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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: SPD476-301	**Study drug:** Mesalazine

Title of the study:

A phase III, randomised, multi-centre, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of SPD476 (mesalazine) given twice daily (2.4g/day) *versus* SPD476 given as a single dose (4.8g/day) in subjects with acute mild to moderate ulcerative colitis

Investigators:

Multi-centre study

Enrolling countries: Australia, Costa Rica, the Czech Republic, India, Mexico, New Zealand, Romania, the Ukraine and the USA.

Coordinating Principal Investigator (PI): [redacted] MD

Study centres:

A total of 52 centres enrolled subjects in this study.

Prof [redacted] was based at the [redacted] USA. Prof [redacted] was a Sub-Investigator for this study.

Publications (reference):

None

Study period: 30 Sep 2003 to 17 Jan 2005	**Clinical phase:** III

Objectives:

Primary

To compare the percentage of subjects in remission after 8 weeks of treatment for SPD476 2.4g/day given twice daily ([BID] ie 1.2g dosed BID) *versus* placebo, and SPD476 4.8g/day given once daily (QD) *versus* placebo (this definition was in accordance with statistical analysis plan [SAP] version 3.0). Remission was defined as an 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.

Secondary

- 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 the UC-DAI score from baseline to 8 weeks of treatment between the three treatment groups
- 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 compare the time to withdrawal 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.

Methodology:

This was a randomised, phase III, multi-centre, double-blind, parallel group, placebo-controlled study to assess the safety and efficacy of SPD476 2.4g/day BID and SPD476 4.8g/day QD. Eligible subjects were randomised to receive SPD476 2.4g/day BID, SPD476 4.8g/day QD or placebo in a 1:1:1 ratio.

Subjects visited their designated clinic on five different occasions: at the Screening Visit (Week -1), Baseline

Visit (Week 0), Visit 3 (Week 2), Visit 4 (Week 4) and the End of Study (Week 8)/Early Withdrawal Visit.

Assessments were conducted throughout the study to determine the efficacy, safety, and tolerability of the study drug. The UC-DAI was used to assess treatment efficacy. Subjects reported their ulcerative colitis (UC) symptoms (rectal bleeding and stool frequency) via an interactive voice response system (IVRS) throughout the study. A sigmoidoscopy and Physician's Global Assessment (PGA) were performed at the Baseline and End of Study/Early Withdrawal Visits. The sigmoidoscopy and PGA at the End of Study/Early Withdrawal Visit were to be performed by the same Investigator/endoscopist who performed them at the Baseline Visit.

Subjects were not allowed to take rescue medication (any alternative UC treatment including other mesalazine-containing products) during the study, with the exception of the screening period in which they were permitted to continue on a stable dose (≤2.0g/day) of the mesalazine treatment they were taking prior to the Screening Visit. If subjects required rescue medication, they were withdrawn and given an appropriate alternative UC treatment as determined by their Investigator. Drug compliance was evaluated at Visits 3 and 4, and at the End of Study/Early Withdrawal Visit. Any unused medication and used packaging was returned at these visits; new medication was dispensed at Visits 3 and 4.

Subjects who were in remission at the end of the 8-week treatment period of this study were given the opportunity to enrol into the open-label Maintenance Phase of extension study SPD476-303. Those who were not in remission (UC-DAI score >1) at the End of Study/Early Withdrawal Visit of this study were given the opportunity to enrol into the Acute Phase of extension study SPD476-303. Subjects who withdrew before Visit 3 (Week 2) were not eligible for the extension study. The Investigator was to follow up with those subjects who did not enter the extension study 30 days after the End of Study/Early Withdrawal Visit and report related non-serious adverse events (AEs) and all serious adverse events (SAEs) that occurred.

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

Subjects were allocated to receive SPD476 2.4g/day BID, SPD476 4.8g/day QD or placebo in a 1:1:1 ratio.

Number of subjects	Placebo	SPD476 2.4g/day BID	SPD476 4.8g/day QD	Total
Planned	85	85	85	255
Randomised	93	93	94	280
Withdrawn	41	17	21	79
Completed	52	76	73	201
ITT population	85	88	89	262
PP population	76	81	79	236
Safety population	93	93	94	280

ITT = Intent-to-treat, PP = Per Protocol

Diagnosis and main criteria for admission:

Subjects had to fulfil the following criteria for inclusion into the study:

- 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 sterilised) were eligible, as were women of child-bearing potential (WOCP) 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 ≤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 a PGA of ≤2). Diagnosis of UC originally had to be established by sigmoidoscopy, colonoscopy, or barium enema and have compatible histology
- Subjects who, in the Investigator's opinion, were not likely to respond to mesalazine doses of 2.4g/day were not included.

Subjects who fulfilled any of the following criteria were excluded from the study:

- 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 >2.0g/day. If a subject had a recent mesalazine dose reduction from >2.0g/day to ≤2.0g/day and relapsed within 2 weeks of that dose reduction he/she was not eligible

- Subjects with Crohn's Disease, proctitis (where the extent of inflammation was ≤15cm from the anus), bleeding disorders, or active peptic ulcer disease
- Subjects with asthma if they were known to be mesalazine-sensitive
- Subjects who in the Investigator's opinion were at immediate or significant risk of toxic megacolon
- 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 immunosuppressants within 6 weeks prior to baseline
- Subjects who used antibiotics within 7 days prior to baseline
- Subjects who used any anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, Cox-2 inhibitors, or ibuprofen on a repeat basis within 7 days prior to baseline
- Subjects who had unsuccessfully treated their current UC relapse with steroids and/or doses of mesalazine >2.0g/day
- Subjects who had moderate or severe renal impairment (defined as a creatinine level of >2mg/dL) were contra-indicated for treatment with mesalazine compounds.

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

SPD476 is a polymeric matrix formulation that displays both delayed- and extended-release of mesalazine in the gastrointestinal tract. Each tablet of SPD476 contained 1.2g of the active ingredient mesalazine and was administered orally in daily doses of 2.4g/day BID or 4.8g/day QD.

Batch numbers of the [redacted] 1.2g tablets were [redacted] and [redacted]

Duration of treatment:

- Duration of screening period: 3-7 days
- Duration of enrolment period: 12 months
- Duration of treatment period: 8 weeks
- Duration of follow-up: 30 days

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

In order to blind the study treatments, placebo tablets were identical in appearance to SPD476, but contained no mesalazine.

Batch numbers of the placebo tablets were [redacted] [redacted] and [redacted]

Criteria for evaluation:

Efficacy

The primary efficacy endpoint for this study was remission defined as a score of ≤1 on the UC-DAI scale with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from baseline in the sigmoidoscopy score. The UC-DAI consisted of four parameters: rectal bleeding, stool frequency, sigmoidoscopy and PGA. Each of these parameters was assessed on a scale of 0-3, with 3 being the most severe score. The sum of the scores of all parameters determined the UC-DAI score.

Components of the UC-DAI score were used for other evaluations of efficacy, including:

- 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 (added in accordance with Protocol Amendment 4)
- Clinical remission: defined as subjects who scored 0 for both the total stool frequency and the total rectal bleeding score ie a complete resolution of symptoms (added in accordance with Protocol Amendment 4)
- Change from baseline in UC-DAI score
- Change from baseline in symptoms, sigmoidoscopy score and PGA.

Any change in symptoms at Weeks 2, 4 and 8 was assessed via rectal bleeding and stool frequency data. Subjects assessed their own rectal bleeding and stool frequency symptoms and reported them daily to the IVRS

during the study. The Investigator calculated the mean score of each parameter for the last available 3 days in the 5-day period immediately prior to each study visit. No data older than 5 days were used.

Assessment of sigmoidoscopic appearance was performed at baseline and at Week 8 (End of Study/Early Withdrawal Visit) on the worst inflamed area in the rectum or the sigmoid if the rectum was not inflamed.

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

Safety

The safety and tolerability of mesalazine were assessed via AEs, laboratory testing (haematology, biochemistry and urinalysis), physical examination, and vital signs. Time to withdrawal from the start of study medication was also assessed.

Statistical methods:

The Safety population was defined as all randomised subjects who received at least one dose of study medication. The ITT population was defined as all randomised subjects who received at least one dose of study medication with the exception of the 18 subjects enrolled at centres [redacted] (USA), [redacted] (Mexico) and [redacted] (India) who were excluded from the ITT population due to protocol and Good Clinical Practice (GCP) non-compliance issues at the respective centres (in accordance with SAP version 3.0). The PP population was defined as all subjects in the ITT population who were without major protocol violations.

The primary efficacy variable was the proportion of subjects who were in remission at Week 8.

The primary treatment comparisons were:

- SPD476 2.4g/d BID *versus* Placebo
- SPD476 4.8g/d QD *versus* Placebo.

The primary analysis of the primary efficacy variable was performed on the ITT population.

The proportion of subjects in remission at 8 weeks was compared with placebo for both active treatment comparisons 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. The odds ratio between active treatment and placebo together with the associated confidence intervals (CIs) were presented analogous to the significance levels used in the hypothesis testing (in accordance with SAP version 3.0). Subjects who withdrew prematurely from the study or who provided no post-baseline data were considered as not being in remission for the primary analysis (in accordance with SAP version 3.0).

If the primary analysis was statistically significant, an additional analysis adjusting for centre and investigations into heterogeneity was to be performed.

A sensitivity analysis of the primary efficacy variable was performed using the Safety population in order to assess the robustness of the results to the exclusion of the 18 subjects enrolled at centres [redacted] and [redacted]

Additional statistical analyses of the primary efficacy variable and analyses of secondary efficacy variables were considered supportive. Consequently, multiplicity adjustments to the significance levels were not carried out. Unless specified, hypothesis tests at the 0.05 significance level and two-sided 95% CIs were used throughout for supportive analyses. The proportion of subjects with clinical improvement, the proportion of treatment failures and the proportion of subjects in clinical remission at 8 weeks was compared with placebo for both active treatment comparisons using the chi-squared test. Change from baseline in UC-DAI score was compared with placebo for both active treatment comparisons using an analysis of covariance (ANCOVA) with change from baseline as the response variable and baseline UC-DAI score, treatment group and pooled centre as explanatory variables. Change from baseline in sigmoidoscopy score was compared with placebo for both active treatment comparisons using the Mantel-Haenszel chi-squared test. Last observation carried forward (LOCF) analyses were performed as part of the supportive analysis (in accordance with SAP version 3.0). These analyses were denoted as being at endpoint (End of Study [Week 8]/Early Withdrawal Visit).

For all secondary efficacy statistical analyses, the following treatment comparisons were made (in accordance with SAP version 3.0):

- SPD476 2.4g/day BID *versus* Placebo
- SPD476 4.8g/day QD *versus* Placebo
- SPD476 2.4g/d BID *versus* SPD476 4.8g/d QD.

Safety summaries were presented for the Safety population. AEs were coded using the medical dictionary for

drug regulatory activities (MedDRA) version 5.1. Treatment-emergent AEs were summarised descriptively, including summaries by system organ class and preferred term. Summary statistics were presented for laboratory safety variables and vital signs at each timepoint.

Withdrawals from the study were summarised by treatment group and reason. Time to withdrawal from the start of study medication was compared between the three treatment groups using Kaplan-Meier curves.

Summary - results:

Subject demographics

There were no clinically significant differences between the treatment groups with regard to demography at screening. The treatment groups were balanced in terms of age, gender, ethnic origin, height and weight. The majority of subjects were Caucasian and approximately 20% of subjects were of Asian/Pacific Islander origin. The mean age of subjects was approximately 42 years. The majority of subjects had never smoked and less than 10% of subjects in each group currently smoked.

UC history was also generally similar in all treatment groups. There were no notable differences between the groups with regard to the method of diagnosis, full extent of disease, rectal involvement and extra-intestinal manifestations.

Overall, there were no differences between the groups in terms of demography or UC history that would affect the outcome of the study.

Efficacy results

An analysis of the primary endpoint (the proportion of subjects in remission in the SPD476 and placebo groups at Week 8) is presented for the ITT population below.

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

Chi-squared test. The smaller p-value was evaluated at the 0.025 significance level and the larger p-value was evaluated at the 0.05 significance level. CIs presented are analogous to the significance level.

A summary of secondary efficacy results at Week 8 is presented for the ITT population below.

	Placebo (N = 85)	SPD476 2.4g/day BID (N = 88)	SPD476 4.8g/day QD (N = 89)
Clinical improvement (reduction in UC-DAI from baseline of ≥3 points)	25.9%	55.7%***	59.6%***
Treatment failure (unchanged, worsened or missing UC-DAI scores)	54.1%	28.4%***	24.7%***
Clinical remission (scores of 0 for stool frequency and rectal bleeding)	18.8%	37.5%**	32.6%*
Change from baseline in UC-DAI score† (least squares mean change)	-0.79	-2.71***	-3.46***
Sigmoidoscopic improvement†	36.5%	64.8%**	71.9%***

*p <0.05, **p <0.01, ***p <0.001 (*versus* placebo)

†Endpoint data

Safety results

There were 233 AEs reported by a total of 129 subjects.

A summary of treatment-emergent AEs is presented below.

	Placebo (N = 93)		SPD476 2.4g/day BID (N = 93)		SPD476 4.8g/day QD (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)
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)

Most AEs were mild or moderate; only 13 subjects had a severe AE, of which eight were in the placebo group. There were no notable differences between the treatment groups with regard to the incidence of treatment-related AEs, which were experienced by less than 20% of subjects in each group.

AEs experienced by ≥3% of subjects in any treatment group are presented in descending order of frequency below.

Number (%) of subjects	Placebo (N = 93)		SPD476 2.4g/day BID (N = 93)		SPD476 4.8g/day QD (N = 94)	
Colitis ulcerative aggravated	9	(9.7)	6	(6.5)	1	(1.1)
Flatulence	4	(4.3)	3	(3.2)	2	(2.1)
Headache	1	(1.1)	5	(5.4)	2	(2.1)
Nausea	2	(2.2)	3	(3.2)	3	(3.2)
Pyrexia	2	(2.2)	2	(2.2)	3	(3.2)
Diarrhoea nos*	2	(2.2)	4	(4.3)	0	
Dyspepsia	3	(3.2)	2	(2.2)	1	(1.1)
Arthralgia	0		3	(3.2)	1	(1.1)
Nasopharyngitis	1	(1.1)	0		3	(3.2)
Bronchitis nos	3	(3.2)	0		0	

*nos, not otherwise specified

Gastrointestinal disorders, the most frequent treatment-related AEs (experienced by 26 of the 46 subjects with treatment-related AEs), occurred in a greater proportion of subjects in the placebo group (13 subjects [14.0%]) than in the SPD476 groups (eight subjects [8.6%] in the 2.4g/day BID group and five subjects [5.3%] in the 4.8g/day QD group). Aggravated ulcerative colitis, flatulence, nausea, and dyspepsia were the most frequent treatment-related gastrointestinal disorders.

Gastrointestinal disorders were also the most frequent severe AEs (experienced by nine of the 13 subjects), most commonly aggravated ulcerative colitis (three subjects [3.2%] in the placebo group and one subject [1.1%] in the SPD476 2.4g/day BID group). Only two subjects experienced a severe treatment-related AE. [redacted] Both subjects discontinued due to their AE.

Seven subjects experienced a total of eight SAEs (three subjects in the placebo group, two subjects in the SPD476 2.4g/day BID group, and two subjects in the SPD476 4.8g/day QD group). Of these, all but one were gastrointestinal disorders. [redacted]

The most frequent AEs that led to study discontinuation were gastrointestinal disorders, which accounted for all but one of the discontinuations due to AEs. Discontinuation due to AEs occurred more frequently in the placebo group (11 subjects [11.8%]) than in either of the SPD476 groups (five subjects [5.4%] in the 2.4g/day BID group and two subjects [2.1%] in the 4.8g/day QD group). The most frequent AE that led to study discontinuation was aggravated ulcerative colitis (experienced by 10 of the 18 subjects withdrawn due to AEs).

There were no clinically relevant differences between the groups with respect to laboratory parameters, vital signs, or physical examination abnormalities.

Conclusions:

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.

Date of report

05 Aug 2005