remission of active, mild to moderate UC in adults. Both Mesavance doses (2.4g/day and 4.8g/day) were superior over placebo for the primary efficacy endpoint. Both Mesavance doses also provided consistent benefits in secondary efficacy variables. While the studies were not designed to demonstrate superiority of one dose over the other dose (2.4g/day vs 4.8g/day), both Mesavance doses appeared to have similar efficacy profiles across both studies as well as pooled studies, suggesting that the high dose would not provide additional clinical benefits.

1.3.3 Safety

Mesavance was evaluated in 655 UC patients in controlled and open-label trials. Emphasis has been placed on the analysis of the placebo-controlled pool from the 2 pivotal studies since it is only here that unbiased assessment of the safety of the test drug could be made. In both pivotal studies, the majority of subjects received treatment for ≥ 8 weeks. Of a total of 621 UC patients randomized in both studies, 356 received Mesavance 2.4g/day or 4.8g/day, 179 received placebo and 86 received Asacol (approved formulation). Across both studies there were no notable differences between the treatment groups in regard to demographic and baseline characteristics at screening. The population was primarily Caucasian, had a mean age of 42 (<10% was age 65 years or older) and the proportions of males and females were well balanced.

In pooled analyses of safety data, the percentage of subjects who experienced treatment-emergent adverse events (AEs) was similar with placebo and active treatment groups (approximately 35%). More treatment-emergent AEs (all causalities experienced by $\geq 2\%$ of subjects) occurred in the placebo group (119 events) than in each of the Mesavance groups (109 events in the 2.4g/day, 92 events in 4.8g/day). Gastrointestinal (GI) disorders were the most common events in all treatment groups, and were more frequent with placebo treatment (15% vs 24%).

Treatment-related AEs experienced at least by 1% of any Mesavance groups (2.4 g/day and 4.8 g/day) and at the rate greater than placebo were headache (5.6%, 3.4% and 0.6%, respectively), flatulence (4%, 2.8%, and 2.8%, respectively), increased alanine aminotransferase (0.6%, 1.1%, 0%, respectively), alopecia (0%, 1.1%, 0%, respectively) and pruritus (0.6%, 1.1% and 0%, respectively). None of alanine aminotransferase changes were deemed to be clinically significant.

The majority of AEs were mild or moderate in severity. The percentage of patients with severe AEs was higher in the placebo group than in 2.4g/day and 4.8g/day active treatment groups (6.2%, 1.1% and 2.2%, respectively). The most common severe AEs were GI disorders which were mainly symptoms associated with UC. Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with Mesavance in patients experiencing this event. A lower percentage of Mesavance patients discontinued therapy due to AEs compared to placebo (2.2% vs 7.3%). The most frequent AE leading to discontinuation from Mesavance therapy was exacerbation of UC (0.8%).

Ten subjects (5 with placebo, 3 with Mesavance 2.4g/day and 2 with 4.8g/day) experienced a total of 13 serious adverse events (SAEs). The majority of SAEs (10/13 events) were GI disorders, mostly colitis or UC (7/10). All SAEs were reported to be unrelated to study medication except for two cases of pancreatitis in Mesavance group (one with each dose) deemed serious secondary to hospitalization. Both patients recovered from their episodes of pancreatitis. There were no deaths in the Placebo-controlled Pool.

There is an ongoing, long-term (12 to 14 months), open-label, extension study (Study 303) which enrolls subjects from the two placebo-controlled pivotal studies. Interim safety data indicated

that continuing exposure to Mesavance in a long-term maintenance study is not associated with any accumulation of risk.

At the time of this NDA submission, Mesavance has not been approved for use in any country. However, the active ingredient of Mesavance (i.e. mesalamine) is also the active ingredient in a number of products marketed throughout the world and has a well established safety profile.

In conclusion, the overall safety profile of Mesavance was as expected according to the drug class. No new safety issues were identified in the reviewed clinical studies. Both Mesavance doses were safe and well tolerated. The incidence and type of adverse events were similar among the three treatment groups in each placebo controlled study and did not indicate dose related increase in adverse events across the Mesavance groups. Interim safety data indicated that continuing exposure to Mesavance in a long-term maintenance study is not associated with any accumulation of risk.

1.3.4 Dosing Regimen and Administration

The recommended dosage for the induction of remission of active, mild to moderate UC in adults is two to four 1.2g tablets to be taken once daily for a total daily dose of 2.4g to 4.8g.

MO comment: The proposed wording of the total daily dose in the Dosage and Administration Section of the labeling is misleading, as it appears to imply a dose range when in fact two dose levels (2.4g/day and 4.8g/day) were tested in the pivotal trials. Thus, the wording should be modified to indicate a total daily dose of 2.4g or 4.8g.

The doses and regimen used in the pivotal study were based on the data from a small (n=38) phase II dose-ranging study (Study 202). The dose ranging study used once daily regimen and compared doses of 1.2g/day, 2.4g/day and 4.8g/day of Mesavance. Results from this study demonstrated that no subjects in the lowest dose achieved remission. The remission rate was slightly better in the 2.4g/day compared to the 4.8 g/day group.

1.3.5 Drug-Drug Interactions

Drug interaction studies have not been conducted with Mesavance.

1.3.6 Special Populations

Safety and effectiveness of Mesavance in pediatric patients have not been studied. There have been no studies with Mesavance in subjects with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with Mesavance. The clinical program did not include sufficient number of subjects aged 65 and older to determine whether they respond differently than younger subjects. Analyses by race would not provide meaningful information as the number of non-Caucasian was very small.

In pooled subgroup analysis by gender, there was a tendency for more females to achieve remission than males in all treatment groups (21%, 45%, 41% vs 14%, 29%, 29%, for placebo,

2.4g/day and 4.8g/day groups, respectively). In regard to the incidence of AEs, females reported slightly higher AEs primarily related to GI disorder than in males for Mesavance group (37.8% vs 30.7%). However, there was no increased risk with the higher dose of Mesavance, and more importantly, the overall incidence was similar to that with placebo group in both genders.

**APPEARS THIS WAY
ON ORIGINAL**

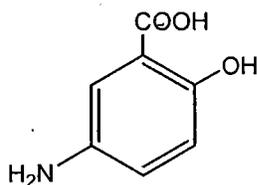
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2 Introduction and Background

2.1 Product Information

Proposed Trade Name: Mesavance
Generic Name: Mesalamine (5-aminosalicylic acid; 5-ASA)
Code Name: SPD476
Chemical Name: 5-amino-2-hydroxybenzoic acid

Structural formula:



Therapeutic Class: Anti-inflammatory
Formulation: Tablet
Proposed indication: Induction of remission of active, mild to moderate UC.

The tablet core is coated with a gastro-resistant pH dependent polymer film, which breaks down at or above pH 7, normally in the terminal ileum. Each tablet contains 1.2g of mesalamine, the active ingredient.

The exact mechanism of action of mesalamine is not fully understood, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways 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 NFκB, a nuclear transcription factor that regulates the transcription of many genes for pro-inflammatory proteins.

Mesalamine is the active ingredient of many products marketed for the treatment of UC for approximately 30 years.

2.2 Currently Available Treatment for Indications

There is an armamentarium of approved mesalamine-containing various oral formulations for the treatment of mildly to moderately active UC, including Sulfasalazine and Colazal® (azo-bond prodrug formulations), Asacol® (delayed release tablets) and Pentasa® (controlled-release capsules). Mesalamine is also marketed as rectal preparations including Canasa® (rectal suppositories) and Rowasa® (rectal suspension enema) for the treatment of distal active UC.

2.3 Availability of Proposed Active Ingredient in the United States

Various oral and rectal mesalamine formulations are approved for marketing in the U.S.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

Pertinent Regulatory Excerpt:

The applicant submitted an IND 66,193 on October 15, 2002 and July 24, 2003 involving a study protocol for a pivotal study 301 and 302, respectively. In the review of both protocols and other pertinent correspondence (meeting minutes May 29, 2003) the Agency agreed with the proposed definition of remission (primary endpoint) and efficacy analysis with the following recommendations: 1) patients with mucosal friability on sigmoidoscopy should not be considered in remission, 2) the Last Observation Carried Forward (LOCF) technique should not be used in primary efficacy analysis, but can be used as supplementary analysis, 3) Subjects who did not take the study drug for the full 8 weeks should be considered treatment failures. The aforementioned recommendations were incorporated into the current NDA submission.

2.6 Other Relevant Background Information

Mesalamine has been available worldwide for the treatment of IBD, specifically for UC for more than 20 years, and as the active component in sulfasalazine for more than 50 years.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

According to the CMC reviewer (Dr. George Lunn), there are no outstanding CMC issues at this time. However, The CMC review was not finalized at the time this review was completed. Any pertinent CMC issues will be addressed in the Medical Team Leader's (Ruyi He, M.D.) secondary review.

3.2 Animal Pharmacology/Toxicology

There are no new animal studies submitted under this application. The applicant referred to NDA 20,049 (Pentasa controlled release capsules) to provide the needed preclinical information. The Agency's Pharmacology reviewer (Dr. David Joseph) recommended that the application should be approved with appropriate labeling changes consistent with the preclinical information in the approved labeling for Pentasa.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of clinical data used in the review are from the clinical trials for Mesavance in the treatment of active, mild to moderate UC (Table 1).

The two pivotal studies (SPD476-301 and SPD476-302) provided the major data for the efficacy and safety review. However, three additional studies including SPD476-201 (an active controlled pilot study using Asacol rectal formulation), SPD476-202 (dose ranging phase 2 study) and an ongoing open-label, 12 to 14 months extension study (SPD476-303) to evaluate the safety and tolerability of Mesavance for the maintenance of UC in remission were reviewed as needed to highlight the proposed indication.

4.2 Tables of Clinical Studies

Table 1 Summary of Clinical Studies

Study reference	Short title	Design	Subjects randomised	Duration of treatment	Treatment arms, daily dose and regimen
SPD476-201	Pilot efficacy study of SPD476 vs Asacol enema	R, DB, PG	79 subjects with active, left-sided UC	8 weeks	SPD476 3.6g/day TID Asacol 4g/day QD (enema)
SPD476-202	Dose-ranging, exploratory study	R, DB, PG	38 subjects with active, mild to moderate UC	8 weeks	SPD476 1.2g/day QD SPD476 2.4g/day QD SPD476 4.8g/day QD
SPD476-301	Efficacy & safety study; placebo vs. SPD476	R, DB, PG placebo-controlled	280 subjects with active, mild to moderate UC	8 weeks	SPD476: 2.4g/day BID SPD476 4.8g/day QD placebo
SPD476-302	Efficacy & safety study; placebo vs. SPD476 and Asacol	R, DB, PG placebo-controlled	343 subjects with active, mild to moderate UC	8 weeks	SPD476 2.4g/day QD SPD476 4.8g/day QD Asacol 2.4g/day TID placebo
SPD476-303 (interim analysis)	12-14 month extension safety study	R*, Open, extension	542 subjects from studies SPD476-301 and -302	Acute Phase: 8 weeks. Maintenance Phase: 12 months	Acute Phase: SPD476 4.8g/day BID Maintenance Phase: SPD476 2.4g/day QD SPD476 2.4g/day BID

QD=once daily; BID=twice daily; TID=three times daily; UC=Ulcerative colitis; R=randomised; DB=double-blind; PG=parallel group

* Only the Maintenance Phase was randomised

4.3 Review Strategy

The applicant submitted the current NDA in the Common Technical Document format (CTD) as an electronic version. In this application, efficacy and safety data of the study drug were generated primarily from 2 pivotal phase III clinical studies. The reviewer thoroughly reviewed the pivotal studies both individually and together as pooled data with equal regard to safety and efficacy. The additional clinical studies submitted in this application were also reviewed as needed to highlight the proposed indication.

The reviewer approached this submission first by focusing upon what the applicant has requested, and what evidence has been submitted in support of the request. In each study, the protocol was examined first, and then the study reports were assessed for safety and efficacy.

The reviewer's final judgment on safety and efficacy for the proposed indication was based on safety profile of the drug and whether the stated primary objective endpoints were achieved. Furthermore, additional information was sought from published clinical data relevant to the drug product and the medical condition being treated. The reviewer also consulted electronic Physician Desk Reference.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) has been consulted for this NDA. The two major studies in the NDA were conducted at multiple centers in many countries. Three sites (two sites in U.S. and one site in Poland) were selected for auditing based on sample size and efficacy results. The sites were inspected by the DSI and the overall assessment in the final report indicated that the studies appear to have been well conducted.

In addition, the quality of data was discussed and reanalyzed for verification purpose by the Agency's Biostatistics reviewer and was found to be acceptable.

4.5 Compliance with Good Clinical Practices

The applicant documented that all studies were conducted in accordance with the current applicable regulations, International Conference on Harmonization (ICH) and local ethical and legal requirements. It was also documented that the studies comply with the principles of the 18th world medical assembly (Helsinki 1964) and amendments of the 29th (Toyo 1975), the 35th (Venice 1983), the 41st (Hong Kong 1988), and the 48th (South Africa 1996) World Medical Assemblies, Declaration of Helsinki.

The applicant documented that patients were informed by the Investigator or an authorized staff member about the nature of the study prior to the start of the study. Each patient signed a study-specific consent form to serve as a participant in the study.

4.6 Financial Disclosures

The applicant certified that they did not enter into a financial agreement with the clinical investigators whereby the value of their compensation could be affected by the outcome of the studies. The applicant also documented that investigators submitted disclosure statements as required by regulations 21 CFR Part 54.

5 CLINICAL PHARMACOLOGY

The exact mechanism of action of mesalamine is not fully understood, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways 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 κ B, a nuclear transcription factor that regulates the transcription of many genes for pro-inflammatory proteins

Mesalamine is the active ingredient of many products marketed for the treatment of UC for approximately 30 years.

5.1 Pharmacokinetics

In the initial submission, the sponsor submitted 6 phase 1 pharmacokinetic (PK) studies and recently an additional food effect and dose proportionality study (SPD476-106) was completed and the result was submitted on August 29, 2006. According to the Agency's Clinical Pharmacology reviewer's (Dr. Sue-Chi Lee) preliminary assessment, some of the PK studies in the initial submission appeared to have stability issues thus the PK data from the affected studies appeared to be questionable. Because of the aforementioned concerns with some of the data, the evaluation of PK data is deferred to the Agency's clinical pharmacology reviewer for appropriate assessment and determination of adequacy of the overall data. The clinical pharmacology review was not finalized at the time this review was completed. Any pertinent clinical pharmacology issue will be addressed in the Medical Team Leader (Ruyi He, M.D.) supplementary review.

5.2 Pharmacodynamics

No information is available.

5.3 Exposure-Response Relationships

No information is available.

6 INTEGRATED REVIEW OF EFFICACY

Of note, in this review, the proposed Trade Name (Mesavance) and Code Name (SPD476) has been used interchangeably in the tables as well as in the text.

6.1 Indication

The proposed indication for Mesavance is the induction of remission of active, mild to moderate UC in adults.

6.1.1 Methods

Efficacy data were generated from two placebo controlled phase III studies (Study 301 and Study 302). While both studies were of similar design, used the same inclusion/exclusion criteria and efficacy endpoints, an additional arm of Asacol 2.4g/day TID (approved formulation) was included in Study 302 as an internal reference. However, for this application the comparison of interest is Mesavance versus placebo. Both studies used Mesavance doses of 2.4g/day and

4.8g/day administered once daily for 8 weeks except for the 2.4g/day group in Study 301, which was given in two divided doses (1.2g BID).

MO comment: The doses and regimen used in the pivotal studies were based on the data from a small (n=38) phase II dose-ranging study (Study 202). The proposed treatment period is consistent with the current practice and approved various mesalamine products.

Eligible subjects were adult males and females with mild to moderate active UC. There were no clinically significant differences between treatment groups in either study in regard to demographic and baseline characteristics. Approximately 50% of subjects was male, the mean age was 42 years and the population was primarily Caucasian. The majority of subjects across treatment groups have never previously smoked and < 10% were current smokers. In the majority (70-88%) of subjects, the disease was classified as left-sided disease, while a small group of patients had pancolitis or involvement of transverse colon.

Of a total of 623 eligible subjects enrolled into two pivotal studies, 603 were included in the efficacy analysis: 262 in Study-301 and 341 (including 86 subjects in Asacol arm) in Study-302. The 20 subjects excluded from the efficacy analysis include 18 subjects from Study 301, due to the non-GCP compliance and 2 subjects from Study 302 due to the positive stool culture. However, the 2 subjects from study 302 did not receive study medication.

6.1.2 General Discussion of Endpoints

- Efficacy Endpoints

In both pivotal studies, the primary efficacy endpoint was the proportion of subjects who were in remission at Week 8. Remission was defined as UC-DAI score of ≤ 1 , with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

Major Secondary Efficacy Endpoints:

- Clinical improvement, defined as a drop in the UC-DAI score of ≥ 3 points from baseline
- Treatment failure, defined as an unchanged, worsened or missing UC-DAI score
- Clinical remission, defined as subjects who scored 0 for both stool frequency and rectal bleeding (i.e., complete resolution of symptoms)
- Change from baseline in sigmoidoscopy scores.

The UC-DAI score was defined as the sum of four parameters including rectal bleeding, stool frequency, mucosal appearance on sigmoidoscopy and physician global assessment (PGA). Each parameter was assessed on scales from 0 to 3, with 3 being the most severe score. It should be pointed out that in both studies, evidence of mucosal friability on sigmoidoscopy was scored a '2' in the sigmoidoscopy portion of the UC-DAI, rather than the usual score of '1', which means that the presence of mucosal friability defines the subject as a non-responder for the primary endpoint. Subjects assessed their own rectal bleeding and stool frequency symptoms and reported them daily to the IVRS during the study. The UC-DAI score, assessment of

sigmoidoscopic appearance and PGA was performed at baseline and at Week 8 (End of Study/Early Withdrawal Visit).

MO comment: It is worth mentioning that there is no rigorous standard to evaluate the efficacy of therapy for UC. While there are many empiric indices for assessment of disease activity in UC, none of them have been formally validated, which makes comparisons with the literature difficult.

- Efficacy Analyses

The primary efficacy analysis included two treatment comparisons: Mesavance 2.4 g/day vs placebo and Mesavance 4.8 g/day vs placebo using the chi-squared test. The study-wise false positive error rate from performing two primary comparisons was controlled using the Bonferroni-Holm method. The treatment comparison with the smaller p-value was evaluated at the 0.025 significance level. If that comparison was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level.

For secondary efficacy analyses, the following treatment comparisons were made:

- SPD476 2.4g/d versus Placebo
- SPD476 4.8g/d versus Placebo
- SPD476 2.4g/d versus SPD476 4.8g/d

It should be noted that multiplicity adjustment was not carried out for performing multiple comparisons for secondary efficacy analyses.

- Subgroup Pooled Analyses

Since the pivotal efficacy studies were of similar design, recruited similar subject populations and used the same efficacy criteria and endpoints, the efficacy data have been pooled to obtain more precise estimates of treatment effects and to allow exploratory subgroup analyses.

For this pooled analysis, the data were grouped into the dose categories of SPD476 2.4g/day, SPD476 4.8g/day and placebo (note that the 2.4g/day group includes both the BID dosing regimen used in study SPD476-301 and the QD dosing regimen used in study SPD476-302). The Asacol group was not included in these analyses since it was only included in one study (Study-302).

The proportion of subjects in remission at week 8 and endpoint were summarized for each of the subgroups (demographic and baseline characteristics at screening) of ITT subjects. The proportion of remitters at week 8 and endpoint were then analyzed using logistic regression.

6.1.3 Study Design

Both pivotal studies (studies 301 and 302) were randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 studies to compare the efficacy and safety of two SPD476 doses versus placebo given in 1:1:1 ratio.

While both studies were almost identical in design, used the same inclusion and exclusion criteria and efficacy endpoints, an additional arm of Asacol 2.4g/day (approved formulation) was included in Study 302 as an internal reference. However, for this application the comparison of interest was Mesavance versus placebo.

MO comment: The study design is appropriate for the study and provides a reasonable assessment of benefit.

6.1.4 Efficacy Findings

The Agency's statistical reviewer verified the applicant's data and concurs with the results of efficacy analyses. The efficacy analyses were performed on the intention-to-treat (ITT) population.

- Primary Efficacy Analyses

In both pivotal studies as well as pooled studies, the primary efficacy analysis demonstrated that at Week 8, both SPD476 2.4g/day and 4.8 g/day doses were superior over placebo (Table 2).

In Study 301, the proportion of subjects in remission was 34.1% and 29.2 %, respectively in the SPD476 2.4g/day and 4.8 g/day group compared to 12.9% in the placebo group (p=0.001 and p=0.009, respectively). Since 18 ITT subjects were excluded from the aforementioned analysis due to Good Clinical Practice non-compliance issues, an additional analysis (sensitivity analysis) was performed in which the 18 subjects were treated as non-responders. In this analysis, the superiority of both active treatments (2.4g/day and 4.8g/day) over placebo was confirmed: 33.3% and 28.7% vs 12.9%; p=0.001 and 0.008, respectively (Table 3).

Similar results were observed in Study 302, in which both active treatment groups were superior over placebo for the primary efficacy endpoint (40.5% and 41.2% vs 22.1%; p=0.010 and p=0.007, respectively).

Table 2 Proportion of Subjects in Remission at Week 8

	SPD476		Placebo n (%)
	2.4g/day n (%)	4.8g/day n (%)	
Study-301	n=88	n=89	n=85
Proportion of Subjects in Remission	30 (34.1)	26 (29.2)	11 (12.9)
p-value	0.001	0.009	
Study-302	n=84	n=85	n=86
Proportion of Subjects in Remission	34 (40.5)	35 (41.2)	19 (22.1)
p-value	0.010	0.007	
Pooled Studies	n=172	n=174	n=171
Proportion of Subjects in Remission	64 (37.2)	61 (35.1)	30 (17.5)
p-value	<0.001	<0.001	

(Compiled by the Reviewer from sponsor's Text Table 12 and Text Table 21, Module 2, Section 2.7.3)

Table 3 Sensitivity Analysis- Primary Efficacy Endpoint (Study 301)

	SPD476		Placebo n (%)
	2.4g/day n (%)	4.8g/day n (%)	
Study-301	n=93	n=94	n=93
Proportion of Subjects in Remission	31 (33.3)	27 (28.7)	12 (12.9)
p-value	0.001	0.008	

(Ref. Text Table 12, Module 2.7.3, Study 301)

MO comment: in each pivotal study as well as pooled studies, the primary efficacy analysis demonstrated that at Week 8, both Mesavance doses were superior over placebo. The remission rates in Study 302 were notably higher for all three treatment groups compared to the rates seen in Study 301, although the reason for disparity is unclear. Both studies were almost identical in study design and conduct with the exception of dosing schedule in the 2.4g/day group which was administered BID in Study 301 and QD in Study 302. The fact that similar magnitude of increased remission rates were also seen in both placebo and Mesavance 4.8g/day QD treatment arms, both of which can be directly compared between studies would indicate that this was study related rather than anomalous to a particular treatment arm. It worth noting hat the two studies were conducted in different groups of countries. It is possible that multinational clinical studies are liable to be characterized by degree of heterogeneity. However, in the reviewer's opinion, the apparent differences in the remission rates has no impact on the overall interpretation of the efficacy data given the efficacy of both Mesavance doses compared to placebo remained comparable in Study 302, and more importantly, the treatment effect is similar to that in Study 301.

While the pivotal studies were not designed to demonstrate superiority of one Mesavance dose over the other dose (2.4g/day vs 4.8g/day), the two doses appeared to have similar efficacy profiles across both studies as well as pooled studies, suggesting that the high dose would not provide additional clinical benefits. Both regimens (QD and BID) of Mesavance 2.4g/day dose are shown to be effective, thus the sponsor's proposal to use a QD regimen is acceptable.

The proposed duration of therapy is consistent with the current clinical practice and approved mesalamine products for the indication.

- **Supportive Analysis**

In Study-302, an exploratory analysis was conducted to compare remission rates between the 4 treatment arms (Table 4). The analysis demonstrated that the proportion of subjects in remission at Week 8 was greater in the SPD476 2.4g/day and 4.8g/day groups compared to the Asacol 2.4g/day and placebo groups (41.2%, 40.5%, 32.6% and 22.1%, respectively). However, the differences between active treatment groups were not statistically significant.

Table 4 Proportion of Subjects in Remission at Week 8 -ITT Population (Study-302)

	Placebo (N=86)	SPD476 2.4g/day QD (N=84)	SPD476 4.8g/day QD (N=85)	Asacol 2.4g/day TID (N=86)
Number of subjects in remission n (%)	19 (22.1)	34 (40.5)	35 (41.2)	28 (32.6)
Comparison of Asacol vs placebo*				
Odds ratio				1.70
95% CI				0.86, 3.36
p-value†				0.124
Comparison of SPD476 vs Asacol*				
Odds ratio		1.41	1.45	
95% CI		0.75, 2.64	0.78, 2.71	
p-value†		0.284	0.243	

Source: Study report SPD476-302, Section 12.1, Table 2.1.1.

* Values from the chi-squared test

† p-value was evaluated at the 0.05 significance level

(Ref. Text Table 13, Module 2, Section 2.7.3)

MO comment: Asacol finding would not provide conclusive comparative efficacy information, as it was tested only in one study. Furthermore, the clinical trials that led to Asacol approval used different efficacy criteria/endpoints, which make comparison across studies difficult.

- **Secondary Efficacy Analyses**

In both pivotal studies, the results of secondary efficacy analyses including clinical improvement, assessment of treatment failure, clinical remission, sigmoidoscopy improvement and change from baseline in UC-DAI score supported the primary efficacy findings by consistently demonstrating greater response with active treatments over placebo (Tables 5 and 6). However, the reader is cautioned that the numerous p-values presented by the sponsor are not adjusted for multiple comparisons that have been performed.

Table 5 Results of Secondary Efficacy Endpoints (%Patients)-Study 301

Secondary Efficacy Variables	SPD476 2.4g/day n=88	SPD476 4.8g/day n=88	Placebo n=85
Clinical Improvement	55.7%***	59.6%***	25.9%
Treatment Failure	28.4%***	24.7%***	54.1%
Clinical Remission	37.5%**	32.6%*	18.8%
Sigmoidoscopic Improvement	64.8%**	71.9%***	36.5%
Change from baseline in UC-DAI score	-2.71***	-3.46***	-0.79

*p < 0.05, **p < 0.01, ***p < 0.001 (each vs placebo)

Ref. copied from sponsor's Table 3 in the proposed labeling.

Table 6 Results of Secondary Efficacy Endpoints (%Patients) -Study 302

Secondary Efficacy Variables	SPD476 2.4g/day n=84	SPD476 4.8g/day n=85	Asacol 2.4g/day n=86	Placebo n=86
Clinical Improvement	60.7%**	64.7%***	55.8%*	39.5%
Treatment Failure	21.4%***	20.0%***	27.9%**	47.7%
Clinical Remission	41.7%**	41.2%**	33.7% ^{NS}	22.1%
Sigmoidoscopic Improvement	70.2%***	76.5%***	60.5%*	41.9%
Change from baseline in UC-DAI score	-3.34**	-3.58**	-3.11*	-1.94

*p < 0.05, **p < 0.01, ***p < 0.001 (each vs placebo); NS = not significant

Ref. copied from sponsor's Tables 4 in the proposed labeling.

- Primary Efficacy Analyses by Subgroup (Pooled Pivotal Studies)**

Results of primary efficacy analyses by subgroups are summarized in Table 7.

The subgroup efficacy analysis by gender demonstrated that both active treatment groups were superior over placebo in both males and females. In males the remission rate was 29.4% with 2.4g/day and 28.7% with 4.8g/day compared to 14.3% with placebo (p=0.016 and p=0.019, respectively). Similar results were seen in females: 44.8% with 2.4g/day and 41.4% with 4.8g/day compared to 20.7% with placebo (p=<0.001 and p=0.004, respectively).

In a subgroup with moderate disease, both active treatments were superior over placebo for the primary efficacy endpoint: 33% with 2.4g/day and 35% with 4.8g/day compared to 16% with placebo (p=0.004 and p=0.001, respectively). In subjects with mild disease, superiority over placebo was achieved with the 2.4g/day group (45% vs 21%; p=0.004), while the efficacy was greater with 4.8g/day than with placebo, the difference did not reach a statistical significance (36% vs 21%; p=0.061).

Significantly greater proportion of subjects with left-sided disease achieved remission with both 2.4g/day and 4.8g/day groups compared to placebo group (37% and 33% vs 19%; p=<0.001 and

p=0.006, respectively). Similar results were observed in subjects with proximal disease (37%, and 43% vs 14%; p=0.034 and 0.005, respectively), however, the number of subjects in this group was small.

Analysis by age and race would not provide meaningful information given the small number of patients aged ≥ 65 years (<10%) and a small number of non-Caucasians in the clinical program.

Table 7 Proportion of Subjects in Remission by Subgroup (Pooled Studies)

Subgroups	Placebo n=171 n/N (%)	SPD476	
		2.4 g/day n=172 n/N (%)	4.8 g/day n=174 n/N (%)
Gender			
Male (n=256)	12/84 (14.3)	25/85 (29.4)	25/87 (28.7)
p-value (active vs placebo)		0.016	0.019
Female (n=261)	18/87 (20.7)	39/87 (44.8)	36/87 (41.4)
p-value (active vs placebo)		<0.001	0.004
Disease Activity			
Mild (n=195)	12/58 (20.6)	30/67 (44.8)	25/70 (35.7)
p-value (active vs placebo)		0.004	0.061
Moderate (n=319)	18/112 (16.1)	34/104 (32.7)	36/103 (35.0)
p-value (active vs placebo)		0.004	0.001
Disease Extent			
Left-sided (n=404)	24/129 (18.6)	51/137 (37.2)	46/138 (33.3)
p-value (active vs placebo)		<0.001	0.006
Other (n=112)	6/42 (14.3)	13/35 (37.1)	15/35 (42.9)
p-value (active vs placebo)		0.034	0.005

Compiled by the Reviewer (Ref. Text Tables 37, 41 and 43; Module 2, section 2.7.3)

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

In the reviewer's opinion, both studies (Study 301 and Study 302) successfully demonstrated that Mesavance is effective in the induction of remission of active, mild to moderate UC in adults. Both Mesavance doses (2.4g/day and 4.8g/day) were superior over placebo for the primary efficacy endpoint. Both Mesavance doses also provided consistent benefits in secondary efficacy variables. While the studies were not designed to demonstrate superiority of one dose over the other dose (2.4g/day vs 4.8g/day), both Mesavance doses appeared to have similar efficacy profiles across both studies as well as pooled studies, suggesting that the high dose would not provide additional clinical benefits.

7 INTEGRATED REVIEW OF SAFETY

7.1 *Methods and Findings*

Mesavance has been evaluated in 655 UC patients in controlled and open-label trials. Emphasis has been placed on the analysis of the placebo-controlled pool from the 2 pivotal studies since it is only here that unbiased assessment of the safety of the study drug could be made. In both studies, the majority of subjects in all active treatment group received treatment for ≥ 8 weeks. The median exposure with placebo was very similar to that in the active treatment group. Of a total of 621 UC patients, 356 received 2.4g/day or 4.8g/day Mesavance, 179 received placebo and 86 received Asacol (approved formulation). There were no notable differences between the treatment groups in regard to demographic and baseline characteristics at screening. The population was primarily Caucasians, the proportions of male and female subjects were similar and the mean age was 42 years.

In pooled analyses of safety data, the percentage of subjects who experienced treatment-emergent AEs was similar with placebo and active treatment groups (approximately 35%). More treatment-emergent AEs (all causalities experienced by $\geq 2\%$ of subjects) occurred in the placebo group (119 events) than in each of the Mesavance treatment groups (109 events in the 2.4g/day, 92 events in 4.8 g/day). Gastrointestinal (GI) disorders were the most common events in all treatment groups, and were more frequent with placebo treatment (15% vs 24%).

Treatment-related AEs experienced at least by 1% of any Mesavance groups (2.4 g/day and 4.8 g/day groups) and at the rate greater than placebo were headache (5.6%, 3.4% and 1%, respectively), flatulence (4%, 2.8%, and 2.8%, respectively), increased ALT (0.6%, 1.1%, 0%, respectively), alopecia (0%, 1.1%, 0%, respectively) and pruritus (0.6%, 1.1% and 0%, respectively). None of the ALT changes were deemed to be clinically significant.

The majority of AEs were mild or moderate in severity. The percentage of patients with severe AEs was higher in the placebo group (6.2% in placebo; 1.1% in 2.4g/day; 2.2% in 4.8g/day). The most common severe AEs were GI disorders which were mainly symptoms associated with UC. Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with Mesavance in patients experiencing this event. A lower percentage of Mesavance patients discontinued therapy due to AEs compared to placebo (2.2% vs 7.3%). The most frequent AE leading to discontinuation from Mesavance therapy was exacerbation of UC (0.8%).

Ten subjects (5 with placebo, 3 with Mesavance 2.4g/day and 2 with Mesavance 4.8g/day) experienced a total of 13 serious adverse events (SAEs). The majority of SAEs were GI disorders (10/13 events), mostly colitis or UC (7/10). All SAEs were reported to be unrelated to study medication except for two cases of pancreatitis (one each with 2.4g/day and 4.8g/day) deemed serious secondary to hospitalization. Both of these patients recovered from their episodes of pancreatitis.

Safety profile from two 8-week phase II studies (Studies 201 and 202) were similar with the safety profile observed in the placebo controlled studies.

There is an ongoing, long-term (12 to 14 months), open-label, extension study (Study 303) which enrolled subjects from the two placebo-controlled pivotal studies, and comprises an 8-week acute phase using Mesavance 4.8 g/day BID and a randomized maintenance phase using Mesavance 2.4 g/day QD vs 2.4 g/day BID. Subjects from pivotal studies (studies 301 and 302) who had not achieved remission could enroll into acute phase of study. The maintenance phase comprised subjects in remission, either at the end of the pivotal studies, or after the acute phase of study. Interim data indicate that continuing exposure to Mesavance in a long-term maintenance study is not associated with any accumulation of risk. The safety profile of Mesavance 2.4g/day (QD or BID) in maintenance therapy to date is consistent with the safety profile observed in the 8-week placebo controlled studies.

Mesavance is not currently approved for marketing in any country. However, the active ingredient (mesalamine) of Mesavance is also the active ingredient in a number of products marketed throughout the world. In view of the extensive clinical use of mesalamine products to treat UC, the safety data presented under this application appear acceptable.

7.1.1 Deaths

There were no death in phase II and phase III studies.

There were two deaths in the long-term, open-label extension study (Study-303). Subject 71105 experienced a fall that resulted in death; this was termed suicide based upon the diagnosis on the death certificate. He was severely intoxicated and fell from the balcony. Subject 56210 received a fatal electric shock while cleaning a car with a vacuum cleaner.

None of the fatal SAEs were considered study drug related by the investigator. A review of the narrative did not suggest the events were related to study drug.

7.1.2 Other Serious Adverse Events

In the placebo-controlled Pool, the incidence of SAEs was low and consistent with the presence of acute UC. Ten subjects (5 receiving placebo, 3 receiving SPD476 2.4g/day and 2 receiving SPD476 4.8g/day) experienced a total of 13 SAEs. Of these 13 events, ten were GI disorders (7 placebo, 2 with SPD476 2.4g/day and 1 with SPD476 4.8g/day), 2 were pancreatitis (one from 2.4 g/day and the other from 4.8 g/day) and 1 gastroenteritis. With the exception of the two cases of pancreatitis (one reported as possibly related and one as probably related), all other SAEs were reported to be unrelated to study medication. Both of the patients recovered from their episodes of pancreatitis.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In Placebo-controlled Pool, premature discontinuations occurred more frequently with placebo group than with SPD476 group (41.9% vs 18.7%), Table 8. There was no difference between the SPD476 treatment groups (18.4% and 19.0% with 2.4g/day and 4.8g/day, respectively). However, fewer subjects receiving the higher dose of SPD476 discontinued owing to AEs (1.1% and 3.4% of subjects receiving SPD476 4.8g/day and 2.4g/day, respectively).

The most frequent reason for premature discontinuation in all treatment groups was lack of efficacy; however, the proportion was greater with placebo than with SPD476 group (26.8% vs 11.2%). Discontinuation due to AEs was the second common reason occurring in 7.3% receiving placebo and 2.2% subjects receiving SPD476.

Table 8 Subjects Disposition-Placebo-controlled Pool

Number (%) of subjects	Placebo		SPD476 2.4g/day		SPD476 4.8g/day		All SPD476	
Randomised	179		179		179		358	
Safety Population n (%)	179	(100.0)	177	(98.9)	179	(100.0)	356	(99.4)
Took study medication	179	(100.0)	177	(98.9)	179	(100.0)	356	(99.4)
Completed study	104	(58.1)	146	(81.6)	145	(81.0)	291	(81.3)
Number (%) of subjects who discontinued	75	(41.9)	33	(18.4)	34	(19.0)	67	(18.7)
Reason for discontinuation								
AE/SAE	13	(7.3)	6	(3.4)	2	(1.1)	8	(2.2)
Non-compliance	1	(0.6)	2	(1.1)	1	(0.6)	3	(0.8)
Lack of efficacy	48	(26.8)	18	(10.1)	22	(12.3)	40	(11.2)
Subject request	6	(3.4)	4	(2.2)	3	(1.7)	7	(2.0)
Lost to follow-up	1	(0.6)	0	0	3	(1.7)	3	(0.8)
Protocol violation	4	(2.2)	0	0	2	(1.1)	2	(0.6)
Other	2	(1.1)	2	(1.1)	0	0	2	(0.6)

Ref. Text Table 5, Model 2.7.4

7.1.3.2 Adverse events associated with dropouts

In the placebo controlled pools, discontinuation due to AEs occurred in 7.3% receiving placebo, and 2.2% subjects receiving SPD476 (Table 9). Most withdrawals were due to GI events associated with UC. Two subjects (one receiving SPD476 2.4g/day and one 4.8g/day) were withdrawn from Study-301 after experiencing a severe treatment-related AE of pancreatitis, reported to be possibly and probably related to study drug, respectively.

In a long-term open-label study (Study 303), there were 15 AEs that resulted in withdrawal (ten during the acute and five during the maintenance phase). The majority of discontinuations in

both phases were due to GI disorders associated with UC. The majority was reported to be unrelated to study treatment and only one (severe pancreatitis) was reported as probably related to treatment.

MO comment: There appears to be no dose-response regarding dropouts due to AEs.

Table 9 Treatment-Emergent AEs Leading to Discontinuation Placebo-controlled Pool

System organ class Preferred term	Placebo (N = 179)		SPD476 2.4g/day (N = 177)		SPD476 4.8g/day (N = 179)		All SPD476 (N = 356)	
Number (%) of subjects Number of subjects withdrawn due to an AE	13	(7.3)	6	(3.4)	2	(1.1)	8	(2.2)
Gastrointestinal disorders	13	(7.3)	4	(2.3)	2	(1.1)	8	(1.7)
Colitis	1	(0.6)	0		0		0	
Colitis ulcerative	9	(5.0)	2	(1.1)	1	(0.6)	3	(0.8)
Colonic haemorrhage	1	(0.6)	0		0		0	
Diarrhoea	0		1	(0.6)	0		1	(0.3)
Dyspepsia	1	(0.6)	0		0		0	
Frequent bowel movements	2	(1.1)	0		0		0	
Pancreatitis	0		1	(0.6)	1	(0.6)	2	(0.6)
General disorders and administration site conditions	0		1	(0.6)	0		1	(0.3)
Asthenia	0		1	(0.6)	0		1	(0.3)
Psychiatric disorders	0		1	(0.6)	0		1	(0.3)
Anxiety	0		1	(0.6)	0		1	(0.3)

Source: Appendix 2.7.4.8.4, Table 2.3.4

Percentages are based on the number of subjects in the safety population for each treatment group.

Ref. Text Table 16, Module 4, 2.7.4.

7.1.3.3 Other significant adverse events

Apart from AEs that resulted in discontinuation, there were no other significant AEs.

7.1.4 Other Search Strategies

The safety data from each pivotal study were reviewed separately and the results were compared to the sponsor's integrated summary of safety. The narrative of SAEs was reviewed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In pivotal clinical trials, safety monitoring included a full physical examination, vital signs, full review of systems, urinalysis, biochemistry and hematology evaluations. A full biochemistry and complete hematology evaluations were performed at selected visits (screening visit, week-4 visit and end of study/early withdrawal). Urine pregnancy tests were obtained at the beginning and

end of study. During the maintenance study (Study 303), safety was monitored at Months 1, 3, 6, 9 and 12. Electrocardiogram (ECG) measurements were evaluated in healthy volunteers.

In order to avoid bias in eliciting AEs, subjects were questioned in a non-leading way at all study visits about changes in their health or concomitant medication usage since their last visit, this information was collated prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments deemed clinically significant by the investigator were assessed as AEs. All AEs (related, unrelated, serious and non-serious) were recorded from the time of informed consent was signed until the end of treatment exposure, and documented on the CRF and source documents. Furthermore, AEs were recorded 30 days following the last exposure to the study product.

A change in a safety laboratory investigation value could represent an AE if the change was clinically relevant or if, during treatment, a parameter was observed to shift from a normal value to a pathological one or an already pathological value worsened to a greater extent. The investigator was responsible for deciding whether a change in a laboratory parameter was clinically significant and, therefore, represented an adverse event.

MO comment: the applicant's methods of eliciting AE data appear acceptable.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) and were categorized by System Organ Class (SOC).

MO comment: in the Reviewer's opinion, AE categorization and preferred terms used in the clinical program are acceptable.

7.1.5.3 Incidence of common adverse events

In the placebo-controlled pool, the percentage of subjects who experienced treatment-emergent AEs was similar with placebo and active treatment groups (approximately 35%). More treatment-emergent AEs (all causalities experienced by $\geq 2\%$ of subjects) occurred in the placebo group (119 events) than in each of the Mesavance treatment groups (109 events in the 2.4g/day, 92 events in 4.8 g/day). Gastrointestinal disorders were the most common events in all treatment groups, and were more frequent with placebo treatment (24% with placebo; 18% with 2.4g/day; 15% with 4.8g/day group). The most common individual events with Mesavance were headache, where the incidence was considerably higher than with placebo (0.6% with placebo, 5.6% with 2.4g/day; 3.4% with 4.8g/day), and flatulence, where the incidence was similar (2.8%; 4% and 2.8%, respectively).

Treatment-emergent AEs (all causalities) during the open-label maintenance phase experienced by $\geq 2\%$ of subjects in any treatment group are presented by SOC and preferred term in Table 11. Overall, similar percentage of subjects (15%) in both treatment groups (SPD476 dosage of 2.4g/day QD vs 2.4g/day BID) experienced AEs during the maintenance phase. Gastrointestinal

disorders were the most frequently reported AEs in both treatment groups. Individual AEs were infrequent, occurring in no more than three subjects in any treatment group.

7.1.5.4 Common adverse event tables

Table 10 Treatment-Emergent AEs (All Causalities) Experienced by $\geq 2\%$ of Subjects: Placebo-controlled Pool

System organ class Preferred term	Placebo (N = 179)	SPD476 2.4g/day (N = 177)	SPD476 4.8g/day (N = 179)	All SPD476 (N = 356)
Number (%) of subjects				
Number of subjects with ≥ 1 AE	62 (34.6)	64 (36.2)	58 (32.4)	122 (34.3)
Number of events	119	109	92	201
Gastrointestinal disorders	43 (24.0)	32 (18.1)	21 (11.7)	53 (14.8)
Abdominal pain	5 (2.8)	4 (2.3)	2 (1.1)	6 (1.7)
Colitis ulcerative	11 (6.1)	7 (4.0)	1 (0.6)	8 (2.2)
Diarrhoea	3 (1.7)	4 (2.3)	0	4 (1.1)
Flatulence	5 (2.8)	7 (4.0)	5 (2.8)	12 (3.4)
Nausea	4 (2.2)	3 (1.7)	5 (2.8)	8 (2.2)
Infections and infestations	10 (5.6)	8 (3.4)	14 (7.8)	20 (5.6)
Nasopharyngitis	1 (0.6)	0	4 (2.2)	4 (1.1)
Nervous system disorders	4 (2.2)	10 (5.6)	8 (4.5)	18 (5.1)
Headache	1 (0.6)	10 (5.6)	6 (3.4)	16 (4.5)
Skin and subcutaneous tissue disorders	4 (2.2)	4 (2.3)	9 (5.0)	13 (3.7)
Musculoskeletal and connective tissue disorders	7 (3.9)	8 (4.5)	5 (2.8)	13 (3.7)
General disorders and administration site conditions	7 (3.9)	7 (4.0)	7 (3.9)	14 (3.9)
Pyrexia	3 (1.7)	2 (1.1)	4 (2.2)	6 (1.7)
Investigations	7 (3.9)	5 (2.8)	7 (3.9)	12 (3.4)
Weight decreased	4 (2.2)	1 (0.6)	0	1 (0.3)
Blood and lymphatic system disorders	2 (1.1)	4 (2.3)	0	4 (1.1)
Metabolism and nutrition disorders	4 (2.2)	1 (0.6)	3 (1.7)	4 (1.1)

Source: Appendix 2.7.4.8.4, Table 2.3.1

Percentages are based on the number of subjects in the Safety Population for each treatment group.

Ref. Text Table 8, Module 2, section 2.7.4.

Table 11 Treatment-Emergent AEs (All Causalities) Experienced by $\geq 2\%$ of Subjects : Study SPD476-303 Maintenance Phase (Interim Data)

System Organ Class	SPD476 2.4g/day QD (N = 215)	SPD476 2.4g/day BID (N = 218)	Overall (N = 433)
Number (%) of subjects			
Total	30 (14.0)	33 (15.1)	63 (14.5)
Gastrointestinal disorders	11 (5.1)	12 (5.5)	23 (5.3)
Infections and infestations	6 (2.8)	10 (4.6)	16 (3.7)
Investigations	6 (2.8)	5 (2.3)	11 (2.6)
Blood and lymphatic system disorders	4 (1.9)	5 (2.3)	9 (2.1)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	5 (2.3)	7 (1.6)

Source: Text Table 24 of the Interim Study Report for SPD476-303 (v1.0; 31 August 2005)

Ref. Text Table 13, Module 2, section 2.7.4.

7.1.5.5 Identifying common and drug-related adverse events

In the placebo-controlled pool, the incidence of treatment-related AEs that can reasonably be considered drug-related was similar across the active treatment groups, and there was no evidence of an increased incidence with the higher dose of SPD476 for any individual AE.

Treatment-related AEs experienced at least by 1% of any Mesavance groups (2.4 g/day and 4.8 g/day) and at the rate greater than placebo were headache (5.6%, 3.4% and 0.6%, respectively),

flatulence (4%, 2.8%, and 2.8%, respectively), increased alanine aminotransferase (0.6%, 1.1%, 0%, respectively), alopecia (0%, 1.1%, 0%, respectively) and pruritus (0.6%, 1.1% and 0%, respectively). None of alanine aminotransferase changes were deemed to be clinically significant.

7.1.5.6 Additional analyses and explorations

The incidence of AEs that was primarily related to GI disorder was slightly higher in females than in males for Mesavance group (37.8% vs 30.7%). However, there was no increased risk with the higher dose of Mesavance, and more importantly, the overall incidence was similar to that with placebo group in both genders.

The clinical program did not include sufficient number of subjects aged 65 and older (<10%) to determine whether they respond differently than younger subjects. Similarly, analyses by race would not provide meaningful information as the number of non-Caucasian was very small.

7.1.6 Less Common Adverse Events

A review of less common AEs did not identify any specific safety concern.

7.1.7 Laboratory Findings

There were no laboratory findings of clinical importance in regard to values over time, individual patient changes or individual clinically important abnormalities.

7.1.7.1 Overview of laboratory testing in the development program

Criteria for identifying Clinically Significant Laboratory Abnormalities (CSLA) were predefined in the protocol (Tables 12 and 13).

Table 12 Hematology Normal Ranges and Defined Outlier Criteria

Parameter	SI unit	Gender	SI Lower Limit	SI Upper Limit	Outlier Criteria
Basophils	%		0	2	>10
Eosinophils	%		0	6	>10
Erythrocytes	10 ¹² /L	F	4.2	5.8	<3
		M	4.5	6.3	<3
Haematocrit	V/V	F	0.34	0.50	<0.32
		M	0.39	0.53	<0.37
Haemoglobin	mmol/L	F	7.44	9.92	<5.89
		M	8.68	11.16	<7.13
Leukocytes	10 ⁹ /L		4.3	11	<2.8, >16.0
Lymphocytes	%		25	45	<10, >50
MCH	pg		27	32	-
MCHC	mmol/L		19.8	22.3	-
MCV	fL		78	102	-
Monocytes	%		2	10	>25
Neutrophils	%		50	65	<40
Platelet count	10 ⁹ /L		144	440	<75, >700

Ref. Text Table 24, Module 2.7.4

Table 13 Biochemistry Normal Ranges and Defined Outlier Criteria

Parameter	SI unit	Gender/Age	SI Lower Limit	SI Upper Limit	Outlier Criteria
Albumin	g/L		30	50	<30
Alkaline Phosphatase	U/L	15-19 years	0	267	>3 x ULN
		≥20 years	31	121	>3 x ULN
Calcium	mmol/L		2	2.75	<1.96, >2.87
Creatinine	umol/L	F	0	84.9	>176.8
		M	0	102.9	>176.8
GGT	U/L	F	6	32	>3 x ULN
		M	10	49	>3 x ULN
AST	U/L	F	1	32	>3 x ULN
		M	1	39	>3 x ULN
ALT	U/L	F	1	30	>3 x ULN
		M	1	39	>3 x ULN
Glucose	mmol/L		3.33	7.77	<3.06, >8.90
Potassium	mmol/L		3.5	5.5	<3, >6
Sodium	mmol/L		136	148	<125, >160
Total bilirubin	umol/L		1.7	18.8	>34.2
Total protein	g/L		66	87	<50, >90
Urea	mmol/L		3.33	8.33	>9.99

Ref. Text Table 25, Module 2.7.4

7.1.7.3 Standard analyses and explorations of laboratory data

Hematology and biochemistry parameters are presented as changes from screening to Weeks 4, 8 and endpoint (end of study or withdrawal) for Placebo-controlled Pool. Urinalysis parameters are presented as changes from screening to Week 8 and endpoint. A change in a safety laboratory investigation value could represent an AE if the change was clinically relevant or if, during treatment, a parameter was observed to shift from a normal value to a pathological one, or an already pathological value worsened to a greater extent. The investigator was responsible for deciding whether a change in a laboratory parameter was clinically significant and, therefore, represented an adverse event.

7.1.7.3.1 Analyses focused on measures of central tendency

In the placebo-controlled pool, the mean data for all hematology and biochemistry parameters were unremarkable and there were no notable mean changes in any group across the course of study.

Changes from screening in mean ALT, AST and GGT values indicated a trend to increase with SPD476 4.8g/day; however, overall mean values for these parameters remained within normal limits at all time-points and no group mean changes were of clinical significance. None of the ALT, AST or GGT changes were deemed to be clinically important.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There was a trend for the incidence of AST, ALT and total bilirubin outliers to increase slightly

with increasing SPD476 daily dose and when compared to placebo. However, the number of subject was too small to draw any conclusion, thus the clinical significance of this finding is unknown.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no dropouts due to laboratory abnormalities in this clinical program.

7.1.7.4 Additional analyses and explorations

There were no additional analyses and exploration performed in this clinical program.

7.1.7.5 Special assessments

There were no special assessments performed in this clinical program.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In this clinical program, vital signs (blood pressure, heart rate, respiratory rate and temperature) were assessed at screening, baseline, Weeks 2, 4, 8 and endpoint (end of study or withdrawal) for the Placebo-controlled Pool. Analyses are presented as changes from baseline and are also presented by dose and frequency of dosing. The protocol defined criteria for identifying clinically significant vital sign abnormalities are summarized in Table 14.

Table 14 Vital Signs Normal Ranges and Defined Outlier Criteria

Parameter	Outlier Criteria
Pulse	+/-25 bpm change from baseline
Diastolic Blood Pressure	+/-20 mmHg change from baseline
Systolic Blood Pressure	+/-20 mmHg change from baseline

Ref. Text Table 29, Module 2.7.3

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Examination of the vital signs data from two placebo controlled studies revealed no adverse event signal.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

There were no notable or clinically significant mean changes from baseline in vital signs

over time in any treatment group. There was no indication of any dose relationship or effect of dosage regimen on any parameter.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were 41 vital signs outliers from 38 subjects in the clinical program. The incidence of both high and low outliers was small for all parameters and was similar for the SPD476 groups and placebo. The only notable difference between the two doses of SPD476 was in the incidence of low SBP outliers (6.1% of subjects vs 2.8% with 4.8g/day and 2.4g/day, respectively). However, the incidence with the higher dose was similar to that observed with placebo treatment (5.0%).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no dropouts due to vital sign abnormalities in this clinical program.

7.1.9 Electrocardiograms (ECGs)

Electrocardiogram (ECG) data were collected from studies in healthy volunteers. There were no notable changes in 12-lead ECG parameters from screening to the end-of-study/early termination visits. No volunteers had changes from screening in QTc intervals of ≥ 30 msec at any time-point, except for Subject 0001, who had a pre-dose QTc interval of 469 msec on Day 1 of Treatment Period 1, compared to 435 msec at screening. However, this subject had a QTC interval reading of 447 msec in a recheck performed approximately 15 minutes prior to dosing on the same day; therefore, the change from screening was within the specified range. Most volunteers had QTc intervals of ≤ 450 msec at all time-points.

7.1.9.4 Additional analyses and explorations

There were no additional analyses and exploration performed in this NDA.

7.1.10 Immunogenicity

Not Applicable

7.1.11 Human Carcinogenicity

The NDA did not include human carcinogenicity studies.

7.1.12 Special Safety Studies

The NDA did not include special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The sponsor indicated that there is no evidence in the SPD476 database, to suggest any withdrawal or rebound effects and no instance of drug abuse has been reported.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant and lactating females were excluded from participating in the SPD476 clinical trials.

7.1.15 Assessment of Effect on Growth

Not Applicable

7.1.16 Overdose Experience

There have been no reports of overdose with SPD476.

7.1.17 Postmarketing Experience

SPD476 has not been marketed for use in any country at the time of this NDA submission. However, the active ingredient (mesalamine) of SPD476 is present in a number of marketed products throughout the world, and has a well established safety profile.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

SPD476 safety data have been collected from two phase II and two phase 3 clinical trials. In addition, an interim safety data from an ongoing long-term, open-label study to evaluate safety and tolerability of SPD476 for the maintenance of UC in remission have been reported. For the clinical trial involving subjects with acute disease (8-week therapy), the two large placebo controlled pivotal studies (Study 301 and Study 302) provided the major safety data. Emphasis has been placed on the analysis of the placebo-controlled data since it is only here that unbiased assessment of the safety of the test drug could be made. In two 8-week placebo-controlled pivotal studies involving 535 UC patients, 177 received SPD476 2.4g/day, 179 received SPD476 4.8g/day and 179 received placebo (Table 15). The majority of subjects in all treatment group received treatment for ≥ 8 weeks. The median exposure with placebo was very similar to that in the active treatment groups (7.9 weeks placebo vs 8.0 weeks all SPD476)

Long-term safety was evaluated using the interim data analysis from maintenance phase of long-term, open-label extension study (Study 303). The maintenance phase comprised subjects in remission, either at the end of the pivotal studies, or after the acute phase of Study 303. As of March 4, 2005, 443 patients in remission were enrolled into maintenance phase with median

treatment duration of 13 weeks (Table 16). Additional safety information from 120-day safety update is summarized under section 7.2.9 of this review.

Table 15 Overall Duration of Exposure: Placebo-controlled Pool

	Placebo (N = 179)	SPD476 2.4g/day (N = 177)	SPD476 4.8g/day (N = 179)	ALL SPD476 (N = 356)
Exposure in weeks: n (%)				
0 to <2	14 (7.8)	6 (3.4)	3 (1.7)	9 (2.5)
2 to <4	39 (21.8)	15 (8.5)	16 (8.9)	31 (8.7)
4 to <8	37 (20.7)	35 (19.8)	45 (25.1)	80 (22.5)
≥8	85 (47.5)	121 (68.4)	111 (62.0)	232 (65.2)
Missing	4 (2.2)	0	4 (2.2)	4 (1.1)
n	175	177	175	352
Median	7.9	8.0	8.0	8.0
Min, Max	0, 10	0, 10	0, 10	0, 10
Sum	1062	1297	1288	2585

Ref. Text Table 1, Module 2.7.4

Table 16 Duration of Treatment Exposure: Maintenance Phase of Study-303 (Interim Data)

	SPD476 2.4g/day QD (N = 215)	SPD476 2.4g/day BID (N = 218)	Overall (N = 433)
Overall (weeks)*; n (%)			
0 to <4	7 (3.3)	8 (3.7)	15 (3.5)
4 to <12	42 (19.5)	48 (22.0)	90 (20.8)
12 to <24	109 (50.7)	100 (45.9)	209 (48.3)
24 to <36	40 (18.6)	47 (21.6)	87 (20.1)
36 to 48	14 (6.5)	13 (6.0)	27 (6.2)
>48	3 (1.4)	2 (0.9)	5 (1.2)
Median	13.1	13.1	13.1
Min, max	0.1, 56.4	0.1, 53.1	0.1, 56.4

Source: TextTable20 of the Interim Study Report for SPD476-303 (v1.0; 31 August 2005)

* Calculated from day of last dose in maintenance phase - day of first dose in maintenance phase + 1

Percentages are based on the number of subjects in the Safety Population dosed during the maintenance phase in each treatment group.

7.2.1.1 Study type and design/patient enumeration

The safety data for SPD476 comprises five clinical studies in subjects with UC (Table 17): a phase 2 active controlled study comparing SPD746 3.6g /day TID vs Asacol enema 4g/day QD for 8 weeks (n=79); a phase 2 dose ranging study including SPD476 1.2 g/day, 2.4 g/day and 4.8 g/day for 8 weeks (n=38); 2 placebo-controlled phase 3 studies comparing SPD746 2.4g/day and 4.8g/day vs placebo for 8 weeks (n=280 and n=343, respectively); and the fifth study is an ongoing, long-term, open-label extension study which enrolled subjects from the two placebo-controlled pivotal studies, and comprises an 8-week acute phase using SPD476 4.8 g/day BID and a randomized maintenance phase using SPD476 2.4 g/day QD vs 2.4 g/day BID. Subjects from studies from placebo-controlled studies who had not achieved remission could enroll into

acute phase of long-term open-label study. The maintenance phase comprised subjects in remission, either at the end of the pivotal studies, or after the acute phase of open-label study.

Table 17 Summary of clinical studies

Study reference	Short title	Design	Subjects randomised	Duration of treatment	Treatment arms, daily dose and regimen
SPD476-201	Pilot efficacy study of SPD476 vs Asacol enema	R, DB, PG	79 subjects with active, left-sided UC	8 weeks	SPD476 3.6g/day TID Asacol 4g/day QD (enema)
SPD476-202	Dose-ranging, exploratory study	R, DB, PG	38 subjects with active, mild to moderate UC	8 weeks	SPD476 1.2g/day QD SPD476 2.4g/day QD SPD476 4.8g/day QD
SPD476-301	Efficacy & safety study, placebo vs. SPD476	R, DB, PG placebo-controlled	280 subjects with active, mild to moderate UC	8 weeks	SPD476: 2.4g/day BID SPD476 4.8g/day QD placebo
SPD476-302	Efficacy & safety study, placebo vs. SPD476 and Asacol	R, DB, PG placebo-controlled	343 subjects with active, mild to moderate UC	8 weeks	SPD476 2.4g/day QD SPD476 4.8g/day QD Asacol 2.4g/day TID placebo
SPD476-303 (interim analysis)	12-14 month extension safety study	R*, Open, extension	542 subjects from studies SPD476-301 and -302	Acute Phase: 8 weeks. Maintenance Phase: 12 months	Acute Phase: SPD476 4.8g/day BID Maintenance Phase: SPD476 2.4g/day QD SPD476 2.4g/day BID

QD=once daily; BID=twice daily; TID=three times daily; UC=Ulcerative colitis; R=randomised; DB=double-blind; PG=parallel group
 * Only the Maintenance Phase was randomised

7.2.1.2 Demographics

Demographic characteristics of placebo controlled pool are summarized in Table 18. Baseline characteristics were comparable between treatment groups. The population was primarily Caucasian, had a mean age of 42 years (< 10% were age 65 years or older) and gender distribution was similar across the groups.

Table 18 Demographic Characteristics: Placebo-controlled Pool

	Placebo (N = 179)	SPD476 2.4g/day (N = 177)	SPD476 4.8g/day (N = 179)	All SPD476 (N = 356)
Gender; n (%)				
Male	90 (50.3)	65 (48.0)	91 (50.8)	176 (49.4)
Ethnic origin; n (%)				
Caucasian	144 (80.4)	142 (80.2)	141 (78.8)	283 (79.5)
Black	3 (1.7)	4 (2.3)	3 (1.7)	7 (2.0)
Hispanic	8 (4.5)	8 (4.5)	7 (3.9)	15 (4.2)
Asian/Pacific Islander	19 (10.6)	18 (10.2)	24 (13.4)	42 (11.8)
Other	5 (2.8)	5 (2.8)	4 (2.2)	9 (2.5)
Age (years)				
Mean (SD)	42.6 (12.95)	41.6 (12.70)	43.1 (13.31)	42.3 (13.01)
Age category 1				
<65 years	170 (95.0)	169 (95.5)	164 (91.6)	333 (93.5)
≥65 years	9 (5.0)	8 (4.5)	15 (8.4)	23 (6.5)
Age category 2				
<55 years	145 (81.0)	147 (83.1)	143 (79.9)	290 (81.5)
≥55 years	34 (19.0)	30 (16.9)	36 (20.1)	66 (18.5)

Ref Text Table 4, Module 2.7.4

7.2.1.3 Extent of exposure (dose/duration)

The two pivotal studies (Study 301 and Study 302) were similar in design, inclusion/exclusion criteria, endpoints, total daily dose and duration of therapy (8 weeks). In two 8-week placebo-

controlled pivotal studies involving 535 UC patients, 177 received SPD476 2.4 g/day, 179 received SPD476 4.8 g/day and 179 received placebo. The majority of subjects in all active treatment group received treatment for ≥ 8 weeks. The median exposure with placebo was very similar to that in the active treatment groups (7.9 weeks placebo vs 8.0 weeks all SPD476).

In addition, long-term safety was evaluated using the interim data analysis from maintenance phase of long-term, open-label, extension study (Study 303). The maintenance phase comprised subjects in remission, either at the end of the pivotal studies, or after the acute phase of Study 303. As of March 4, 2005, 443 patients in remission were enrolled into maintenance phase with median treatment duration of 13 weeks. In the maintenance phase patients were randomized to either SPD746 2.4g/day QD or 2.4g/day BID. Additional safety information from 120-day safety update is summarized under section 7.2.9 of this review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The studies relevant to safety evaluation have been outlined under Section 7.2.1.1 of this review.

7.2.2.2 Postmarketing experience

SPD476 has not been marketed for use in any country at the time of this submission. However, the active ingredient of SPD476 (i.e., mesalamine) is present in a number of marketed products and has a well established safety profile.

7.2.2.3 Literature

The applicant provided a few articles electronically with this application. The reviewer performed additional literature search utilizing the Agency's on line database as well as resources and used them in describing various sections of this review.

7.2.3 Adequacy of Overall Clinical Experience

The study design and the protocol defined endpoints are acceptable. The trials were limited in their lack of sufficient geriatric population and racial subsets.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Agency did not request and this application did not include any new animal studies.

7.2.5 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments appear adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

During the drug development, the sponsor found that mesalamine was unstable in plasma samples stored at -20°C. As a result, the PK data from most of phase I studies appeared to be questionable according to the Biopharm reviewer's preliminary assessment. It is indicated that the biological samples from Study SPD476-105 were stored at -80°C for up to 59 days and, therefore, this study was not affected by the stability issues discussed above. In addition, the sponsor has recently conducted a new food effect and dose proportionality study (SPD476-106) and the study result was submitted on August 29, 2006.

Due to the aforementioned stability issue, evaluation and comment on the adequacy of PK data is differed to the Division's clinical pharmacology reviewer. The clinical pharmacology review was not finalized at the time this review was completed. Any pertinent clinical pharmacology issue will be addressed in the Medical Team Leader (Ruyi He, M.D.) supplementary review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The studies were appropriately designed to allow for adequate analysis of safety. Overall, the pivotal studies demonstrated that the two doses tested are safe and well tolerated. The overall safety profile of SPD746 was as expected according to the drug class.

7.2.8 Assessment of Quality and Completeness of Data

The data necessary to conduct safety review were included in the NDA. Overall, the applicant's quality of assessment appears acceptable.

7.2.9 Additional Submissions, Including Safety Update

The AE analyses in the 4-month safety update from an ongoing open-label, log-term study (Study-303, data cut-off 01/24/06) and the original summary of clinical safety (12/19/2005) show an overall similarity. The occurrence of AEs in the acute and maintenance phases of Study-303 was low. Most AEs events, including SAEs and AEs that led to withdrawal, were GI disorders and most of these were related to the underlying disease state of the study population. Laboratory test and vital signs results were unremarkable.

The safety update also includes SAEs recorded in two other ongoing active controlled studies (Study 304 and Study 306) as of 01/06/06.

- Two SAEs were reported in two subjects in Study 304
A 20-year-old Caucasian female (Subject 24503) experienced a miscarriage. Concomitant medications at the time of the event included progesterone. The subject was reported to be a smoker (8 cigarettes daily). The Investigator confirmed that the subject had no other relevant

medical history that could affect the outcome of the pregnancy. The subject started study drug on 02 September 2005 and stopped study drug on 20 September 2005. On 20 September 2005, the subject was reported to be pregnant. On _____ the subject experienced a miscarriage. On _____ the subject underwent curettage of the uterus without complications. The event is considered unexpected by the Investigator.

A 49-year-old Caucasian female (Subject 33102) experienced appendicitis. The subject started study drug on 01 October 2005 that was then interrupted due to the event on _____ (duration of interruption is unknown, but believed to be not more than two days). The subject was admitted to hospital and underwent an emergency laparoscopic appendectomy without complication. The principal Investigator reported that the event was unrelated to the use of study drug.

- Four SAEs were reported in three subjects in Study 306.

Subject 013 experienced a perianal abscess. Subject 219 experienced haematuria and renal colic. Both events were considered unrelated to the study drug by the Investigator. Subject 289 experienced acute pancreatitis, but continued receiving study drug and the condition improved. The relationship of the study drug to the event of pancreatitis was considered unknown by the Investigator.

MO comment: Data from both ongoing active controlled studies (Studies 304 and 306) have not been unblinded. The clinical significance of the aforementioned findings is unknown.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the two 8-week placebo controlled studies, treatment-related AEs experienced at least by 1% of any Mesavance group (2.4 g/day, 4.8 g/day) and at the rate greater than placebo were headache (5.6%, 3.4%, and 0.6%, respectively), flatulence (4%, 2.8% and 2.8%, respectively), increased alanine aminotransferase (0.6%, 1.1%, 0%, respectively), alopecia (0%, 1.1%, 0%, respectively) and pruritus (0.6%, 1.1% and 0%, respectively). None of alanine aminotransferase changes were deemed to be clinically significant. A rare AE that was probably/possibly drug-related was acute pancreatitis as outlined elsewhere.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The incidence of AEs in pooled data and individual study data has been reviewed and summarized under Section 7.1.5.3 and Appendix 10, respectively, of this review.

Comparison of AEs across the pivotal studies showed that the overall incidence of treatment-emergent AE was higher in study 301 (affecting $\geq 40\%$ of subjects per treatment group compared to 20% per treatment group in study 302). The disparity was greatest between the placebo arms of the two studies (50.5% vs 17.4%). In both studies, the events were predominantly GI disorder associated with UC. The study designs are similar and there are no differences in the methods of collecting data which could explain this apparent disparity. One difference between the study designs is the regimen of the 2.4g/day SPD476 groups: QD in study 302 and BID in study 301. However, one cannot attribute the higher AE rate in study 301 to BID rather than QD dosing, because a similar difference between the studies in AEs rates was observed in the 4.8g/day QD and the placebo groups, whose regimens were identical in each study.

The most obvious general difference between the studies is that they were conducted in different groups of countries. In spite of a subset analysis of safety data by country revealing no consistent clinically significant differences, it is possible that the observed difference in AEs rates may have something to do with the higher propensity of one group of countries to report AEs than another. It is possible that multinational clinical studies are liable to be characterized by degree of heterogeneity.

After a careful review of the data, the reviewer concurs with the sponsor's conclusion that the difference between studies in AE rates has little impact on the interpretation of the overall safety data. There were no novel AEs reported in study 301 and the incidence and type of AEs was similar among three treatment groups.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for drug-demographic interactions

Safety and effectiveness of SPD467 in pediatric patients have not been studied. The clinical program did not include sufficient number of subjects aged 65 and older to determine whether they respond differently than younger subjects. Analyses by race would not provide meaningful information as the number of non-Caucasian was very small.

The incidence of AEs primarily related to GI disorder was slightly higher in females (All SPD476; 37.8% vs 30.7%). However, there was no increased risk with the higher dose of SPD476, and importantly, the overall incidence was similar to that with placebo in both genders.

7.4.3 Causality Determination

The overall safety data including data from placebo-controlled trials do not suggest that use of SPD476 is associated with any new safety signal. The overall safety profile was as expected according to the drug class.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosage for the induction of remission in adults with active, mild to moderate UC is two to four 1.2g tablets to be taken once daily for a total daily dose of 2.4g to 4.8g.

MO comment: The proposed wording of the total daily dose (—) in the Dosage and Administration Section of the labeling is misleading, as it appears to imply a dose range, when in fact two dose levels (2.4g/day and 4.8g/day) were tested in pivotal trials. Thus, the wording should be modified to indicate a total daily dose of 2.4g or 4.8g.

The doses and regimen used in the pivotal study were based on the data from a small (n=38) phase II dose-ranging study (Study 202). The dose ranging study used once daily regimen and compared doses of 1.2g/day, 2.4g/day, and 4.8g/day of Mesavance. Results from this study demonstrated that no subjects in the lowest dose achieved remission. The remission rate was slightly better in the 2.4g/day group than the 4.8g/day group.

8.2 Drug-Drug Interactions

Drug interaction studies have not been conducted with Mesavance.

8.3 Special Populations

Safety and effectiveness of SPD476 in pediatric patients have not been studied. There have been no studies with Mesavance in subjects with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with Mesavance. The clinical program did not include sufficient number of subjects aged 65 and older to determine whether they respond differently than younger subjects. Analyses by race would not provide meaningful information as the number of non-Caucasian was very small.

In a subgroup efficacy analysis (pooled pivotal studies) by gender, there was a tendency for more females to achieve remission than males in all treatment groups (21%, 45%, 41% vs 14%, 29%, 18%, for placebo, 2.4 g/day and 4.8 g/day groups, respectively). In regard to safety analysis by gender, the incidence of AEs was slightly higher in females than in males for Mesavance group (37.8% vs 30.7%). However, there was no increased risk with the higher dose of Mesavance, and more importantly, the overall incidence was similar to that with placebo group in both genders.

8.4 Pediatrics

The request for deferral was granted for pediatric assessments of SPD476 for the indication until the efficacy and safety data are available in adults. The sponsor is required to

The request for a partial waiver for children < 6 years of age was denied due to the inadequate justification (large tablet size). The applicant was advised to develop age-appropriate formulations, or provide a rationale why this is not possible (advise letter dated August 3, 2006).

8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting required for this NDA.

8.6 Literature Review

The applicant provided a few articles electronically with this application. The reviewer performed additional literature search utilizing the Agency's on line database as well as resources and used them in describing various sections of this review.

8.7 Postmarketing Risk Management Plan

There are no applicable issues related to risk management in this NDA.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

Mesavance has been demonstrated to be safe and effective in induction of remission of active, mild to moderate UC in adults. Both Mesavance doses (2.4g/day and 4.8g/day) had similar efficacy and safety profiles for the indication. The pivotal studies were not designed to demonstrate superiority of one dose over the other dose of Mesavance.

In two similarly designed 8-week placebo-controlled phase III clinical studies (Studies 301 and 302) involving 517 subjects with mild to moderate active UC, the sponsor was able to demonstrate clinically meaningful and statistically significant efficacy findings. Both Mesavance doses were safe and well tolerated in each placebo-controlled study. The incidence and type of adverse events were similar across the treatment groups in each placebo-controlled study and did not indicate dose related increase in adverse events across the Mesavance groups. Interim safety data indicated that continuing exposure to Mesavance in a long-term extension study (Study 303) is not associated with any accumulation of risk.

9.2 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation for approval of Mesavance for the induction of remission of active, mild to

moderate ulcerative colitis in adults pending satisfactory labeling negotiations with the sponsor. The recommended dose is 2.4g/day QD or 4.8g/day QD for 8 weeks.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no applicable activities related to risk management for this NDA.

9.3.2 Required Phase 4 Commitments

No phase 4 requests are required for this approval. The Division granted deferral for pediatric assessments for the indication until the efficacy and safety data are available in adults. The sponsor is required to _____

The request for a partial waiver for children < 6 years of age was denied due to the inadequate justification (i.e. large tablet size). The applicant was advised to develop age-appropriate formulations, or provide a rationale why this is not possible (advise letter dated August 3, 2006).

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests for this NDA.

9.4 Labeling Review

The clinical section of the proposed labeling is reviewed under appendix 10.3 of this review.

9.5 Comments to Applicant

The reviewer has no additional comments to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

The clinical data upon which this application is submitted is based on two phase III placebo-controlled studies (Study-301 and Study-302). While both studies were of similar design, used the same inclusion/exclusion criteria and efficacy endpoints, an additional arm of Asacol 2.4g/day (approved formulation) was included in Study 302 as an internal reference. However, for this application the comparison of interest was two Mesavance doses vs placebo. Both studies used Mesavance doses of 2.4g/day and 4.8g/day administered once daily for 8 weeks except for the 2.4g/day group in Study 301, which was given in two divided doses (1.2g BID).

10.1.1 STUDY-301

PROTOCOL SUMMARY

Title: A phase III, randomized, multi-centre, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of SPD476 2.4g/day given twice daily and SPD476 4.8g/day given once daily in subjects with mild to moderate active UC.

Investigators

A total of 52 centers enrolled subjects in U.S and non-U.S countries.

Study period: 30 September 2003 to 17 January 2005

Objectives

The primary objective was to compare the percentage of subjects in remission after 8 weeks of treatment for SPD476 2.4g/day given twice daily (1.2g BID) versus placebo, and SPD476 4.8g/day given once daily (QD) versus placebo.

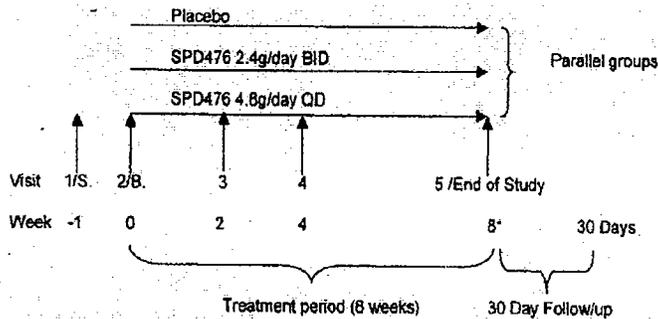
Major Secondary objectives:

- To compare the percentage of subjects achieving clinical improvement at Week 8 as defined by a drop of ≥ 3 points from baseline in the overall UC-DAI score for the three treatment groups
- To compare the percentage of subjects in remission after 8 weeks of treatment between the two doses of SPD476
- To compare the change in symptoms (rectal bleeding and stool frequency) from baseline to 2, 4, and 8 weeks of treatment between the three treatment groups
- To compare the change in sigmoidoscopic (mucosal) appearance from baseline to 8 weeks of treatment between the three treatment groups

- To assess the safety and tolerability of SPD476 administered as 2.4g/day BID and 4.8g/day QD as compared to placebo.

Study Design

This was a randomized, multi-centre, double-blind, 3-arm, parallel group, placebo-controlled phase III study to assess the safety and efficacy of SPD476 2.4g/day administered twice daily (1.2g BID) and SPD476 4.8g/day administered once daily (QD). Eligible subjects were randomized to receive SPD476 2.4g/day, SPD476 4.8g/day or placebo in a 1:1:1 ratio. Doses of study medication were to be taken with food.



*All subjects who are enrolled in SPD476-301 and remain on study drug until Visit 3 will be offered the opportunity to enter a 12-month extension clinical trial, SPD476-303 providing they meet all inclusion criteria.

MO comment: The study design is adequate to achieve the study objective.

Inclusion Criteria

- Men and women aged 18 and over
- Women not of childbearing potential (defined as those who were post-menopausal for at least 12 consecutive months or those who were surgically sterilized) were eligible, as were women of child-bearing potential who agreed to use an effective contraceptive method while on study treatment and agreed not to become pregnant during the 30 days after the last dose of the study drug
- Subjects who were newly diagnosed or had a diagnosis of relapsing (relapsed \leq 6 weeks to baseline) mild to moderate UC (total score of 4-10 on the UC-DAI and with a sigmoidoscopy score of 1 and PGA of <2).

Exclusion Criteria

- Subjects who, in the investigator's opinion, were not likely to respond to mesalazine doses of 2.4g/day were not included
- Subjects with severe UC according to the PGA or subjects who had relapsed for > 6 weeks prior to baseline
- Subjects who had relapsed on maintenance therapy with doses of mesalazine > 2.0 g/day.
- Subjects with Crohn's Disease, proctitis (where the extent of inflammation was ≤ 15 cm from the anus), bleeding disorders, or active peptic ulcer disease

- Subjects with stool cultures that were positive for enteric pathogens
- Subjects who had previous resective colonic surgery
- Subjects who used systemic or rectal steroids within 4 weeks prior to baseline
- Subjects who used immunosuppressant within 6 weeks prior to baseline
- Subjects who had moderate or severe renal impairment (defined as a creatinine level of > 2 mg/dL)

MO comment: inclusion and exclusion criteria are appropriate for the study.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects who were in remission at Week 8. Remission was defined as a UC-DAI score of ≤ 1 , with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

Major Secondary Efficacy Endpoints

- Clinical improvement, defined as a drop in the UC-DAI score of ≥ 3 points from baseline
- Treatment failure, defined as an unchanged, worsened or missing UC-DAI score
- Clinical remission, defined as subjects who scored 0 for the stool frequency and rectal bleeding scores (i.e. a complete resolution of symptoms)
- Change from baseline in sigmoidoscopy score.

The UC-DAI score is defined as the sum of four parameters including rectal bleeding, stool frequency, mucosal appearance on sigmoidoscopy and PGA. Each parameter was assessed on scales from 0 to 3, with 3 being the most severe score. It should be pointed out that in both studies any sigmoidoscopy evidence of mucosal friability was scored a '2' in the sigmoidoscopy portion of the UC-DAI rather than the usual score of '1', which means that the presence of friability defines the subject as a non-responder for the primary endpoint. Subjects assessed their own rectal bleeding and stool frequency symptoms and reported them daily to the IVRS during the study. The UC-DAI score, assessment of sigmoidoscopic mucosal appearance and PGA were performed at baseline and at Week 8 (End of Study/Early Withdrawal Visit).

MO comment: It is worth mentioning that there is no rigorous standard to evaluate the efficacy of therapy for UC. While there are many empiric indices for the measurement of disease activity in UC, none of them have been formally validated, which makes comparison with the literature difficult.

Safety Evaluation

The safety and tolerability of study medication was assessed by monitoring adverse events (AEs), laboratory testing (hematology, biochemistry and urinalysis), physical examination, and vital signs.

Study Procedure

During the study period, subjects visited the clinic on five different occasions (Table 19). A visit window of +/- 3 days was permitted for visits 3, 4, 6. Starting from the day of the Screening Visit, subjects were instructed to phone the IVRS every day within 1 hour before going to bed to record their symptoms (stool frequency and rectal bleeding) for that day. Subject symptoms data were retrieved from the IVRS for the last available 3 days immediately prior to each study visit, except the Screening Visit, for which data were retrieved via subject recall from the last available 3 days prior to the visit. The average of the scores of the last available 3 days was calculated for each parameter and recorded in the CRF. A sigmoidoscopy and PGA were performed at baseline and at the End of Study or Early Withdrawal Visit.

Table 19 Study Schedule

Visit Number	1 Screening	2 Baseline (Randomization)	3	4	5 ^a End of Study/Early Termination
Week ¹	-1	0	2	4	8
Informed Consent	X				
In/Exclusion Criteria	X	X			
Medical History	X				
Demographics	X				
Physical examination Including Weight & Height ⁶	X				X
Vital Signs (BP and Pulse)	X	X	X	X	X
Serum Pregnancy Test ²	X				X
Urinalysis (Dipstick) ⁴	X				X
Stool culture	X				X
Hematology ⁷	X			X	X
Biochemistry ⁷	X			X	X
Sigmoidoscopy (UC-DAI)		X			X
Physicians Global Assessment (UC-DAI)		X			X
Symptoms assessment (UC- DAI) ⁸	X ⁹	X	X	X	X
Diary Card distributed/review	X	X	X	X	X
Study medication dispensed		X	X	X	
Adverse Event		X	X	X	X
Concomitant medication	X	X	X	X	X
Drug Compliance			X	X	X
30 Day Follow-up ³					X

1. A visit window of +/- 3 days will be permitted for visits 3, 4, 5.
2. Serum beta HCG pregnancy test will be completed for all women of childbearing potential. A negative serum pregnancy test must be obtained prior to study drug administration.
3. Investigator/designee is to follow-up with the subject 30 days following the end of study visit and report any SAEs that occur.
4. If any of the urine dip-stick parameters are abnormal, a urine sample will be sent to the central laboratory for analysis and microscopic examination.
5. If the subject does not complete 8 weeks of treatment, all procedures listed for the End of Study /Early Termination visit (week 8) should be completed as soon as possible following the subject's last dose.
6. Height will be measured at screening only.
7. Hematology and biochemistry assessments will be performed by a central laboratory.
8. Symptoms, i.e., stool frequency and rectal bleeding, will be assessed from the data recorded on the subject's diary card. Only the last 3 days prior to the study visit will be assessed.
9. Symptom assessment for 3 days prior to screening visit is made per subject recall, not diary cards.

Ref. Text Table 1, Module 5.3.5.1 (Study-301)

Randomization Method

Subjects were assigned to one of three treatment groups, namely, SPD476 2.4g/day SPD476 4.8g/day, and placebo using a 1:1:1 allocation. Three-digit randomization numbers were allocated sequentially to subjects via an IVRS following confirmation of eligibility. Randomization procedures were organized centrally and were not stratified by centre as the

number of subjects in each centre was expected to be small. Once a randomization number was assigned, it was not used again if, for example, a subject was withdrawn from the study.

Treatment Compliance

Subjects were instructed to bring their unused study medication and used packaging to every visit. At the end of the study, the clinical monitor returned all unused and un-dispensed study medication to the depot from which study medication was originally supplied and delivery records were reconciled against usage and returned stocks based on entries in the drug accountability forms. Subject compliance was calculated at the end of the study using the following formula: Number of doses taken from first dose to last dose / number of doses that should have been taken from first dose to last dose x 100. Subjects who had taken 80% -120% of the medication under study were regarded as being compliant.

Concomitant Therapy

Any concomitant medication taken by the subject at baseline was to be kept at a stable dose during the study. Subjects were advised not to take indigestion remedies at the same time of day as study medication. Subjects were not permitted to use any of the medications listed below and were withdrawn from the study if they did:

- Systemic or rectal corticosteroids
- Sulphasalazine or mesalazine products other than SPD476
- Immunosuppressive agents
- NSAIDs, anti-diarrheal, laxatives, antibiotics and drugs that cause constipation were to be avoided; however, prophylactic use of aspirin (325mg/day) for cardiac disease was permitted throughout the study. Paracetamol was recommended for mild acute pain.

Protocol Amendments

- Protocol Amendments 1 and 2 were finalized prior to subject enrolment and were incorporated into the planned analyses.

The following amendments were finalized after subject enrolment had commenced:

- Protocol Amendment 3 (dated 03 May 2004) was introduced to specify that all study medication would be stored at room temperature 15-25°C/59-77°F based on stability data.
- Protocol Amendment 4 (dated 27 Sep 2004) was introduced for the following main reasons:
 - To define treatment failure as an unchanged, worsened, or missing UC-DAI score; and to define clinical remission as a combined symptom score of 0 (i.e. rectal bleeding and stool frequency symptoms absent)
 - To clarify that subjects who had previous resective colonic surgery would not be eligible for the study
 - To amend the handling of missing and incomplete data to document that the LOCF method would no longer be used for imputation of UC-DAI scores from the Early

- Withdrawal Visit to Week 8 in the case of subjects withdrawing early, although LOCF analysis could be performed on secondary variables as supportive analyses
- To add to the primary efficacy variable definition that subjects who withdrew prematurely from the study, provided no post baseline data, or had a missing or incomplete UC-DAI score would be assessed as not being in remission
 - To add that pair-wise comparisons of the two study doses and a treatment failure analysis would be performed; and to include a statistical analysis of the UC-DAI, change in sigmoidoscopy score and also an exploratory analysis of symptoms recorded on the IVRS in order to support the primary findings

STATISTICAL METHODS

Data Set Analyzed

The intent-to-treat (ITT) population was defined as all randomized subjects who received at least one dose of study medication. The per-protocol (PP) population was defined as all subjects in the ITT population who were without major protocol violations.

Efficacy Analyses

For primary efficacy analysis the primary treatment comparisons were:

- SPD476 2.4g/day versus Placebo
- SPD476 4.8g/day versus Placebo.

The proportion of subjects in remission at week-8 was compared with placebo for both active treatments using the chi-squared test. The study-wise false positive error rate from performing two primary comparisons was controlled using the Bonferroni-Holm method. The treatment comparison with the smaller p-value was evaluated at the 0.025 significance level. If that comparison was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level.

Secondary Efficacy Analyses

For all secondary efficacy analyses, the following treatment comparisons were made:

- SPD476 2.4g/day versus Placebo
- SPD476 4.8g/day versus Placebo
- SPD476 2.4g/day versus SPD476 4.8g/day.

The sponsor indicated that analyses of secondary efficacy variables were considered supportive, thus multiplicity adjustments to the significance levels were not carried out. Hypothesis tests at the 0.05 significance level and two-sided 95% CIs were used throughout for supportive analyses.

RESULTS (Study 301)

Patient Disposition

The study was initiated on September 23, 2003 and completed on January 17, 2005. A total of 280 subjects were enrolled at 52 centers in U.S. and non-U.S. countries (Table 20). The majority of the subjects were enrolled in three countries including Ukraine, India and U.S.

Table 20 Subject Disposition – Randomized Subjects

	Placebo	SPD476 2.4g/day	SPD476 4.8g/day
Randomized	N=93	N=93	N=94
	n (%)	n (%)	n (%)
Australia	1 (1.1)	0	2 (2.1)
Czech Republic	6 (6.5)	4 (4.3)	6 (6.4)
Mexico	6 (6.5)	7 (7.5)	5 (5.3)
New Zealand	4 (4.3)	3 (3.2)	5 (5.3)
Romania	3 (3.2)	6 (6.5)	2 (2.1)
Ukraine	23 (24.7)	30 (32.3)	25 (26.6)
India	22 (23.7)	22 (23.7)	27 (28.7)
USA	28 (30.1)	21 (22.6)	22 (23.4)

(Ref. Text Table 3, Section 6, Model 5.3.5.1, Study-301)

Premature Study Discontinuation

Seventy-nine subjects discontinued from the study prematurely (Table 21). Discontinuations were more frequent in the placebo group compared to SPD476 2.4g/day and 4.8 g/day groups (44.1%, 18.3% and 22.3%, respectively). The most frequent reason for premature discontinuation in all groups was lack of efficacy and it was greater in the placebo group compared to SPD476 2.4g/day and 4.8 g/day groups (25.8%, 7.5% and 11.7%, respectively). Discontinuations due to adverse event (AE) or serious adverse event (SAE) were also more frequent in the placebo group.

Table 21 Reasons for Premature Study Discontinuation.

	Placebo (N = 93)		SPD476 2.4g/day BID (N = 93)		SPD476 4.8g/day QD (N = 94)	
Subjects (%) who discontinued	41	(44.1)	17	(18.3)	21	(22.3)
Lack of efficacy	24	(25.8)	7	(7.5)	11	(11.7)
AE/SAE	11	(11.8)	5	(5.4)	2	(2.1)
Protocol violation	4	(4.3)	0		1	(1.1)
Subject request	0		3	(3.2)	2	(2.1)
Lost to follow-up	1	(1.1)	0		3	(3.2)
Non-compliance	1	(1.1)	2	(2.2)	1	(1.1)

Source: Section 12, Table 1.1.

Note: an End of Study CRF page was not completed for subject 22209 (SPD476 4.8g/day QD).

(Ref. Text Table 4, Model 5.3.5.1, Study 301)

Demographic and Other Baseline Characteristics

There were no clinically significant differences between the treatment groups in regard to demographic and baseline characteristics at screening (Tables 22 and 23, respectively). Approximately 50% of subjects was male and the mean age was 42 years. The mean height and weight was 167 cm and 69 kg, respectively. The population was primarily Caucasian and approximately 20% of subjects were of Asian/Pacific Islander origin. The majority of subjects had never smoked and less than 10% of subjects in each treatment group currently smoked.

Most subjects had a history of UC and was generally similar in all treatment groups, while newly diagnosed subjects were slightly less frequent in the 2.4g/day group. Most subjects were diagnosed by colonoscopy and all subjects but one had compatible histology. Mean time since diagnosis was slightly greater in the 4.8g/day group, although mean duration of the current episode was generally similar in all groups. Most subjects across treatment groups had left-sided disease (77-89%), while < 20% had pancolitis.

Table 22 Demographic Characteristics – ITT Population

	Placebo (N = 85)		SPD476 2.4g/day BID (N = 86)		SPD476 4.8g/day QD (N = 89)	
Gender; n (%)						
Male	41	(48.2)	46	(52.3)	48	(53.9)
Female	44	(51.8)	42	(47.7)	41	(46.1)
Age (years)						
Mean (SD)	42.6	(11.68)	40.2	(11.97)	41.8	(13.62)
Median	42.0		40.0		39.0	
Min, Max	21	76	20	67	18	73
Height (cm)						
Mean (SD)	167.7	(9.93)	168.3	(10.91)	167.8	(9.54)
Median	167.0		168.5		167.0	
Min, Max	140	186	130	191	145	192
Weight* (kg)						
Mean (SD)	69.0	(16.87)	68.1	(17.20)	70.8	(18.03)
Median	65.6		63.2		67.3	
Min, Max	31	115	40	119	38	135
Ethnic origin; n (%)						
Caucasian	56	(65.9)	57	(64.8)	54	(60.7)
Black	3	(3.5)	3	(3.4)	3	(3.4)
Hispanic	5	(5.9)	6	(6.8)	6	(6.7)
Asian/Pacific Islander	16	(18.8)	17	(19.3)	22	(24.7)
Other	5	(5.9)	5	(5.7)	4	(4.5)
Smoking history; n (%)						
Never smoked	62	(72.9)	67	(76.1)	68	(76.4)
Previously smoked	20	(23.5)	17	(19.3)	13	(14.5)
Currently smokes	3	(3.5)	4	(4.5)	8	(8.9)

Source: Section 12, Tables 1.2.1 and 3.3.1

* Weight data were recorded for the Safety population.

(Ref. Text Table 5, section 6, Model 5.3.5.1, study-301)

Table 23 Ulcerative Colitis History – ITT Population.

	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Diagnosis: n (%)			
Newly diagnosed	16 (18.8)	10 (11.4)	22 (24.7)
History of ulcerative colitis	69 (81.2)	78 (88.6)	67 (75.3)
Time since diagnosis (weeks)			
Mean (SD)	226.1 (282.94)	216.1 (298.59)	266.8 (396.84)
Median	113.1	87.6	92.1
Min, Max	0 1187	1 1627	0 2123
Method of diagnosis: n (%)			
Sigmoidoscopy	19 (22.4)	29 (33.0)	26 (29.2)
Colonoscopy	69 (81.2)	66 (75.0)	64 (71.9)
Barium enema	7 (8.2)	6 (6.8)	7 (7.9)
Compatible histology	84 (98.8)	88 (100.0)	89 (100.0)
Number of relapses in last 2 years; n (%)			
0	12 (14.1)	9 (10.2)	19 (21.3)
1-2	31 (36.5)	49 (55.7)	37 (41.6)
3-4	27 (31.8)	25 (28.4)	20 (22.5)
5-6	9 (10.6)	4 (4.5)	5 (5.6)
≥7	4 (4.7)	0	5 (5.6)
Duration of current episode (days)			
Mean (SD)	26.6 (38.74)	21.4 (17.02)	20.6 (10.10)
Median	21.0	21.0	21.0
Min, Max	4 384	1 147	4 42
Full extent of disease* (cm)			
N	75	74	78
Mean (SD)	48.2 (26.80)	48.9 (23.30)	55.2 (26.21)
Median	40.0	45.0	50.0
Min, Max	10 120	20 120	12 140
Classification of disease: n (%)			
Left-sided†	66 (77.6)	78 (88.6)	71 (79.8)
Involvement of transverse colon	4 (4.7)	4 (4.5)	6 (6.7)
Pancolitis	15 (17.6)	6 (6.8)	11 (12.4)
Rectal involvement: n (%)			
Yes	72 (84.7)	75 (85.2)	74 (83.1)
Extra-intestinal manifestations: n (%)			
Yes	3 (3.5)	5 (5.7)	1 (1.1)

Source: Section 12, Table 1.3.1.

Notes: For the method of diagnosis, subjects could be included in more than one category. The number of relapses and the full extent of disease were not recorded for all subjects.

* Measured from the anal margin. † Involvement of sigmoid and/or descending colon.

(Ref. Text Table 6, section 6, Model 5.3.5.1)

Medical/Surgical History at Screening

There were no notable differences between the treatment groups in regard to medical/surgical history abnormalities at screening (Table 24). The only medical/surgical history abnormalities experienced by ≥10% of subjects in any group were surgical and medical procedures (30%), gastrointestinal disorders (12%), and infections and infestations (10%). Individual medical/surgical histories occurred infrequently, each being experienced by no more than 5% of subjects in any treatment group with the exception of appendectomy (7.5%, 6.5% and 3.2% of subjects in the placebo, SPD476 2.4g/day and SPD476 4.8g/day groups, respectively), tonsillectomy (1.1%, 4.3% and 5.3% of subjects, respectively) and tubal ligation (4.3%, 1.1% and 5.3% of subjects, respectively).

Table 24 Medical/Surgical History at Screening Experienced by ≥ 10% of Subjects

System organ class	Placebo (N = 93)	SPD476 2.4g/day BID (N = 93)	SPD476 4.8g/day QD (N = 94)
Surgical and medical procedures	30 (32.3)	25 (26.9)	29 (30.9)
Gastrointestinal disorders	12 (12.9)	13 (14.0)	8 (8.5)
Infections and infestations	13 (14.0)	9 (9.7)	6 (6.4)

Source: Section 12, Table 1.6.

(Ref. Text Table 7, section 6, Model 5.3.5.1, Study 301)

Concomitant Therapy

In general, the majority of concomitant medications were taken by a similar proportion of subjects in each treatment group (Table 25). The most frequent concomitant medications taken during the treatment period were anilides (8%), aminosalicic acid and similar agents (7%), proton-pump inhibitors (6%) and enemas (5%). For all subjects but two, aminosalicic acid and similar agents were stopped on study day 1.

Table 25 Concomitant Medication Taken by ≥ 5% of Subjects

Number (%) of subjects	Placebo (N = 93)	SPD476 2.4g/day BID (N = 93)	SPD476 4.8g/day QD (N = 94)
Anilides	4 (4.3)	9 (9.7)	9 (9.6)
Tylenol	0	3 (3.2)	5 (5.3)
Aminosalicic acid and similar agents	8 (8.6)	6 (6.5)	6 (6.4)
Proton pump inhibitors	9 (9.7)	5 (5.4)	4 (4.3)
Enemas	4 (4.3)	6 (6.5)	4 (4.3)
ACE inhibitors, plain	3 (3.2)	3 (3.2)	5 (5.3)
Benzodiazepine derivatives	6 (6.5)	1 (1.1)	4 (4.3)
Beta-blocking agents, selective	3 (3.2)	1 (1.1)	5 (5.3)
Selective serotonin reuptake inhibitors	8 (8.6)	0	1 (1.1)

Source: Section 12, Table 1.8.

Note: ACE, angiotensin-converting enzyme.

(Ref. Text Table 10, section 6, Model 5.3.5.1, Study 301)

Treatment Compliance

Most subjects in all treatment groups were compliant with study medication (Table 26). Twelve subjects took <80% of the required amount of study medication (four in each treatment group) and two subjects took >120% of the required amount of study medication (one in each active treatment group).

Table 26 Overall Compliance with Study Medication

	Placebo (N = 93)	SPD476 2.4g/day BID (N = 93)	SPD476 4.8g/day QD (N = 94)
Overall compliance,* n (%)			
<80%	4 (4.3)	4 (4.3)	4 (4.3)
80-120%	85 (91.4)	88 (94.6)	85 (90.4)
>120%	0	1 (1.1)	1 (1.1)
Not available	4 (4.3)	0	4 (4.3)

Source: Section 12, Table 1.9.

*Overall compliance was defined as [(number of doses taken from first dose to last dose) / (number of doses that should have been taken from first dose to last dose)] * 100.

(Ref. Text Table 11, section 6, Model 5.3.5.1, Study 301)

Protocol Deviations

Major protocol deviations occurred infrequently and there were generally no notable differences between the treatment groups, although subjects who were non-compliant in regard to study medication were slightly more frequent in the SPD476 4.8g/day group (Table 27).

Table 27 Major Protocol Deviations

Number (%) of subjects	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Subject did not have 80 to 120% overall compliance	4 (4.7)	5 (5.7)	9 (10.1)
Subjects who had been in relapse for >6 weeks prior to baseline	2 (2.4)	1 (1.1)	1 (1.1)
Subjects with UC-DAI <4 or sigmoidoscopy score <1	3 (3.5)	0	1 (1.1)
Subjects with Crohn's Disease, proctitis (where the extent of inflammation was ≤15cm from the anus)	2 (2.4)	0	0
Subjects with a positive stool culture for enteric pathogens* and subjects with <i>Clostridium difficile</i> toxin present or with ova or parasites as detected by microscopy	0	0	1 (1.1)
Subjects who had relapsed on maintenance therapy with doses of mesalazine >2.0g/day	0	1 (1.1)	0
Subjects whose original diagnosis had not been established by compatible histology	1 (1.2)	0	0

Source: Section 12, Table 1.10.

* Enteric pathogens included *Salmonella*, *Shigella*, *Yersinia*, *Aeromonas*, *Plesiomonas* or *Campylobacter*.

Subjects could have more than one protocol deviation.

(Ref. Text Table 12, section 6, Model 5.3.5.1, Study 301)

EFFICACY EVALUATION

Analyses of Primary Efficacy Endpoint

In the ITT analysis, at Week 8 significantly greater proportion of subjects achieved remission in the SPD476 2.4g/day group compared to the placebo group (34.1% vs 12.9%, p=0.001), a difference that was statistically significant in favor of active treatment (Table 28). The odds of remission for subjects taking SPD476 2.4g/day were approximately 3.5 times greater than for subjects taking placebo. Similar results were seen in the SPD476 4.8 g/day group compared to placebo group (29.2% vs 12.9%, p=0.009). The PP analysis showed similar results, in which 14% (11/76) of subjects was in remission in the placebo group compared to 37% (30/81) in SPD476 2.4 g/day and 32% (26/79) in 4.8 g/day groups (p=0.001 and 0.007, respectively).

Table 28 Subjects in Remission (Primary Efficacy Endpoint) at Week 8

	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

Source: Section 12, Table 2.1.1.

* Values from the chi-squared test.

† Study-wise, false-positive error rate was controlled using the Bonferroni-Holm method. The treatment comparison with the smaller p-value was evaluated at the 0.025 significance level. If this was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level. CIs presented are analogous to the significance level.

(Ref. Text Table 14, section 6, Model 5.3.5.1, Study 301)

Additional Analysis of Primary efficacy Endpoints

Since 18 subjects were excluded from the aforementioned analysis due to Good Clinical Practice non-compliance issues, an additional analysis (sensitivity analysis) was performed in which the 18 subjects were treated as non-responders. In this analysis, the superiority of both active treatments over placebo was confirmed (Table 29).

Table 29 Sensitivity Analysis Primary Endpoint

	Subjects (%) in remission	Odds ratio	CI	p-value†
Placebo; N = 93	12 (12.9)			
SPD476 2.4g/day BID; N = 93 versus placebo*	31 (33.3)	3.38	(1.44, 7.90)	0.001
SPD476 4.8g/day QD; N = 94 versus placebo*	27 (28.7)	2.72	(1.28, 5.78)	0.008

Source: Section 12, Table 2.8.1.

* Values from the chi-squared test.

† Study-wise false-positive error rate was controlled using the Bonferroni-Holm method. The treatment comparison with the smaller p-value was evaluated at the 0.025 significance level. If this was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level. CIs presented are analogous to the significance level.

(Ref. Text Table 26, section 6, Model 5.3.5.1, Study 301)

MO comment: Both SPD476 doses were superior over placebo. Whilst the study was not designed to demonstrate superiority of one SPD476 dose over the other dose, the 2 doses tested (2.4g/day and 4.8g/day) appeared to have similar efficacy profiles, suggesting that the high dose would not provide additional clinical benefits over the low dose.

Analyses of Secondary Efficacy Variables

The results of secondary efficacy analyses supported the findings of primary efficacy analysis by consistently demonstrating greater efficacy with active treatments over placebo (Tables 30).

Table 30 Results of Secondary Efficacy Endpoints (%Patients)

Secondary Efficacy Variables	SPD476 2.4g/day n=88	SPD476 4.8g/day n=88	Placebo n=85
Clinical Improvement	55.7%***	59.6%***	25.9%
Treatment Failure	28.4%***	24.7%***	54.1%
Clinical Remission	37.5%**	32.6%*	18.8%
Sigmoidoscopic Improvement	64.8%**	71.9%***	36.5%
Change from baseline in UC-DAI score	-2.71***	-3.46***	-0.79
*p < 0.05, **p < 0.01, ***p < 0.001 (each vs placebo)			

Ref. copied from Table 3, sponsor's proposed labeling

Analysis of stool frequency score demonstrated that the proportion of subjects with scores <1 increased in all groups from baseline to Week 8 and endpoint, although a greater increase was observed in the SPD476 groups compared to the placebo group (Table 31).

Table 31 Average Stool Frequency Score

	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Baseline			
Mean (SD)	1.746 (0.9134)	1.527 (0.8316)	1.667 (0.7598)
Score: n (%)			
<1	13 (15.3)	18 (20.5)	9 (10.1)
1 to <2	29 (34.1)	34 (38.6)	37 (41.6)
≥2	42 (49.4)	36 (40.9)	42 (47.2)
Week 2			
<1	22 (25.9)	31 (35.2)	30 (33.7)
1 to <2	17 (20.0)	23 (26.1)	32 (36.0)
≥2	26 (30.6)	26 (29.5)	16 (18.0)
Week 4			
<1	19 (22.4)	33 (37.5)	35 (39.3)
1 to <2	21 (24.7)	28 (31.8)	34 (38.2)
≥2	15 (17.6)	13 (14.8)	6 (6.7)
Week 8			
<1	28 (30.6)	45 (51.1)	53 (59.6)
1 to <2	13 (15.3)	16 (18.2)	12 (13.5)
≥2	9 (10.6)	11 (12.5)	5 (5.6)
Endpoint			
<1	27 (31.8)	49 (55.7)	56 (61.8)
1 to <2	19 (22.4)	19 (21.6)	15 (16.9)
≥2	35 (41.2)	18 (20.5)	13 (14.6)

Source: Section 12, Table 2.7.1.

Note: baseline stool frequency scores recorded for subject 13002 in the placebo group and subject 12907 in the SPD476 4.8g/day QD group were not used as they were recorded after the visit date.

Percentages are based on the number of subjects in the ITT population for each treatment group.

(Ref. Text Table 22, section 6, Model 5.3.5.1, Study 301)

Regarding analysis of rectal bleeding score, the proportion of subjects with scores <1 increased in all groups from baseline to Week 8 and endpoint although the increase was greater in the SPD476 groups compared to the placebo group (Table 32). Marked differences between the SPD476 and placebo groups were observed as early as Week 2.

Table 32 Average Rectal Bleeding Score

	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Baseline			
Mean (SD)	1.27 (0.754)	1.10 (0.727)	1.19 (0.641)
Score: n (%)			
<1	18 (21.2)	24 (27.3)	28 (31.5)
1 to <2	40 (47.1)	46 (52.3)	37 (41.6)
≥2	26 (30.6)	18 (20.5)	23 (25.8)
Week 2			
<1	29 (34.1)	43 (48.9)	57 (64.0)
1 to <2	26 (30.6)	28 (31.8)	13 (14.6)
≥2	10 (11.8)	9 (10.2)	8 (9.0)
Week 4			
<1	30 (35.3)	55 (62.5)	56 (62.9)
1 to <2	19 (22.4)	16 (18.2)	17 (19.1)
≥2	6 (7.1)	3 (3.4)	2 (2.2)
Week 8			
<1	32 (37.6)	56 (63.6)	63 (70.8)
1 to <2	10 (11.8)	10 (11.4)	6 (6.7)
≥2	6 (7.1)	6 (6.8)	1 (1.1)
Endpoint			
<1	37 (43.5)	64 (72.7)	67 (75.3)
1 to <2	19 (22.4)	11 (12.5)	11 (12.4)
≥2	25 (29.4)	11 (12.5)	5 (5.6)

Source: Section 12, Table 2.7.5.

Note: baseline rectal bleeding scores recorded for subject 13002 in the placebo group and subject 12907 in the SPD476 4.8g/day QD group were not used as they were recorded after the visit date.

Percentages are based on the number of subjects in the ITT population for each treatment group.

(Ref. Text Table 23, section 6, Model 5.3.5.1, Study 301)

At Week 8, the proportion of subjects with improved sigmoidoscopy scores was greater in the SPD476 4.8g/day and SPD476 2.4g/day groups compared to the placebo group: 69.7%, 61.4%

and 35.3%, respectively (Table 33). However, it should be noted that a greater proportion of subjects from the placebo group had unknown value (subjects who had withdrawn prior to Week 8) at week 8 compared to active treatment groups (approximately 44% vs 20%).

Table 33 Results of Sigmoidoscopy Score

Number (%) of subjects	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Baseline			
1 (mild)	13 (15.3)	19 (21.6)	13 (14.6)
2 (moderate)	64 (75.3)	65 (73.9)	74 (83.1)
3 (severe)	8 (9.4)	4 (4.5)	2 (2.2)
Change at Week 8			
Improved	30 (35.3)	54 (61.4)	62 (69.7)
Same	17 (20.0)	15 (17.0)	7 (7.9)
Worsened	1 (1.2)	3 (3.4)	1 (1.1)
Unknown [‡]	37 (43.5)	16 (18.2)	19 (21.3)
p-value [†]			
versus placebo		0.300	0.002
versus SPD476 4.8g/day QD		0.040	
Change at endpoint			
Improved	31 (36.5)	57 (64.8)	64 (71.9)
Same	43 (50.6)	24 (27.3)	15 (16.9)
Worsened	6 (7.1)	5 (5.7)	2 (2.2)
Unknown	5 (5.9)	2 (2.3)	8 (9.0)
p-value [†]			
versus placebo		0.002	<0.001
versus SPD476 4.8g/day QD		0.059	

Source: Section 12, Table 2.7.11.

* Change from baseline. Unknown changes were not included in the analysis.

† p-value from the Mantel-Haenszel chi-squared test with the alternative hypothesis of linear association at Week 8 or endpoint.

‡ Unknown values include those of subjects who had withdrawn prior to Week 8.

(Ref. Text Table 24, section 6, Model 5.3.5.1, Study 301)

MO comment: the results of secondary efficacy analyses supported the findings of primary efficacy analysis, however, the reader is cautioned that the numerous p-values presented by the sponsor are not adjusted for multiple comparisons that have been performed.

Analysis of Centre Effect

An analysis of the effect of centre on the proportion of subjects in remission at Week 8 is presented for the ITT population in Table 34.

In Eastern Europe, remission rates for all treatment groups were slightly greater than the overall rates observed. In India, remission rates for all treatment groups were slightly lower. Remission rates in the USA were lower in both active treatment groups compared to the overall rates; however, it was considerably lower for 4.8g/day group. The p-value from the treatment pooled centre interaction was 0.9245, indicating that there was no difference in treatment effect over pooled centers.

Table 34 Analysis of Centre Effect on the Proportion of Subjects in Remission

	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Subjects per pooled centre			
Australasia*	5	3	7
Eastern Europe†	32	40	33
India	19	21	25
Mexico‡	3	5	4
USA	26	19	20
Subjects (%) in remission§			
Australasia*	11 (12.9)	30 (34.1)	26 (29.2)
Eastern Europe†	6 (18.8)	18 (45.0)	15 (45.5)
India	2 (10.5)	7 (33.3)	6 (24.0)
Mexico‡	0	0	1 (25.0)
USA	3 (11.5)	5 (26.3)	1 (5.0)
p-value¶	0.9245		

Source: Section 12, Table 2.3.1.

* The Australasia pooled centre consisted of subjects from Australia and New Zealand.

† The Eastern Europe pooled centre consisted of subjects from Romania, Ukraine and the Czech Republic.

‡ The Mexico pooled centre also contained one site from Costa Rica.

§ Subjects who had a UC-DAI score of ≤1 with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

¶ p-value from the treatment* pooled centre interaction from a logistic regression model with treatment, pooled centre and treatment* pooled centre as factors.

(Ref. Text Table 16, section 6, Model 5.3.5.1, Study 301)

MO comment: the variability in remission rates across the pooled centers may be due to the small number of subjects within each centre.

SAFETY EVALUATION

Extent of Exposure

The overall mean duration of treatment exposure was 6.9 weeks. Subjects in both SPD476 groups were exposed to treatment for slightly longer than subjects in the placebo group (approximately 7 weeks versus 6 weeks) and more subjects in the placebo group than in the SPD476 groups had <4 weeks exposure to study treatment (Table 35).

Table 35 Duration of Treatment Exposure – Safety Population

Exposure in weeks;* n (%)	Placebo (N = 93)	SPD476 2.4g/day BID (N = 93)	SPD476 4.8g/day QD (N = 94)
0 to <2	4 (4.3)	4 (4.3)	2 (2.1)
2 to <4	25 (26.9)	10 (10.8)	10 (10.6)
4 to 8	30 (32.3)	36 (38.7)	41 (43.6)
>8	30 (32.3)	43 (46.2)	37 (39.4)
N	89	93	90
Mean (SD)	6.04 (2.796)	7.30 (2.283)	7.24 (2.175)
Median	8.00	8.00	8.00
Min, Max	0.7, 10.1	0.4, 10.1	1.0, 9.4

Ref. Text Table 27, Module 5, Section 8.1 (Study-301)

Overall Incidence of Adverse Events (AEs)

One-hundred and twenty-nine subjects (46%) experienced treatment-emergent AEs (Table 36). Approximately 50% of subjects in the placebo and SPD476 2.4g/day BID treatment groups experienced at least one treatment-emergent AE, compared with 40% of subjects in the SPD476 4.8g/day QD group. Most were of mild or moderate intensity; only 13 subjects had a severe event, of which eight were in the placebo group. There were no notable differences between the treatment groups in regard to the incidence of treatment-related AEs, which were experienced by less than 20% of subjects in each group.

There were no deaths during the study and only seven subjects experienced eight SAEs. Withdrawals due to AEs were less frequent in the SPD476 groups than in the placebo group. There was no evidence of any dose related increase in AEs across the SPD476 groups.

Table 36 Treatment-Emergent Adverse Events – Safety Population

	Placebo		SPD476 2.4g/day BID		SPD476 4.8g/day QD	
	(N = 93)		(N = 93)		(N = 94)	
Number (%) of subjects with:						
Any AE	47	(50.5)	44	(47.3)	38	(40.4)
Any mild AE	26	(28.0)	35	(37.6)	28	(29.8)
Any moderate AE	25	(26.9)	14	(15.1)	15	(16.0)
Any severe AE	8	(8.6)	2	(2.2)	3	(3.2)
Any treatment-related AE	17	(18.3)	15	(16.1)	14	(14.9)
Any SAE	3	(3.2)	2	(2.2)	2	(2.1)
AE that led to withdrawal	11	(11.8)	5	(5.4)	2	(2.1)

Ref. Text Table 28 Module 5, Section 8.1 (Study-301)

Most Common Treatment-emergent AEs

Gastrointestinal (GI) disorders, the most frequently reported AEs in all treatment groups, were experienced by more subjects in the placebo group than in the SPD476 groups, with the lowest incidence occurring in the SPD476 4.8g/day QD group (Tables 37 and 38). The most frequently reported GI disorder was colitis ulcerative aggravated, which occurred in nine subjects (9.7%) in the placebo group compared to six (6.5%) and one (1.1%) subject in the SPD476 2.4g/day BID and SPD476 4.8g/day QD group, respectively. No hepatobiliary disorders were experienced in any treatment group. Renal and urinary disorders (acute glomerulonephritis and haematuria) were experienced by two subjects in the SPD476 2.4g/day BID group; neither event was considered to be related to study medication.

Table 37 Treatment-Emergent AEs Experienced by $\geq 2\%$ of Subjects – Safety Population

System organ class Preferred term	Placebo (N = 93)		SPD476 2.4g/day BID (N = 93)		SPD476 4.8g/day QD (N = 94)	
	Number (%) of subjects					
Total	47	(50.5)	44	(47.3)	38	(40.4)
Gastrointestinal disorders	35	(37.6)	22	(23.7)	15	(16.0)
Colitis ulcerative aggravated	9	(9.7)	6	(6.5)	1	(1.1)
Flatulence	4	(4.3)	3	(3.2)	2	(2.1)
Dyspepsia	3	(3.2)	2	(2.2)	1	(1.1)
Abdominal pain nos	2	(2.2)	1	(1.1)	2	(2.1)
Abdominal pain upper	2	(2.2)	2	(2.2)	1	(1.1)
Anal discomfort	2	(2.2)	0		0	
Diarrhea nos	2	(2.2)	4	(4.3)	0	
Frequent bowel movements	2	(2.2)	0		0	
Nausea	2	(2.2)	3	(3.2)	3	(3.2)
Abdominal distension	1	(1.1)	2	(2.2)	2	(2.1)
Musculoskeletal and connective tissue disorders	5	(5.4)	8	(8.6)	4	(4.3)
Arthralgia	0		3	(3.2)	1	(1.1)
Back pain	1	(1.1)	2	(2.2)	1	(1.1)
Skin and subcutaneous tissue disorders	3	(3.2)	4	(4.3)	9	(9.6)
Pruritus	1	(1.1)	1	(1.1)	2	(2.1)
Alopecia	0		0		2	(2.1)
Infections and infestations	4	(4.3)	4	(4.3)	6	(6.4)
Herpes zoster	0		0		2	(2.1)
Upper respiratory tract infection	0		2	(2.2)	0	
General disorders and administration site conditions	5	(5.4)	4	(4.3)	4	(4.3)
Pyrexia	2	(2.2)	2	(2.2)	3	(3.2)
Investigations	3	(3.2)	2	(2.2)	7	(7.4)
ALT increased	0		1	(1.1)	2	(2.1)
Haemoglobin decreased	2	(2.2)	0		0	
Respiratory, thoracic, and mediastinal disorders	6	(6.5)	2	(2.2)	4	(4.3)
Bronchitis nos	3	(3.2)	0		0	
Nasopharyngitis	1	(1.1)	0		3	(3.2)

Ref. Text Table 29 Module 5, Section 8.1 (Study-301)

Table 38 (continued) Treatment-Emergent AEs Experienced by $\geq 2\%$ of Subjects

System organ class Preferred term	Placebo (N = 93)		SPD476 2.4g/day BID (N = 93)		SPD476 4.8g/day QD (N = 94)	
	Number (%) of subjects					
Nervous system disorders	1	(1.1)	5	(5.4)	3	(3.2)
Headache	1	(1.1)	5	(5.4)	2	(2.1)
Dizziness	0		2	(2.2)	0	
Metabolism and nutrition disorders	3	(3.2)	0		3	(3.2)
Anorexia	2	(2.2)	0		0	
Psychiatric disorders	2	(2.2)	3	(3.2)	0	
Anxiety	0		2	(2.2)	0	
Blood and lymphatic system disorders	2	(2.2)	2	(2.2)	0	
Anaemia nos	1	(1.1)	2	(2.2)	0	
Eye disorders	0		2	(2.2)	1	(1.1)
Renal and urinary disorders	0		2	(2.2)	0	
Cardiac disorders	0		0		2	(2.1)

Ref. Text Table 29 Module 5, Section 8.1 (Study-301)

Severe Treatment-Emergent AEs

The most frequent severe AEs were GI disorders experienced by nine of the 13 subjects, most commonly aggravated UC (Table 39). In the SPD476 groups, only one subject had severe aggravated UC (in the 2.4g/day BID group), although one subject in each SPD476 group had severe pancreatitis compared with none in the placebo group.

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Table 39 Severe Treatment-Emergent Adverse Events

System organ class Preferred term	Placebo (N = 93)		SPD476 2.4g/day BID (N = 93)		SPD476 4.8g/day QD (N = 94)	
	Number	(%)	Number	(%)	Number	(%)
Number (%) of subjects						
Total	8	(8.6)	2	(2.2)	3	(3.2)
Gastrointestinal disorders	6	(6.5)	2	(2.2)	1	(1.1)
Colitis ulcerative aggravated†	3	(3.2)	1	(1.1)	0	
Diarrhea nos	1	(1.1)	0		0	
Frequent bowel movements	2	(2.2)	0		0	
Pancreatitis nos†	0		1	(1.1)	1	(1.1)
Infections and infestations	1	(1.1)	0		1	(1.1)
Sinusitis nos	1	(1.1)	0		0	
Tonsillitis	1	(1.1)	0		0	
Gastroenteritis viral nos†	0		0		1	(1.1)
Nervous system disorders	1	(1.1)	0		0	
Headache	1	(1.1)	0		0	
Respiratory, thoracic, and mediastinal disorders	1	(1.1)	0		0	
Bronchitis nos	1	(1.1)	0		0	
Metabolism and nutrition disorders	0		0		1	(1.1)
Fluid retention	0		0		1	(1.1)

Ref. Text Table 30, Module 5, Section 8.1 (Study-301)

† All severe cases of these events were SAEs.

Treatment-Related AEs

Treatment-related AEs experienced by $\geq 2\%$ of subjects occurred in similar proportion of subjects in all treatment groups (Table 40). However, GI disorders, the most frequent treatment-related AEs occurred in a greater proportion of subjects in the placebo group (13 subjects [14.0%]) than in the SPD476 groups (8 subjects [8.6%] in the 2.4g/day BID group and 5 subjects [5.3%] in the 4.8g/day QD group). Aggravated UC, flatulence, nausea, and dyspepsia were the most frequent treatment-related gastrointestinal disorders.

In the SPD476 2.4g/day BID group, headache was the most frequent treatment-related AE (5 subjects [5.4%]), no cases of treatment-related headache were reported in the SPD476 4.8g/day QD group or in the placebo group. In the SPD476 4.8g/day QD group, skin and subcutaneous tissue disorders were the most frequent treatment-related AEs, predominantly pruritus and alopecia.

Table 40 Treatment-Related AEs Experienced by $\geq 2\%$ of Subjects

System organ class Preferred term	Placebo		SPD476 2.4g/day BID		SPD476 4.8g/day QD	
	(N = 93)		(N = 93)		(N = 94)	
Number (%) of subjects						
Total	17	(18.3)	15	(16.1)	14	(14.9)
Gastrointestinal disorders	13	(14.0)	8	(8.6)	5	(5.3)
Colitis ulcerative aggravated	3	(3.2)	1	(1.1)	1	(1.1)
Flatulence	3	(3.2)	1	(1.1)	1	(1.1)
Nausea	2	(2.2)	1	(1.1)	2	(2.1)
Dyspepsia	2	(2.2)	1	(1.1)	1	(1.1)
Abdominal pain upper	2	(2.2)	0		0	
Skin and subcutaneous tissue disorders	1	(1.1)	2	(2.2)	6	(6.4)
Pruritus	0		1	(1.1)	2	(2.1)
Alopecia	0		0		2	(2.1)
Nervous system disorders	0		5	(5.4)	1	(1.1)
Headache	0		5	(5.4)	0	
Dizziness	0		2	(2.2)	0	
Investigations	1	(1.1)	1	(1.1)	2	(2.1)
ALT increased	0		1	(1.1)	2	(2.1)
General disorders/administration site conditions	0		2	(2.2)	0	

Source: Section 12, Table 3.2.5.

Ref. Text Table 31 Module 5, Section 8.1 (Study-301)

Deaths, Other Serious Adverse Events (SAEs), Discontinuations due to Adverse Events and Other Significant Adverse Events

There were no deaths during the study. Seven subjects experienced a total of eight SAEs: three subjects [3.2%] in the placebo group, two subjects [2.2%] in the SPD476 2.4g/day BID group, and two subjects [2.1%] in the SPD476 4.8g/day QD group (Table 41). Of these, all but one was GI disorders. All SAEs were considered to be unrelated to the study medication with the exception of the two cases of pancreatitis experienced by subjects 11902 (possibly-related) and 17301 (probably-related), and all were severe except for the one moderate case of colitis. Only one SAE did not result in withdrawal (viral gastroenteritis experienced by subject 11701) but all resolved.

Table 41 Treatment-Emergent Serious Adverse Events

Treatment group	Subject	System organ class	Preferred term	Intensity
Placebo	12906	Gastrointestinal disorders	Colitis ulcerative aggravated*	Severe
	18210	Gastrointestinal disorders	Colitis aggravated*	Moderate
	21804	Gastrointestinal disorders	Colitis ulcerative aggravated*	Severe
		Gastrointestinal disorders	Colitis ulcerative aggravated†	Severe
SPD476 2.4g/day BID	11902	Gastrointestinal disorders	Pancreatitis nos*	Severe
	26001	Gastrointestinal disorders	Colitis ulcerative aggravated*	Severe
SPD476 4.8g/day QD	11701	Infections and infestations	Gastroenteritis viral nos	Severe
	17301	Gastrointestinal disorders	Pancreatitis nos*	Severe

* Subject withdrawn due to this SAE.

† Event occurred 22 days after withdrawal.

Ref. Text Table 32 Module 5, Section 8.1 (Study-301)

Study Discontinuation Due to AEs

The most frequent AEs that led to study discontinuation were GI disorders, which accounted for all but one of the discontinuations due to AEs (Table 42). Discontinuation due to AEs occurred more frequently in the placebo group (11.8%) than in either of the SPD476 groups (5.4% in the 2.4g/day BID group and 2.1% in the 4.8g/day QD group).

The most frequent AE that led to study discontinuation was aggravated UC, which was experienced by 10 of the 18 subjects withdrawn due to AEs. This occurred more frequently in the placebo group than in either of the SPD476 groups.

Table 42 Treatment-Emergent Adverse Events That Resulted in Study Discontinuation

System organ class Preferred term	Placebo		SPD476 2.4g/day BID		SPD476 4.8g/day QD	
	(N = 93)		(N = 93)		(N = 94)	
Number (%) of subjects						
Total	11	(11.8)	5	(5.4)	2	(2.1)
Gastrointestinal disorders	11	(11.8)	4	(4.3)	2	(2.1)
Colitis ulcerative aggravated	7	(7.5)	2*	(2.2)	1	(1.1)
Frequent bowel movements	2	(2.2)	0		0	
Pancreatitis nos	0		1	(1.1)	1	(1.1)
Colitis aggravated	1	(1.1)	0		0	
Diarrhea nos	0		1	(1.1)	0	
Dyspepsia	1	(1.1)	0		0	
Psychiatric disorders	0		1	(1.1)	0	
Anxiety	0		1	(1.1)	0	

* In addition to the two subjects presented, subject 26508 experienced an unrelated AE of colitis ulcerative aggravated that resulted in permanent discontinuation of study drug. This subject was withdrawn due to lack of efficacy.

Ref. Text Table 33 Module 5, Section 8.1 (Study-301)

Clinical Laboratory Evaluation

Summary of hematology and biochemistry values and changes from baseline at Weeks 4 and 8, and endpoint are presented in the sponsor's Module 5, Section 12, Table 3.4.1 and Table 3.4.2, respectively. The mean data for all hematology and biochemistry parameters analyzed were unremarkable and there were no notable mean changes in any group across the course of the study.

MO comment: The overall safety data from Study 301 demonstrated that administration of SPD476 was safe and well-tolerated. There was no evidence of any notable changes in the safety profile of SPD476 with increasing dose.

10.1.2 STUDY-302

Title: Phase III, randomized, multicenter, double-dummy, parallel-group, placebo-controlled study to evaluate the efficacy and safety of SPD476 2.4 g/day and 4.8 g/day given once daily, with reference to Asacol 0.8 g three times daily in subjects with mild to moderate acute UC.

The protocol for Study 302 is almost identical to that of Study 301 which is summarized under appendix 10.1.1. of this review with 2 exceptions: in Study 302, an additional arm of Asacol 2.4g/day (approved formulation) was included as an internal reference (note that the assessment of the efficacy of Asacol was not part of the primary efficacy analysis), and the SPD476 2.4g/day dose was given once daily in Study 302, whereas it was given in two divided doses in Study 301.

RESULTS

Patient Disposition

The study was initiated on December 4, 2003 and completed on October 20, 2004. A total of 343 subjects were randomized into the study at 49 centers in 10 foreign countries (Table 43). The majority of the subjects were enrolled in two countries, namely, Poland (38%) and Russia (33%).

All subjects but two (SPD476 2.4g/day group) took at least one dose of study medication. Over 80% of subjects in the active treatment groups completed the study compared to 61% in the placebo group.

Table 43 Subject Disposition – Randomized Subjects

	Placebo	SPD476 2.4g/day	SPD476 4.8g/day	Asacol
Randomized	N= 86	N=86	N=85	N=86
	n (%)	n (%)	n (%)	n (%)
Estonia	2 (2.3)	3 (3.5)	2 (2.4)	3 (3.5)
France	0	1 (1.2)	1 (1.2)	1 (1.2)
Germany	1 (1.2)	3 (3.5)	2 (2.4)	4 (4.7)
Hungary	7 (8.1)	7 (8.1)	9 (10.6)	8 (9.3)
Israel	4 (4.7)	4 (4.7)	1 (1.2)	5 (5.8)
Latvia	1 (1.2)	2 (2.3)	4 (4.7)	2 (2.3)
Lithuania	4 (4.7)	3 (3.5)	2 (2.4)	5 (5.8)
Poland	37 (43.0)	32 (37.2)	33 (38.8)	30 (34.9)
Russia	28 (32.6)	29 (33.7)	30 (35.3)	26 (30.2)
Spain	2 (2.3)	2 (2.3)	1 (1.2)	2 (2.3)

(Ref. Text Table 3, Model 5.3.5.1, Study 302)

Premature Discontinuation

Although lack of efficacy was the most frequent reason for premature discontinuation in all groups, the proportion of subjects who discontinued due to lack of efficacy was greatest in the placebo group (27.9% versus 12%), Table 44. Discontinuations due to other reasons were infrequent and there were no notable differences between the groups.

Table 44 Reasons for Premature Study Discontinuation

	Placebo (N = 86)	SPD476 2.4g/day (N = 86)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Number (%) of subjects who discontinued	34 (39.5)	16 (18.6)	13 (15.3)	16 (18.6)
Lack of efficacy	24 (27.9)	11 (12.8)	11 (12.9)	10 (11.6)
Subject request	6 (7.0)	1 (1.2)	1 (1.2)	2 (2.3)
Other*	2 (2.3)	2† (2.3)	0	1 (1.2)
AE/SAE	2 (2.3)	1 (1.2)	0	1 (1.2)
Protocol violation	0	0	1 (1.2)	1 (1.2)
Lost to follow-up	0	0	0	1 (1.2)

Source: Section 12.1, Table 1.1 and Appendix 2, Listing 2.1.

* Placebo: subject 58206 – tablets too large and too many, subject 63603 – disease exacerbation; SPD476 2.4g/day QD: subject 63604 – disease exacerbation, subject 63606 – enrolled in error; Asacol 2.4g/day TID: subject 62208 – exacerbation of UC.

† In addition to these two subjects, subject 62803 in the SPD476 2.4g/day QD group had a positive stool culture result but was randomized in error. The subject did not take any study medication and was excluded from the study as a screen failure.

(Ref. Text Table 4, Model 5.3.5.1, Study 302)

Demographic and Baseline Characteristics

There were no clinically significant differences between the treatment groups in regard to demographic and baseline characteristics at screening (Tables 45 and 46, respectively). All subjects were Caucasian, the proportions of males and females were similar across treatment groups and the mean age was approximately 43 years. The majority of subjects had never smoked and less than 10% of subjects in each group currently smoked.

There were no clinically significant differences between the treatment groups in regard to UC history. The majority (85-88%) of subjects in each treatment groups had a history of UC and a similar proportion of subjects in each treatment group were newly diagnosed (13%). The method of diagnosis, mean time since diagnosis and number of relapses experienced in the last 2 years were generally similar across the treatment groups. The majority (70-80%) of patients in all treatment groups had left-sided disease, while 17-21% of patients had pancolitis.

Table 45 Demographic Characteristics – ITT Population

	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Gender; n (%)				
Male	43 (50.0)	39 (46.4)	39 (45.9)	41 (47.7)
Female	43 (50.0)	45 (53.6)	46 (54.1)	45 (52.3)
Age (years)				
Mean (SD)	43.2 (14.06)	43.3 (13.30)	44.6 (13.13)	41.9 (13.34)
Median	44.5	45.0	45.0	43.0
Min, Max	19 74	21 78	19 76	18 76
Height (cm)				
Mean (SD)	169.9 (9.19)	169.7 (8.88)	169.7 (9.88)	170.6 (9.65)
Median	170.5	170.0	170.0	170.0
Min, Max	142 192	150 190	148 191	144 198
Weight* (Kg)				
Mean (SD)	68.7 (14.36)	73.3 (14.87)	73.0 (14.33)	72.6 (15.65)
Median	68.0	72.0	71.0	70.5
Min, Max	40.2 99.0	43.0 126.0	42.5 120.0	46.0 124.0
Ethnic origin; n (%)				
Caucasian	86 (100.0)	84 (100.0)	85 (100.0)	86 (100.0)
Smoking history; n (%)				
Never smoked	51 (59.3)	56 (66.7)	62 (72.9)	63 (73.3)
Previously smoked	28 (32.6)	20 (23.8)	17 (20.0)	18 (20.9)
Currently smokes	7 (8.1)	8 (9.5)	6 (7.1)	5 (5.8)

Source: Section 12.1, Tables 1.2 and 3.3.1.
 * Weight data were recorded for the Safety population.

(Ref. Text Table 5, Model 5.3.5.1, Study 302)

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Table 46 Ulcerative Colitis History – ITT Population

	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Diagnosis: n (%)				
Newly diagnosed	10 (11.6)	11 (13.1)	12 (14.1)	13 (15.1)
History of UC	76 (88.4)	73 (86.9)	73 (85.9)	73 (84.9)
Time since diagnosis (weeks)				
Mean (SD)	293.1 (324.6)	290.4 (333.9)	282.7 (380.9)	244.4 (260.3)
Median	179.1	161.4	136.0	122.0
Min, Max	1 1224	1 1639	0 2212	0 1045
Method of diagnosis: n (%)				
Sigmoidoscopy	33 (38.4)	33 (39.3)	34 (40.0)	33 (38.4)
Colonoscopy	65 (75.0)	65 (77.4)	68 (80.0)	66 (76.7)
Barium enema	10 (11.0)	5 (6.0)	9 (10.6)	10 (11.6)
Compatible histology	66 (100.0)	63 (98.9)	65 (100.0)	66 (100.0)
Number of relapses in last 2 years: n (%)				
0	8 (9.3)	8 (9.5)	8 (9.4)	6 (7.0)
1-2	62 (60.6)	36 (46.4)	40 (47.1)	44 (51.2)
3-4	21 (24.4)	27 (32.1)	28 (32.9)	20 (23.3)
5-6	1 (1.2)	6 (7.1)	4 (4.7)	8 (9.3)
≥7	2 (2.3)	1 (1.2)	1 (1.2)	2 (2.3)
Duration of current episode (days)				
Mean (SD)	22.4 (11.61)	21.3 (9.10)	20.7 (8.46)	21.5 (10.65)
Median	21.0	21.0	21.0	21.0
Min, Max	5 84	6 42	3 35	7 70
Full extent of disease* (cm)				
N	60	58	62	69
Mean (SD)	48.9 (31.63)	56.1 (32.61)	50.4 (34.68)	52.4 (26.26)
Median	35.0	41.0	40.0	45.0
Min, Max	15 150	26 160	15 160	15 150
Classification of disease: n (%)				
Left-sided†	63 (73.3)	59 (70.2)	67 (78.9)	69 (80.2)
Involvement of transverse colon	6 (7.0)	7 (8.3)	4 (4.7)	2 (2.3)
Pancolitis	17 (19.6)	18 (21.4)	14 (16.5)	15 (17.4)

Notes: For the method of diagnosis, subjects could be included in more than one category. Full extent of disease was not recorded for all subjects.

* Measured from the anal margin.

† Involvement of sigmoid and/or descending colon.

(Ref. Text Table 5, Model 5.3.5.1, Study 302)

Prior Therapy

There were no notable differences between the treatment groups regarding medications taken prior to baseline (Table 47). The most frequent prior medications were aminosalicylic acid (51.3% of subjects overall). All other prior medications were taken by no more than four subjects in any treatment group.

Table 47 Prior Medications Taken by ≥ 5% of Subjects

Number (%) of subjects	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Aminosalicylic acid and similar agents	44 (51.2)	46 (54.8)	40 (47.1)	45 (52.3)
Mesalazine*	20 (23.3)	25 (29.8)	24 (28.2)	28 (32.6)
Sulfasalazine†	25 (29.1)	22 (26.2)	17 (20.0)	17 (19.8)
Benzodiazepine derivatives	6 (7.0)	6 (7.1)	2 (2.4)	7 (8.1)

Source: Section 12.1, Table 1.7.

* Mesalazine includes medications coded as mesalazine, mesalamine and Lixacol.

† Sulfasalazine includes medications coded as Salazopyrin, sulfasalazin and sulfasalazine.

(Ref. Text Table 8, Model 5.3.5.1, Study 302)

Treatment Compliance

Most subjects in all treatment groups were compliant as per protocol with study medication Table 48.

Table 48 Compliance With Study Medication – Safety Population

	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Overall compliance; n (%)				
<80%	0	2 (2.4)	5 (5.9)	2 (2.3)
80 – 120%	84 (97.7)	82 (97.6)	78 (91.8)	82 (95.3)
>120%	2 (2.3)	0	2 (2.4)	1 (1.2)

Source: Section 12.1, Table 1.9.

Note: Subject 63001 in the Asacol 2.4g/day TID group took study medication but overall compliance was not calculated for this subject as she was lost to follow-up.

Overall compliance was defined as ((number of doses taken from first dose to last dose) / (number of doses that should have been taken from first dose to last dose))*100%.

(Ref. Text Table 10, Model 5.3.5.1, Study 302)

Protocol Deviations

Overall, major protocol deviations occurred infrequently and there were no notable differences between the treatment groups, although subjects who were non-compliant with study medication were slightly more frequent in the 4.8g/day group (Table 49).

Table 49 Major Protocol Deviations – ITT Population

Number (%) of subjects	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Subject did not have 80 to 120% overall compliance	2 (2.3)	2 (2.4)	6 (7.1)	2 (2.3)
Subjects with UC-DAI <4 or sigmoidoscopy score <1	1 (1.2)	1 (1.2)	0	1 (1.2)
Subjects who had relapsed on maintenance therapy with doses of mesalazine >2.0g/day	1 (1.2)	1 (1.2)	0	1 (1.2)
Subjects with Crohn's Disease, proctitis (where the extent of inflammation was ≤15cm from the anus)	1 (1.2)	0	1 (1.2)	0
Subjects whose original diagnosis had not been established by compatible histology	0	1 (1.2)	0	0
Subjects who had unsuccessfully treated their current relapse with steroids and/or mesalazine >2.0g/day	0	1 (1.2)	0	0

Source: Section 12.1, Table 1.10.

Note: subjects could have more than one protocol deviation.

(Ref. Text Table 11, Model 5.3.5.1, Study 302)

EFFICACY EVALUATION

Of a total of 343 patients randomized into the study, 341 subjects were included in the ITT analysis. Two subjects (# 62803 and # 63606) were excluded from the ITT population (SPD476 2.4 g/day treatment group) because they had a positive stool culture result but were randomized in error. Both subjects did not receive any study medication.

Primary Efficacy Analysis

In the ITT analysis, 40.5% of subjects in the SPD476 2.4g/day group and 41.2% in the SPD476 4.8g/day group were in remission at Week 8 compared to 22.1% in the placebo group, the differences were statistically significant in favor of active treatments (p=0.010 and p=0.007, respectively (Table 50).

Table 50 Subjects in Remission at Week 8 – ITT Population

	Subjects in remission (%)	Odds ratio	CI	p value [†]
Placebo; N = 86	19 (22.1)			
SPD476 2.4g/day; N = 84 versus placebo*	34 (40.5)	2.40	(1.23, 4.69)	0.010
SPD476 4.8g/day; N = 85 versus placebo*	35 (41.2)	2.47	(1.15, 5.30)	0.007

Source: Section 12.1, Table 2.1.1.

* Values from the chi-squared test.

† Study-wise false-positive error rate was controlled using the Bonferroni-Holm method. The treatment comparison with the smaller p-value was evaluated at the 0.025 significance level. If this was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level. CIs presented are analogous to the significance level.

(Ref. Text Table 13, Model 5.3.5.1, Study 302)

MO comment. Both active treatments were superior over placebo. While the study was not designed to demonstrate superiority of one active dose over the other dose, both dose levels (2.4g/day and 4.8g/day) appeared to have similar efficacy profiles, suggesting that the high dose would not provide additional clinical benefits over the low dose.

Supportive Analysis

The proportion of subjects in remission at Week 8 was greater in the SPD476 4.8g/day and 2.4g/day groups compared to the Asacol 2.4g/day and placebo groups: 41.2%, 40.5%, 32.6% and 22.1%, respectively (Table 51). However, the differences between active treatment groups were not statistically significant.

MO comment: Asacol finding would not provide conclusive comparative efficacy information, as it was tested in only one study. Furthermore, the clinical trials that led to Asacol approval used different efficacy criteria and endpoints, which make comparison across studies difficult.

Table 51 Subjects in Remission at Week 8 – ITT Population

	Subjects in remission (%)	Odds ratio	95% CI	p value†
Placebo; N = 86	19 (22.1)			
SPD476 2.4g/day; N = 84	34 (40.5)	0.97	(0.53, 1.79)	0.926
versus SPD476 4.8g/day*		1.41	(0.75, 2.64)	0.284
SPD476 4.8g/day; N = 85	35 (41.2)	1.45	(0.78, 2.71)	0.243
versus Asacol*				
Asacol; N = 86	28 (32.5)	1.70	(0.86, 3.36)	0.124
versus placebo*				

Source: Section 12.1, Table 2.1.1.

* Values from the chi-squared test.

† p-value was evaluated at the 0.05 significance level.

(Ref. Text Table 14, Model 5.3.5.1, Study 302)

Secondary Efficacy Analyses

The results of secondary efficacy analyses supported the findings of primary efficacy analysis by demonstrating greater efficacy with active treatments over placebo (Tables 52).

Table 52 Results of Secondary Efficacy Endpoints (% Patients)

Secondary Efficacy Variables	SPD476 2.4g/day n=84	SPD476 4.8g/day n=85	Asacol 2.4g/day n=86	Placebo n=86
Clinical Improvement	60.7%**	64.7%***	55.8%*	39.5%
Treatment Failure	21.4%***	20.0%***	27.9%**	47.7%
Clinical Remission	41.7%**	41.2%**	33.7% ^{NS}	22.1%
Sigmoidoscopic Improvement	70.2%***	76.5%***	60.5%*	41.9%
Change from baseline in UC-DAI score	-3.34**	-3.58**	-3.11*	-1.94

*p < 0.05, **p < 0.01, ***p < 0.001 (each vs placebo); NS = not significant

Ref. copied from Table 4, sponsor's proposed labeling.

In regard to analysis of stool frequency score, the proportion of subjects with a stool frequency score of < 1 at Week 8 and endpoint was greater in the SPD476 and Asacol 2.4g/day groups compared to the placebo group (Table 53). Similarly, all groups showed a reduction in rectal bleeding score from baseline to Week 8 and endpoint, but the proportion of subjects with a score of <1 at Week 8 and endpoint was greater in the SPD476 and Asacol 2.4g/day groups compared to the placebo group (Table 54). Sigmoidoscopy exam demonstrated that at Week 8, the proportion of subjects with improved sigmoidoscopy scores was greater in the SPD476 4.8g/day and 2.4g/day groups compared to the Asacol 2.4g/day and placebo groups: 76.5%, 69.0%, 58.1% and 41.9%, respectively at Week 8; similar scores were observed at endpoint (Table 55). At Week 8, differences between SPD476 4.8g/day and placebo were statistically significant (p = 0.002), while differences between SPD476 2.4g/day and placebo and between Asacol 2.4g/day and placebo did not reach a statistical significance.

Table 53 Average Stool Frequency Score – ITT Population

	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Baseline				
Mean (SD)	1.686 (0.7291)	1.675 (0.7607)	1.482 (0.6872)	1.647 (0.7665)
Score; n (%)				
<1	10 (11.8)	7 (8.3)	12 (14.1)	9 (10.5)
1 to <2	32 (37.2)	37 (44.0)	46 (54.1)	38 (44.2)
≥2	44 (51.2)	39 (46.4)	27 (31.8)	38 (44.2)
Week 2				
<1	20 (23.3)	28 (33.3)	20 (23.5)	23 (26.7)
1 to <2	30 (34.9)	28 (33.3)	44 (51.8)	35 (40.7)
≥2	21 (24.4)	24 (28.6)	18 (21.2)	21 (24.4)
Week 4				
<1	16 (18.6)	36 (42.9)	29 (34.1)	37 (43.0)
1 to <2	26 (30.2)	27 (32.1)	37 (43.5)	28 (32.6)
≥2	16 (18.6)	11 (13.1)	9 (10.6)	9 (10.5)
Week 8				
<1	31 (36.0)	45 (53.6)	47 (55.3)	48 (55.5)
1 to <2	14 (16.3)	19 (22.6)	18 (21.2)	18 (20.9)
≥2	7 (8.1)	6 (7.1)	7 (8.2)	6 (7.0)
Endpoint				
<1	31 (36.0)	45 (53.6)	49 (57.6)	47 (54.7)
1 to <2	21 (24.4)	23 (27.4)	23 (27.1)	19 (22.1)
≥2	27 (31.4)	16 (19.0)	13 (15.3)	17 (19.8)

Source: Section 12.1, Table 2.7.1.

Note: subject 06205 in the SPD476 2.4g/day QD group and subject 55404 in the Asacol group had no stool frequency scores recorded at baseline.

Percentages are based on the number of subjects in the ITT population for each treatment group.

Table 54 Average Rectal Bleeding Score – ITT Population

	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 85)	Asacol (N = 86)
Baseline				
Mean (SD)	1.260 (0.7256)	1.185 (0.7218)	1.141 (0.6180)	1.231 (0.7053)
Score; n (%)				
<1	20 (23.3)	21 (25.0)	20 (23.5)	20 (23.3)
1 to <2	42 (48.8)	40 (47.6)	49 (57.6)	40 (46.5)
≥2	24 (27.9)	22 (26.2)	16 (18.8)	25 (29.1)
Week 2				
<1	35 (40.7)	40 (47.6)	41 (48.2)	34 (39.5)
1 to <2	20 (23.3)	29 (34.5)	28 (32.9)	32 (37.2)
≥2	16 (18.6)	11 (13.1)	13 (15.3)	13 (15.1)
Week 4				
<1	32 (37.2)	52 (61.9)	52 (61.2)	51 (59.3)
1 to <2	19 (22.1)	17 (20.2)	18 (21.2)	18 (20.9)
≥2	7 (8.1)	5 (6.0)	5 (5.8)	5 (5.8)
Week 8				
<1	35 (40.7)	55 (65.5)	58 (68.2)	54 (62.8)
1 to <2	13 (15.1)	13 (15.6)	12 (14.1)	11 (12.8)
≥2	4 (4.7)	2 (2.4)	2 (2.4)	5 (5.8)
Endpoint				
<1	39 (45.3)	58 (69.0)	63 (74.1)	57 (66.3)
1 to <2	25 (29.1)	18 (21.4)	15 (17.6)	13 (15.1)
≥2	15 (17.4)	8 (9.5)	7 (8.2)	13 (15.1)

(Ref. Text Table 22, Model 5.3.5.1, Study 302)

Table 55 Results of Sigmoidoscopy Score – ITT Population

Number (%) of subjects	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 86)	Asacol (N = 86)
Baseline				
0 (normal)	0	0	0	0
1 (mild)	12 (14.0)	12 (14.3)	14 (16.0)	15 (20.9)
2 (moderate)	65 (76.7)	64 (76.2)	62 (72.9)	61 (70.9)
3 (severe)	8 (9.3)	8 (9.5)	9 (10.5)	6 (7.0)
Missing score	0	0	0	1 (1.2)
Change at Week 8				
Improved	36 (41.9)	56 (69.0)	65 (79.5)	50 (58.1)
Same	14 (16.3)	11 (13.1)	7 (8.2)	19 (22.1)
Worsened	2 (2.3)	1 (1.2)	0	1 (1.2)
Unknown	34 (39.5)	14 (16.7)	13 (15.3)	16 (18.6)
p-value [†]				
SPD476 vs placebo		0.074	0.002	
SPD476 2.4g/day vs SPD476 4.8g/day		0.163		
SPD476 vs Asacol		0.144	0.004	
Asacol vs placebo				0.627
Change at endpoint				
Improved	36 (41.9)	59 (70.2)	65 (79.5)	52 (60.5)
Same	36 (41.9)	22 (26.2)	16 (18.8)	27 (31.4)
Worsened	6 (7.0)	1 (1.2)	3 (3.5)	3 (3.5)
Unknown	8 (9.3)	2 (2.4)	1 (1.2)	4 (4.7)
p-value [†]				
SPD476 vs placebo		<0.001	<0.001	
SPD476 2.4g/day vs SPD476 4.8g/day		0.692		
SPD476 vs Asacol		0.182	0.006	
Asacol vs placebo				0.026

Source: Section 12.1, Table 2.7.11.

Note: vs. = versus.

* Change from Baseline. Unknown changes were not included in the analysis.

† p-value from the Mantel-Haenszel chi-squared test with the alternative hypothesis of linear association at Week 8 or endpoint.

(Ref. Text Table 23, Model 5.3.5.1, Study 302)

MO comment: the results of secondary efficacy analyses supported the findings of primary efficacy analysis, however, the reader is cautioned that the numerous p-values presented by the sponsor are not adjusted for multiple comparisons that have been performed.

Analysis of Center Effect

Remission rates in Poland and Russia, the pooled centers that enrolled the majority of subjects were similar to the overall remission rates (Table 56). Remission rates in the other pooled centers followed a similar trend, although some differences were observed, most likely as a result of the small number of subjects in certain pooled centers. The p-value from the treatment pooled centre interaction was 0.5473, indicating that there was no difference in treatment effect.

Table 56 Analysis of Centre Effect on the Proportion of Subjects in Remission at Week 8

	Placebo (N = 86)	SPD476 2.4g/day (N = 84)	SPD476 4.8g/day (N = 86)	Asacol (N = 86)
Number of subjects per pooled centre				
Hungary	7	7	9	8
Israel	4	4	1	5
Poland	37	30	33	30
Russia	28	29	30	26
The Baltic States [†]	7	8	8	10
Western Europe [‡]	3	5	4	7
Subjects in remission[§]: n (%)				
Hungary	19 (22.1)	34 (40.5)	35 (41.2)	28 (32.6)
Israel	2 (28.6)	3 (42.9)	2 (22.2)	3 (37.5)
Poland	0	1 (25.0)	0	1 (20.0)
Poland	6 (16.2)	13 (43.3)	13 (39.4)	11 (36.7)
Russia	6 (21.4)	12 (41.4)	15 (50.0)	9 (34.6)
The Baltic States [†]	5 (71.4)	4 (50.0)	2 (25.0)	3 (30.0)
Western Europe [‡]	0	1 (16.7)	3 (75.0)	1 (14.3)
p-value [§]			0.5473	

Source: Section 12.1, Table 2.3.1.

* The Baltic States pooled centre consisted of subjects from Estonia, Latvia and Lithuania.

† The Western Europe pooled centre consisted of subjects from France, Germany and Spain.

‡ Subjects who had a UC-DAI score of ≤1 with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

§ p-value from the treatment-pooled centre interaction from a logistic regression model with treatment, pooled centre and treatment-pooled centre as factors.

(Ref. Text Table 15, Model 5.3.5.1, Study 302)

SAFETY EVALUATION

Of the 343 subjects randomized, 341 subjects received at least one dose of study medication and were included in the safety population, two subjects (subjects 62803 and 63606 in SPD476 2.4g/day QD) were randomized in error and did not receive any study medication.

Extent of Exposure

The majority of subjects in all treatment groups received treatment for ≥ 4 weeks (Table 57). Mean duration of exposure to study treatment and the sum of exposure were slightly greater in the active treatment groups compared to the placebo group. More subjects in the placebo group had < 2 weeks exposure to study treatment.

Table 57 Duration of Treatment Exposure – Safety Population

	Placebo		SPD476 2.4g/day		SPD476 4.8g/day		Asacol	
	(N = 86)		(N = 84)		(N = 85)		(N = 86)	
Exposure in weeks*, n (%)								
0 to <2	10	(11.6)	2	(2.4)	1	(1.2)	4	(4.7)
2 to <4	14	(16.3)	5	(6.0)	6	(7.1)	5	(5.8)
4 to 8	46	(53.5)	46	(54.8)	42	(49.4)	45	(52.3)
>8	16	(18.6)	31	(36.9)	36	(42.4)	31	(36.0)
Mean (SD)	6.10	(2.667)	7.36	(1.878)	7.49	(1.819)	7.29	(2.095)

Ref. Text Table 27, Module 5.3.5.1, Study 302)

Overall Incidence of Adverse Events (AEs)

Treatment-emergent AEs were experienced by 72 subjects in the safety population and occurred to a similar extent between the treatment groups (Table 58). The majority of AEs were of mild or moderate intensity; only five subjects had a severe adverse event (3 in the placebo group and 1 in each of the SPD476 4.8g/day QD and Asacol groups). Treatment-related AEs were experienced by eight subjects (9.3%) in the placebo group, 10 subjects (11.9%) in the SPD476 2.4g/day group, 12 subjects (14.1%) in the SPD476 4.8g/day group and six subjects (7.0%) in the Asacol group.

Serious adverse events (SAEs) and AEs leading to withdrawal were very infrequent. For SAEs, there were 2 subjects [2.3%] each in the placebo and Asacol groups and one subject [1.2%] in the SPD476 2.4g/day group. For AEs leading to withdrawal, there were 2 subjects [2.3%] in the placebo group and one subject [1.2%] each in the SPD476 2.4g/day and Asacol groups. No SAEs or AEs leading to withdrawal were experienced in the SPD476 4.8g/day group.

Table 58 Treatment-Emergent Adverse Events – Safety Population

	Placebo		SPD476 2.4g/day		SPD476 4.8g/day		Asacol	
	(N = 86)		(N = 84)		(N = 85)		(N = 86)	
Number (%) of subjects with:								
Any AE	15	(17.4)	20	(23.8)	20	(23.5)	17	(19.8)
Any mild AE	5	(5.8)	15	(17.9)	15	(17.6)	11	(12.8)
Any moderate AE	7	(8.1)	9	(10.7)	6	(7.1)	9	(10.5)
Any severe AE	3	(3.5)	0		1	(1.2)	1	(1.2)
Any treatment-related AE	8	(9.3)	10	(11.9)	12	(14.1)	6	(7.0)
Any SAE	2	(2.3)	1	(1.2)	0		2	(2.3)
AE that led to withdrawal	2	(2.3)	1	(1.2)	0		1	(1.2)

Ref. Text Table 28, Module 5.3.5.1, Study 302)

Most Common Treatment-Emergent AEs

In general, there were no notable differences between the placebo, SPD476 and Asacol groups or between the two doses of SPD476 in regard to the types or frequencies of AEs experienced (Table 59). The most frequently reported AEs in all groups were GI disorders. The most frequent AEs by preferred term were headache (6.0% in the SPD476 2.4g/day group, 4.7% in the SPD476 4.8g/day group and 3.5% in the Asacol 2.4g/day group), flatulence (1.2% in the placebo group, 4.8% in the SPD476 2.4g/day group, 3.5% in the SPD476 4.8g/day group and 1.2% in the Asacol 2.4g/day group) and abdominal pain nos (3.5% in the placebo group, 3.6% in the SPD476 2.4g/day group and 2.3% in the Asacol 2.4g/day group).

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Table 59 Treatment-Emergent Adverse Events Experienced by $\geq 2\%$ of Subjects

System organ class Preferred term	Placebo		SPD476 2.4g/day		SPD476 4.8g/day		Asacol	
Number (%) of subjects	(N = 86)		(N = 84)		(N = 85)		(N = 86)	
Gastrointestinal disorders	8	(9.3)	10	(11.9)	7	(8.2)	7	(8.1)
Flatulence	1	(1.2)	4	(4.8)	3	(3.5)	1	(1.2)
Abdominal pain nos	3	(3.5)	3	(3.6)	0		2	(2.3)
Nausea	2	(2.3)	0		2	(2.4)	2	(2.3)
Colitis ulcerative aggravated	1	(1.2)	1	(1.2)	0		2	(2.3)
Nervous system disorders	3	(3.5)	5	(6.0)	5	(5.9)	3	(3.5)
Headache	0		5	(6.0)	4	(4.7)	3	(3.5)
Dizziness	3	(3.5)	0		1	(1.2)	0	
Investigations	4	(4.7)	3	(3.6)	1	(1.2)	2	(2.3)
Weight decreased	4	(4.7)	1	(1.2)	0		0	
General disorders and administration site conditions	2	(2.3)	3	(3.6)	1	(1.2)	1	(1.2)
Asthenia	2	(2.3)	2	(2.4)	1	(1.2)	0	
Infections and infestations	2	(2.3)	2	(2.4)	2	(2.4)	0	
Respiratory, thoracic and mediastinal disorders	0		0		2	(2.4)	3	(3.5)
Pharyngitis	0		0		0		2	(2.3)
Musculoskeletal and connective tissue disorders	2	(2.3)	0		1	(1.2)	1	(1.2)
Arthralgia	2	(2.3)	0		1	(1.2)	0	
Blood and lymphatic system disorders	0		2	(2.4)	0		0	

Ref. Text Table 29, Module 5.3.5.1, Study 302)

Treatment-Related AEs

Thirty-six subjects experienced a total of 49 treatment-related AEs (Table 60). Individual AEs occurred infrequently and there were no notable differences between treatments groups in regard to the types or frequencies of treatment-related AEs experienced. The most frequent treatment-related AEs were flatulence (1.2% in the placebo group, 4.8% in the SPD476 2.4g/day group, 2.4% in the SPD476 4.8g/day group and 1.2% in the Asacol group) and headache (1.2% in the SPD476 2.4g/day group, 3.5% in the SPD476 4.8g/day group and 2.3% in the Asacol group)

Table 60 Treatment-Related Adverse Events

System organ class Preferred term Number (%) of subjects	Placebo (N = 86)		SPD476 2.4g/day (N = 84)		SPD476 4.8g/day (N = 85)		Asacol 2.4 g/day (N = 86)	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Total	8	(9.3)	10	(11.9)	12	(14.1)	6	(7.0)
Gastrointestinal disorders	6	(7.0)	7	(8.3)	3	(3.5)	3	(3.5)
Flatulence	1	(1.2)	4	(4.8)	2	(2.4)	1	(1.2)
Abdominal pain nos	3	(3.5)	1	(1.2)	0		2	(2.3)
Nausea	2	(2.3)	0		2	(2.4)	1	(1.2)
Diarrhea nos	1	(1.2)	0		0		0	
Dyspepsia	0		1	(1.2)	0		0	
Rectal polyp	0		1	(1.2)	0		0	
Vomiting nos	0		1	(1.2)	0		0	
Nervous system disorders	2	(2.3)	1	(1.2)	4	(4.7)	2	(2.3)
Headache	0		1	(1.2)	3	(3.5)	2	(2.3)
Dizziness	2	(2.3)	0		1	(1.2)	0	
Investigations	2	(2.3)	1	(1.2)	1	(1.2)	0	
Weight decreased	2	(2.3)	0		0		0	
Liver function test nos abnormal	0		0		1	(1.2)	0	
Platelet count decreased	0		1	(1.2)	0		0	
General disorders & administration site conditions	1	(1.2)	1	(1.2)	1	(1.2)	0	
Asthenia	1	(1.2)	1	(1.2)	1	(1.2)	0	
Pyrexia	1	(1.2)	0		0		0	
Musculoskeletal and connective tissue disorders	1	(1.2)	0		1	(1.2)	0	
Arthralgia	1	(1.2)	0		1	(1.2)	0	
Skin and subcutaneous tissue disorders	0		1	(1.2)	1	(1.2)	0	
Prurigo	0		0		1	(1.2)	0	
Urticaria nos	0		1	(1.2)	0		0	
Hepatobiliary disorders	0		0		1	(1.2)	0	
Reproductive system and breast disorders	0		0		0		1	(1.2)
Menorrhagia	0		0		0		1	(1.2)
Vascular disorders	0		0		1	(1.2)	0	
Hypertension nos	0		0		1	(1.2)	0	

Ref. Text Table 31, Module 5.3.5.1, Study 302)

Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events

There were no deaths during the study. Five subjects (2 in the placebo group, 2 in the Asacol group, 1 in the SPD476 2.4g/day group, and none in the SPD476 4.8g/day group) experienced a total of eight SAEs. Of the eight SAEs, six experienced in the placebo and Asacol group were GI disorders (aggravated UC), and two SAEs experienced in the SPD476 2.4g/day group were perianal abscess and urinary retention. No SAEs were considered to be related to study medication and all SAEs were resolved at the end of the study.

In total, four subjects (2 in the placebo group, one in the SPD476 2.4g/day group, 1 in the Asacol group, and none in the SPD476 4.8g/day QD group) discontinued from the study due to an AE. With the exception of the non-serious event of asthenia in the SPD476 2.4g/day group, all events that resulted in discontinuation were GI disorder (aggravated UC). No AEs or SAEs that resulted in discontinuation were considered to be related to study medication.

Clinical Laboratory Evaluation

No clinically significant mean hematology and biochemistry values and no notable changes from baseline were observed in any group.

Changes from baseline in GGT and ALT values are presented in Table 61. A slight trend towards increasing GGT and ALT was observed in the SPD476 4.8g/day and Asacol groups, however, overall mean values for these parameters remained within the normal range at all time points.

Table 61 Change from Baseline in GGT and ALT Values – Safety Population

mean (SD)	Placebo		SPD476 2.4g/day		SPD476 4.8g/day		Asacol 2.4 g/day	
GGT (U/L)								
Week 4	-1.0	(8.65)	-1.5	(15.81)	10.7	(46.21)	-0.1	(15.95)
Week 8	-1.2	(17.09)	-5.7	(35.32)	9.3	(39.28)	3.0	(23.28)
Endpoint	-1.2	(14.49)	-4.0	(32.96)	8.9	(37.63)	2.4	(21.63)
ALT (U/L)								
Week 4	-4.3	(16.99)	2.1	(15.22)	1.5	(17.25)	1.9	(8.65)
Week 8	-2.8	(21.71)	1.5	(15.89)	3.6	(19.92)	5.0	(18.39)
Endpoint	-2.0	(17.85)	0.9	(14.86)	2.6	(20.29)	3.8	(17.34)

Ref. Text Table 33, Module 5.3.5.1, Study 302)

Week 4: placebo N = 58, SPD476 2.4g/day N = 74, SPD476 4.8g/day N = 75, Asacol 2.4g/day N = 74

Week 8: placebo N = 51, SPD476 2.4g/day N = 70, SPD476 4.8g/day N = 72, Asacol 2.4g/day N = 70

Endpoint: placebo N = 78, SPD476 2.4g/day N = 83, SPD476 4.8g/day N = 84, Asacol 2.4g/day N = 82

MO comment: Review of safety data from Study 302 demonstrated that SPD476 was safe and well tolerated, and there was no evidence of a dose-response relationship for any safety parameter.

10.2 List of Abbreviations

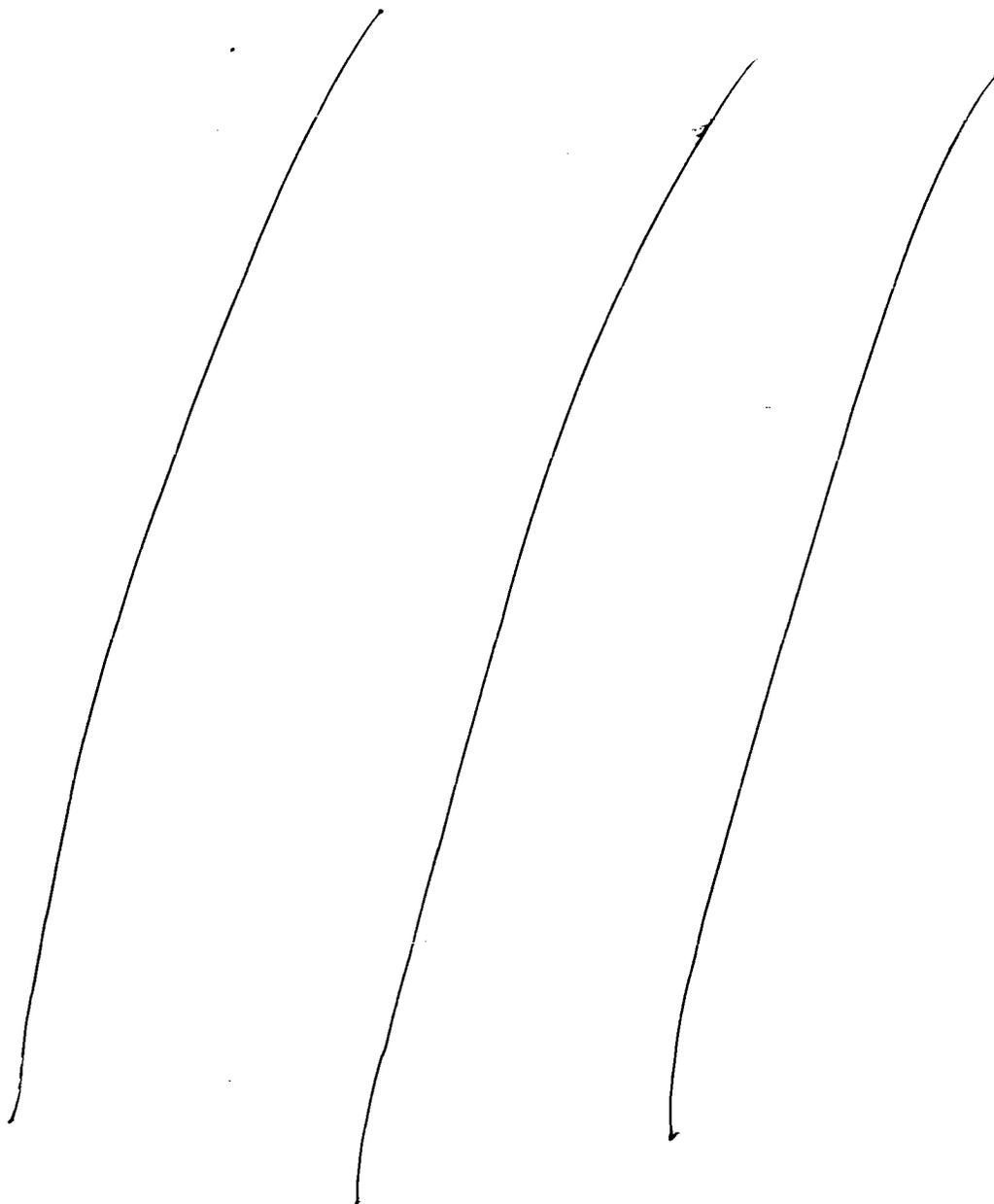
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
BARC	Bioanalytical Research Corporation
BID	Twice Daily
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Clinical Research Organization
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HEENT	Head, Eyes, Ears, Nose and Throat
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
LSM	Least Squares Mean
Max	Maximum
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	Minimum
NOS	not otherwise specified
NSAID	Non-Steroidal Anti-Inflammatory Drug
PEG	Polyethylene Glycol
PGA	Physician's Global Assessment
PI	Principal Investigator
PP	Per Protocol
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
UC	Ulcerative Colitis
UC-DAI	Ulcerative Colitis-Disease Activity Index
WOCP	Women of Child-bearing Potential

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Clinical Review
Fathia Gibril, MD, MHSc
NDA 22-000
Mesavance (Mesalamine)

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