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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

SYNOPSIS

Study number: SPD476-303	**Study drug:** SPD476 (Mesalazine)

Title of the study:

A phase III, randomised, multi-centre, open-label, 12 to 14 month extension study to evaluate the safety and tolerability of SPD476 (mesalazine) given once daily *versus* twice daily for the maintenance of ulcerative colitis in remission.

Investigators:

Multi-centre study

Enrolling countries: Australia, Costa Rica, Czech Republic, Estonia, France, Germany, Hungary, India, Israel, Latvia, Lituania, Mexico, New Zealand, Poland, Romania, Russia, Spain, the Ukraine and the US.

Coordinating Principal Investigator (PI): Prof. [redacted]

Study centre(s):

There were 101 enrolling centres in this study.

Prof. [redacted] is based in the [redacted] UK. Prof. [redacted] acted as the coordinating PI but was not based at any of the study centres that participated in the study.

Publications (reference):

None

Study period: 26 Nov 2003 to 13 March 2006	**Clinical phase:** III

Objectives:

Note: The following convention will be used in most of the text and all of the tables and listings in this Clinical Study Report:

- 2.4g/day administered as 1.2g bd will be written as 2.4g/d bd.
- 4.8g/day administered as 2.4g bd will be written as 4.8g/d bd.

Primary

Maintenance Phase:

- The primary objective of this study was to assess the safety and tolerability of SPD476 2.4g/day (2.4g dosed once daily [QD]) and SPD476 2.4g/day (1.2g dosed twice daily [BID]) in a long-term (12-month) study.

Note: This study was defined as a 12-14 month extension study due to the additional 2 months of treatment that subjects could receive for acute disease if they entered the Acute Phase.

Secondary

The secondary objectives of this study were as follows:

Acute Phase

- To evaluate the percentage of subjects in the Acute Phase who were in remission (an ulcerative colitis disease activity index [UC-DAI] score of $\leq$1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from study SPD476-301 [301] or SPD476-302 [302] baseline in the sigmoidoscopy score [friability moved from score of 1 to 2]) at the end of the treatment period with SPD476 4.8g/day (2.4g dosed BID)
- To assess the safety and tolerability of SPD476 4.8g/day (2.4g dosed BID) (this objective was added in accordance with Protocol Amendment 5).

Maintenance Phase

- To compare the time to relapse between the two treatment groups, SPD476 2.4g/day (2.4g dosed QD) and SPD476 2.4g/day (1.2g dosed BID) over 12 months
- To compare subject compliance between the two treatment groups, SPD476 2.4g/day (2.4g dosed QD) and SPD476 2.4g/day (1.2g dosed BID)

- To compare the percentage of subjects in remission at the end of the 12-month treatment period between the two treatment groups, SPD476 2.4g/day (2.4g dosed QD) and SPD476 2.4g/day (1.2g dosed BID)
- To compare Patient Questionnaire scores between treatment groups. (This objective was added in accordance with Protocol Amendment 5).

Methodology:

This was a randomised, phase III, multi-centre, open-label, long-term extension study (an extension of protocols SPD476-301 [parent study 301] and SPD476-302 [parent study 302]). The study consisted of two treatment phases, an Acute Phase and a Maintenance Phase.

Subjects were recruited into the Acute Phase if they were not in remission (UC-DAI remission criteria not met) at the End of Study/Early Withdrawal Visit of studies 301 or 302. Subjects in the Acute Phase received SPD476 4.8g/day BID (2.4g dosed BID) for 8 weeks. These subjects visited the clinic on three occasions over 2 months. If Acute Phase subjects were deemed to be in remission after 2 months, they were given the opportunity to enter the Maintenance Phase. Subjects reported symptoms (rectal bleeding and stool frequency) to an interactive voice response system (IVRS) daily during the Acute Phase. Subjects in the Acute Phase who did not achieve remission or who were withdrawn within 8 weeks were to complete all End of Study/Early Withdrawal Visit procedures.

Subjects were able to enter the Maintenance Phase if they were in remission (UC-DAI $\leq$1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from parent study baseline in the sigmoidoscopy score) at the End of Study/Early Withdrawal Visit in studies 301 or 302, or at the end of the Acute Phase. Subjects in the Maintenance Phase were to receive SPD476 2.4g/day (2.4g dosed QD or 1.2g dosed BID) for up to 12 months and to visit the clinic on six occasions over 12 months. Symptoms were discussed with subjects at all visits. Subjects in the Maintenance Phase who withdrew early from the study or who were withdrawn due to a relapse (where relapse was defined as a requirement for alternative treatment [any medication other than SPD476] for ulcerative colitis [UC]) were also to complete all End of Study/Early Withdrawal Visit procedures. Those subjects were to be given appropriate alternative treatment as determined by their primary physician.

The first visit of this study (303), ie Visit A1 (Acute Phase) or Visit M1 (Maintenance Phase), was the same as the End of Study/Early Withdrawal Visit of study 301 or 302. Visit M1 could also be Visit A3 for subjects who proceeded from the Acute Phase into the Maintenance Phase. Eligibility criteria were reviewed at Visit A1 and Visit M1. A sigmoidoscopy was performed to assess mucosal appearance at Visit A1 (as part of the End of Study/Early Withdrawal Visit of study 301 or 302), Visit A3 (End of Study/Early Withdrawal Visit of the Acute Phase), Visit M1 (as part of Visit A3, or the End of Study/Early Withdrawal Visit of study 301 or 302) and Visit M6 (End of Study/Early Withdrawal Visit of the Maintenance Phase). The UC-DAI score was calculated at these visits to determine if the subject was in remission.

Vital signs, adverse events (AEs), concomitant medications and study drug compliance were assessed at all study visits. A physical examination, blood draws (for safety analysis) and urinalysis were performed at all visits except Visit A2.

The investigator/designee was to follow up with the subject 30 days post last dose of the study drug and report any related non-serious AEs and all serious adverse events (SAEs) that occurred.

Number of subjects (total and for each treatment arm):

Acute Phase subjects received SPD476 4.8g/day BID. Maintenance Phase subjects were randomised in a 1:1 ratio to receive either SPD476 2.4g/day QD or SPD476 2.4g/day BID (1.2g BID).

	Acute Phase	**Maintenance Phase**		
	SPD476 4.8g/day BID	SPD476 2.4g/day QD	SPD476 2.4g/day BID	Overall
Planned	400	175	175	350
Enrolled	312	n/a	n/a	459
Randomised	n/a	225	234	459
Withdrawn	99	43	39	82
Completed	250	182	195	377
Efficacy	304	219	232	451
Safety	312	225	234	459

Diagnosis and main criteria for admission:

All subjects had to understand and be able, willing and likely to comply with study procedures and restrictions.

Inclusion criteria

- Subjects had to sign the study 303 informed consent form (indicating that they were aware of the investigational nature of the study), meet all eligibility requirements and have completed all assessments of the study 301 or 302 End of Study/Early Withdrawal Visit
- Subjects were eligible to enter the Acute Phase if they did not achieve remission at the End of Study/Early Withdrawal Visits in study 301 or 302
- Subjects were eligible to enter directly into the Maintenance Phase if they were in remission at the End of Study/Early Withdrawal Visits in study 301 or 302 or at Visit A3 of the Acute Phase in the current study
- Women of child-bearing potential (WOCP) had to use an acceptable contraceptive method while on study treatment
- Subjects and investigators had to agree that participation in the Acute and/or Maintenance Phase of this study was in the best interest of the subject.

Exclusion criteria

Subjects who withdrew from study 301 or 302 before Visit 3 (Week 2), or subjects who withdrew from study 301 or 302 due to a possibly or probably related severe AE or SAE, were not eligible to enter this study.

Test product, dose and mode of administration, batch no.:

SPD476 is a polymeric matrix formulation that displays both delayed and extended release of 5-aminosalicylic acid (5-ASA, or mesalazine) in the gastrointestinal tract. Each SPD476 tablet contained 1.2g of the active ingredient mesalazine and was administered orally. SPD476 batch numbers were as follows: [redacted] and [redacted]

The total daily dose for subjects in the Acute Phase was:

- SPD476 4.8g/day, 2 tablets SPD476 1.2g dosed BID.

The total daily dose for subjects in the Maintenance Phase was:

- SPD476 2.4g/day, 2 tablets SPD476 1.2g dosed QD, or
- SPD476 2.4g/day, 1 tablet SPD476 1.2g dosed BID.

Duration of treatment:

Duration of treatment period: Acute Phase, 2 months; Maintenance Phase, 12 months. Subjects entering the Acute Phase and progressing to the Maintenance Phase could receive study treatment for a total of 14 months.

Duration of follow-up: 30 days

Reference therapy, dose and mode of administration, batch no.:

None.

Criteria for evaluation:

The safety and tolerability of the study medication was assessed by AE monitoring, laboratory testing (haematology and biochemistry), urinalysis, physical examination and vital signs. Compliance was assessed by monitoring the number of tablets dispensed to and returned by subjects.

The efficacy endpoints for this study were time to relapse for the Maintenance phase and the percentage of subjects in remission at the end of the study for the Acute and Maintenance phases. Relapse was defined as a requirement for alternative treatment for UC. Remission was defined as a UC-DAI score of $\leq$1 with a score of 0 for rectal bleeding and stool frequency and at least a 1-point reduction in the sigmoidoscopy score from the baseline of study 301 or 302.

The UC-DAI consisted of rectal bleeding, stool frequency and sigmoidoscopy scores and the physician's global assessment (PGA). Each of these parameters was assessed on a scale of 0 to 3, with 3 being the most severe score. The sum of scores for all four parameters determined the UC-DAI score. Assessment of sigmoidoscopic appearance was performed in the worst inflamed area in the rectum or in the sigmoid if the rectum was not inflamed. The same area was to be evaluated throughout the study. The sigmoidoscopy and PGA at Visits A1 and A3 and M1 and M6 were to be performed by the same investigator/endoscopist.

Statistical methods:

The safety population included all subjects dosed in either the Acute Phase or the Maintenance Phase of the study. The efficacy population included all subjects dosed in either the Acute Phase or the Maintenance Phase of the study, except for 18 subjects from three study centres (USA, Mexico and India) affected by GCP and non-compliance issues. The Efficacy Evaluable population was defined as all subjects who received at least one dose of study medication in the Maintenance Phase of the extension study, excluding subjects who did not take the treatment to which they were assigned; and subjects who did not meet the relaxed remission criteria defined as: a total UC-DAI score of ≤1.333, with a score of zero for rectal bleeding, a score of ≤1 for total stool frequency over 3 days and a sigmoidoscopy score reduction of 1 point or more from baseline of study 301 or 302, where total rectal bleeding and total stool frequency score is the sum of the last 3 diary days prior to the study visit.

Subject disposition was summarised according to subject completion/withdrawal experience in parent studies 301 and 302 and in both phases of this study. Demographic and baseline data collected prior to receiving treatment in study 301 or 302 was summarised for the various groups of subjects in the extension study.

The above summaries were presented overall, and (where applicable) split further by which study the subject came from (study 301 or 302) and which treatment was received in that study, whether or not the subject achieved remission in study 301 or 302, whether or not the Maintenance Phase was preceded by the Acute Phase, and which treatment was received in the Maintenance Phase.

The proportion of subjects who were in remission at Visit A3 (Month 2) of the Acute Phase, and at Visit M6 (Month 12) of the Maintenance Phase were summarised overall and (where applicable) by tables split similarly to those described above. Summary statistics were presented for efficacy variables, their changes from baseline (prior to the start of study 301 or 302) and their changes from the start of the relevant extension study phase. These summaries were presented overall and (where applicable) by Maintenance Phase treatment.

AEs were coded using MedDRA version 5.1. Any AEs that emerged (either started or worsened) during either phase of the extension study were summarised descriptively, including summaries by organ class system and preferred term. These summaries were presented overall, and split by the various factors described above, as applicable.

Summary statistics were presented for laboratory safety variables and vital signs, their changes from baseline (prior to the start of study 301 or 302), and their changes from the start of the relevant extension study phase. These summaries were presented overall and (where applicable) by the Maintenance Phase treatment.

Summary – Results:

Subject demographics

Demographic and baseline (parent study 301 or 302) characteristics were similar for subjects in both the Acute Phase and the Maintenance Phase of this study (study 303). The majority of subjects were Caucasian. Subjects were well matched in terms of gender, age (mean age was approximately 40 years), smoking history (the majority of subjects never smoked) and baseline UC-DAI score in parent studies 301 or 302 (mean score was 6.6 [± 1.5] points in the Acute Phase of 303 and 6.4 [± 1.5] points in the Maintenance Phase of 303). UC history data were generally similar for both Maintenance Phase treatment groups and between parent study treatment groups in the Acute Phase. The majority of subjects had a history of UC in both study phases (84.0% [Acute Phase], 85.6% [Maintenance Phase]) and approximately 15% of subjects (16.0% [Acute Phase], 14.4% [Maintenance Phase]) in both study phases were newly diagnosed ie diagnosed at screening prior to commencing study treatment in parent studies 301 and 302. The majority of subjects were historically diagnosed via colonoscopy and all subjects, except for one in the Maintenance Phase SPD476 2.4g/day QD group, were diagnosed with compatible histology. The majority of subjects had ≤2 relapses in the 2 years prior to study entry and left-sided UC with rectal involvement (mean extent of disease approximately 50 cm).

Efficacy results:

Efficacy was a secondary objective for this extension study.

Acute Phase

Remission was achieved in 59.5% of subjects who completed the Acute Phase (Month 2). A response to treatment was observed for subjects entering from all parent study treatment groups.

Maintenance Phase

The proportion of subjects withdrawing due to relapse in the Maintenance Phase was low. Both treatment groups had similar times to relapse for the duration of the Maintenance Phase. At 12 months (360 days), the proportion of subjects who had not relapsed was approximately 88% in the SPD476 2.4g/day QD group and

92% in the SPD476 2.4g/day BID group.

At Visit M1 (Month 0) of the Maintenance Phase, 78.1% of subjects in the SPD476 2.4g/day QD group and 82.3% of subjects in the SPD476 2.4g/day BID group were in remission according to the strict criteria employed in this study (UC-DAI ≤1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from parent study baseline in the sigmoidoscopy score). The remainder of subjects (SPD476 2.4g/day QD, 21.9%; SPD476 2.4g/day BID, 17.7%) were not in remission according to the strict criteria, but were in the investigators' opinion well enough to enter the Maintenance Phase.

At Month 12, 64.4% of subjects in the SPD476 2.4g/day QD group and 68.5% of subjects in the SPD476 2.4g/day BID group met the strict remission criteria; no statistically significant differences were observed between treatment groups.

At Month 12, remission was observed in 75.8% of subjects who entered the Maintenance Phase directly from studies 301 and 302 (SPD476 2.4g/day QD, 74.6%; SPD476 2.4g/day BID, 77.0%) and 55.9% (SPD476 2.4g/day QD, 52.5%; SPD476 2.4g/day BID, 59.1%) of subjects who entered the Maintenance Phase following prior treatment in the Acute Phase.

Remission was observed in an identical percentage of subjects from both parent studies. A response to treatment was observed for subjects entering from all parent study treatment groups; however, no clear trend between remission and parent study treatment and no statistically significant differences were observed at Month 12 between SPD476 2.4g/day QD and SPD476 2.4g/day BID groups split by parent study treatments.

Most subjects in both treatment groups were satisfied with the Maintenance Phase study treatment in terms of number of tablets taken at one time, number of times taken per day and size of study medication tablets, as assessed by the patient questionnaire. A greater percentage of subjects were extremely satisfied with regard to the number of tablets taken at one time in the SPD476 2.4g/day QD group than in the SPD476 2.4g/day BID group (68.4% *vs* 53.4%).

Safety results:

Acute Phase
The majority of subjects (65.7%) in the Acute Phase received study treatment for >8 weeks; the mean duration of exposure to SPD476 4.8g/day BID was 8.1 (±1.7) weeks.

The mean compliance to study treatment in the Acute Phase was 97.8% and the majority of subjects (94.6%) were 80 to 120% compliant to study treatment.

A summary of treatment-emergent AEs observed in the Acute Phase is presented below.

Summary of Treatment-Emergent Adverse Events – Acute Phase (N = 312)		
Number (%) of subjects with:		
Any AE	72	(23.1)
Any mild AE	51	(16.3)
Any moderate AE	25	(8.0)
Any severe AE	8	(2.6)
Any treatment-related AE	27	(8.7)
Any SAE	9	(2.9)
Any AE that led to withdrawal	9	(2.9)
Any AE that led to death	1	(0.3)

Overall, 72 subjects (23.1%) experienced treatment-emergent AEs during the Acute Phase and 27 of these subjects (8.7%) had treatment-related AEs; the majority of AEs were mild or moderate. Consistent with parent study and Maintenance Phase results, gastrointestinal disorders were the most frequently reported category of AE (26 subjects, 8.3%). Nine subjects withdrew from the Acute Phase due to five AEs and four SAEs, most of which were gastrointestinal disorders. One SAE and two AEs that led to withdrawal (pancreatitis nos [SAE], headache nos aggravated, and colitis ulcerative aggravated) were assessed as probably related to study treatment and another AE (colitis ulcerative aggravated) was assessed as possibly related to study treatment. Nine subjects experienced nine SAEs, most of which were gastrointestinal disorders. No SAEs were assessed as related to study treatment, except for the one aforementioned SAE that led to withdrawal. One SAE (suicide [subject fell while intoxicated with alcohol]), assessed as unrelated to study treatment, led to subject death. Three renal and urinary disorder AEs (dysuria, nephrolithiasis and renal pain) occurred in the Acute Phase, all of which were assessed as unrelated to study treatment. No subject experienced a hepatobiliary AE.

Maintenance Phase
The majority of subjects (79.1%) in the Maintenance Phase received study treatment for >48 weeks (12 months). The mean duration of exposure to study treatment in the Maintenance Phase was 47.6 (± 11.3) weeks; there were no notable differences between treatment groups with regard to duration of treatment

exposure. The mean compliance to study treatment in the Maintenance Phase was 98.7% and the majority of subjects (94.6%) were 80 to 120% compliant to study treatment. A summary of treatment-emergent AEs observed in the Maintenance Phase is presented below.

Overall, 174 subjects (37.9%) experienced treatment-emergent AEs and 47 of these subjects (10.2%) experienced treatment-related AEs in the Maintenance Phase; the majority were moderate or mild and occurred to a similar extent in both treatment groups. Consistent with parent study results, gastrointestinal disorders were the most frequently reported AEs. Eighteen subjects (3.9%) experienced 22 SAEs in the Maintenance Phase: nine subjects in the SPD476 2.4g/day QD group had ten SAEs, and nine subjects in the SPD476 2.4g/day BID group had 12 SAEs. Most were gastrointestinal disorders. One SAE (liver function tests not otherwise specified [nos] abnormal) was assessed as possibly related to treatment with SPD476 2.4g/day QD. One SAE led to subject death (electric shock).

Summary of Treatment-Emergent Adverse Events – Maintenance Phase

	SPD476 2.4g/day QD (N = 225)		SPD476 2.4g/day BID (N = 234)		Overall (N = 459)	
Number (%) of subjects with:						
Any AE	88	(39.1)	86	(36.8)	174	(37.9)
Any mild AE	62	(27.6)	63	(26.9)	125	(27.2)
Any moderate AE	44	(19.6)	38	(16.2)	82	(17.9)
Any severe AE	7	(3.1)	5	(2.1)	12	(2.6)
Any treatment-related AE	25	(11.1)	22	(9.4)	47	(10.2)
Any SAE	9	(4.0)	9	(3.8)	18	(3.9)
Any AE that led to withdrawal	11	(4.9)	10	(4.3)	21	(4.6)
Any AE that led to death	0	(0.0)	1	(0.4)	1	(0.2)

Twenty-one subjects (4.6%) withdrew from the Maintenance Phase due to AEs (11 subjects [SPD476 2.4g/day QD], ten subjects [SPD476 2.4g/day BID]), most of which were gastrointestinal disorders. Two AEs of colitis ulcerative aggravated (both in the SPD476 2.4g/day QD group) that led to withdrawal were assessed as probably related to study treatment and one SAE and another AE (liver function tests nos abnormal [SAE], SPD476 2.4g/day QD group; arthralgia, SPD476 2.4g/day BID group) that led to withdrawal were assessed as possibly related to study treatment. Seven subjects had renal and urinary disorder AEs: four events of haematuria (two in each treatment group), one event of cystitis nos in the SPD476 2.4g/day BID group, and individual events of calculus ureteric, nephrolithiasis and nocturia in SPD476 2.4g/day QD group, all were assessed as unrelated to study treatment. One subject in the SPD476 2.4g/day QD had two hepatobiliary disorder events of cholecystitis chronic nos [AE] and hepatitis chronic nos [SAE], both of which were assessed as unrelated to study treatment.

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

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Date of report

09 October 2006