CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-000
Drug Name:	Li salda (mesalamine delayed-release tablets)
Indication(s):	Induction of remission in mild-to-moderate ulcerative colitis
Applicant:	Shire Pharmaceuticals
Date(s):	PDUFA goal date 10/21/06, extended to 1/19/07
Review Priority:	Standard, with major amendment
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Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data in this NDA support the efficacy of Lialda in inducing remission in ulcerative colitis. Lialda appears to be equally efficacious at both of the doses studied, 2.4 g/day and 4.8 g/day.

1.2 Brief Overview of Clinical Studies

The applicant conducted two Phase III studies in support of the efficacy of Lialda, SPD476-301 and -302. These are reviewed here.

The studies are of similar design, with the primary difference being the dosing of the lower dose of Lialda (twice daily in study 301 and once a day in study 302, for a total of 2.4g/day in both). Both studies were randomized, multi-center and multinational, double-blind parallel-group, and placebo-controlled. They were designed to evaluate the safety and efficacy of Lialda, given at 2.4g/day or at a higher dose of 4.8g/day in subjects with acute mild to moderate ulcerative colitis.

Eligible subjects were adult males and females with mild to moderate active UC, defined as 4-10 on the ulcerative colitis disease activity index (UC-DAI) with a sigmoidoscopy score of >= 1 and a PGA of <= 2. (The UC-DAI consists of four parameters: rectal bleeding, stool frequency, sigmoidoscopy and Physician's global assessment (PGA). Each of these parameters is assessed on a scale of 0-3, with 3 being the most severe score. The sum of the scores of all parameters determines the UC-DAI score.)

In study 301, a total of 280 patients were randomized to receive either placebo (n=93), Lialda 2.4 g/day BID (n=93) or Lialda 4.8 g/day QD (n=94); a total of 201 patients completed the 8 week study (52, 76, and 73, respectively).

In study 302, a total of 343 patients were randomized to receive either placebo (n=86), Lialda 2.4 g/day QD (n=86), Lialda 4.8 g/day QD (n=85), or Asacol 2.4g/day TID; a total of 264 patients completed the 8 week study (52, 70, 72, and 70, respectively). Mesalamine 2.4g/day TID is considered to be standard of care; Asacol is an approved mesalamine product and was included at a dose of 2.4g/day TID as a reference arm.

Subjects visited their designated clinic on five different occasions: at Screening (week -1), Baseline (week 0), Visit 3 (week 2), Visit 4 (week 4) and End-of-study (week 8)/early withdrawal visit.

Subjects reported their UC symptoms (rectal bleeding and stool frequency) via an interactive voice response system (IVRS) throughout the study. A sigmoidoscopy and PGA were performed at baseline and final visit, by the same endoscopist. Rescue medication was not allowed.

Efficacy Assessment

The UC-DAI was used to assess efficacy. The **primary efficacy variable** was the proportion of subjects in remission at week 8. Remission was 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.

1.3 Statistical Issues and Findings

Lialda was significantly more efficacious than placebo. Remission rates among subjects with mild and moderate UC were 34 % for Lialda 2.4 g/day, 29% for Lialda 4.8 g/day, and 13% for placebo in study 301; and 40 % for Lialda 2.4 g/day, 41% for Lialda 4.8 g/day, and 22% for placebo in study 302. Results on secondary efficacy measures supported this finding.

2. INTRODUCTION

2.1 Overview

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but age of onset can vary widely. UC is more common in whites vs. non-whites and in women vs. men. The disease is manifest as mucosal inflammation and mucosal ulceration that occurs in the colon in a continuous segment beginning with the rectum. Extent of involvement varies, but it can include the entire colon. Involved areas classically show inflammatory changes that are limited to the mucosa, and, depending on severity, there may be extensive, broad-based ulceration. Clinically, UC presents as a chronic relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain, but there may be long quiescent periods between attacks. There may also be systemic manifestations of the disease, with involvement of joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a very significant risk of colon cancer with longstanding disease, such that pancolitis of 10 years duration or longer has a 20- to 30-fold increased risk of cancer compared to the general population.

Approved therapies for UC include corticosteroids for acute attacks of UC and mesalamine (5-aminosalicylic acid; 5-ASA) in various oral and rectal formulations to treat mildly or moderately active UC (including, for certain products, maintenance of remission). Also used, but

unapproved, therapies include azathioprine and 6-mercaptopurine. Use of any of the preceding has come to be considered part of "conventional therapy." Remicade is approved for induction of remission in moderately to severely active UC with inadequate response to conventional therapy.

The product under review, Lialda, is a mesalamine delayed-release tablet. Each tablet contains 1.2g of 5-ASA.

2.2 Data Sources

This NDA was submitted electronically and accessed through the CDER EDR.

In addition, case report forms were sent separately in response to an information request dated 01 June 2006.

Site 633 in Study 302 showed unusually high response rates in all treatment groups (approximately 67% in remission on average, compared to the overall average rate of 34% in study 302). The case report forms for this site were individually examined and the corresponding electronic records were checked against the values recorded on the CRFs; no inconsistencies were found. (This site was one of three sites selected for auditing based on sample size and efficacy results. The sites were inspected by the DSI; the overall assessment in the final report indicated that the studies appear to have been well conducted and no irregularities were found.)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The applicant conducted two Phase III studies in support of the indication, SPD476-301 and -302, and these are reviewed here. The studies are of similar design, with the primary difference being the dosing of the lower dose of Lialda (twice daily in study 301 and once a day in study 302, for a total of 2.4g/day in both).

An additional study, -303, an open-label extension of these studies, is not reviewed here.

Note that both the trade name Lialda and the code name SPD476 are used in the text and tables of this review.

SPD476-301

Design

Study 301 was a randomized, multi-center and multinational, double-blind parallel-group, placebo-controlled study to evaluate the safety and efficacy of Lialda, given twice daily (2.4g/day total) or given as a single and higher dose (4.8g/day) in subjects with acute mild to moderate ulcerative colitis. Enrolling countries included Australia, Costa Rica, the Czech Republic, India, Mexico New Zealand Romania, Ukraine and the United States; 52 centers enrolled subjects in this study. A total of 280 patients were randomized to receive either placebo (n=93), Lialda 2.4 g/day BID (n=93) or Lialda 4.8 g/day QD (n=94); a total of 201 patients completed the 8 week study (52, 76, and 73, respectively).

Eligible subjects were adult males and females with mild to moderate active UC, defined as 4-10 on the ulcerative colitis disease activity index (UC-DAI) with a sigmoidoscopy score of >= 1 and a PGA of <= 2. (The UC-DAI consists of four parameters: rectal bleeding, stool frequency, sigmoidoscopy and Physician's global assessment (PGA). Each of these parameters is assessed on a scale of 0-3, with 3 being the most severe score. The sum of the scores of all parameters determines the UC-DAI score.)

Subjects visited their designated clinic on five different occasions: at Screening (week -1), Baseline (week 0), Visit 3 (week 2), visit 4 (week 4) and End of study (week 8)/early withdrawal visit.

Subjects reported their UC symptoms (rectal bleeding and stool frequency) via an interactive voice response system (IVRS) throughout the study. A sigmoidoscopy and PGA were performed at baseline and final visit, by the same endoscopist. Rescue medication was not allowed.

Efficacy Assessment

The ulcerative colitis disease activity index (UC-DAI) was used to assess efficacy. The UC-DAI consists of four parameters: rectal bleeding, stool frequency, sigmoidoscopy and Physician's global assessment (PGA). Each of these parameters is 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.

Populations

The safety population was defined as all randomized subjects who received at least one dose of study medication; the ITT population was defined as all randomized subjects who received at least one dose of study medication with the exception of 18 subjects who were excluded due to protocol and good clinical practice non-compliance issues at their respective centers (**); and the per-protocol population as all subjects in the ITT population who were without major protocol violations.

Table 1. Study 301. Number of subjects (total and for each treatment arm)
Subjects were allocated to receive Lialda 2.4g/day BID, Lialda 4.8g/day QD or placebo in a 1:1:1 ratio.

Number of subjects	Placebo	Lialda 2.4g/day BID	Lialda 4.8g/day QD	Total
Planned	85	85	85	255
Randomized	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

Premature Study Discontinuation

Seventy-nine subjects discontinued from the study prematurely (Table 2). Discontinuations were more frequent in the placebo group compared to Lialda 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 Lialda 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 2 Study 301. 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)

Endpoints

The **primary efficacy variable** was the proportion of subjects in remission at week 8. Remission was 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.

Secondary efficacy endpoints included clinical improvement (reduction in UC-DAI score from baseline of >= 3 points), treatment failure (unchanged, worsened or missing UC-DAI scores),

clinical remission (scores of 0 for stool frequency and rectal bleeding), and sigmoidoscopic improvement. These endpoints were evaluated at week 8.

Analysis

To evaluate remission at week 8, Lialda 2.4g/d BID and Lialda 4.8g/d QD were each compared to placebo using a chi-squared test for comparison of proportions. The 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 that comparison was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level.

The ITT population was used for the primary analysis. A sensitivity analysis of the primary variable was performed using the safety population, in which the 18 patients excluded from the ITT population were counted as non-responders (i.e., not in remission).

Subjects who withdrew prematurely from the study were considered as not being in remission.

The proportion of subjects with clinical improvement, proportion of treatment failures, and proportion of subjects in clinical remission at 8 weeks was compared with placebo for both active treatments using a chi-square test. Change from baseline in UC-DAI score was compared with placebo for both active treatments using ANCOVA with baseline UC-DAI score, treatment group and pooled center as explanatory variables. Change from baseline in sigmoidoscopy score was compared with placebo using the Mantel-Haensel chi-squared test.

Analyses of secondary variables were considered supportive and therefore multiplicity adjustments were not carried out.

Study 301 Results

Demographics

The treatment groups were similar in demographic characteristics. The proportions of male and female subjects in each group were approximately equal. The majority of subjects were Caucasian and approximately 20% were of Asian/Pacific Islander origin. The mean age of subjects was approximately 40 years, with 10 subjects older than 65 (3, 2 and 5 in placebo, 2.4 g/d and 4.8 g/d, respectively.)The majority of subjects had never smoked and less than 10% of subjects in each treatment group currently smoked.

Table 3. Study 301. Demographic Characteristics – ITT Population

	Placebo (N = 86)		SPD476 2.4g/day BID (N = 88)		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	16	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	66.8		63.2		67.3	
Min, Max	31	115	40	119	36	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)	6	(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	(14.6)
Currently smokes	3	(3.5)	4	(4.5)	8	(9.0)

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)

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

Primary endpoint

The results for the proportion of subjects in remission at week 8 are given below for the ITT population.

Table 4. Study 301. Proportion of Subjects in Remission at Week 8

	Lialda		Placebo
	2.4g/day n =88	4.8g/day n =89	n =85
	n (%)	n (%)	n (%)
Subjects in Remission	30 (34)	26 (29)	11 (13)
p-value	0.001	0.009	

A significantly greater proportion of subjects were in remission in Lialda 2.4g/day and 4.8g/day groups compared to placebo group (34% and 29% versus 12%). The odds of remission on active treatment were approximately 3 times that of placebo. Of note is that little difference is seen in the results for 2.4 g/d and 4.8 g/d.

A sensitivity analysis of the safety population, including the 18 subjects excluded from the ITT population counted here as non-responders, supported these results: 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.

Secondary endpoints

A summary of secondary efficacy results in study 301 at Week 8 is given below. Analyses of secondary efficacy variables supported a finding of greater efficacy in both active treatment groups compared to placebo group.

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

Secondary Efficacy Variables	Lialda 2.4g/day n=88	Lialda 4.8g/day n=88	Placebo n=85
Clinical Improvement	56%***	60%***	26%
Treatment Failure	28%***	25%***	54%
Clinical Remission	38%**	33%*	19%
Sigmoidoscopic Improvement	65%**	72%***	37%
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

Clinical improvement was achieved in 55% (49/88) of subjects in Lialda 2.4g/day and 59% (53/89) in 4.8g/day group compared to 25% (22/85) in the placebo group. Similarly, a

significantly higher proportion of subjects achieved clinical remission in both active treatment groups compared to placebo group (38% and 33% vs. 19%). 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). In regard to treatment failure, a significantly higher proportion of subjects was classified as treatment failure in the placebo group (54%, 46/85) compared to Lialda 2.4g/day (28%, 25/88) and 4.8g/day groups (24%, 22/89).

SPD476-302

Design

Study 302 was a randomized, multi-center and multinational, double-blind parallel-group, placebo-controlled study to evaluate the safety and efficacy of Lialda given once a day at either 2.4g/day or 4.8g/day in subjects with acute mild to moderate ulcerative colitis. Enrolling countries included Germany, Spain, France, Poland, Hungary, Russia, Israel, Latvia, Lithuania and Estonia; 49 centers enrolled subjects in this study. A total of 343 patients were randomized to receive either placebo (n=86), Lialda 2.4 g/day QD (n=86), Lialda 4.8 g/day QD (n=85), or Asacol 2.4g/day TID; a total of 264 patients completed the 8 week study (52, 70, 72, and 70, respectively). Mesalamine 2.4g/day TID is considered to be standard of care; Asacol is an approved mesalamine product and was included at a dose of 2.4g/day TID as a reference arm.

Eligible subjects were adult males and females with mild to moderate active UC, defined as 4-10 on the ulcerative colitis disease activity index (UC-DAI) with a sigmoidoscopy score of >= 1 and a PGA of <= 2.

Subjects visited their designated clinic on five different occasions: at Screening (week -1), Baseline (week 0), Visit 3 (week 2), Visit 4 (week 4) and End of study (week 8)/early withdrawal visit.

Subjects reported their UC symptoms (rectal bleeding and stool frequency) via an interactive voice response system (IVRS) throughout the study. A sigmoidoscopy and PGA were performed at baseline and final visit, by the same endoscopist. Rescue medication was not allowed.

Efficacy assessment

The ulcerative colitis disease activity index (UC-DAI) was used to assess efficacy. The UC-DAI consists of four parameters: rectal bleeding, stool frequency, sigmoidoscopy and Physician's global assessment (PGA). Each of these parameters is 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.

Populations

The safety and ITT populations were defined as all randomized subjects who received at least one dose of study medication; and the per-protocol population as all subjects in the ITT population who were without major protocol violations.

Table 6. Study 302. Number of subjects (total and for each treatment arm):
Subjects were allocated to receive treatment (placebo, Lialda 2.4g/day QD, Lialda4.8g/day QD or Asacol 2.4g/day TID) in a 1:1:1:1 ratio.

Number of subjects	Placebo	Lialda 2.4g/day QD	Lialda 4.8g/day QD	Asacol 2.4g TID	Total
Planned	85	85	85	85	340
Randomized	86	86	85	86	343
Withdrawn	34	16	13	16	79
Completed	52	70	72	70	264
ITT population	86	84	85	86	341
PP population	82	78	78	83	321
Safety population	86	84	85	86	341

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

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 6. Discontinuations due to other reasons were infrequent and there were no notable differences between the groups.

Table 6. Study 302. 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 randomised 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)

Endpoints

The **primary efficacy variable** was the proportion of subjects in remission at week 8. Remission was 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.

Secondary efficacy endpoints included clinical improvement (reduction in UC-DAI score from baseline of >= 3 points), treatment failure (unchanged, worsened or missing UC-DAI scores), clinical remission (scores of 0 for stool frequency and rectal bleeding), and change from baseline in the individual components of the UC-DAI score, including symptoms scores, sigmoidoscopy score and PGA score.

Analysis

To evaluate remission at week 8, Lialda 2.4g/d QD and Lialda 4.8g/d QD were each compared to Placebo using a chi-squared test for comparison of proportions. The 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 that comparison was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level.

The ITT population was used for the primary analysis.

Subjects who withdrew prematurely from the study were considered as not being in remission.

The study was not designed to demonstrate non-inferiority of Lialda against Asacol; however, the comparison was included as a supportive analysis.

The proportion of subjects with clinical improvement, proportion of treatment failures, and proportion of subjects in clinical remission at 8 weeks was compared with placebo for both active treatments using a chi-square test. Change from baseline in UC-DAI score was compared with placebo for both active treatments using ANCOVA with baseline UC-DAI score, treatment group and pooled center as explanatory variables. Change from baseline in sigmoidoscopy score was compared with placebo using the Mantel-Haensel chi-squared test.

Analyses of secondary variables were considered supportive and therefore multiplicity adjustments were not carried out.

Study 302 Results

Demographics

The treatment groups were similar in demographic characteristics. The proportions of male and female subjects in each group were approximately equal. All subjects were Caucasian. The

mean age of subjects was approximately 43 years, with 22 subjects older than 65 (5, 6, 6, and 5 in placebo, 2.4 g/d, 4.8 g/d, and Asacol, respectively.)The majority of subjects had never smoked and less than 10% of subjects in each treatment group currently smoked.

Table 7. Study 302. 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	(8.68)	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)

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

Primary endpoint

The results for the proportion of subjects in remission at week 8 are given below for the ITT population.

Table 8. Study 302. Proportion of Subjects in Remission at Week 8

	Lialda		**Asacol**	**Placebo**
	2.4g/day n=84	**4.8g/day** n =85	n =86	n =86
	n (%)	n (%)	n (%)	n (%)
Subjects in Remission	34 (40)	35 (41)	28 (33)	19 (22)
p-value (treatment v. placebo)	0.010	0.007		

Secondary endpoints

A summary of secondary efficacy results in study 302 at Week 8 is given below. Analyses of secondary efficacy variables supported a finding of greater efficacy in both Lialda treatment groups compared to placebo group.

Table 9. Study 302. Results of Secondary Efficacy Endpoints (%Patients)

Secondary Efficacy Variables	Lialda 2.4g/day n=84	Lialda 4.8g/day n=85	Asacol 2.4g/day n=86	Placebo n=86
Clinical Improvement	61%**	65%***	56%*	40%
Treatment Failure	21%***	20%***	28%**	48%
Clinical Remission	42%**	41%**	34%NS	22%
Sigmoidoscopic Improvement	70%***	77%***	61%*	42%
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

A greater proportion of subjects achieved clinical improvement in the Lialda 2.4g/day (60%, 51/84) and 4.8g/day group (64%, 55/85) compared to the placebo group (39%, 34/86). Similarly, a 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%). 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). Significantly higher proportion of subjects was classified as treatment failure in the placebo group (48%, 41/86) compared to Lialda 2.4g/day (21%, 18/84) and 4.8g/day groups (20%, 20/85). 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.

3.2 Evaluation of Safety

There were no important differences between placebo and Lialda in terms of safety. For more details, see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

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% of females vs. 14%, 29%, 29% of males, for placebo, 2.4g/day and 4.8g/day groups, respectively).

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 also would not provide meaningful information as there were few non-whites.

The safety and effectiveness of Lialda in pediatric patients have not been studied.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Lialda was significantly more efficacious than placebo. Remission rates among subjects with mild and moderate UC were 34 % for Lialda 2.4 g/day, 29% for Lialda 4.8 g/day, and 13% for placebo in study 301; and 40 % for Lialda 2.4 g/day, 41% for Lialda 4.8 g/day, and 22% for placebo in study 302. Results on secondary efficacy measures supported this finding.

5.2 Conclusions and Recommendations

The data in this NDA support the efficacy of Lialda in inducing remission in ulcerative colitis. Lialda appears to be equally efficacious at both of the doses studied.

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